Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 4

The Eye and Ear

BRIAN P. WILCOCK
Ontario Veterinary College, Canada

THE EYE

I. General Considerations

The role of the veterinary pathologist in the diagnosis of ocular disease is greatly influenced by the accuracy with which the eye can be examined in the living animal. Some of its tissues, such as the lens, do not lend themselves well to pathologic techniques. Some focal lesions, especially of the posterior segment, may be readily visible and magnified with the ophthalmoscope but difficult to locate histologically. The reluctance of many pathologists to embrace ophthalmic pathology stems from the disappointing quality of sections made from formalin-fixed globes processed by routine methods, and from unfamiliarity with the complex terminology shared by clinical ophthalmologists and ophthalmic pathologists. At least equally daunting is the need to be familiar with the ever-growing list of inherited disorders that occur in purebred dogs, the species which indisputably dominates veterinary ophthalmology. In many instances, the correct diagnosis requires the correlation of the structural lesion with the age, breed, and specific clinical features of the disease to a much greater degree than is the case with most other body systems.

The eye undergoes very rapid postmortem change that not only obscures subtle degenerative lesions but also mimics genuine developmental or degenerative diseases. Even with a globe obtained within minutes of death or surgical removal, improper handling of the specimen frequently results in a section of poor quality. The globe can be speedily and gently removed by grasping the third eyelid with forceps and applying traction to the globe while making a circumferential incision at the fornix. Blunt curved scissors inserted through this incision may be used to sever extraocular muscles and optic nerve, and allow the globe to be removed from the orbit. All orbital fat and extraocular muscles should be gently removed from the sclera to permit rapid penetration of fixative to the retina. The choice of fixative depends on the disease suspected and on the type of examination to which the eye will be subjected. Formalin has the advantage of ready availability, little danger of overfixation, and adequate preservation of color and macroscopic detail for photography. Also, it permits localization in the bisected globe of lesions identified ophthalmoscopically, and the use of electron microscopy should such examination be warranted by the findings of light microscopy. However, formalin penetrates the sclera slowly, and there are postmortem changes, including retinal detachment, even in globes fixed immediately after death or surgery. Rapid-acting fixatives such as Zenker's, Helly's or Bouin's are preferred for globes in which preservation of histologic detail is paramount. All render the globe and its refractive media opaque and less suitable for macroscopic photography than does formalin. All require strict attention to the duration of fixation and thorough postfixation washing in water (Zenker's, Helly's) or 70% ethanol (Bouin's). Regardless of the method of fixation, all eyes benefit from hardening in 70% ethanol over about 24 hr to prevent retinal detachment when trimming the globe for embedding. A mixture of equal parts cold 4% buffered glutaraldehyde and 10% neutral formalin has been recommended as an ocular fixative for both light and electron microscopy.

In all domestic animals, the preferred section for histology is made from a midsagittal slab which includes optic nerve, thereby allowing examination of both tapetal and nontapetal fundus in the same section.

Bibliography

Dodds, W. J. *et al.* The frequencies of inherited blood and eye diseases as determined by genetic screening programs. *J Am Anim Hosp Assoc* **17:** 697–704, 1981.

Duke-Elder, S. "System of Ophthalmology," Vol. I–XV. St. Louis, Missouri, Mosby, 1964.

Fine, B. S., and Yanoff, M. "Ocular Histology," 2nd Ed. Hagerstown, Maryland, Harper & Row, 1979.

Gelatt, K. N. Feline ophthalmology. *Compend Cont Ed* **1:** 576–583, 1979.
Gelatt, K. N. (ed.). "Veterinary Ophthalmology." Philadelphia, Pennsylvania, Lea & Febiger, 1981.
Jensen, H. E. Histological changes in the canine eye related to aging. *Proc Am Coll Vet Ophthalmol,* 3–15, 1974.
Martin, C. L., and Anderson, B. G. Ocular anatomy. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 58–64. Philadelphia, Pennsylvania, Lea & Febiger, 1981.
Peiffer, R. L. (ed.). "Comparative Ophthalmic Pathology." Springfield, Illinois, Charles C Thomas, 1983.
Prince, J. H. *et al.* "Anatomy and Histology of the Eye and Orbit in Domestic Animals." Springfield, Illinois, Charles C Thomas, 1960.
Rubin, L. F. "Atlas of Veterinary Ophthalmoscopy." Philadelphia, Pennsylvania, Lea & Febiger, 1974.
Rubin, L. F. "Inherited Eye Disease in Purebred Dogs." Philadelphia, Pennsylvania, Williams & Wilkins, 1989.
Saunders, L. Z., and Rubin, L. F. "Ophthalmic Pathology of Animals." Basel, Switzerland, Karger, 1975.
Smolin, G., and O'Connor, G. R. "Ocular Immunology," Philadelphia, Pennsylvania, Lea & Febiger, 1981.
Spencer, W. H. (ed.). "Opththalmic Pathology." Philadelphia, Pennsylvania, W. B. Saunders, 1985.
Stryer, L. The molecules of visual excitation. *Sci Am,* July 1987, 42–50.
Walls, G. L. (ed.). "The Vertebrate Eye and its Adaptive Radiation." New York, Hafner Publishing, 1967.
Yanoff, M., and Fine, B. S. "Ocular Pathology." 3rd Ed., Philadelphia, Pennsylvania, J. B. Lippincott, 1989.

II. Developmental Anomalies

Ocular developmental defects are common in domestic animals, particularly in purebred dog breeds in which extensive linebreeding has been used to increase the predictability of the phenotype. Many of the defects involve the eyelids and result from accentuation of anatomic peculiarities of the breed, such as entropion from deliberate enophthalmos or misdirected hairs from overly prominent facial folds. Such anomalies are clinically obvious and amenable to surgery, and rarely require the attention of a pathologist.

Anomalies of the globe are usually multiple, which reflects the interdependence of the various parts of the developing eye. Without proper consideration of ocular embryology, the lesions found in anomalous eyes can be a catolog of observations rather than predictable results of single errors in organogenesis. It is also important to recognize the differences in normal ocular structure among the various species, and the different rates at which mature form is attained. For example, the retina of carnivore eyes remains immature until about 6 weeks postnatally, whereas that of ruminants and horses is mature at birth.

The primary optic vesicle is an evagination of the forebrain that, with differential growth of brain and surface ectoderm, becomes separated from the presumptive diencephalon by the optic stalk. The apposition of primary optic vesicle to overlying surface ectoderm induces a focal ectodermal thickening, the lens placode. The placode

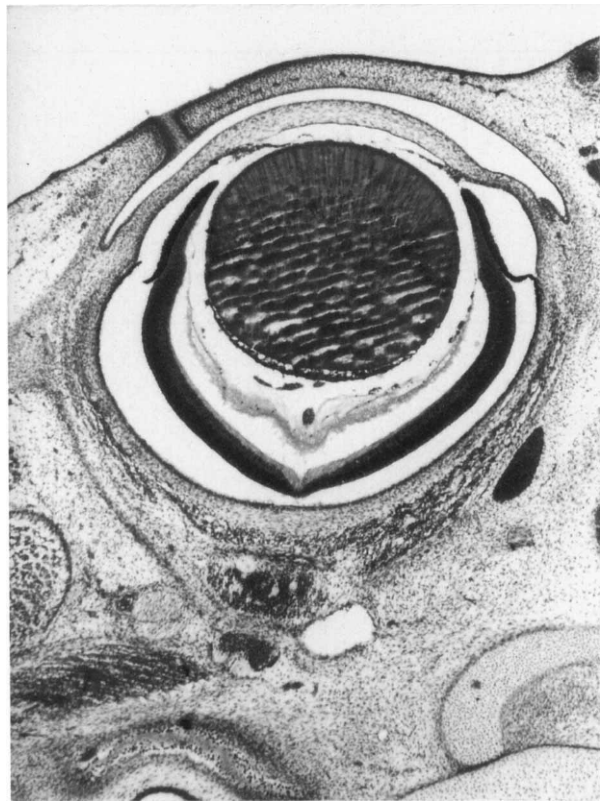

Fig. 4.1 Canine embryo, 34 days gestation. Lids fused, cornea fully formed. Large lens surrounded by complete vascular tunic derived posteriorly from hyaloid artery and anteriorly from the future pupillary membrane. Iris not yet formed. Retina almost fills cavity of optic vesicle.

grows to form a primitive lens vesicle. It is the developing lens which orchestrates the invagination of the optic vesicle to form the bilayered optic cup and bring the lining neuroectoderm into the apposition that provides the future photoreceptor and pigment epithelial layers. Surrounding the optic cup is a mass of mesenchyme, derived from neural crest, that will form the vascular and fibrous tunics of the eye under the induction of the differentiating neuroectoderm (Fig. 4.1). Ocular adnexa and muscles form independently and seem not to require normal development of the globe, as evidenced by the presence of normal lacrimal gland, lids, and extraocular muscles in most cases of severe microphthalmos.

Bibliography

Aguirre, G. D., Rubin, L. F., and Bistner, S. I. Development of the canine eye. *Am J Vet Res* **33:** 2399–2414, 1972.
Bellhorn, R. W. A survey of ocular findings in 16- to-24-week-old beagles. *J Am Vet Med Assoc* **162:** 139–141, 1973.
Bellhorn, R. W. A survey of ocular findings in eight- to-ten-month-old beagles. *J Am Vet Med Assoc* **164:** 1114–1116, 1974.
Bistner, S. I. Embryology of the canine and bovine eyes. *In* "Veterinary Ophthalmology," K. N. Gelatt (ed.), pp. 3–11. Philadelphia, Pennsylvania, Lea & Febiger, 1981.

Bistner, S. I., Rubin, L. F., and Aguirre, G. Development of the bovine eye. *Am J Vet Res* **34**: 7–12, 1973.
Donovan, A. The postnatal development of the cat retina. *Exp Eye Res* **5**: 249–254, 1966.
Duke-Elder, S. "System of Ophthalmology," Vol. III, parts 1 and 2. St. Louis, Missouri, Mosby, 1964.
Garner, A., and Griffiths, P. Bilateral congenital ocular defects in a foal. *Br J Ophthalmol* **53**: 513–517, 1969.
Gelatt, K. N., Leipold, H. W., and Huston, K. Congenital ophthalmic anomalies in cattle. *Mod Vet Pract* **57**: 105–109, 1976.
Greene, H. J. *et al.* Congenital defects in cattle. *Ir Vet J* **27**: 37–44, 1973.
Hu, F., and Montagna, W. The development of pigment cells in the eyes of rhesus monkeys. *Am J Anat* **132**: 119–132, 1971.
Huston, R., Saperstein, G., and Leipold, H. W. Congenital defects in foals. *Equine Med Surg* **1**: 146–161, 1977.
Mann, I. "Developmental Abnormalities of the Eye," 2nd Ed. Philadelphia, Pennsylvania, Lippincott, 1957.
Martin, C. L., and Anderson, B. G. Ocular anatomy. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 58-64. Philadelphia, Pennsylvania Lea & Febiger, 1981.
Pei, Y. F., and Rhodin, J. A. G. The prenatal development of the mouse eye. *Anat Rec* **168**: 105–125, 1970.
Priester, W. A. Congenital ocular defects in cattle, horses, cats, and dogs. *J Am Vet Med Assoc* **160**: 1504–1511, 1972.
Riis, R. C. Equine ophthalmology. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 509–570. Philadelphia, Pennsylvania, Lea & Febiger, 1981.
Saunders, L. Z., and Rubin, L. F. "Ophthalmic Pathology of Animals. An Atlas and Reference Book." Basel, Switzerland, Karger, 1975.
Selby, L. A., Hopps, H. C., and Edmonds, L. D. Comparative aspects of congenital malformations in man and swine. *J Am Vet Med Assoc* **159**: 1485–1490, 1971.
Weidman, T. A., and Kuwabara, T. Development of the rat retina. *Invest Ophthalmol Vis Sci* **8**: 60–69, 1969.

A. Defective Organogenesis

Failure of the eye to attain even the stage of optic cup is not a rare occurrence and is usually of unknown cause. The defect is usually bilateral but asymmetrical, and the severity of the defect relates to the stage of organogenesis at which the insult occurred. Failure of formation of the primary vesicle, or its early and complete regression, is true anophthalmos and is very rare. Failure of optic vesicle invagination gives rise to the very rare congenital cystic eye. Incomplete invagination results in congenital retinal nonattachment. Failure of division (or subsequent fusion) of the optic primordium as it grows from the telencephalon results in cyclopia, or synophthalmos, a single dysplastic midline globe.

1. Anophthalmos and Microphthalmos

Anophthalmos, total absence of ocular tissue, is a very rare lesion and almost all cases described are more correctly termed severe microphthalmos in that some vestige of eye is found in serially sectioned orbital content. The usefulness of distinguishing between the two is questionable, and many authors have adopted the term clinical anophthalmos for all such cases. Concurrent anomalies of skeletal and central nervous systems are common.

Macroscopic examination of orbital content usually reveals a normal lacrimal gland and vestigial extraocular muscles. The globe is usually recognized as an irregular mass of black pigment, with structures such as cornea or optic nerve variably recognizable. Histologically, there is almost always a mass of pigmented neurectoderm, reminiscent of ciliary processes, and some effort at retinal differentiation. There is frequently some remnant of lens, a finding which suggests regression of an embryonic globe that had reached at least the stage of optic cup. One or more plates of cartilage, presumably derived from third eyelid analog, are common.

2. Cyclopia and Synophthalmos

Damage to the prosencephalon prior to the outgrowth of the optic vesicles may result in improper separation of paired cranial midline structures, including eyes. Cyclopia defines a fetal malformation characterized by a single median orbit containing a single globe. Most specimens have some duplication of intraocular structures such as lens, iris, or hyaloid vessels and are thus more properly considered incomplete separation or early fusion (synophthalmos) (Fig. 4.2). Some specimens have two dysplastic globes within a single orbit. Severe cranial anomalies accompany cyclopia and synophthalmos, including absent or deformed ears, a median proboscis, cranioschisis, cleft palate, and brain anomalies ranging from microcephaly to hydranencephaly and hydrocephalus.

Cyclopianlike malformations have been reported in sheep, chickens, and dogs, and as inherited defects in cattle, with the most thoroughly documented cases being

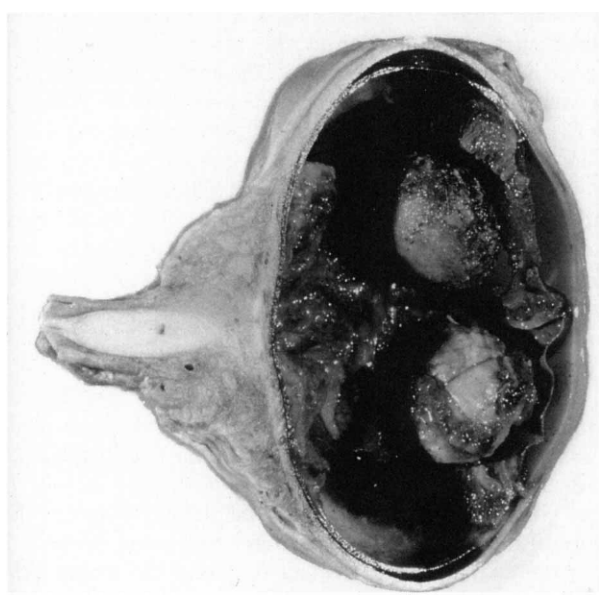

Fig. 4.2 Globe from typical cyclopian calf. Duplication of lens and pupil indicates synophthalmos rather than true cyclopia.

in sheep grazing alpine pastures rich in the legume *Veratrum californicum*. Fresh and dried plants contain three steroidal alkaloids—jervine, cyclopamine, and cycloposine—capable of damaging the developing neural groove of the fetal lamb. Ewes eating the plant on gestational day 15 have lambs with the cyclopian malformation, for it is at that time that the neural groove has formed and the first cranial somites are forming. A similar syndrome has been produced in kids and calves by maternal feeding of the plant on day 14 of gestation. Ingestion of the alkaloids prior to day 15 in sheep may cause fetal death but no anomalies, and exposure soon after day 15 may cause various skeletal abnormalities but not cyclopia.

In naturally occurring outbreaks, affected lambs have deformities ranging from cyclopia with microcephaly to relatively normal lambs with harelip and cleft palate. Prolonged gestation is common in the case of severely malformed fetuses.

3. Cystic Eye and Retinal Nonattachment

Failure of apposition of the optic vesicle to the cranial ectoderm results in failure of lens induction, which in turn removes the major stimulus for the invagination of the optic vesicle to form the optic cup. Persistence of the primary optic vesicle is seen as a cystic eye (Fig. 4.3), consisting of a scleral sheet lined by neurectoderm of variable neurosensory and pigmentary differentiation. The absence of lens and of bilayered iridociliary epithelium distinguish this rare lesion from the more common dysplastic eye of secondary microphthalmos.

Incomplete invagination of the optic vesicle allows persistence of the cavity of the primary optic vesicle and prevents attachment of the presumptive neurosensory retina to the developing retinal pigment epithelium. In the postnatal globe, retinal nonattachment cannot easily be distinguished from acquired retinal separation (Fig. 4.4). In each instance, the retina is extensively folded and may have improper differentiation of neuronal layers. The diagnosis of retinal nonattachment is assisted if there is also lack of apposition between the two layers of neurectoderm covering the anterior uvea (destined to be iridal and ciliary epithelium) and if retinal rosettes are evident. In addition, since nonattachment is an early and fundamental error in organogenesis, such eyes usually lack a lens and probably will be microphthalmic with multiple anomalies.

4. Coloboma

The mildest and latest defect in organogenesis results from failure of complete fusion of the lips of the embryonic fissure, a slitlike but normal channel in the floor of the optic cup and stalk through which the vasoformative mesoderm and stromal mesenchyme enter the globe. Failure of closure of the fissure may occur anywhere along its length, but the channel persists most frequently as a notchlike defect of the caudal pole at, or just ventral to, the optic disk and is lined by an outpouching of dysplastic neurectoderm. If the defect is sufficiently large, the outpouching

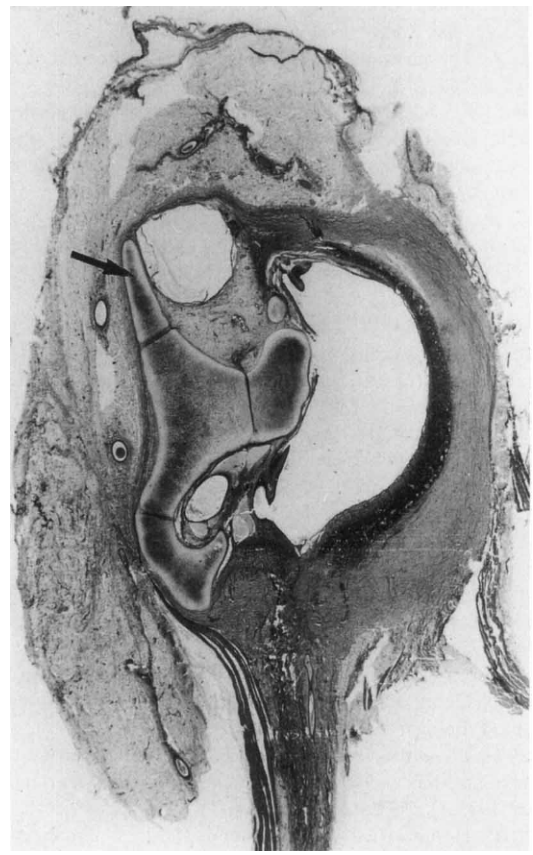

Fig. 4.3 Severe microphthalmos. Foal. There is no lens, no apparent attempt at invagination, and no neurosensory retinal differentiation. Persistence of the cavity of the optic vesicle qualifies this as a cystic eye. Cartilage plate (arrow) is probably analog of third eyelid.

of neurectoderm induces a similar bulge in the sclera, termed **scleral ectasia** (Fig. 4.5). Occasionally such ectasias are so large as to form a retrobulbar cyst as large as the globe itself (Fig. 4.6). Regardless of size, the lining of the scleral coloboma is formed by neurectoderm that bulged through the defect in the optic cup. Abortive neurosensory differentiation within the cyst wall is common (Fig. 4.7).

Colobomas occur in all domestic species but are especially frequent in collie dogs as one manifestation of the collie eye anomaly. They are rare in horses and cattle, and in both species, most cases have been reported in blue-eyed or incompletely albino animals. In Charolais cattle, colobomas of or near the optic disk are inherited as an autosomal dominant trait with incomplete penetrance. The lesion is bilateral but not necessarily equal in severity. Colobomas of iris or eyelid also occur but are rarely significant to ocular function and even more rarely receive histologic examination. Colobomas not aligned with the embryonic fissure also occur, but their pathogenesis is unknown.

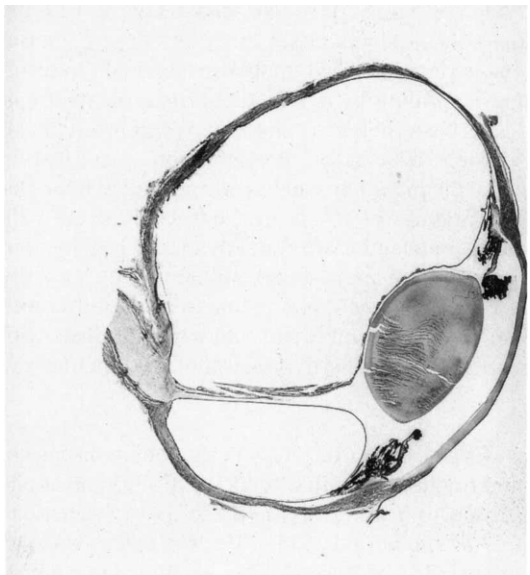

Fig. 4.4 Microphthalmos. Foal. There is congenital retinal detachment.

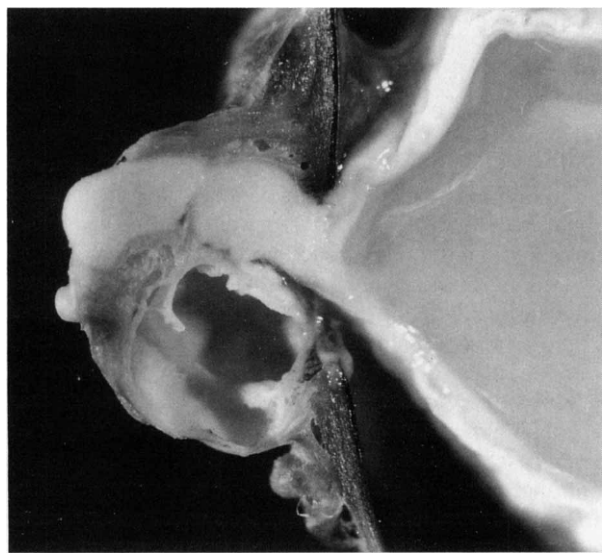

Fig. 4.5 Scleral ectasia and retinal separation. Collie. Cavity within the ectasia is analogous to the cavity of the primary optic vesicle.

B. Defective Differentiation

Subsequent to formation of the optic cup, ocular differentiation involves continued differentiation of neurectoderm into retinal and uveal neuroepithelium, and induction of primitive periocular mesenchyme to form the fibrous and vascular tunics of the globe. The normal development of retinal pigment epithelium from the neurectoderm of the posterior half of the optic vesicle seems prerequisite for these differentiations to occur. Aberrant differentiation of the surface ectoderm destined to form corneal epithelium and lens is infrequent except for those *in utero* degenerative diseases of the lens which lead to congenital cataract.

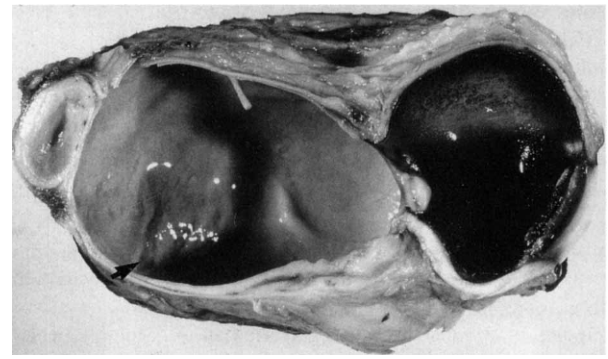

Fig. 4.6 Retrobulbar cyst (arrow) formed by coloboma and massive scleral ectasia. Calf. Globe is small. Retina is completely separated.

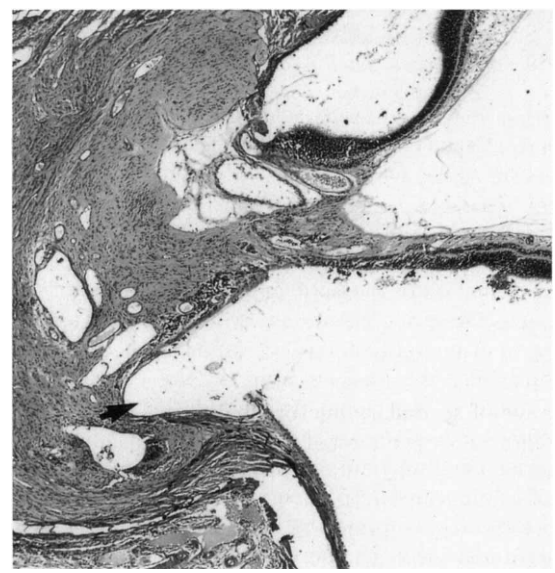

Fig. 4.7 Coloboma (arrow) at the optic disk. Collie pup with collie eye anomaly. Dysplastic neuroectoderm lines the defect and attempts to form sensory retina.

It is traditional to present specific ocular anomalies as they relate to structures of the adult eye, and thus as anomalies of cornea, iris, lens, retina, and so on. This approach correlates well with the clinical examination of the eye, but an understanding of the evolution of anomalies may best be gained if seen in terms of defective differentiation of the germ layers. For this reason, anomalies of ocular differentiation are presented here as anomalies of mesenchyme, ectoderm, and neurectoderm. Ocular neurectoderm is the primary organizer of ocular differentiation.

Bibliography

Bendixen, H. C. Littery occurrence of anophthalmia or microphthalmia together with other malformations in swine—presum-

ably due to vitamin A deficiency of the maternal diet. *Acta Pathol Microbiol Scand (Suppl.)* **54:** 161–179, 1944.
Binns, W. *et al.* A congenital cyclopian-like malformation in lambs. *J Am Vet Med Assoc* **134:** 180–183, 1959.
Binns, W. *et al.* Chronologic evaluation of teratogenesis in sheep fed *Veratrum californicum*. *J Am Vet Med Assoc* **147:** 839–842, 1963.
Hale, F. The relation of vitamin A to anophthalmos in pigs. *Am J Ophthalmol* **18:** 1087–1093, 1935.
Leipold, H. W., and Huston, K. Congenital syndrome of anophthalmia—microphthalmia with associated defects in cattle. *Vet Pathol* **5:** 407–418, 1968.
Leipold, H. W., Gelatt, K. N., and Huston, K. Multiple ocular anomalies and hydrocephalus in grade beef shorthorn cattle. *Am J Vet Res* **32:** 1019–1026, 1971.
McCormack, J. Typical colobomas in Charolais bulls. *Vet Med Small Anim Clin* **72:** 1626–1628, 1977.
Rosenfeld, I., and Beath, O. A. Congenital malformations in the eyes of sheep. *J Agric Res* **75:** 93–103, 1947.
Rubin, L. F. Hereditary retinal detachment in Bedlington terriers: A preliminary report. *Small Anim Clin* **3:** 387–389, 1963.
Saunders, L. Z., and Fincher, M. G. Hereditary multiple eye defects in grade Jersey calves. *Cornell Vet* **41:** 351–366, 1957.
Wheeler, C. A., and Collier, L. L. Bilateral colobomas involving the optic discs in a quarter horse. *Eq Vet J (Suppl.)* **10:** 39–41, 1990.

1. Anomalies of Mesenchyme

After formation of the optic cup and separation of the lens vesicle, the periocular mesenchyme undergoes a complex series of migrations, differentiations, and atrophies that determines the final structure of the vascular and fibrous tunics of the globe. At the anterior edge of the optic cup, successive waves of mesenchymal invasion form corneal endothelium, corneal stroma, and the anterior half of the transient perilenticular vascular network. The posterior half is formed by invasion of vasoformative mesoderm and mesenchyme through the embryonic fissure to form the extensive hyaloid artery system (Fig. 4.1). Another mesenchymal wave accompanies the ingrowth of the neurectoderm at the anterior lip of the optic cup to form the iris stroma. Its peripheral portion later atrophies to form the porous filtration angle of the anterior chamber, a process that may not be completed in carnivores until several weeks after birth. The choroid and sclera are induced by the developing retinal pigment epithelium to form from the mesenchyme surrounding the caudal half of the optic cup.

Anomalies of mesenchyme may result from defective ingrowth or differentiation, as with choroidal and iris hypoplasia, but more frequent are the defects associated with incomplete atrophy of the normally transient embryonal mesenchyme of the intraocular vasculature or filtration angle, such as occurs with persistent pupillary membrane and some primary glaucomas.

a. CHOROIDAL HYPOPLASIA. This is a relatively common lesion in the eye of dogs by virtue of its prevalence in the collie breed as the hallmark of collie eye anomaly, and a very similar syndrome occurs in Australian shepherd dogs and Shetland sheepdogs. It is also seen in a variety of dog breeds in association with genes for color dilution (merle, dapple, and harlequin). The hypoplasia is thought to result from induction failure by a defective retinal pigment epithelium. The basic defect is not clearly established but may be related to defective pigmentation, a suggestion supported by the prevalence of iris and choroidal hypoplasia in white animals of all species, especially those with blue irises. Some degree of retinal dysplasia is also common, an observation which bears on the role of normally developing retinal pigment epithelium in ocular differentiation. Even in otherwise normal (nonwhite) animals with a blue iris, there is usually hypoplasia of the tapetum and choroid.

b. COLLIE EYE ANOMALY. This is a common disease of smooth and rough collies, first reported in 1953 and at one time estimated to have affected 90% of North American collies. During the period 1975–1979, the defect was still present in over 70% of 20,000 collies examined in a voluntary screening program. Prevalence in Europe and the United Kingdom is lower (30–60%). The basic defect, patchy to diffuse choroidal hypoplasia, is inherited as an autosomal recessive trait, but the numerous associated defects are more unpredictable in their familial pattern. Similar syndromes are reported in Border collies, Shetland sheepdogs, and Australian shepherd dogs, and are probably of similar pathogenesis. The prevalence in these breeds, as in rough collies, has marked geographic variation.

The ophthalmoscopic findings include one or more of retinal vessel tortuosity, focal to diffuse choroidal and tapetal hypoplasia, typical coloboma, and retinal separation with intraocular hemorrhage. Other observations that are occasionally made in eyes of affected dogs are enophthalmos, microphthalmos, and corneal stromal mineralization. The disease is always bilateral but not necessarily equal. Even the mild, visually insignificant lesion of focal choroidal hypoplasia is genetically significant.

Macroscopic examination of the bisected globe reveals abnormal pallor of the posterior segment of the globe. If the globe is transilluminated, the sclera and choroid are focally or diffusely more translucent than normal. The pallor and translucency imply choroidal hypoplasia. Within or adjacent to the optic disk there may be a colobomatous pit of variable size, the lining of which is continuous with the retina. Accompanying the larger type of pit is a bulge in the overlying sclera, called **scleral ectasia** or **posterior staphyloma.** If there is retinal separation, it is usually complete, with the only sites of attachment being at the abnormal optic disk and at the ora ciliaris (Fig. 4.8). In such cases, there may be extensive intravitreal hemorrhage and retinal tears. Almost all collie eyes with retinal separation have large optic disk colobomas. Detachment from the ora ciliaris may also occur, leaving the folded retina on the floor of the globe (Fig. 4.9).

The histologic lesion found in all affected eyes is choroidal hypoplasia, which virtually always is diffuse, despite

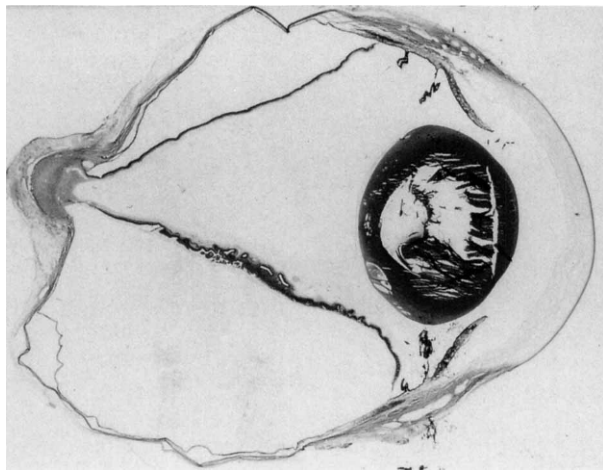

Fig. 4.8 Retinal separation. Collie eye anomaly. There is coloboma at the optic disk. Choroid and sclera are thin. Retinal folding does not constitute dysplasia.

ophthalmoscopic observation of a lesion that appears to be only focal. The choroid is thin and poorly pigmented, and the tapetum is thinner than normal or even absent (Fig. 4.10A,B). Retinal pigment epithelium is poorly pigmented even in nontapetal fundus and may be vacuolated. Because the choroid and tapetum in the normal dog do not reach adult thickness until about 4 months postpartum, aged-matched control eyes are essential if overinterpretation of normal choroidal immaturity is to be avoided.

Histologic examination of eyes with optic disk colobomas reveals the bulging of dysplastic neurectoderm, continuous with retina, into the pit in the nerve head. The neurectoderm may show jumbled differentiation into ganglion cells, photoreceptor rosettes, glial cells, or pigment epithelium. Rosettes are common in the neurosensory retina adjacent to affected disks or embedded in the optic disk itself. In some specimens, there are degenerative retinal lesions overlying severely hypoplastic choroid. Edematous clefts are seen in the nerve fiber layer, and ganglion cells may be severely vacuolated.

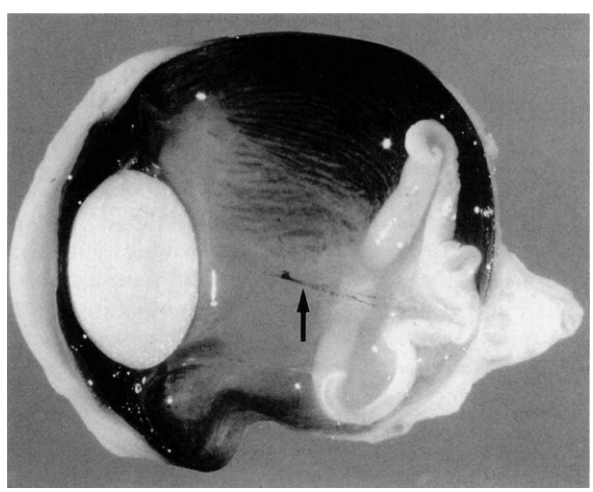

Fig. 4.9 Retinal separation from ora ciliaris. Collie eye anomaly. Note hypopigmented choroid and prominent hyaloid artery (arrow).

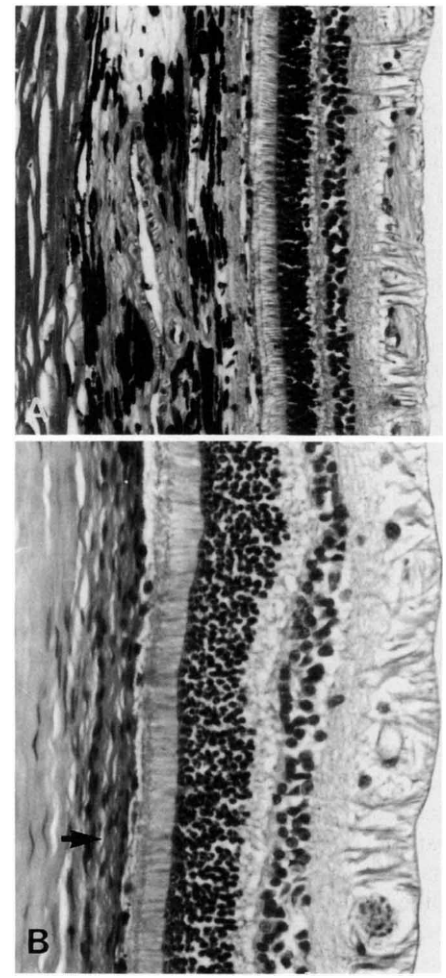

Fig. 4.10 (A) Normal posterior pole of the globe of 13-week-old puppy. Tapetum present but thin (normal for puppy). Choroidal thickness approximates that of retina. (B) Posterior pole just dorsal to the optic disk of 13-week-old collie with collie eye anomaly. Tapetum is absent. Choroid (arrow) severely hypoplastic.

Other retinal lesions include retinal folds and detachment. The folds are seen on histologic section as tubes of fully differentiated retina cut in cross section or tangentially, and are thought to represent folds in a neurosensory retina that at least temporarily has grown in excess of the space available for it within the optic cup. These folds correspond to the clinically detectable vermiform streaks on the fundus, and gradually disappear as the dog (and eye) matures, allowing the growth of scleral shell to catch up with that of retina. Presumably it is a more severe imbalance in growth of inner and outer layers of the optic cup which predisposes to retinal separation in about 10%

of eyes with this syndrome, as a retina which is too small attempts to stretch from optic disk to ora ciliaris by the shortest route.

Focal fibroblastic metaplasia and mineralization is occasionally seen in the subepithelial corneal stroma of dogs with collie eye anomaly, but a similar defect is seen in anomalous eyes of other breeds; a genetic link to the collie eye defect is not established. Tortuosity of retinal veins, a controversial clinical lesion sometimes considered part of collie eye anomaly, has no described histologic counterpart.

The earliest lesion of this anomaly is defective differentiation of primitive retinal pigment epithelium to form rosettelike structures near the optic disk. Proper differentiation of both pigment epithelium and neurosensory retina requires obliteration of the lumen of the primary optic vesicle, which allows the two neurectodermal layers to come into apposition. Whether the earliest lesion of collie eye anomaly results from inherently defective differentiation of pigment epithelium or from imperfect apposition of the two neurectodermal layers has not been resolved, but a central role of the pigment epithelium in determining ocular morphology suggests that the primary defect is in maturation of the presumptive retinal pigment epithelium. Anomalous development of choroid and sclera, including coloboma, is not seen in fetuses up to 45 gestational days but is seen in neonates. This suggests that the defect is in choroidal maturation rather than in formation. Another manifestation of mesenchymal maldevelopment is delayed atrophy and remodeling in the anterior chamber. The filtration angle may be closed, iris stroma may be attached to the corneal endothelium by a mesenchymal bridge, and remnants of anterior perilenticular mesenchyme are unusually prominent. Pigmentation of iridal neurectoderm is sparse. As these neonatal anterior segment lesions are not seen at the age (8–20 weeks) when puppies are examined ophthalmoscopically, it is presumed that they reflect only delayed mesenchymal remodeling.

2. Defects of Anterior Segment Mesenchyme

Hypoplasia of the iris is a rare defect that may occur alone or in conjunction with multiple ocular defects. It is relatively most frequent in horses, where it may be inherited and associated with cataract and conjunctival dermoids. The defect presumably results from incomplete inward migration of the anterior lip of the optic cup, with resultant lack of a neurectodermal scaffold to guide the migration of presumptive iris stroma. The hypoplasia is usually severe, and most cases are clinically described as aniridia. Histologic examination of such eyes usually reveals the vestigial iris as a triangular mesenchymal stump covered posteriorly by normal-appearing pigmented epithelium (Fig. 4.11A). The trabecular meshwork within the filtration angles may be malformed, but the ciliary apparatus is usually normal. The lens often is cataractous (Fig. 4.11B) and sometimes ectopic or hypoplastic. Glaucoma has been described as a sequel in horses (but not in other species), and would be an expected sequel in severely affected eyes in any species.

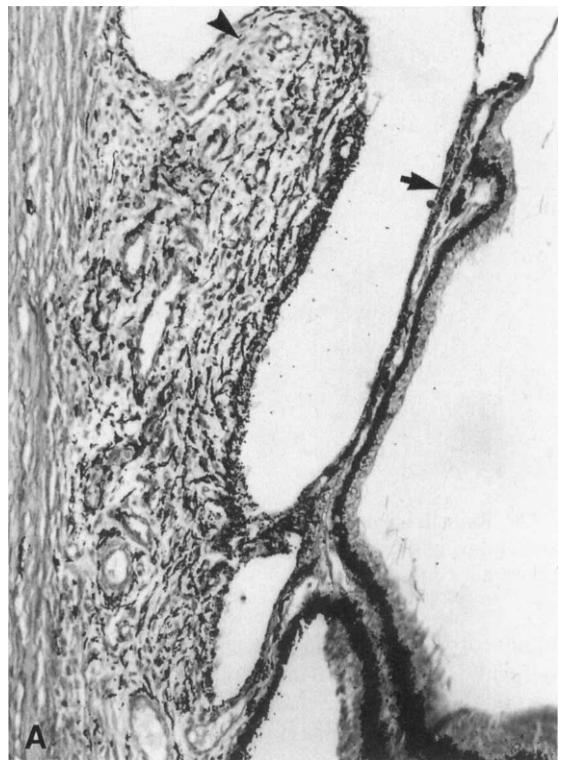

Fig. 4.11A Iris hypoplasia (arrow) and goniodysgenesis (arrowhead). Dog. Stroma and epithelium are inadequate.

Hypopigmentation of the iris may be unilateral (heterochromia iridis) or bilateral (ocular albinism). The iris is normal except for incomplete development of pigment granules in the cytoplasm of otherwise normal stromal and epithelial cells. Tapetum and, less reliably, choroid of affected eyes usually are hypoplastic.

Incomplete atrophy of the anterior chamber mesenchyme is relatively common in dogs and occurs occasionally in other domestic species. During organogenesis, three waves of mesenchyme migrate between the surface ectoderm and the anterior rim of the optic cup. The first two waves form corneal endothelium and stroma. The third wave forms a sheet stretching across the face of the lens and future iris. It differentiates centrally into the anterior half of the perilenticular vascular tunic and atrophies late in gestation or in the early postnatal period. Failure to atrophy results in **persistent pupillary membrane.** The more peripheral portions of the third mesenchymal wave differentiate into iris stroma and trabecular meshwork, the latter by a combination of atrophy and remodeling that continues until the third postnatal week in dogs.

Much less common are those defects grouped under the general category of anterior segment dysplasia or **anterior segment cleavage syndromes,** which include multiple

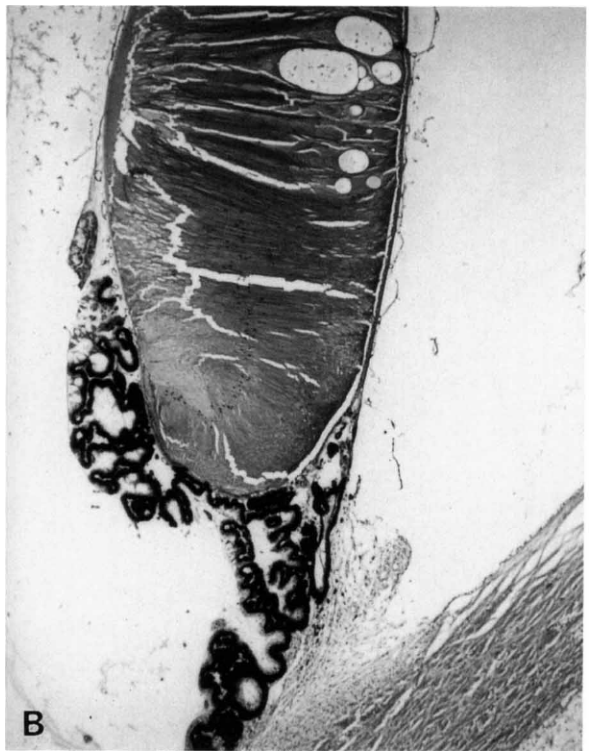

Fig. 4.11B Iris hypoplasia, congenital cataract and dysplasia of ciliary processes. Piglet, one of three affected.

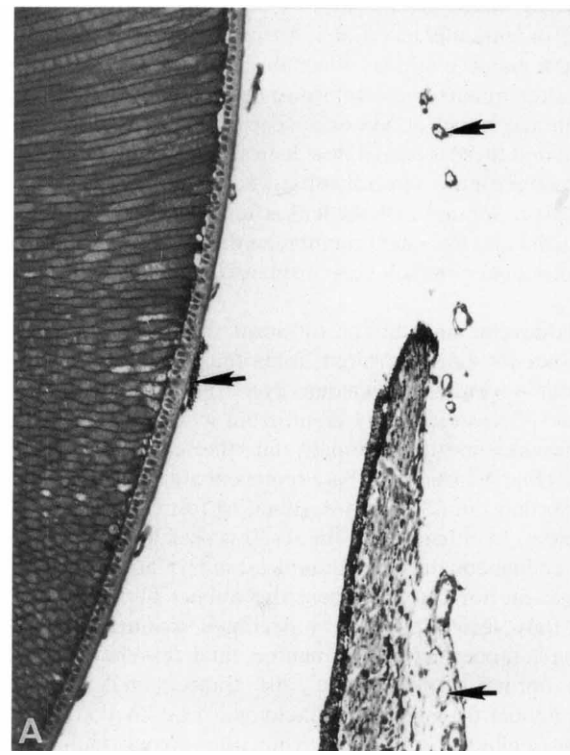

Fig. 4.12A Persistence of anterior tunica vasculosa lentis. Portions are seen as fine vascular channels on anterior lens capsule, in the pupil, and on anterior surface of iris (arrows).

anomalies of cornea, lens, and anterior uvea that stem from disordered development of anterior segment mesenchyme. Such eyes are commonly microphthalmic and usually have microphakia, cataract, and congenital corneal opacities at sites of congenital synechiae.

Persistent pupillary membrane refers to the delayed or incomplete atrophy of the anterior perilenticular vascular network that, in the fetus, originates from the minor arterial circle of the iris and invests the developing lens. Atrophy is frequently incomplete at birth and, in dogs, persistent remnants are common up to about 6 months of age. These insignificant and usually bloodless strands are seen as short, threadlike protrusions from the area of the minor arterial circle (iris collarette), and they may insert elsewhere on the iris, cross the pupil, or extend blindly into the anterior chamber (Fig. 4.12A). Persistent pupillary membranes achieve clinical significance in two ways. First, the size and number of strands crossing the pupil may be such that vision is obstructed. Second, strands that contact lens or cornea are associated with focal dysplasia of lens or corneal endothelium, clinically seen as opacity (Fig. 4.12B).

Histologic descriptions are mainly from studies in basenji dogs, in which persistent pupillary membrane occurs as an autosomal recessive trait of variable penetrance. In this breed, atrophy of the pupillary membrane is abnormally slow even in dogs free of the defect in adult life, and remnants in puppies up to 8 months old are common. The membranes are seen as thin endothelial tubes, invested with a thin adventitial stroma, extending from vessels in the iris stroma near the collarette. The tubes are usually empty, but in severely affected eyes may contain erythrocytes, and the adventitia may contain melanin. The tubes

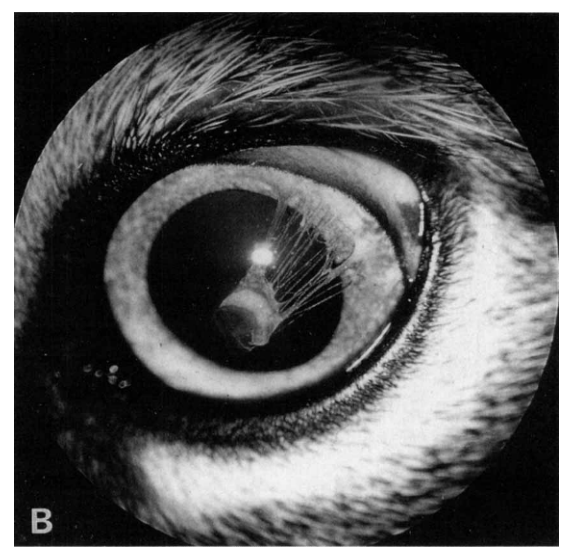

Fig. 4.12B Persistent pupillary membrane. Dog. Central crescent insertion is on the anterior pole of the lens.

weave in and out of the plane of section en route to corneal, iridic, or lenticular insertions. At sites of corneal insertion, corneal endothelium is either absent or dysplastic, with the latter manifested as fibrous metaplasia. Descemet's membrane is malformed or absent in the areas of attachment, and there is associated deep stromal corneal edema to account for the clinically observed, minute gray stromal opacities. Contact with the lens is accompanied by similar epithelial and basement membrane dysplasia, resulting in one or more epithelial, subcapsular, or polar cortical cataracts.

Maldevelopment of the **filtration angle (goniodysgenesis)** occurs as a prevalent, inherited condition in dogs and in severely anomalous eyes of animals of any species. The defect may result from incomplete atrophy of mesenchyme that normally fills the fetal iridocorneal angle (Fig. 4.13A,B), or may represent a true dysplasia of the fibrillar condensation destined to form the pectinate ligament. In either event, the result is seen as an imperforate or inadequately perforated mesodermal sheet separating anterior chamber from the trabecular meshwork. The only lesion may be a pectinate ligament that is thicker, more heavily pigmented, and less fenestrated than normal. Alternatively, the trabecular meshwork may appear as a solid mesenchymal mass that may not be distinguishable from postglaucoma compression and fibrosis of a developmentally normal filtration angle (see Glaucoma).

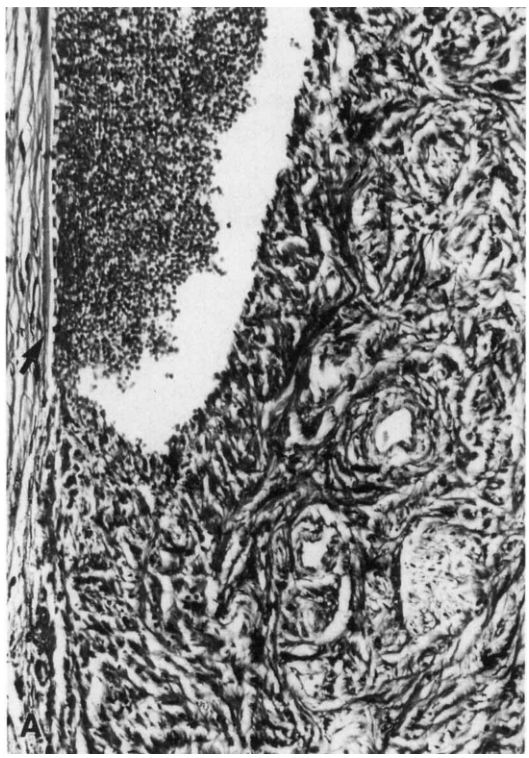

Fig. 4.13A Goniodysgenesis. Calf. Note dense mesoderm in the area that should be the open lattice of the trabecular meshwork. Termination of Descemet's membrane, where the pectinate ligament should insert (arrow).

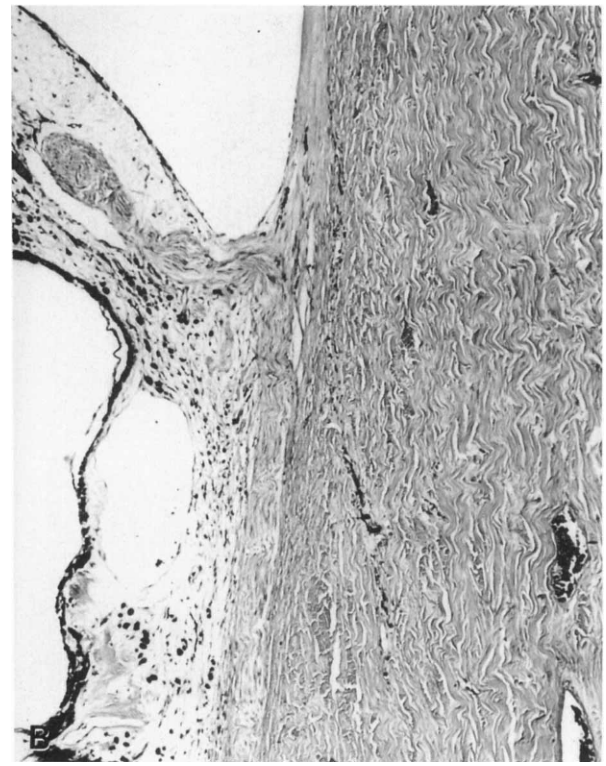

Fig. 4.13B Goniodysgenesis. Ciliary cleft is filled with primitive mesenchyme and has no development of trabecular meshwork.

3. Incomplete Atrophy of Posterior Segment Mesenchyme

Incomplete atrophy of posterior segment mesenchyme may result in the mild and common lesion of **persistent hyaloid artery,** or in the much rarer but clinically more significant lesions of **persistent posterior perilenticular vascular tunic** with or without concurrent persistence of the primary vitreous. The hyaloid artery and its branches are formed from mesenchyme that enters the optic cup through the embryonic fissure prior to its closure. The vessel traverses the optic cup from optic disk to lens, there it ramifies over the posterior lens surface and joins with the branches of the anterior chamber pupillary membrane to form a complete perilenticular vascular tunic. As with its anterior chamber counterpart, the hyaloid system undergoes almost complete atrophy before birth. Persistence of some vestige into adult life is common and clinically insignificant. In ruminants the most common remnant is Bergmeister's papilla, a cone of glial tissue with a vascular core which extends from optic disk for a few millimeters into the vitreous. In calves until about 2 months of age, the vestigial hyaloid system may still contain blood. In carnivores, it is the anterior perilenticular portion that normally persists for

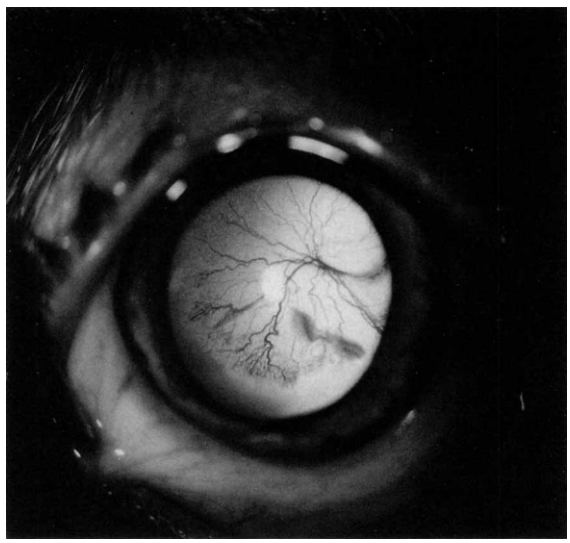

Fig. 4.14 Persistence of hyaloid artery and posterior tunica vasculosa lentis. Dog. Posterior polar cataract is the almost inevitable consequence as seen here.

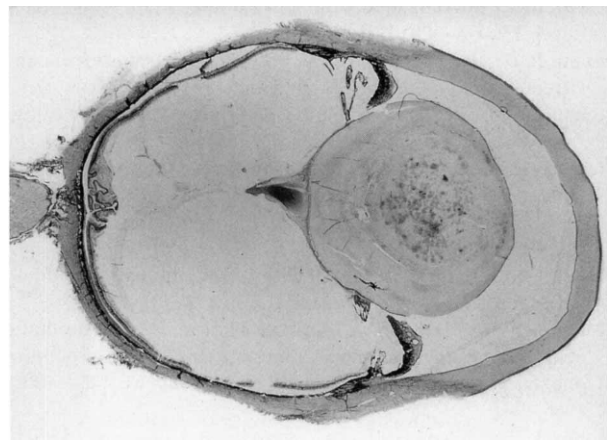

Fig. 4.15 Persistent hyperplastic primary vitreous. A fibrocartilaginous plaque adheres to an elongated lens (lenticonus) and extends to the posterior pole. Retina is dysplastic near the optic disk.

several weeks postnatally. Bloodless remnants of the main hyaloid artery are common in dogs and ruminants up to several years of age.

Much less common is undue persistence and even hyperplasia of the anterior end of the hyaloid system, the **posterior tunica vasculosa lentis** (Fig. 4.14). In humans the retained tissue may be predominantly fibrous and is thought to be a metaplastic derivative of the neurectodermal primary vitreous which accompanies the hyaloid vasculature. This rare anomaly, also called **persistent hyperplastic primary vitreous,** is typically unilateral in humans and is accompanied by microphthalmos, microphakia, retinal detachment, shallow anterior chamber, and embryonic filtration angles. The several reports of this anomaly in dogs have described a unilateral or bilateral retrolental vascular or fibrovascular network, usually without any reported anomalies other than the expected posterior polar cataract. Such lesions are better described as persistent posterior tunica vasculosa lentis. In Doberman pinschers and Staffordshire bull terriers, the defect is inherited and forms a spectrum that includes persistent pupillary membrane, cataract, lenticonus, and microphthalmia, as well as persistence of variable amounts of primary vitreous and posterior tunica vasculosa lentis (Fig. 4.15). The defects are detected as early as gestational day 30, at which time hyperplasia of posterior tunica vasculosa lentis is already obvious. Posterior polar cataracts and preretinal membranes are observed by day 37.

Bibliography

Arnbjerg, J., and Jensen, O. A. Spontaneous microphthalmia in two Doberman puppies with anterior chamber cleavage syndrome. *J Am Anim Hosp Assoc* **18:** 481–484, 1982.

Barnett, K. C., and Grimes, T. D. Unilateral persistence and hyperplasia of the primary vitreous in the dog. *J Small Anim Pract* **14:** 561–565, 1973.

Barnett, K. C., and Knight, G. C. Persistent pupillary membrane and associated defects in the basenji. *Vet Rec* **85:** 242–249, 1969.

Bertram, T., Coignoul, F., and Cheville, N. Ocular dysgenesis in Australian shepherd dogs. *J Am Anim Hosp Assoc* **20:** 177–182, 1984.

Bistner, S., Shaw, D., and Riis, R. C. Diseases of the uveal tract (Part I). *Compend Cont Ed* **1:** 868–876, 1979.

Boevé, M. H., van der Linde-Sipman, T., and Stades, F. C. Early morphogenesis of persistent hyperplastic tunica vasculosa lentis and primary vitreous. *Invest Ophthalmol Vis Sci* **29:** 1076–1086, 1988.

Creel, D. Inappropriate use of albino animals in research. *Pharmacol Biochem Behav* **12:** 969–977, 1980.

Eriksson, K. Hereditary aniridia with secondary cataract in horses. *Nord Vet Med* **7:** 773–793, 1955.

Gelatt, K. N. The canine glaucomas. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 390–434. Philadelphia, Pennsylvania, Lea & Febiger, 1981.

Gelatt, K. N., and McGill, L. D. Clinical characteristics of microphthalmia with colobomas of the Australian shepherd dog. *J Am Vet Med Assoc* **162:** 393–396, 1973.

Gelatt, K. N., Huston, K., and Leipold, H. W. Ocular anomalies in incomplete albino cattle. *Am J Vet Res* **30:** 1313–1316, 1969.

Grimes, T. D., and Mullaney, J. Persistent hyperplastic primary vitreous in a greyhound. *Vet Rec* **85:** 607–611, 1969.

Joyce, J. R. *et al.* Iridal hypoplasia (aniridia) accompanied by limbic dermoids and cataracts in a group of related quarterhorses. *Eq Vet J (Suppl)* **10:** 26–28, 1990.

Latshaw, W. K., Wyman, M., and Benzke, W. G. Embryologic development of an anomaly of ocular fundus in the collie dog. *Am J Vet Res* **30:** 211–217, 1969.

Lucus, D. R. Ocular associations of dappling in the coat colours of dogs. II. Histology. *J Comp Pathol* **53:** 260–266, 1954.

Martin, C. L. Development of pectinate ligament structure of the dog: Study by scanning electron microscopy. *Am J Vet Res* **35:** 1433–1439, 1974.

Peiffer, R. L., Gelatt, K. N., and Gwin, R. M. Persistent primary

vitreous and pigmented cataract in a dog. *J Am Anim Hosp Assoc* **13:** 478–480, 1977.
Pruett, R. C., and Schepens, C. L. Posterior hyperplastic primary vitreous. *Am J Ophthalmol* **69:** 535–543, 1970.
Rebhun, W. C. Persistent hyperplastic primary vitreous in a dog. *J Am Vet Med Assoc* **169:** 620–622, 1976.
Reese, A. B. Persistent hyperplastic primary vitreous. *Am J Ophthalmol* **40:** 317–331, 1955.
Roberts, S. R. Color dilution and hereditary defects in collie dogs. *Am J Ophthalmol* **63:** 1762–1775, 1967.
Roberts, S. R., and Bistner, S. I. Persistent pupillary membrane in basenji dogs. *J Am Vet Med Assoc* **153:** 533–542, 1968.
Roberts, S. R., Dellaporta, A., and Winter, F. C. The collie ectasia syndrome. Pathologic alterations in the eyes of puppies one to fourteen days of age. *Am J Ophthalmol* **61:** 1458–1466, 1966.
Rubin, L. F., Nelson, E. J., and Sharp, C. A. Collie eye anomaly in Australian shepherd dogs. *Prog Vet Comp Ophthalmol* **1:** 105–108, 1991.
Smelser, G. K., and Azanics, V. The development of the trabecular meshwork in primate eyes. *Am J Ophthalmol* **71:** 366–385, 1971.
Stades, F. C. Persistent hyperplastic tunica vasculosa lentis and persistent hyperplastic primary vitreous in 90 closely-related Doberman pinschers: Clinical aspects. *J Am Anim Hosp Assoc* **16:** 739–751, 1980.
Van der Linde-Sipman, J. S., Stades, F. C., and DeWolff-Rouendaal, D. Persistent hyperplastic tunica vasculosa lentes and persistent hyperplastic primary vitreous in the Doberman pinscher. Pathological aspects. *J Am Anim Hosp Assoc* **19:** 791–802, 1983.
Yakely, W. L., *et al.* Genetic transmission of an ocular fundus anomaly in collies. *J Am Vet Med Assoc* **152:** 457–461, 1968.

4. Anomalies of Neurectoderm

Included under this heading are anomalies of retina, optic nerve, and of neuroepithelium of iris and ciliary body. Of these, retinal anomalies are by far the most frequent and most significant.

a. RETINAL DYSPLASIA Retinal dysplasia is a general term denoting abnormal retinal differentiation, characterized by jumbling of retinal layers and by glial proliferation. Retinal dysplasia is common in dogs and in cattle, and results from failure of proper apposition of the two layers of the optic cup, from failure of proper induction by an inherently defective retinal pigment epithelium, or from necrosis of the developing retina. Regardless of pathogenesis, the dysplastic retina is characterized by retinal folds, retinal rosettes, patchy to diffuse blending of nuclear layers, loss of retinal cells, and glial scars. The folds and rosettes are the histologic counterparts of the vermiform streaks seen on the fundus with the ophthalmoscope. The hallmark of retinal dysplasia is the rosette, composed of a central lumen surrounded by one to three layers of neuroblasts. The three-layered rosette is the most common in naturally occurring cases in animals, and shows more or less complete retinal differentiation. Most such rosettes are probably retinal folds cut transversely. The lumen contains pink fibrils resembling photoreceptors and is bounded by a thin membrane resembling the normal outer limiting membrane. One- and two-layered rosettes are encountered infrequently and consist of a lumen surrounded by undifferentiated neuroblasts.

There are good examples of each class of retinal dysplasia among naturally occurring diseases of domestic animals in which the retinal lesion is the major or sole ocular change. In addition, anomalous retinal differentiation is to be expected in any severely anomalous globe, such as those with cyclopia, microphthalmos, or large colobomas. In dogs, the location, ophthalmoscopic appearance, and effect on vision vary from breed to breed but tend to be uniform within each breed, a fact used by clinical ophthalmologists when attempting to distinguish inherited dysplasias from those occurring as isolated anomalies or as sequelae to *in utero* infections.

The first type, that resultant from retinal nonattachment, should probably be considered extensive retinal folding rather than true dysplasia, unless actual disorganization and blending of neural layers can be demonstrated. There may be associated cataract. Cases with retinal nonattachment have extensively folded retinas, since the distance to be traversed from disk to ora ciliaris in a straight line is shorter than the convex route taken by attached retina, and redundant retina is obliged to fold upon itself.

The second type, which is probably the one seen with greatest frequency in dogs and in the greatest variety of breeds, is retinal folding and subtle disorganization of the outer nuclear layer. The defect may be nonprogressive and clinically insignificant or progress to complete retinal separation and blindness, with the outcome greatly influenced by the specific breed in which the defect occurs. In English springer spaniels, in which this type of dysplasia has been most extensively studied, changes are seen as early as gestational day 45 and always by day 55. Focal infolding of the neuroblastic layer away from the retinal pigment epithelium and focal loss of the junctions between the neuroblasts (the outer limiting membrane) are the early changes, followed by overt focal retinal separation and extensive retinal folding. In all breeds in which this type of dysplasia has been adequately studied, it is inherited as a simple autosomal trait. The primary defect is probably related to faulty induction by the pigment epithelium, resulting in a focal dysregulation of retinal growth that leads to the retinal folding.

Retinal dysplasia occurs in combination with chondrodysplasia in several dog breeds, but particularly in Labrador retrievers. Cataract and persistent hyaloid remnants may accompany the retinal lesion. In this breed, all the defects are the result of a single gene, with recessive effects on the skeleton and incompletely dominant effects on the eye.

Another common example of retinal dysplasia, thought to be secondary to defects of retinal pigment epithelium, is seen in collie eye anomaly, in which foci of dysplastic retina are common in the peripapillary retina, in the optic disk, and in the wall of the colobomas. Some of these foci, which may include rosettes, are thought to represent dysplastic differentiation of primitive retinal pigment epi-

thelium. Others, however, routinely disappear as the eye grows, suggesting that the folding results from a temporary imbalance between retinal and scleral growth. Since the other defects of choroidal and scleral formation and maturation in this syndrome are attributed to faulty induction by a defective retinal pigment epithelium (RPE), it is reasonable to attribute the retinal folding to the same mechanism.

In the third category, retinal necrosis, are found the most complex examples of retinal dysplasia in domestic animals. A wide variety of viral and physico–chemical insults to the embryonic eye may cause retinal maldevelopment, but naturally occurring examples are almost exclusively viral. Since the carnivore retina continues to develop for about 6 weeks after birth, the opportunity is great for injury postnatally to produce retinal maldevelopment in puppies and kittens. Retinal maturation is most rapid in central (peripapillary) retina and progressively less toward the periphery, so that occasionally dysplastic lesions may be encountered only in peripheral retina, suggesting a viral (or other) injury quite close to the 6-week-old limit for dysplasia of this pathogenesis. Mature retina will scar but will not develop lesions of dysplasia.

The specific viruses implicated in domestic animals are bovine virus diarrhea virus in cattle, bluetongue virus in sheep, herpesvirus in dogs, and both parvovirus and leukemia virus in cats. The histologic lesion is similar for all diseases, with variation in lesions caused by the same virus in one species as great as the variation caused by different viruses in different species. The most significant clue suggesting viral rather than genetic cause is the presence of residual inflammation and postnecrotic scarring in retina, optic nerve, and perhaps subtly, in choroid. Injured retinal pigment epithelium undergoes one or more of reactive hyperplasia, migration into injured retina as discrete pigmented cells in areas of scarred retina, or metaplastic formation of multilayered fibroglial plaques in place of normal simple cuboidal epithelium (Fig. 4.16A,B). Disorganization of nuclear layers and rosette formation are seen, as in other types of dysplasia.

Infection of calves with bovine virus diarrhea virus between 79 and 150 gestation days is the most frequently encountered and thoroughly studied retinal dysplasia of known viral etiology. Work with other viruses has been too limited to allow definition of the susceptible period in fetal development or of the full range of resultant lesions. The limited descriptions of the other viral-induced retinal lesions suggest that the sequence of events is probably quite similar for all such agents.

The initial ocular lesion is nonsuppurative panuveitis and retinitis with multifocal retinal and choroidal necrosis. The acute inflammatory disease gradually subsides over several weeks, and most cases of spontaneous abortion or neonatal death retain scant vestige of previous inflammation. Those ocular structures already well differentiated at the time of the endophthalmitis (cornea, uvea, optic nerve) may undergo atrophy and scarring or be left virtually untouched. Other tissues such as retina are actively

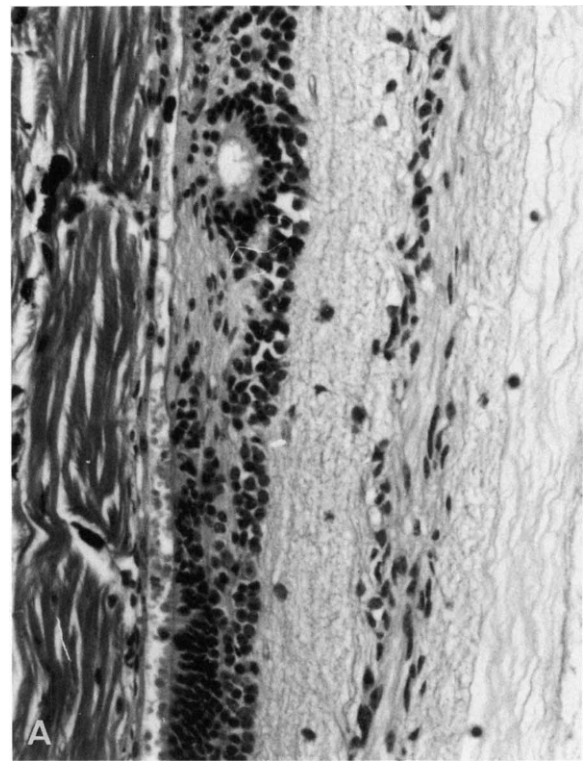

Fig. 4.16A Retinal dysplasia. BVD virus. Calf. Focal retinal scar with loss of outer nuclear layer and photoreceptors. Abortive regeneration with small rosette. Blending of inner and outer nuclear layers. Note lack of ganglion cells.

differentiating and exhibit a combination of this atrophy and scarring as well as abortive regeneration and arrested differentiation. Retinal pigment epithelium in most examples (bluetongue being an apparent exception) is infected and subsequently injured. The result is a patchy alternation of abortive retinal regeneration, hyperplastic pigment epithelium, and postnecrotic glial scarring (Fig. 4.17). The lesions are usually more severe in nontapetal retina and are bilateral but not necessarily symmetrical. It seems reasonable to speculate that those naturally occurring cases in which the dysplasia is confined to peripheral retina represent late viral infection when only peripheral retina is still differentiating.

Because the virus has affinity for other neural tissues, all calves with retinal dysplasia induced by bovine viral diarrhea virus also have cerebellar atrophy, and some have hydrocephalus or hydranencephaly. A similar association with hydrocephalus and other brain anomalies has been described for feline parvovirus infection in cats, bluetongue virus infection in sheep, and in a possibly hereditary syndrome in white shorthorn and Hereford cattle. In the latter two instances, the involvement of virus could not be excluded based on published information.

b. Optic Nerve Hypoplasia Hypoplasia is the most common anomaly of the optic nerve. The defect may be

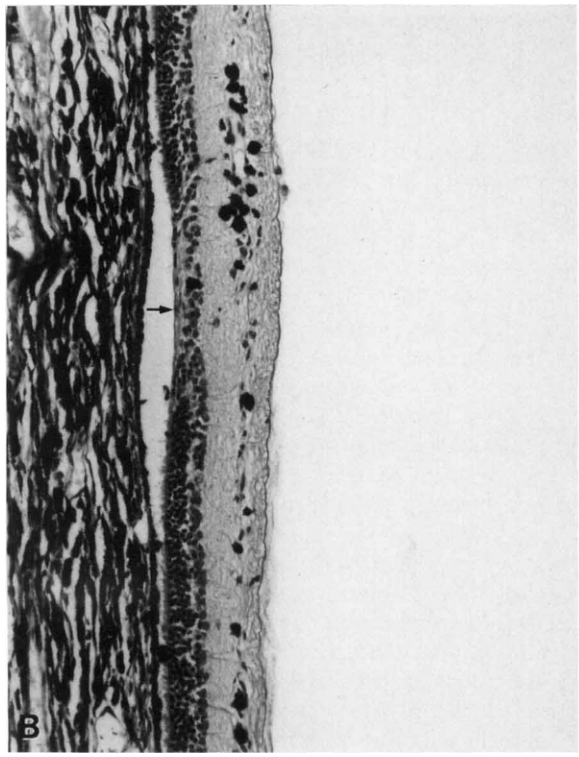

Fig. 4.16B Calf, BVD. Pigment-laden cells from retinal pigment epithelium have migrated into ganglion cell layer. Postnecrotic scar (arrow) with loss of photoreceptors and outer nuclear layer.

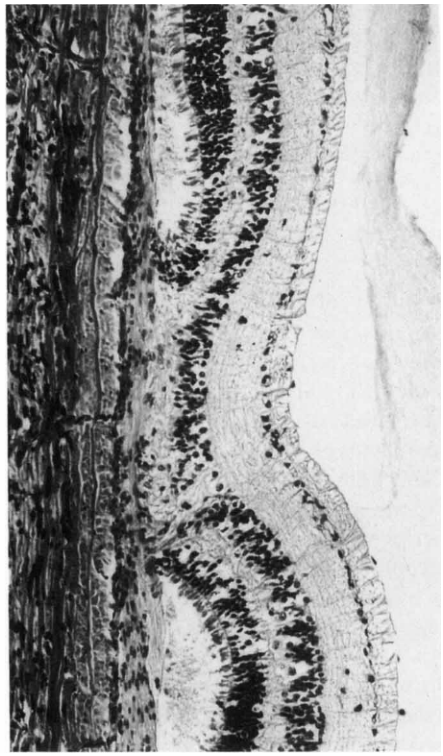

Fig. 4.17 Focal chorioretinal scar with loss of outer nuclear layer and fibrous metaplasia of adjacent retinal pigment epithelium. Calf, prenatal BVD infection.

unilateral or bilateral, and usually occurs in eyes with other anomalies and particularly in eyes with retinal dysplasia. In most instances, the so-called hypoplasia is more likely to be atrophy as the inevitable result of the destruction of ganglion cells in viral, toxic, genetic, or idiopathic retinal disease (Fig. 4.18). The only clear example of an alternative pathogenesis is that associated with maternal deficiency of vitamin A in cattle, in which atrophy of the developing optic nerve results from failure of remodeling of the optic nerve foramen and subsequent stenosis. A similar lesion occurs in pigs, but in that species, hypovitaminosis A seems more indiscriminately teratogenic, and optic nerve hypoplasia is accompanied by diffuse ocular dysplasia and multiple systemic anomalies. Hypoplasia is a relatively frequent clinical diagnosis in toy breeds of dogs, without apparent visual defects (and thus rarely receives histologic examination). Most examples are probably hypomyelination of the optic disk, which results from premature halt of myelinated nerve fibers at, or posterior to, the lamina cribrosa. The opposite, with myelin extending too far into the nerve fiber layer of the peripapillary retina, is also seen in dogs and is a frequent but insignificant occurrence in horses.

Inherited optic nerve hypoplasia is documented in one strain of laboratory mice, although it may accompany inherited retinal dysplasia or multiple inherited anomalies

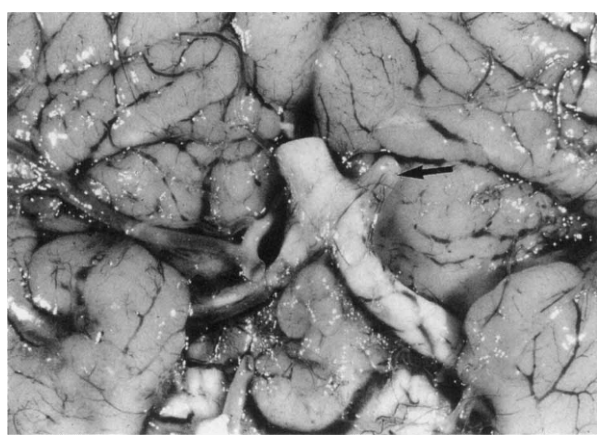

Fig. 4.18 Optic chiasm. Foal with unilateral secondary (degenerative) microphthalmos. Small left optic nerve (arrow) due to prenatal atrophy following ganglion cell destruction.

in any species. Histologic examination of affected eyes reveals few if any ganglion cells and a thin and moth-eaten nerve fiber layer.

Bibliography

Albert, D. M. Retinal neoplasia and dysplasia. I. Induction by feline leukemia virus. *Invest Ophthalmol* **16:** 325–337, 1977.

Albert, D. M. *et al.* Canine herpes-induced retinal dysplasia and

associated ocular anomalies. *Invest Ophthalmol* **15:** 267–278, 1976.
Ashton, N., Barnett, K. C., and Sachs, D. D. Retinal dysplasia in Sealyham terriers. *J Pathol Bact* **96:** 269–272, 1968.
Barnett, K. C. Comparative aspects of canine hereditary eye disease. *Adv Vet Sci* **20:** 39–67, 1976.
Barnett, K. C., Bjorck, G. R., and Kock, E. Hereditary retinal dysplasia in the Labrador retriever in England and Sweden. *J Small Anim Pract* **10:** 755–759, 1969.
Barnett, K. C., and Grimes, T. D. Bilateral aplasia of the optic nerve in a cat. *Br J Ophthalmol* **58:** 663–667, 1974.
Barrie, K. N., and Gelatt, K. N. Diseases of the canine posterior segment: The ocular fundus. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 480–484, Philadelphia, Pennsylvania, Lea & Febiger, 1981.
Bistner, S. I., Rubin, L. F., and Saunders, L. Z. The ocular lesions of bovine viral diarrhea-mucosal disease. *Vet Pathol* **7:** 275–286, 1970.
Brown, T. T. *et al.* Pathogenetic studies of infection of the bovine fetus with bovine viral diarrhea virus. II. Ocular lesions. *Vet Pathol* **12:** 393–404, 1975.
Carrig, C. B. *et al.* Retinal dysplasia associated with skeletal abnormalities in Labrador retrievers. *J Am Vet Med Assoc* **170:** 49–57, 1977.
Gelatt, K. N. Inherited retinopathies in the dog. *Compend Cont Ed* **1:** 307–313, 1979.
Gelatt, K. N., Leipold, H. W., and Coffman, J. R. Bilateral optic nerve hypoplasia in a colt. *J Am Vet Med Assoc* **155:** 627–631, 1969.
Greene, H. J., and Leipold, H. W. Hereditary internal hydrocephalus and retinal dysplasia in shorthorn calves. *Cornell Vet* **64:** 367–375, 1974.
Hayes, K. C., Nielsen, G. W., and Eaton, H. D. Pathogenesis of the optic nerve lesion in vitamin A-deficient calves. *Arch Ophthalmol* **80:** 777–787, 1968.
Heywood, R., and Wells, G. A. H. A retinal dysplasia in the beagle dog. *Vet Rec* **87:** 178–180, 1970.
Keller, W. F. *et al.* Retinal dysplasia in English springer spaniels. *Proc Am Coll Vet Ophthalmol* 63–66, 1977.
Kennedy, P. C., Kendrick, J. W., and Stormont, C. Adenohypophyseal aplasia, an inherited defect associated with abnormal gestation in Guernsey cattle. *Cornell Vet* **47:** 160–178, 1957.
Kern, T. J., and Riis, R. C. Optic nerve hypoplasia in three miniature poodles. *J Am Vet Med Assoc* **178:** 49–54, 1981.
Lahav, M., and Albert, D. M. Clinical and histopathologic classification of retinal dysplasia. *Am J Ophthalmol* **75:** 648–667, 1974.
Lavach, J. D., Murphy, J. M., and Severin, G. A. Retinal dysplasia in the English springer spaniel. *J Am Anim Hosp Assoc* **14:** 192–199, 1978.
MacMillan, A. D. Retinal dysplasia in the dog and cat. *Vet Clin North Am* **10:** 411–415, 1980.
Nelson, D. L., and MacMillan, A. D. Multifocal retinal dysplasia in field trial Labrador retrievers. *Proc Am Coll Vet Ophthalmol* 11–23, 1978.
O'Toole, D. *et al.* Retinal dysplasia of English springer spaniel dogs: Light microscopy of the postnatal lesions. *Vet Pathol* **20:** 298–211, 1983.
Percy, D. H. *et al.* Lesions in puppies surviving infection with canine herpes virus. *Vet Pathol* **8:** 37–53, 1971.
Percy, D. H., Scott, F. W., and Albert, D. M. Retinal dysplasia due to feline panleukopenia virus infection. *J Am Vet Med Assoc* **167:** 935–937, 1975.
Sheffield, B., and Fishman, D. A. Intercellular junctions in the developing neural retina of the chick embryo. *Ztschr Zellforsch* **104:** 405–418, 1970.
Silverstein, A. M., Osburn, B. I., and Prendergast, R. A. The pathogenesis of retinal dysplasia. *Am J Ophthalmol* **72:** 13–21, 1971.
Silverstein, A. M. *et al.* An experimental virus-induced retinal dysplasia in the fetal lamb. *Am J Ophthalmol* **72:** 22–34, 1971.
Whitely, H. E. Dysplastic canine retinal morphogenesis. *Invest Ophthalmol Vis Sci* **32:** 1492–1498, 1991.

5. Anomalies of Surface Ectoderm

From fetal surface ectoderm are derived corneal epithelium, lens, lacrimal apparatus, and the epithelial portions of the eyelids and associated adnexa. Seldom are anomalies of these structures the subject of histopathologic study, inasmuch as they are clinically obvious and of significance only if they result in corneal irritation, impaired vision, or unacceptable appearance.

Excessively large or small palpebral fissures are part of current fashion in some dog breeds. Micropalpebral fissure frequently leads to entropion as the lid margin curls inward, and resultant corneal abrasion necessitates surgical correction. Congenital entropion also occurs as sporadic flock epizootics in lambs, but whether this is a structural deformity or the result of eyelid spasm is unclear. Entropion associated with microphthalmos occurs in all species. Other eyelid defects include colobomas, which are focal to diffuse examples of eyelid agenesis, and delayed separation of the eyelid fusion, which is the normal state during organogenesis.

Disorders of cilia are very common in dogs but uncommon in other species. Congenital defects include one or more of ectopic cilia, misdirected but otherwise normal cilia (trichiasis), the occurrence of a second row of cilia from the orifice of normal or atrophic Meibomian glands (distichiasis), and excessively large cilia (trichomegaly). In each instance, the significance of the anomaly depends on the presence or absence of corneal irritation.

The lacrimal gland and its ducts develop from an isolated bud of surface ectoderm and, although anomalies must surely exist, they have not been investigated. Failure of patency of the lacrimal puncta occurs in dogs and horses and manifests as excessive tearing. Ectopic or supernumerary openings have been reported in dogs and in cattle.

a. CORNEAL ANOMALIES Primary corneal maldevelopment is rare in all species. The category may be expanded to include corneal dystrophies, defined as bilateral, inherited, and usually central corneal opacities that, despite their typically adult onset, presumably have a congenital basis. These rare lesions will be discussed with degenerative diseases of the adult cornea.

Corneal anomalies may be ectodermal or mesenchymal, and may affect one or more of corneal size, shape, or transparency. **Microcornea** refers to a small but histologically normal cornea in an otherwise normal globe. A small cornea occurring in a microphthalmic globe is expected

and does not merit a separate description. Mild microcornea of no clinical significance is reportedly common in certain dog breeds. **Megalocornea** has not been reported in domestic animals except in predictable association with congenital buphthalmos.

Dermoid is a congenital lesion of cornea or conjunctiva characterized by focal skinlike differentiation, and as such is properly termed a **choristoma.** They occur in all species. There is one report of a geographically high prevalence of multiple and sometimes bilateral dermoids as an inherited phenomenon in polled Hereford cattle in the American midwest, but ordinarily they seem to occur as single, random anomalies of unknown pathogenesis. Defective induction (skin instead of corneal epithelium) by the invading corneal stromal mesenchyme is the most popular speculation.

The degree of differentiation varies, but most consist of stratified squamous keratinized and variably pigmented epithelium overlying an irregular dermis containing hair, sweat glands, and sebaceous glands. Very rarely, cartilage or bone is seen. The degree of adnexal differentiation varies widely but may approach that of normal skin (Fig. 4.19A,B,C). At the edge of the dermoid, the dermal collagen reorients to blend with the regular stroma of cornea, and the epidermis transforms itself to corneal epithelium. Surgical removal may be for cosmetic reasons, or may be required if dermoid hairs irritate the cornea or if the position of the dermoid interferes with vision. In most instances of corneal dermoid, the choristoma is attached to the surface of a corneal stroma of normal thickness, so excision of the dermoid should not risk perforation of the globe.

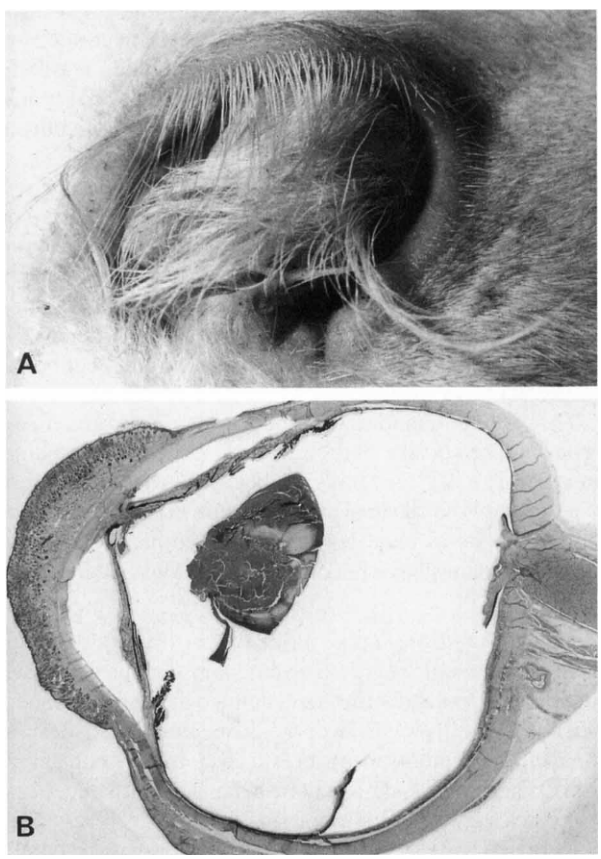

Fig. 4.19 Corneal dermoid, calf. (A) Notchlike defect in lower lid is a coloboma. (B) Globe from (A). Anterior rupture of lens capsule with well-organized anterior synechia, probably from foreign-body perforation.

Congenital corneal opacities are usually caused by anomalous formation of the anterior chamber, particularly congenital anterior synechiae and persistent pupillary membranes. Adherence of anterior chamber structures to the corneal endothelium, or perhaps their interposition during ingrowth of the corneal endothelium, results in focal absence of the corneal endothelium and disorganization of adjacent corneal stroma. Grossly, the affected cornea has deep stromal opacity caused by stromal edema or fibrosis in the area of the defective endothelium. Pigment, originating from adherent uveal strands, may be found in the corneal stroma. The opacity may be diffuse or focal, depending on the extent of uveal–corneal adhesion. Diffuse, congenital corneal opacity occurs in Holstein–Friesian cattle in England and Germany. The histologic lesion is diffuse corneal edema, but its pathogenesis is unknown. The cornea remains permanently opaque.

Corneal opacity caused by noncellular depositions occurs in dogs and is usually of adult onset despite an apparently genetic basis. The exception is multifocal, subepithelial deposition of basophilic, periodic acid-Shiff positive material in the corneas of puppies with collie eye anomaly or other mesodermal dysgeneses. The material is of unknown origin and may be the histologic counterpart of the transient, multifocal, subepithelial opacities seen quite commonly in 2 to 3-week-old puppies whose eyes are otherwise normal and thus unavailable for histologic examination.

b. ANOMALIES OF LENS The lens may be abnormally small, abnormally shaped, ectopic, or cataractous. Of these, only ectopia and cataract are common.

Aphakia is the congenital absence of lens, and it may be primary or secondary. It is claimed that primary aphakia is possible only in a rudimentary globe because of the central role of lens in the induction of invagination of the primary optic vesicle. Any globe with the structure of optic cup, regardless of how dysplastic, must have had a lens early in organogenesis, and its absence later must be the result of degeneration. This assumption is an extrapolation from work done many years ago in chicken embryos; while no work has been published to refute this contention, there is no work in mammals to confirm it. In the one report of aphakia in modern literature that includes histologic examination, several other puppies had small lenses, and all had invaginated optic cups with iris and retina. There was no conclusion about the nature of the injury to the developing eyes or the timing of such injury.

Microphakia, or congenitally small lens, is reported in

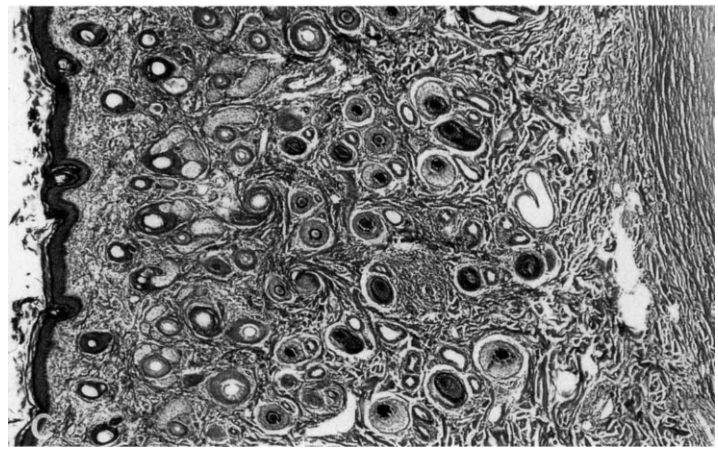

Fig. 4.19C Same eye as in (A) and (B). Development approaches that of normal skin. Note abrupt transition to dense regular corneal stroma at deep margin of dermoid.

dogs, calves, and cats, but is nonetheless rare. Most such reports describe the defect in association with ectopia lentis, microphthalmos, and anterior chamber mesenchymal anomalies. Such lenses are spherical and almost always are cataractous.

Lenticonus and **lentiglobus** are rare defects of lens shape characterized by an abrupt change in capsular configuration so that the lens acquires a globular or conical protrusion. The defect is usually polar and, in animals, usually posterior. From scattered and very old descriptions, it is difficult to define the "typical" histology of such lesions or their pathogenesis. The defect usually appears as a focal overgrowth of cortical lens fibers covered by thin posterior lens capsule and retained posterior epithelium. Of four relatively recent descriptions, all of dog eyes, all had congenital cataract but only in one did the cataract involve the protruding lens fibers themselves. Other ocular lesions reported include hyperplasia of tunica vasculosa lentis, rupture of the lens protrusion, and dysplasia of ciliary epithelium. At least in Doberman pinscher dogs, the posterior lentiglobus or lenticonus accompanying hyperplastic tunica vasculosa lentis appears to be an acquired defect caused by the abnormal fibrovascular elements adherent to lens.

Congenitally ectopic lenses occur in all species but are relatively common only in dogs and horses. Much more common than congenital luxations are spontaneous luxations in adult dogs, which may be associated with acquired lesions of the zonule. The reason for the particular susceptibility of small terriers and poodles to spontaneous lens luxation is unknown.

Congenital cataract occurs in most severely anomalous eyes but may occur as an isolated ocular lesion (Fig. 4.20). When cataract is present in eyes with multiple anomalies, it usually results from persistence of some part of perilenticular vasoformative mesoderm, but may also result from intraocular inflammation or toxic degeneration. Persistence of pupillary membrane or hyaloid system frequently results in multiple epithelial defects and subcapsular opacities at the sites of mesodermal contact with the lens.

In dogs, congenital primary cataracts are frequently hereditary but, as with corneal and retinal diseases, most hereditary cataracts are not congenital. Subtle, nonprogressive nuclear or cortical opacities are common but clinically insignificant in dogs and are of unknown pathogenesis. Primary and usually diffuse cataract is the most

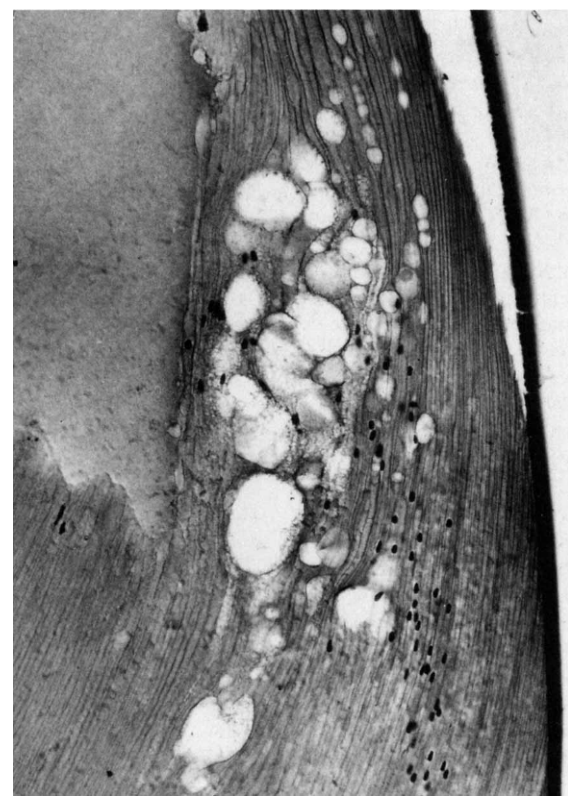

Fig. 4.20 "Bladder cells" in congenital cataract. Dog.

common ocular anomaly of horses. The pathogenesis is unknown, but there is usually no other ocular lesion. Congenital nuclear cataracts have been described as an inherited lesion in Morgan horses in the United States of America.

Congenital cataract is rare in cattle, swine, sheep, and goats. In cattle, hereditary congenital cataract occurs in Holstein–Friesians and in Jerseys and is thought to be an autosomal recessive trait. It is also seen as an infrequent result of fetal infection with the virus of bovine virus diarrhea.

There is a single report of bilateral, complete cataracts in a litter of Persian kittens, but there are no examples in swine or small ruminants except in association with multiple ocular defects.

The pathology of congenital cataract is the same as that of acquired cataract and is discussed later. It may be nuclear, cortical or capsular, focal or diffuse, stationary or progressive.

Bibliography

Aguirre, G. D., and Bistner, S. I. Microphakia with lenticular luxation and subluxation in cats. *Vet Med Small Anim Clin* **66:** 498–500, 1973.

Aguirre, G. D., and Bistner, S. I. Posterior lenticonus in the dog. *Cornell Vet* **63:** 455–461, 1973.

Barrie, K. P. *et al.* Posterior lenticonus, microphthalmia, congenital cataracts and retinal folds in an old English sheepdog. *J Am Anim Hosp Assoc* **15:** 715–717, 1979.

Barkyoumb, S. D., and Leipold, H. W. Nature and cause of bilateral ocular dermoids in Hereford cattle. *Vet Pathol* **21:** 316–324, 1984.

Beech, J., Aguirre, G., and Gross, S. Congenital nuclear cataracts in the Morgan horse. *J Am Vet Med Assoc* **184:** 1363–1365, 1984.

Brightman, A. H., Everitt, J., and Bevier, G. Epibulbar solid dermoid choristoma in a pig. *Vet Pathol* **22:** 292–294, 1985.

Gelatt, K. N. Cataracts in cattle. *J Am Vet Med Assoc* **159:** 195–200, 1971.

Gwin, R. M., and Gelatt, K. N. The canine lens. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 435–473. Philadelphia, Pennsylvania, Lea & Febiger, 1981.

Lavach, J. D., and Severin, G. A. Posterior lenticonus and lenticonus internum in a dog. *J Am Anim Hosp Assoc* **13:** 685–687, 1977.

Martin, C. L. Zonular defects in the dog: A clinical and scanning electron microscopic study. *J Am Anim Hosp Assoc* **14:** 571–579, 1978.

Martin, C. L., and Leipold, H. W. Aphakia and multiple ocular defects in Saint Bernard puppies. *Vet Med Small Anim Clin* **69:** 448–453, 1974.

Olesen, H. P., Jensen, O. A., and Norn, M. S. Congenital hereditary cataract in cocker spaniels. *J Small Anim Pract* **15:** 741–749, 1974.

Peiffer, R. L. Bilateral congenital aphakia and retinal detachment in a cat. *J Am Anim Hosp Assoc* **18:** 128–130, 1982.

Peiffer, R. L., and Gelatt, K. N. Congenital cataracts in a Persian kitten. *Vet Med Small Anim Clin* **70:** 1334–1335, 1975.

Rubin, L. F. Cataracts in golden retrievers. *J Am Vet Med Assoc* **165:** 457–458, 1974.

Rubin, L. F., Koch, S. A., and Huber, R. J. Hereditary cataracts in miniature schnauzers. *J Am Vet Med Assoc* **154:** 1456–1458, 1969.

Takei, Y., and Mizuno, K. Electron microscopic studies on zonules. *Graefes Arch Klin Exp Ophthalmol* **202:** 237–244, 1977.

Trelstad, R. L., and Coulombre, A. J. Morphogenesis of the collagenous stroma in the chick cornea. *J Cell Biol* **50:** 840–858, 1971.

III. Ocular Adnexa

The adnexa include eyelids, nictitating membrane, and lacrimal and accessory lacrimal glands. Developmental, degenerative, inflammatory, and neoplastic diseases of these structures are commonly encountered in clinical practice, but only the neoplasms and proliferative inflammatory lesions are regularly submitted for histologic examination.

A. Eyelids

Disorders of size and configuration of the palpebral fissure are common in purebred dogs, as are anomalies of number or placement of cilia. None requires histologic evaluation.

The outer lid surface is skin and thus may suffer any of the afflictions of that tissue so that the evaluation of blepharitis uses the nomenclature and logic of dermatopathology (see Chapter 5). The inner (bulbar) surface is conjunctiva, and its diseases are discussed later.

External hordeolum or **stye** is a suppurative adenitis of the adnexal glands of Zeis or Moll. **Internal hordeolum** is suppurative inflammation of the meibomian gland. With persistent inflammation, the leakage of sebaceous secretion into adjacent soft tissue stimulates a granulomatous inflammation not unlike its epidermal counterpart, furunculosis. In this location, the nodular firm swelling is called a **chalazion.** Grossly, chalazion may be confused with meibomian adenoma and, in fact, frequently accompanies such adenomas.

B. Lacrimal System

Acquired disease of the lacrimal system is probably quite common in dogs if one includes keratoconjunctivitis sicca (see Keratitis) and eversion of the gland of the third eyelid.

Dacryoadenitis is inflammation of the lacrimal gland, and may result from involvement in orbital cellulitis or orbital trauma, spread from severe intraocular inflammation, incidental involvement in systemic diseases such as malignant catarrhal fever, feline infectious peritonitis, and canine distemper; or apparently specific immunologic assault. Specific dacryoadenitis caused by a coronavirus is extremely common in laboratory rats, in which acute necrotizing inflammation of lacrimal, Harderian, and salivary glands results in eventual fibrosis and squamous metaplasia of affected glands. Residual lesions in mildly affected rats are multiple lymphoid aggregates in the glandular interstitium. Similar changes are often seen in dogs with keratoconjunctivitis sicca, and in the absence of dem-

onstrated viral cause, are assumed to represent autoimmune lacrimal adenitis. The analogous lesion in humans with Sjögren's syndrome is associated with influx of numerous T-helper cells into the gland, but no studies have yet been published to prove this immune pathogenesis for canine lacrimal adenitis and atrophy. However, the efficacy of cyclosporine, which acts primarily by suppression of T-helper cells, in reversing canine lacrimal adenitis provides evidence for such a pathogenesis.

Protrusion of the **nictitans gland** is quite common in dogs, and is thought to reflect a congenital laxity in the connective tissue anchoring the gland to the cartilage of the third eyelid. Because the resultant eversion is unsightly and resembles a neoplasm, these lesions frequently are excised, even although the membrana nictitans may be normal except for overlying conjunctival inflammation from exposure and abrasion. Since this gland sometimes supplies a significant proportion of total lacrimal secretion, its surgical removal may be followed by keratoconjunctivitis sicca in dogs that have less than optimal function of the primary lacrimal gland. In dogs with keratoconjunctivitis sicca, the gland may suffer the same lymphocytic interstitial adenitis, fibrosis, and atrophy as affects the lacrimal gland itself.

C. Conjunctiva

At the orifice of the meibomian glands, the epidermis of the lid undergoes abrupt transition to the pseudostratified columnar mucous membrane typical of the palpebral and bulbar conjunctivae. Goblet cells increase in number from the lid margin to the fornix, but ordinarily are absent in bulbar conjunctiva. Lymphoid aggregates are common in the subepithelial connective tissue, particularly below the bulbar conjunctiva and the inner aspect of the nictitating membrane. These aggregates are more prominent in the conjunctiva of horses than in other domestic species. Whether this is normal or a reflection of increased antigenic stimulation of the conjunctiva in the dusty environment of many horse stables is unknown. The transition from conjunctival to corneal epithelium occurs at, or slightly central to, the corneoscleral junction, and is marked by gradual loss of pigment, rete ridges, subepithelial blood vessels, and lymphoid tissue.

The general pathology of the conjunctiva is similar to that of other mucous membranes. Acute conjunctival injury, whether physical, chemical, or microbial, results in hyperemia and unusually severe edema. Evacuation of goblet cells and cellular exudation from the very labile conjunctival vessels add to the excessive lacrimation caused by any ocular irritation. The ocular discharge progresses from serous to mucoid and perhaps purulent with increasing severity of insult. Chronic irritation results in epithelial hyperplasia, hyperplasia of goblet cells and lymphoid aggregates, or even squamous metaplasia progressing to keratinization. The goblet cell hyperplasia is a very uncommon lesion when compared to squamous metaplasia and lymphoid hyperplasia. Lymphoid hyperplasia may be so marked as to result in grossly visible white nodules that may require surgical or chemical removal to reduce irritation of the adjacent cornea. While lymphoid hyperplasia is characteristic of a number of etiologically specific conjunctival diseases, it is best considered a nonspecific response to any chronic antigenic stimulation. Conjunctivitis frequently accompanies other ocular disease, notably keratitis, uveitis, and glaucoma. Conversely, conjunctival inflammation may spread to cornea, uvea, and orbit, although only secondary corneal involvement is common.

The causes of conjunctivitis include every class of noxious stimulus, including allergy and desiccation. Alleged bacterial causes, based on isolations from conjunctival swabs, are usually not distinguishable from the normal varied conjunctival flora. At least in dogs, the isolation of gram-negative organisms, especially coliforms, *Pseudomonas,* and *Proteus,* should be considered significant in light of the almost exclusively gram-positive flora of normal conjuctiva. Conjunctivitis occurs in a wide variety of multisystem diseases such as canine distemper and ehrlichiosis, equine viral arteritis and babesiosis, bovine virus diarrhea, malignant catarrhal fever, hog cholera, rinderpest, African swine fever, and others. Conjunctivitis accompanies most viral and allergic diseases of the upper respiratory tract. Only those diseases in which conjunctivitis is prominent or the only sign are discussed here.

Infectious bovine rhinotracheitis is usually accompanied by serous to purulent conjunctivitis that can be confused clinically with infectious bovine keratoconjunctivitis caused by *Moraxella bovis.* However, corneal involvement with rhinotracheitis is uncommon and is never the central suppurating ulcer typical of infectious keratoconjunctivitis. In an unpredictable number of animals, multifocal white glistening nodules, 1–2 mm in diameter, may be seen on the palpebral or bulbar conjunctiva. They appear as early as 3 days after instillation of virus into conjunctival sac, and represent hyperplastic lymphoid aggregates. Overlying conjunctiva may be ulcerated, and the defect filled with fibrin. Infectious bovine rhinotracheitis is discussed with the Respiratory (Volume 2, Chapter 6), Alimentary (Volume 2, Chapter 1), and Female Genital Systems (Volume 3, Chapter 4).

Feline infectious conjunctivitis is common and is caused by mycoplasma, chlamydia, or one of the upper respiratory tract viruses (herpesvirus, calicivirus, reovirus). Combined infections occur and are perhaps the rule. Usually the condition occurs in association with upper respiratory or oral lesions that may suggest an etiologic diagnosis. *Mycoplasma felis* or *M. gateae* may cause conjunctivitis unassociated with other signs in immunosuppressed cats, but instillation of organisms into the conjunctival sac of cats without prior corticosteroid administration does not cause disease. The conjunctivitis is pseudodiphtheritic and initially is unilateral. Histologically there is nonspecific erosive and suppurative conjunctivitis. Diagnosis requires the demonstration of coccoid bodies in the periphery of conjunctival epithelial cells.

1. Parasitic Conjunctivitis

Parasitic conjunctivitis is relatively common worldwide and may be caused by members of the genera *Thelazia, Habronema, Draschia, Onchocerca,* and several members of the family Oestridae. Of these, only *Thelazia* is truly an ocular parasite; the others cause eyelid, conjunctival, or orbital disease incidentally in the course of larval migration.

Members of the genus *Thelazia* are thin, rapidly motile nematodes 7–20 mm in length that inhabit the conjunctival sac and lacrimal duct of a variety of wild and domestic mammals. Their prevalence is much greater than the prevalence of conjunctivitis, suggesting that their number must be greater than usual before signs of conjunctival irritation are observed. The genus is found worldwide, and a listing of every species in every host is not justified here. The commonest species associated with conjunctivitis in domestic animals are *T. lacrymalis* in horses in Europe and North America, *T. rhodesis* in ruminants worldwide and *T. californiensis* in many species including dog, cat, bear, coyote, deer, and humans. Female worms are viviparous, and larvae free in lacrimal secretions are consumed by flies of the genus *Musca,* in which they develop for 15 to 30 days. The third-stage infective larvae migrate to the fly's proboscis and are returned to the conjunctival sac as the fly feeds.

Ocular habronemiasis results from deposition of larvae by the fly intermediate host, usually *Musca domestica* or *Stomoxys calcitrans,* in the moisture of the medial canthus of horses. Larvae of *Habronema muscae, H. microstoma,* or *Draschia (Habronema) megastomum* are the culprits. The burrowing larvae cause an ulcerative, oozing lesion about 0.5–1.0 cm in diameter at the medial canthus, which becomes progressively more nodular as granulomatous reaction to the larvae mounts. Mineralized granules may be found within the lesion along with caseous debris, liquefaction, and viable larvae. The histologic lesion is similar to that of cutaneous habronemiasis, namely chronic granulomatous inflammation surrounding live or dead larvae and eosinophils.

2. Ophthalmomyiasis

A syndrome of periocular and even intraocular invasion by fly larvae occurs in various species, including humans. Its various manifestations are known collectively as ophthalmomyiasis. Specific oculovascular myiasis, uitpeuloog or gedoelstial myiasis, is a disease of domestic ruminants and horses caused by invasion and migration of larvae of *Gedoelstia* spp. of Oestridae. The *Gedoelstia* are parasites of the blue wildebeest and hartebeest, the larvae being deposited in the eye, rather than in the nares, as is the habit of *Oestrus ovis.* The most important member of the genus in terms of frequent aberrant parasitism in domestic species is *G. hassleri,* which, in its natural antelope host, migrates to the nasal cavity via the vascular system and cerebral meninges and subdural space. The parasitism is not clinically significant in the antelope, but in domestic species which are aberrant hosts, severe ocular and neural disease occurs, sometimes on a large scale. The disease is seasonal and occurs particularly in domestic ruminants in contact with wildebeest.

The ocular lesions vary from a transient mild conjunctivitis to a destructive ophthalmitis with orbital or periorbital edema or abscessation affecting one or both eyes. Neurological signs of varied pattern are common in sheep, partly due to the larvae directly and partly to thrombophlebitis marking their route of invasion. Thrombosis may be very extensive, may involve the jugular vessels and endocardium, and may cause sudden death when coronary vessels are affected.

Larval migration may be into conjunctival sac, orbital tissues, or into the eye itself. In the last instance, ophthalmomyiasis interna, the globe is often destroyed by the larval penetration. However, a syndrome of relatively harmless larval migration in the subretinal space or within vitreous has been reported in humans. The characteristic subretinal linear tracks may be accompanied by focal retinal separation, preretinal and subretinal hemorrhage, and focal proliferations of retinal pigment epithelium. Two reported cases in cats had similar subretinal tracks, hyperplasia of pigment epithelium, and retinal hemorrhages. In one, the live motile larva was detected either on the face of, or just within, the retina. Subsequent examination failed to detect the larva, and the eye lesions resolved except for the subretinal tracks and pigment clumps.

The penetration is usually by a single larva despite numerous eggs or larvae within conjunctiva. The larva may die within the globe or continue its migration by uneventful exit from the globe via sclera, optic nerve, or vessel adventitia.

3. Allergic Conjunctivitis

Presumed allergic conjunctivitis occurs in all species, but is most likely to be investigated in dogs. Rarely is a specific allergen identified and, like its counterparts in allergic skin diseases, the diagnosis is based on the failure to demonstrate infectious or mechanical causes, response to corticosteroid therapy, and sometimes a convincing association with environmental changes. Biopsy is rarely warranted but, when taken during the acute disease, may show epithelial changes ranging from erosion to hyperplasia to squamous metaplasia, with eosinophils around dilated subepithelial blood vessels and percolating throughout the epithelium. More chronic lesions, which are the more usual to be biopsied, have squamous metaplasia and lymphocytic–plasmacytic linear, perivascular, or nodular infiltrates. The linear infiltrates predominate in a poorly characterized interface plasmacytic conjunctivitis more or less specific for German shepherd dogs. The bulbar surface of third eyelid is the favorite location, and many believe this lesion (sometimes referred to as plasmoma) to be the conjunctival variant of pannus keratitis.

Bibliography

Barrie, K. P., and Gelatt, K. N. Diseases of the eyelids (part I). *Compend Cont Ed* **1**: 405–410, 1979.

Barrie, K. P., and Parshall, C. J. Eyelid pyogranulomas in four dogs. *J Am Anim Hosp Assoc* **14**: 433–438, 1979.
Basson, P. A. Studies on specific oculo-vascular myiasis of domestic animals (uitpeuloog): I. Historical review. II. Experimental transmission. III. Symptomatology, pathology, aetiology and epizootiology. *Onderstepoort J Vet Res* **29**: 81–87, 203–209, 211–240, 1962.
Basson, P. A. Gedoelstial myiasis in antelopes in southern Africa. *Onderstepoort J Vet Res* **33**: 77–91, 1966.
Hughes, J. P., Olander, H. J., and Wada, M. Keratoconjunctivitis associated with infectious bovine rhinotracheitis. *J Am Vet Med Assoc* **145**: 32–39, 1964.
Lavach, J. D., and Gelatt, K. N. Diseases of the eyelids (part II). *Compend Cont Ed* **1**: 485–492, 1979.
Mason, G. I. Bilateral ophthalmomyiasis interna. *Am J Ophthalmol* **91**: 65–70, 1981.
Patton, S., and McCracken, M. D. The occurrence and effect of thelazia in horses. *Equine Pract* **3**: 53–57, 1981.
Raphel, C. F. Diseases of the equine eyelid. *Compend Cont Ed* **4**: S14–S21, 1982.

IV. The Cornea

The cornea of domestic mammals is a horizontal ellipse varying from 0.6 to 2.0 mm in thickness among the various species. In general, the larger and older the animal, the thicker the cornea. It appears as a structural and physiologic modification of sclera, and when chronically injured may lose the specialized features of cornea and resemble limbic sclera both ophthalmoscopically and histologically. Embryologically, however, the epithelium is derived from surface ectoderm, and the stroma is from neural crest mesenchyme, in contrast to the vascular–mesenchymal (non-neural) origin for sclera.

The major attribute of cornea is its clarity, and the loss of clarity is the most obvious indicator of corneal disease. The clarity results from several highly specialized anatomic and physiologic features: an unusually regular, nonkeratinized, and nonpigmented surface epithelium; an avascular, cell-poor stroma composed of very thin collagen (mostly type I) fibrils arranged in orderly lamellae (Fig. 4.21A); and a high degree of stromal dehydration maintained primarily by an Na-K-dependent adenosine triphosphatase (ATPase) pump in the cell membrane of the corneal endothelium. This dehydration is passively protected by the hydrophobic corneal epithelium and by the lack of stromal vascularity.

The reaction of cornea to injury is strongly influenced by these anatomic and physiologic features. The acutely injured cornea cannot respond with acute inflammation because it lacks blood vessels. Instead, edema is the hallmark of early corneal injury. The edema may result from injury to the corneal epithelium or endothelium (Fig. 4.21B,C), and is described below. With long-standing corneal disease, the cornea may undergo metaplasia to resemble limbic sclera and thus acquire the full range of inflammatory responses available to vascularized tissue. The chronically irritated epithelium undergoes epidermal metaplasia with the appearance of rete ridges, basilar pigmentation, and surface keratinization. The stroma acquires a capillary network and dermislike irregular fibroplasia. These changes, while they enable the cornea to survive in a hostile environment and to combat the inflammatory stimulus, also deprive it of its transparency.

Fig. 4.21A Normal canine cornea. Uniform, nonkeratinized epithelium. Stroma is poorly cellular and compact. The corneal endothelium is frequently torn or missing as the result of sectioning artefact.

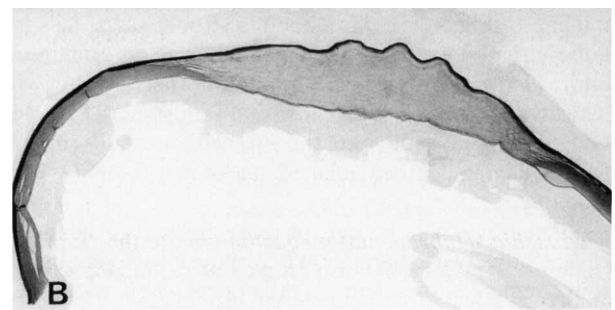

Fig. 4.21B Central corneal edema from abrasion of the corneal endothelium by lens. Foal, congenital anterior lens luxation.

Corneal injury may result from physical or chemical trauma, microbial agents, increased intraocular pressure and, rarely, from inborn errors of metabolism. Specific features of some of these injuries will be discussed later, but those features common to most corneal injuries are presented here.

A. Corneal Edema

Corneal edema occurs rapidly following injury and results from imbibition of lacrimal water through damaged corneal epithelium or failure of electrolyte (and thus water) extrusion by the corneal endothelium. If the epithelial or endothelial defect is focal, the resultant edema is limited to the stroma adjacent to the defect. The edematous cornea is clinically opaque, and may be up to five times its normal

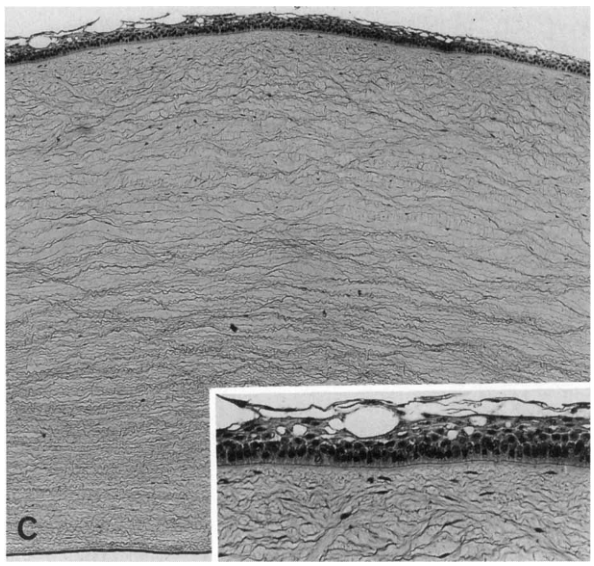

Fig. 4.21C Edema of cornea and epithelial keratitis. Ox. Phenothiazine photosensitivity. Inset. Detail of epithelium.

thickness (Fig. 4.21B). Edematous stroma stains less intensely than normal, and collagen lamellae are separated into a fine feltwork of pale-staining fibrils by excessive hydration of the proteoglycan ground substance. Percolation of stromal fluid into the epithelium results in the intercellular and intracellular edema known as **bullous keratopathy.**

Edema may also be part of more chronic corneal disease. Corneal vascularization in response to severe injury is accompanied by edema, as the porous new capillaries leak fluid into the interstitial spaces. A small amount of peripheral corneal edema frequently accompanies the peripheral stromal vascularization seen in chronic anterior uveitis of any cause. Sometimes the edema is unexpectedly diffuse, severe, and may persist even after the uveitis itself has subsided. Such eyes have a neutrophilic or lymphocytic destructive endothelialitis, with leukocytes interspersed among the vacuolated, pyknotic endothelial cells (see later under anterior uveitis). Other examples of corneal edema are seen in glaucoma and anterior segment anomalies. In the former, it is assumed that the high aqueous pressure drives fluid into the hydrophilic corneal stroma to a degree that overcomes the endothelial ion pump that dehydrates the stroma under normal conditions. In anterior segment anomalies, persistent pupillary membranes or congenital anterior synechiae cause focal defects in endothelial continuity and thus focal opacities due to deep stromal edema.

Persistent corneal edema seems to predispose to stromal vascularization and fibrosis, but numerous experimental models show that edema *per se* stimulates neither. A natural example of virtually permanent corneal edema occurs in Boston terrier and Chihuahua dogs with endothelial dystrophy, where neither fibrosis nor vascularization occurs despite years of severe diffuse stromal edema. When vascularization and fibrosis occur, they are in response to cytokines released by damaged epithelium, stromal keratocytes, or immigrant leukocytes rather than the edema itself.

B. Corneal Wounds

The healing of corneal wounds varies with the depth of penetration. Those defects involving epithelium alone, or epithelium and superficial stroma, heal by epithelial sliding followed by mitosis. The sliding begins within a few hours and is greatly enhanced by the secretion of fibronectin from adjacent injured epithelium. Mitotic activity, in contrast, is delayed for about 24 hr, is stimulated by epidermal growth factor derived from the injured epithelium and the normal tear film, and is most marked in the corneal basal cells near the limbus. Small defects are covered by flattened epithelial cells from adjacent normal cornea, and such shallow lesions heal completely by subsequent mitosis of basilar epithelium to rebuild epithelial thickness. Even if such abrasions affect the entire corneal surface, sliding and subsequent mitosis from the bulbar conjunctiva eventually lead to corneal restitution. Healing of shallow, uninfected corneal ulcers is rapid. For example, 7-mm ulcers heal within a mean of 11 days in horses.

Initially the epithelium has the characteristics of conjunctiva, including pigment, but within a few weeks it adopts a corneal epithelial configuration. Shallow defects in superficial stroma are filled by epithelial cells, creating an epithelial facet that is permanent but clinically insignificant. Epithelial adhesion to the underlying stroma remains fragile for 6 to 8 weeks until the hemidesmosomal attachments of epithelium to basal lamina reform, and until the new epithelium secretes type VII collagen fibrils that anchor the basal lamina to the stroma. In the interim, the cells adhere to a mixture of fibrin and fibronectin derived from the inflamed conjunctival vessels via the tear film or from the injured cornea itself. In many cases the only evidence of previous shallow ulceration is a thickened basal lamina resulting from secretion by the regenerating epithelium, and gentle undulation of the normally flat epithelial–stromal interface.

Deeper defects that include more than the outer third of stroma must heal by epithelial sliding and replication combined with stromal fibroplasia (Fig. 4.22A). Within a few hours of the insult, neutrophils reach the wound via the tear film, attracted by proteases released by injured epithelium. They migrate into the stroma and control bacterial contamination, degrade damaged collagen, and stimulate both fibroplasia and vascularization via production of various cytokines, especially basic fibroblast growth factor. Repair of the stroma is invariably by fibroplasia and never restores the stroma to complete normalcy. Viable stromal cells (keratocytes) adjacent to the wound undergo fibroblastic metaplasia and secrete large amounts of sulfated ground substance, particularly chondroitin sulfate. Histiocytes that slowly accumulate in the injured stroma may also assume the morphologic characteristics of fibro-

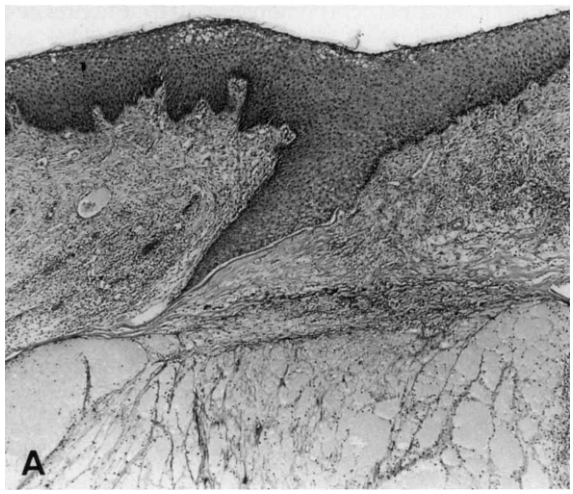

Fig. 4.22A Corneal perforation. Steer. Defect filled by downgrowth of hyperplastic corneal epithelium. Adjacent stroma is vascularized and chronically inflamed. There is anterior synechia.

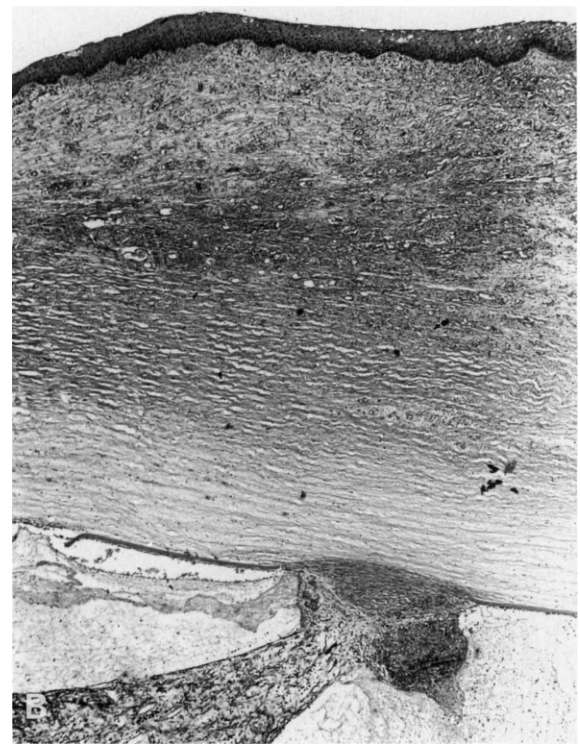

Fig. 4.22B Corneal epidermalization and chronic superficial stromal inflammation with vascularization. Anterior synechia adherent by fibrous plaque that is partly formed by metaplastic corneal endothelium.

blasts. The stimulus for the fibroblasts to form, enlarge, and begin the production of new collagen and ground substance apparently also comes from proliferating reparative epithelium, which produces fibroblast/angioblast stimulatory cytokines. If the defect is not covered by epithelium, or if the animal is neutropenic, stromal fibroplasia is markedly retarded. These events initially occur without stromal vascularization, and nonseptic corneal wounds, even if deep, may heal without vascularization if they do so rapidly. The fibroblastic repair tissue gradually becomes less cellular, the collagen fibrils reorient to resemble more closely the parallel arrays of normal stroma, and the ground substance gradually reverts from an embryonic configuration dominated by chondroitin sulfate to the normal predominance of keratan sulfate. Complete restitution of normal stroma, however, never occurs (Fig. 4.22B), although the residual scar may be subtle and better detected by clinical examination than by histology.

A corneal perforation heals, as does a deep but incompletely penetrating wound, except for the involvement of corneal endothelium and Descemet's membrane. The cut edges of Descemet's elastic membrane retract from the wound, and the transcorneal gap is initially plugged with fibrin. Surface epithelium grows inward along the cut surface of the stroma and is inhibited only by contact with viable corneal endothelium. As with the surface epithelium, the corneal endothelium attempts to bridge the defect by sliding over the fibrin scaffold to restore endothelial continuity. The cells may enlarge severalfold to compensate for endothelial cell loss. Replacement by mitosis begins within about 24 hr in some experimental models, but the regenerative capability of the corneal endothelium in adult animals of most domestic species is very limited, and repair occurs by endothelial sliding and hypertrophy. So potent is this capability that normal stromal dehydration can be maintained even in the face of a 50% reduction in endothelial cell density. The cut ends of Descemet's membrane make no apparent effort at regrowth, but rather the endothelium gradually secretes a new membrane, which may eventually fuse with the old or remain separated from it by a layer of fibrous tissue.

The sequence of epithelial sliding and regeneration, remodeling stromal fibrosis, and endothelial repair is not uniformly successful. Large gaping wounds fill with proliferating epithelium and stromal fibrous tissue, which may protrude through the defect in Descemet's membrane and endothelium and into the anterior chamber. The fibroblasts, most of which are probably derived from keratocytes but which may also evolve via endothelial metaplasia, tend to grow along the posterior surface of Descemet's membrane. Regenerating or sliding endothelium is then separated from the coiled remnants of the original Descemet's membrane by a dense fibrous layer, called a **retrocorneal membrane.** Eventually, the corneal endothelium may resume continuity on the posterior surface of this membrane, secrete a new Descemet's membrane, and result in a cornea with two separate Descemet's membranes. Rarely the downgrowth of surface epithelium may gain access to the anterior chamber, in which it grows uninhibited as if in an organ-culture chamber. Glaucoma from overgrowth of the filtration angle or pupil is the usual consequence.

Bibliography

Bahn, C. F. *et al.* Postnatal development of corneal endothelium. *Invest Ophthalmol Vis Sci* **27**: 44–51, 1986.

Bellhorn, R. W., and Henkind, P. Superficial pigmentary keratitis in the dog. *J Am Vet Med Assoc* **149**: 173–175, 1966.

Brogdon, J. D. *et al.* Effect of epidermal growth factor on healing of corneal endothelial cells in cats. *Am J Vet Res* **50**: 1237–1243, 1989.

Cameron, J. D., Flaxman, B. A., and Yanoff, M. *In vitro* studies of corneal wound healing: Epithelial–endothelial interactions. *Invest Ophthalmol* **13**: 575–579, 1974.

Capella, J. A. Regenerating of endothelium in diseased and injured corneas. *Am J Ophthalmol* **74**: 810–817, 1972.

Catcott, E. J., and Griesemer, R. A. A study of corneal healing in the dog. *Am J Vet Res* **15**: 261–265, 1954.

Cintron, C., Covington, H. I., and Kublin, C. L. Morphologic analyses of proteoglycans in rabbit corneal scars. *Invest Ophthalmol Vis Sci* **31**: 1789–1798, 1990.

Fujikawa, L. S. *et al.* Fibronectin in healing rabbit corneal wounds. *Lab Invest* **45**: 120–129, 1981.

Gipson, I. K., Spurr-Michaud, S. J., and Tisdale, A. S. Anchoring fibrils form a complex network in human and rabbit cornea. *Invest Ophthalmol Vis Sci* **28**: 212–220, 1987.

Hanna, C. Proliferation and migration of epithelial cells during corneal wound repair in the rabbit and rat. *Am J Ophthalmol* **61**: 55, 1966.

Kay, E. P,. Nimni, M. E., and Smith, R. E. Modulation of endothelial cell morphology and collagen synthesis by polymorphonuclear leukocytes. *Invest Ophthalmol Vis Sci* **25**: 502–512, 1984.

Khodadoust, A. A. *et al.* Adhesion of regenerating corneal epithelium. The role of the basement membrane. *Am J Ophthalmol* **65**: 339–348, 1968.

Kitazawa, T. *et al.* The mechanism of accelerated corneal epithelial healing by human epidermal growth factor. *Invest Ophthalmol Vis Sci* **31**: 1773–1778, 1990.

Kuwabara, T., Perkins, D. G., and Cogan, D. G. Sliding of the epithelium in experimental corneal wounds. *Invest Ophthalmol* **15**: 4–14, 1976.

Landshman, N. *et al.* Relationship between morphology and functional ability of regenerated corneal endothelium. *Invest Ophthalmol Vis Sci* **29**: 1100–1109, 1988.

Mathers, W. D. *et al.* Dose-dependent effects of epidermal growth factor on corneal wound healing. *Invest Ophthalmol Vis Sci* **30**: 2403–2406, 1989.

Matsuda, H., and Smelser, G. K. Electron microscopy of corneal wound healing. *Exp Eye Res* **16**: 427–442, 1973.

Maurice, D. M. The transparency of the corneal stroma. *Vision Res* **10**: 107–108, 1970.

Neaderland, M. H. *et al.* Healing of experimentally induced corneal ulcers in horses. *Am J Vet Res* **48**: 427–430, 1987.

Soubrane, G. *et al.* Binding of basic fibroblast growth factor to normal and neovascularized rabbit cornea. *Invest Ophthalmol Vis Sci* **31**: 323–333, 1990.

Van Horn, D. L. *et al.* Regenerative capacity of the corneal endothelium in rabbit and cat. *Invest Ophthalmol* **16**: 597–613, 1977.

Watanabe, K., Nakagawa, S., and Nishida, T. Stimulatory effects of fibronectin and EGF on migration of corneal epithelial cells. *Invest Ophthalmol Vis Sci* **28**: 205–211, 1987.

C. Corneal Dystrophy

Corneal dystrophy should refer to bilateral, inherited, but not necessarily congenital, defects in structure or function of one or more corneal components. These are recognized most frequently as corneal opacities, deposits, or erosions. All are uncommon, but the least uncommon is bilateral recurrent central corneal erosion in middle-aged or old dogs, and occasionally in horses or cats. Stromal dystrophies are discussed with corneal deposits next.

Epithelial-stromal dystrophy (recurrent erosion syndrome) in dogs was first described in boxer dogs (hence the name boxer ulcer) and, while boxers and related breeds may be predisposed, similar recurrent erosions are encountered in a wide variety of breeds. The clinical syndrome is distinctive, characterized by a shallow central corneal erosion with scant edema and no vascularization. The lesion refuses to heal, or repeatedly reulcerates, because of poor adhesion of the epithelium to the underlying stroma or basal lamina. The defect appears not to be in epithelial healing *per se*, since sliding and mitotic activity are normal in affected dogs. Keratectomy specimens reveal poorly adherent hyperplastic epithelium at the ulcer margins, usually with multiple clefts separating epithelium from stroma even in areas distant from the obvious ulcer. The basal lamina is usually not visible with light microscopy, and the epithelium appears to be attempting to adhere to a thin zone of hypocellular, pale-staining stroma. The observation of pyknotic and lytic keratocyte nuclei within this superficial zone suggests that the basic defect is degeneration of the superficial stroma, so that epithelial hemidesmosomes and anchoring collagen fibrils have no firm anchor. Very chronic cases usually acquire superficial stromal granulation tissue appropriate to any chronic ulceration, but its onset is much delayed in comparison to infectious or traumatic ulcers.

Corneal endothelial dystrophy occurs in Boston terriers, Chihuahuas, and several other dog breeds, and causes slowly progressive bilateral corneal edema in mature dogs. The edema usually begins adjacent to the lateral limbus and may initially be unilateral and unaccompanied by other clinical signs. Later, epithelial fluid bullae may rupture to cause painful corneal ulcers and associated inflammation. Despite the persistent stromal edema, fibrosis and vascularization do not occur unless rupture of epithelial bullae initiates keratitis. The primary lesion is spontaneous necrosis of corneal endothelium followed by hypertrophy and sliding of viable endothelium. A marked progressive decrease in overall endothelial cell density results, eventually, in what usually is severe bilateral corneal edema. The reason for the endothelial cell death is unknown. Focal irregularities in Descemet's membrane occur in areas of endothelial loss, presumably a result of new basement membrane production by adjacent reactive endothelium.

A rare, juvenile-onset, genetically transmitted endothelial dystrophy in Manx and domestic short-hair cats is manifest as bilateral, progressive central epithelial and stromal edema. Fluid accumulates within superficial stroma and within the epithelium. Primary morphologic abnormalities are not described in the Manx, but in short-

hairs there is irregularity and vacuolation of corneal endothelium.

D. Corneal Stromal Depositions

Deposition of mineral, lipid, or pigment within the cornea may be primary or occur secondary to chronic corneal injury in any species.

Corneal pigmentation often accompanies chronic corneal irritation in dogs and less frequently in other species, particularly horses. The pigment is melanin and is found in the basal layer of the corneal epithelium and in the superficial stroma. It is the result of a progressive ingrowth of new germinal cells that have retained pigment from the bulbar conjunctiva. The clinical name, pigmentary keratitis, is purely descriptive (Fig. 4.23). The corneal epithelium is invariably hyperplastic and often has the other features of chronically irritated cornea, such as rete ridge formation and keratinization, that characterize corneal epidermalization. There is usually evidence of chronic stromal inflammation, including vascularization. Infrequently, nonepithelial corneal pigmentation is the residual lesion of uveal (iris) adherence to cornea, with uveal melanin left behind as the adhesion resolves.

Corneal lipidosis occurs as apparently spontaneous crystalline corneal stromal opacities in dogs, as a result of persistent hypercholesterolemia, and as part of chronic stromal inflammation. The deposits are usually mixtures of cholesterol, phospholipids, and neutral fats. When the deposition is bilateral and unassociated with previous keratitis or serum lipid abnormality, the lesion qualifies as **corneal stromal dystrophy.** Crystalline lipid-rich corneal dystrophy is common in young Siberian huskies and occurs sporadically in other dog breeds, notably collies, Airedale terriers, beagles, and cavalier King Charles spaniels.

Diets high in cholesterol produce diffuse corneal stromal lipidosis in rabbits, as well as focal lipid deposits in uveal epithelium and stroma. While hyperlipemia is not a feature of most cases of corneal lipidosis in dogs (most of which are spontaneous dystrophies), circumferential peripheral stromal lipidosis is reported in German shepherd dogs with hyperlipoproteinemia resulting from hypothyroidism.

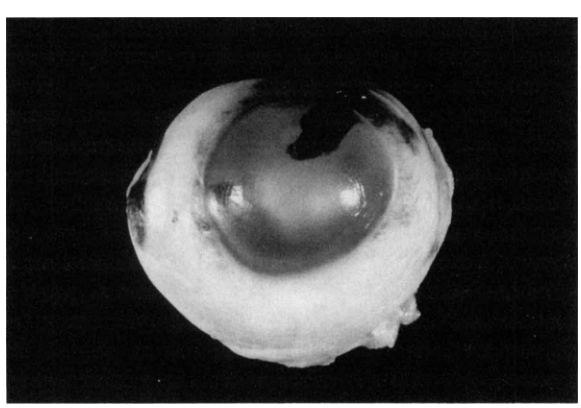

Fig. 4.23 Corneal pigmentation. Pug dog, a breed with normally bulging eyes.

Regardless of pathogenesis, the histologic lesion is similar. Cholesterol crystals and lipid vacuoles are found principally in anterior stroma, and are sometimes surrounded by lipid-laden macrophages and variable numbers of other leukocytes. Vascularization is often present, but its pathogenesis is unknown.

Mineral deposition occurs primarily in the anterior stroma and the epithelial basement membrane. Predisposing corneal changes include desiccation, anesthesia, edema, or inflammation. There are many methods for inducing deposition of calcium salts, but stromal edema seems to be the common denominator in almost all cases. The edema may result from corneal epithelial desiccation (exposure keratitis), uveitis, deliberate corneal trauma, or chemical injury. Hypercalcemia from vitamin D toxicity or hyperparathyroidism exacerbates the mineralization and is essential to lesion development in some experimental models.

An unidentified corneal deposition is often seen in canine eyes suffering from multiple anomalies, particularly those involving uvea. Similar deposits are seen, with less regularity, in the horizonal midportion of the cornea of many normal puppies. Fine basophilic periodic acid-Schiff positive linear deposits are associated with the epithelial basement membrane or superficial stroma. There is some disarray of superficial stromal fibers but no inflammation. The nature and pathogenesis of the deposits are unknown, but most disappear after a few months.

E. Corneal Degeneration

Corneal degeneration is a vague term sometimes used to describe those corneal lesions characterized by noninflammatory loss of epithelial or stromal viability. Diseases such as keratoconjunctivitis sicca and pannus keratopathy are sometimes considered primary degenerative lesions, but their principal manifestation is inflammatory, and they are discussed under keratitis.

The only degenerative, noninflammatory acquired corneal lesion presented here is the **corneal sequestrum** of **cats.** This lesion, also called corneal mummification or corneal nigrum, is initially seen as a central, nonulcerated brown focus in one or both corneas of cats of any age or breed. Persian and Siamese cats are more frequently affected than are other breeds. Histologically, the lesion is bland corneal epithelial desiccation that may be mistaken as artefact. The stroma is hyalinized, featureless, and orange-brown. In older lesions the deep margin of the focus may be marked by a zone of reactive mononuclear leukocytes and, perhaps, a few giant cells. The epithelium is usually absent over the central portion of the biopsy specimen, because lesions have usually ulcerated by the time keratectomy is done. The nature of the pigment and the pathogenesis of this unique disease are unknown. The

sequestrum may eventually slough, and the defect heals by granulation, although most lesions are treated by excision before that stage is reached.

Bibliography

Aguirre, G. D., Rubin, L. F., and Harvey, C. E. Keratoconjunctivitis sicca in dogs. *J Am Vet Med Assoc* **158:** 1566–1579, 1971.

Cooley, P. L., and Dice, P. F. Corneal dystrophy in the dog and cat. *Vet Clin North Am: Small Anim Pract* **20:** 681–692, 1990.

Cooley, P. L., and Wyman, M. Indolent-like corneal ulcers in three horses. *J Am Vet Med Assoc* **188:** 295–297, 1986.

Crispen, S. M. Corneal dystrophies in small animals. *Vet Annual* **22:** 298–310, 1982.

Crispen, S. M., and Barnett, K. C. Arcus lipoides corneae secondary to hypothyroidisim in the Alsatian. *J Small Anim Pract* **19:** 127–142, 1978.

Ekins, M. B., Waring, G. O., and Harris, R. R. Oval lipid corneal opacities in beagles, Part II: Natural history over four years and study of tear function. *J Am Anim Hosp Assoc* **16:** 601–605, 1980.

Formston, C. *et al.* Corneal necrosis in the cat. *J Small Anim Pract* **15:** 19–25, 1974.

Gelatt, K. N., and Samuelson, D. A. Recurrent corneal erosions and epithelial dystrophy in the boxer dog. *J Am Anim Hosp Assoc* **18:** 453–460, 1982.

Gwin, R. M. Primary canine corneal endothelial cell dystrophy: Specular microscopic evaluation, diagnosis, and therapy. *J Am Anim Hosp Assoc* **18:** 471–479, 1982.

Gwin, R. M., and Gelatt, K. N. Bilateral ocular lipidosis in a cottontail rabbit fed an all-milk diet. *J Am Vet Med Assoc* **171:** 887–889, 1977.

Harrington, G. A., and Kelly, D. F. Corneal lipidosis in a dog with bilateral thyroid carcinoma. *Vet Pathol* **17:** 490–493, 1980.

Kirschner, S. E., Niyo, Y., and Betts, D. M. Idiopathic persistent corneal erosions: Clinical and pathological findings in 18 dogs. *J Am Anim Hosp Assoc* **25:** 84–90, 1989.

Martin, C. L., and Dice, P. F. Corneal endothelial dystrophy in the dog. *J Am Anim Hosp Assoc* **18:** 327–336, 1982.

McMillan, A. D. Crystalline corneal opacities in the Siberian husky. *J Am Vet Med Assoc* **175:** 829–832, 1979.

Souri, E. The feline corneal nigrum. *Vet Med Small Anim Clin* **70:** 531–534, 1975.

Startup, F. G. Corneal necrosis and sequestration in the cat: A review and record of 100 cases. *J Small Anim Pract* **29:** 476–486, 1988.

F. Corneal Inflammation

Corneal inflammation is called keratitis and is traditionally divided into epithelial, stromal (interstitial), and ulcerative keratitis. Most lesions reaching a pathologist are ulcerated or show extensive stromal scarring below a healed ulcer. Regardless of cause, corneal inflammation initially follows the stereotyped sequence of edema and leukocyte immigration from tears and distant limbic venules. With severe lesions, corneal stromal vascularization, fibrosis, and epithelial metaplasia with pigmentation may occur.

Keratitis usually results from physical, chemical, or microbial injury to the cornea, but the cornea may also be affected by extension of disease from elsewhere in the eye or adnexa or conjunctiva. The stroma and endothelium may become involved in diseases of the uvea by extension via the aqueous or by direct extension from iris root or ciliary apparatus across the limbus. Purely stromal keratitis is uncommon except as an extension from a severe anterior uveitis.

Purely **epithelial keratitis** is rarely encountered in histologic preparations, because the clinical lesion either is transient and progresses to ulceration (as in acute keratoconjunctivitis sicca) or is so mild that eyes are unavailable for histologic examination. **Superficial punctate keratitis** is, in fact, noninflammatory and consists of multiple fine epithelial opacities that are probably foci of epithelial hydropic change. Intercellular fluid accumulation (bullous keratopathy) is seen as a sequel to corneal edema.

Stromal keratitis is subdivided into superficial and deep. Superficial stromal keratitis is common only in dogs, particularly in German shepherds, as a chronic, nonulcerative proliferative inflammation termed **pannus keratitis,** chronic superficial keratitis, or Uberreiter's syndrome. The clinical disease is distinctive. The early lesion is seen in dogs of either sex, usually in early middle age, as a vascularized opacity growing into the corneal stroma from the limbus. The ingrowth is bilateral, although not always of simultaneous onset, and most frequently originates from the ventrolateral limbus. There is no ulceration, but pigmentation is often marked. The untreated lesion eventually infiltrates the entire cornea, converting the superficial stroma to an opaque membrane resembling granulation tissue.

The histologic appearance varies with the duration of the lesion. The initial lesion is a superficial stromal infiltration of mononuclear cells, especially plasma cells. Subsequently, there is progressive vascularization and fibroplasia in the superficial third of the stroma, accompanied by

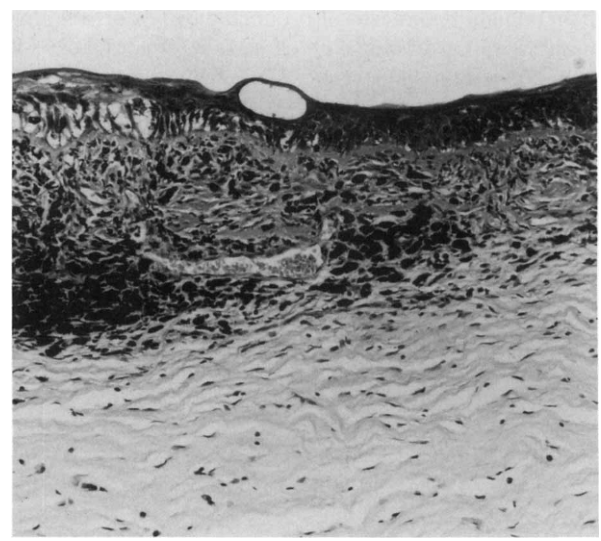

Fig. 4.24 Superficial stromal keratitis (of pannus). Dog. Epithelial hyperplasia, chronic superficial stromal inflammation and pigmentation.

epithelial hyperplasia and pigmentation that may include the stroma (Fig. 4.24). The deep stroma is never affected.

The pathogenesis of the condition is unknown, but an immune reaction to altered corneal epithelial antigens is hypothesized. Its response to continuous corticosteroid administration supports this hypothesis, although direct immunofluorescence tests for intraepithelial or basement membrane immunoglobulin are negative. Infectious agents are not consistently isolated. A histologically similar lesion of the bulbar conjuctiva of third eyelid occurs in the same breed (so-called plasmoma) and may reflect the same (unknown) pathogenesis.

Nonulcerative **deep stromal keratitis** may result from extension from anterior uveitis or from endothelial damage by uveal inflammation, trauma, or glaucoma. Inflammations extending from the anterior uvea are distinctly laminar and initially consist of perilimbic edema and leukocytosis. Later, corneal stromal vascularization occurs as a laminar, perilimbic "brush border" of vessels extending from the vascular plexus at the base of iris and ciliary body. As the uveitis subsides, the corneal lesion regresses until only the empty ghosts of these vessels remain. This lesion is particularly common in the eyes of horses which have suffered one or more bouts of equine recurrent ophthalmitis.

Ulcerative keratitis includes a large group of lesions caused by physical and chemical trauma, desiccation, bacterial or viral infection, and rarely from primary degeneration of the corneal epithelium itself. Regardless of cause, the loss of epithelium initiates a predictable series of corneal reactions caused by tear imbibition, local production of cytokines, and opportunistic microbial contamination of the wound. Imbibition causes superficial stromal edema below the ulcer and is followed by immigration of neutrophils from the tear film and, later, from the limbus. The leukocytes, although somewhat protective against opportunistic pathogens, also add their collagenases, proteases, and stimulatory cytokines to the wound and thereby may contribute to its progression. Epithelial and stromal repair proceeds as already described for corneal wound healing, but the repair fails in those cases in which microbial contamination is well established or in which the cause of the initial ulceration has not been corrected. Common examples of the latter are found in dogs in which corneal trauma by misdirected cilia or facial hair, or desiccation due to lacrimal gland dysfunction, persists.

The usual role of bacteria and fungi in the pathogenesis of corneal ulceration is opportunistic. However, these opportunists contribute significantly to the perpetuation and worsening of the lesion. Proteases and collagenases of microbial, leukocytic, or corneal origin progressively liquefy corneal stroma, a process termed **keratomalacia** (Fig. 4.25). Ulcers contaminated by *Pseudomonas* and *Streptococcus* spp. are particularly prone to rapid liquefaction because of the potent collagenases and proteases produced by these organisms. *Pseudomonas* ulcers have been extensively investigated because of the devastating liquefaction of cornea that commonly accompanies this infection. The bacteria themselves produce numerous proteases and other toxins, which may be important in the establishment of the early infection, but most of the characteristic stromal malacia results from the action of proteases originating from leukocytes, reactive corneal epithelium, or injured stroma. The stroma contains a variety of proenzymes (for collagenases, elastases, gelatinases, and other stromal lysins) that are cleaved by the *Pseudomonas* toxins to produce the active enzymes. Which toxins are produced, and in what quantities, is very strain dependent. The stepwise degradation of stroma is seen histologically as a featureless eosinophilic coagulum, which occurs with progressive septic ulcers regardless of the species of bacterium. The neutrophils may encircle the liquefying focus as a thick wall of live and fragmented cells. The resulting lesion is then called a **ring abscess** (Fig. 4.26) and is seen

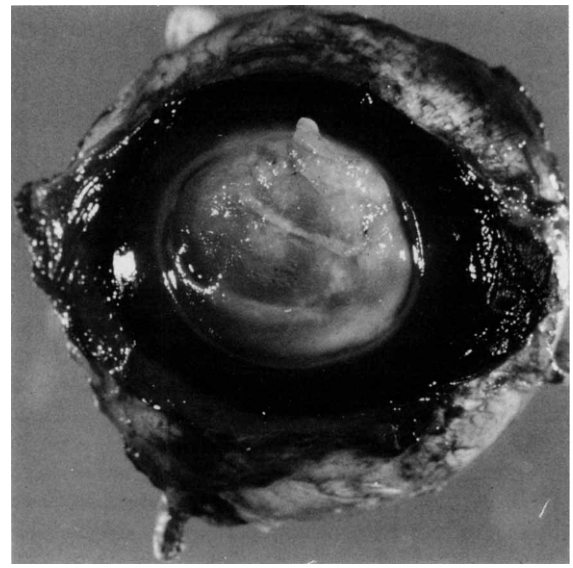

Fig. 4.25 Keratomalacia. Horse with *Pseudomonas* keratitis.

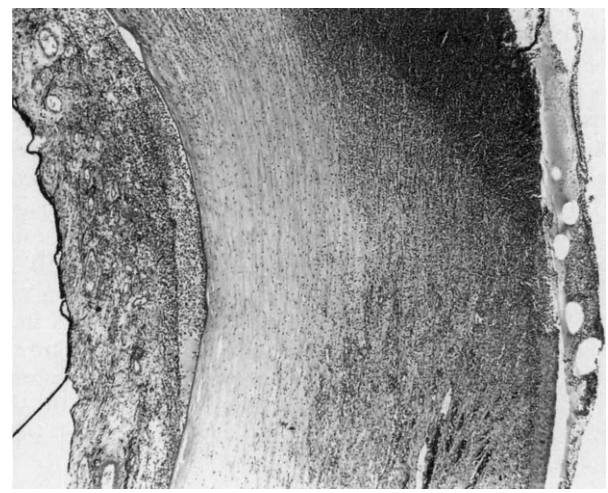

Fig. 4.26 Ring abscess. Calf. Edematous cornea is ulcerated and infiltrated by neutrophils. Leukocytes are within and on the surface of the iris which is adherent to the cornea.

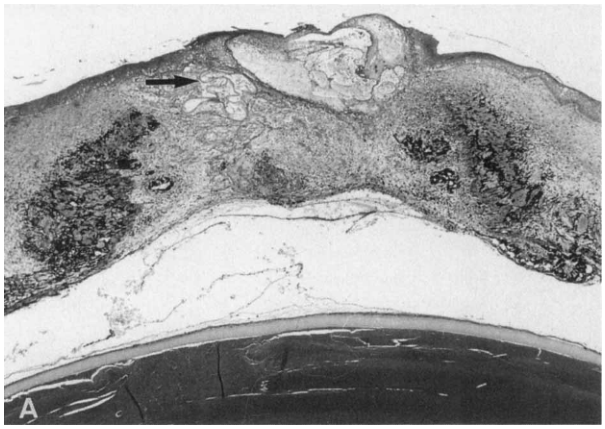

Fig. 4.27A Corneal epithelium is attempting to heal across a fibrin mass plugging the defect. Iris is incorporated into lesion and will form anterior staphyloma. Note coiled remnant of Descemet's membrane (arrow).

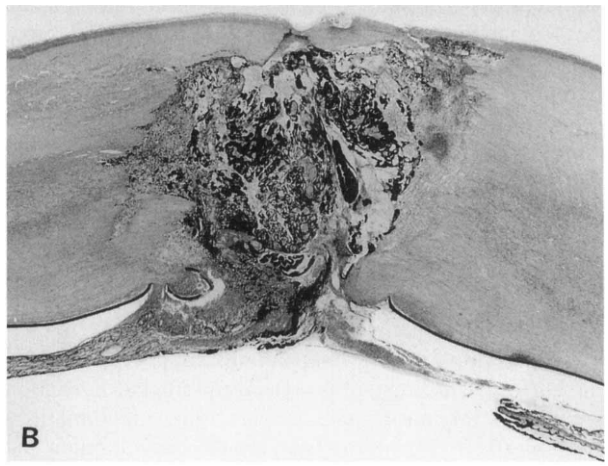

Fig. 4.27B Iris entrapped within cornea following perforation of ulcer (iris prolapse).

more commonly in cattle than any other species, perhaps because of the prevalence of untreated, contaminated corneal ulcers in that species and the prevalence of septic corneal perforation.

The sequelae of ulcerative keratitis involve cornea, conjunctiva, and uvea. The ulcer itself may heal with vascularization and scarring proportional to the severity of the initial lesion. It may persist as a stubborn but nonprogressive lesion, or it may progress to involve more of the stroma and epithelium. Stromal liquefaction that reaches Descemet's membrane results in its forward bulging as a **descemetocele.** This membrane, although resistant to penetration of the microbial agents themselves, is apparently permeable to inflammatory mediators and microbial toxins which diffuse into the anterior chamber. These chemicals, combined with a vasoactive sensory neural reflex from irritated cornea, are responsible for the vasodilation and exudation in anterior uvea which are seen histologically in virtually all globes with deep ulcerative keratitis. Even in nonperforating keratitis, the anterior uveal inflammation may result in sufficient fibrin exudation so as to predispose to focal adhesions, called synechiae, of iris to the injured cornea. In the case of corneal perforation, the iris flows forward to plug the defect and subsequently becomes incorporated into the corneal scarring. This defect is a permanent anterior synechia but is usually called **anterior staphyloma,** meaning a fibrous tunic (i.e., corneal) defect lined by uvea (i.e., iris) (Fig. 4.27A,B).

The conjunctiva is involved in almost all instances of keratitis, either as a victim of the same injury or as the nearest vascularized tissue to the diseased cornea. Hyperemia, cellular exudation, and lymphofollicular hyperplasia are common as the conjunctiva responds to the diffusion of inflammatory mediators of microbial, leukocytic, and tissue origin from the injured cornea.

1. Keratoconjunctivitis Sicca

Necrosis of corneal epithelium caused by desiccation is seen as a common and usually spontaneous condition in dogs, but desiccation secondary to exophthalmos or failure of the blinking reflex is seen in all species. Acute desiccation keratitis is particularly common in calves moribund as a result of neonatal diarrhea or meningoencephalitis, and is seen as bilateral, large, shallow, central corneal ulcers. Depending on the length of time between development of the ulcer and the animal's death, the epithelial loss may be accompanied by stromal edema and neutrophil infiltration. A similar lesion occurs in animals subjected to general anesthetics when failure to blink prevents adequate distribution of tears.

Desiccation keratitis may follow destruction or denervation of lacrimal or accessory lacrimal gland in any species by orbital inflammation, drugs, neoplasia, or trauma. Squamous metaplasia with resultant inadequacy of secretion may be seen with chronic deficiency of vitamin A. Specific lacrimal adenitis with subsequent atrophy is well recognized with coronavirus infection in rats and may be seen in the acute or chronic phases of canine distemper. Similar adenitis probably occurs with other viruses and in other species, but such lesions are poorly documented. Transient keratoconjunctivitis sicca may accompany acute herpetic keratoconjunctivitis in cats.

Keratoconjunctivitis sicca is encountered more commonly in dogs than in any other species, with an overall prevalence in North America of about 1%. Most cases are chronic, progressive, and idiopathic. The reason for greater than expected prevalence in certain breeds (English bulldog, Lhasa Apso, Shih Tzu, West Highland white terrier, and others) is unknown. Because the disease is amenable to medical or surgical management, few specimens are available for histologic examination until the very chronic stages. At this time the lacrimal gland is atrophic with interstitial lymphoid infiltration and fibrosis, but provides no clue as to the initial lesion. The ability of certain immune modulators, notably cyclosporine, to reverse the disease points to some kind of immune-mediated phenomenon, perhaps autoimmunity.

The corneal changes vary with the severity and rapidity of onset of lacrimal deficiency. In acute disease with marked lacrimal deficiency, clinical signs of ulcerative keratitis may occur. The corneal epithelium is thinned, has numerous hydropically degenerate cells, and may suffer full-thickness ulceration. The accompanying stromal changes, including eventual vascularization and fibrosis, are those of ulcerative keratitis. More commonly in dogs, however, the desiccation is not absolute (at least initially), and the epithelial response is protective epidermalization without prior ulceration. Keratinization, marked hyperplasia with rete ridge formation, and pigmentation are commonly seen. Stromal inflammation and vascularization are usually superficial, resulting in a lesion very similar to pannus keratitis. Squamous metaplasia may also occur in the bulbar conjunctiva. The conjunctivitis that clinically is the earliest lesion of keratoconjunctivitis sicca is rarely available for histologic examination.

2. Herpetic Keratitis of Cats

Feline herpetic keratitis caused by feline herpesvirus-1 is seen either as the sole ocular lesion or in concert with conjunctivitis. Clinical signs associated with herpesvirus infections in cats include conjunctivitis, keratitis, rhinotracheitis, and, in neonates, systemic disease with encephalitis and necrosis in visceral organs. Acquired immunity alters the manifestations of the disease and results in different lesions predominating in different age groups. Keratitis is commonest in adult cats and seems to result from activation of latent infection during concurrent immunosuppressive disease or corticosteroid therapy. Concurrent mild respiratory disease may be present. In contrast, the infection in adolescent cats causes a nonspecific bilateral erosive conjunctivitis without keratitis. Intranuclear inclusions are numerous within cells prior to sloughing, and leukocytes are sparse until ulceration permits opportunistic contamination. Upper respiratory disease is almost always present and is typically more severe than that in adults. In adult cats the disease is often unilateral and primarily corneal. It probably reflects recrudescence of latent infection. The typical corneal lesions are multifocal minute corneal erosions and ulcers which have a tendency to coalesce into branching dendritic ulcers. Severe or recurrent lesions in immunosuppressed cats may result in underlying stromal keratitis with lymphocytic infiltration, persistent edema, and vascularization. Inclusion bodies, intranuclear and typical of herpesviruses, are sometimes found in degenerating epithelium at the ulcer's margin. Lesion development is preceded by viral replication within otherwise normal corneal epithelium, and only in immunosuppressed cats is viral antigen abundant within the stroma.

3. Feline Eosinophilic Keratitis

Another uniquely feline ocular lesion is seen clinically as unilateral or bilateral proliferative, superficial stromal keratitis. There is no breed, age, or sex predilection, and no known association with other ocular or systemic disease. Since diagnosis is made by cytologic or histologic examination, this disease is more likely to be seen by pathologists than most other corneal disorders. Scrapings of the surface of the lesion reveal numerous eosinophils and fewer mast cells and other mononuclear leukocytes. Eosinophils may be less conspicuous on histologic examination of keratectomy specimens, perhaps because most seem determined to emigrate through the epithelium and into the tear film. Instead, the stromal lesion is a mixture of macrophages, plasma cells, fibroblasts and, unpredictably, mast cells and eosinophils. The latter are least frequent in older lesions. No bacterial or fungal agents have been seen. While there are histologic similarities to cutaneous eosinophilic ulcer and linear granuloma, no statistical association has been proven, and the lack of understanding of even the cutaneous eosinophilic lesions makes such attempted comparisons of very limited value.

Bibliography

Austad, R., and Oen, E. O. Chronic superficial keratitis (keratitis superficialis chronica) in the dog. I. A review of the literature. *J Small Anim Pract* **19:** 197–210, 1978.

Bedford, P. G. C., and Longstaffe, J. A. Corneal pannus (chronic superficial keratitis) in the German shepherd dog. *J Small Anim Pract* **20:** 41–56, 1979.

Brown, S. I., Bloomfield, S. E., and Tam, W. I. The cornea-destroying enzyme of *Pseudomonas aeruginosa*. *Invest Ophthalmol* **13:** 174–180, 1974.

Gelatt, K. N. Corneal diseases in the dog. *Compend Cont Ed* **1:** 78–84, 1979.

Iglewski, B. H., Burns, R. P., and Gipson, I. K. Pathogenesis of corneal damage from pseudomonas exotoxin A. *Invest Ophthalmol* **16:** 73–76, 1977.

Jones, G.E . *et al.* Mycoplasmas and ovine keratoconjunctivitis. *Vet Rec* **99:** 137–141, 1976.

Kessler, E., Mondino, B. J., and Brown, S. I. The corneal response to *Pseudomonas aeruginosa:* Histopathological and enzymatic characterization. *Invest Ophthalmol* **16:** 116–125, 1977.

Nasisse, M. P. *et al.* Experimental ocular herpesvirus infection in the cat. *Invest Ophthalmol Vis Sci* **30:** 1758–1768, 1989.

Paulsen, M. E. *et al.* Feline eosinophilic keratitis: A review of 15 clinical cases. *J Am Anim Hosp Assoc* **23:** 63–68, 1987.

Slatter, D. H. *et al.* Ubereitter's syndrome (chronic superficial keratitis) in dogs in the Rocky Mountain area—a study of 463 cases. *J Small Anim Pract* **18:** 757–772, 1977.

Steuhl, K-P. *et al.* Relevance of host-derived and bacterial factors in *Pseudomonas aeruginosa* corneal infections. *Invest Ophthalmol Vis Sci* **28:** 1559–1568, 1987.

4. Mycotic Keratitis

Mycotic keratitis is not a specific disease but is often viewed as such because of its consistently poor response to therapy and tendency to progress to corneal perforation. The offending fungus is usually a member of the normal conjunctival flora, and its role in the disease is that of opportunistic contaminant. *Aspergillus* is the most frequent isolate. The condition most often occurs in eyes with traumatic corneal injury, particularly if they have been receiving long-term antibiotic-corticosteroid ther-

apy. Horses seem particularly prone to mycotic keratitis, perhaps related to the mold-laden, dusty environment in which many horses are housed; only rarely does the lesion occur in dogs or cats. Fungi of the genera *Aspergillus* and *Penicillium* are most commonly isolated. Since virtually all stabled horses have fungi as part of their conjunctival flora, seeing the hyphae within the corneal stroma is required for the diagnosis. Isolation from a corneal swab or shallow scraping is not adequate.

The typical early lesion is deep ulcerative keratitis, specific only in the fungi observed within the lesion. Some chronic lesions are exclusively stromal, probably the result of epithelial healing of the initial penetration or because therapy eliminated the infection in the superficial stroma. For whatever reason, the typical equine eye enucleated for mycotic keratitis has an intense neutrophil-rich deep stromal keratitis with several characteristic features: the neutrophils are karyorrhectic, the inflammation is most intense immediately adjacent to Descemet's membrane, and frequently there is lysis of the normally resistant Descemet's membrane, with spillage of the corneal inflammation into the anterior chamber. Fungi are numerous within the malacia of the deep stroma and within Descemet's membrane itself, but rarely if ever are seen within the anterior chamber. They are sparse or absent within the superficial half of the stroma, which explains why corneal scrapings or even keratectomy specimens may fail to reveal the agent. The reason for the apparent targeting of Descemet's membrane is not known, but the presence of the apparent tropism even in untreated eyes suggests that it is a genuine tropism and not just persistence of a previously generalized stromal infection in the site least likely to be reached by topical fungicides.

Bibliography

Bistner, S. I., and Riis, R. C. Clinical aspects of mycotic keratitis in horses. *Cornell Vet* **69:** 364–374, 1979.

Chandler, F. W., Kaplan, W., and Ajello, L. Mycotic keratitis. *In* "Histopathology of Mycotic Diseases," pp. 83–84. Chicago, Illinois, Year Book Medical Publishers, 1980.

Hodgson, D. R., and Jacobs, K. A. Two cases of *Fusarium* keratomycoses in the horse. *Vet Rec* **110:** 520–522, 1982.

Moore, C. P. *et al.* Bacterial and fungal isolates from Equidae with ulcerative keratitis. *J Am Vet Med Assoc* **182:** 600–603, 1983.

Moore, C. P. *et al.* Prevalence of ocular microorganisms in hospitalized and stabled horses. *Am J Vet Res* **49:** 773–777, 1988.

5. Infectious Bovine Keratoconjunctivitis

This disease vies with squamous cell carcinoma as the most important disease of the bovine eye. It occurs worldwide, is most prevalent in summer due to the increase in fly vectors, and has a clinical expression that ranges from initial conjunctivitis and ulcerative keratitis to iris prolapse, glaucoma, and phthisis bulbi. The prevalence of severe sequelae reflects inadequate management of the disease rather than any special virulence of this agent as compared to other infectious causes of keratitis in other species.

The disease behaves as an infectious epizootic within a susceptible population, frequently affecting over 50% of the cattle at risk within 2 weeks of the initial clinical case. Shedding of virulent organisms by a carrier animal is thought to be the usual route of introduction into a previously unexposed group, although a role for various mechanical or biological vectors is also assumed.

Moraxella bovis has been confirmed as the most important causative agent, although agents including *Mycoplasma bovoculi, Mycoplasma conjunctivae, Acholeplasma laidlawii,* and bovine herpesvirus may contribute to lesion severity. Earlier skepticism about the virulence of *M. bovis,* based on the unreliability of reproduction of the disease, isolation of the organism from apparently healthy cattle, and failure of isolation from some overtly affected cattle, has been overcome by detailed information on the pathogenesis of the disease. It is now clear that virulence of *M. bovis* is associated with hemolytic, leucocytolytic, piliated strains, which predominate in the eyes of only affected cattle. Nonpiliated, nonhemolytic strains predominate in healthy cattle and are probably part of the normal conjunctival flora. The use of immunofluorescence has demonstrated *M. bovis* in many of the naturally occurring cases for which the results of culture were negative. In naturally occurring outbreaks, the number of isolations of hemolytic *M. bovis* falls to almost zero as the outbreak wanes, but a few chronically affected carriers remain as the most important source of virulent bacteria for outbreaks of disease in the next summer.

In addition to variation in the virulence of different strains of *M. bovis,* sunlight, dust, and perhaps, concurrent infection with infectious bovine rhinotracheitis virus increase the severity of the disease. Calves are usually affected more severely than cattle older than 2 years, although absolute resistance to infection seems fragile. The protective effect of serum antibody against the disease is controversial. Specific immunoglobulin A (IgA) is found in tears of infected calves, and there is substantial evidence that locally produced IgA is strongly protective.

Following experimental inoculation of virulent *M. bovis* onto the cornea, pilus-mediated adhesion and production of bacterial cytotoxin result in microscopic ulceration in as little as 12 hr. Initial adhesion is to older surface epithelium ("dark cells") and results in the development of microscopic pits in the cell surface. *Moraxella* is found within degenerate epithelial cells, but it is not known whether invasion is necessary for subsequent cellular destruction. In field epizootics, the earliest lesion is bulbar conjunctival edema and hyperemia, followed in 24 to 48 hr by the appearance of a shallow, central corneal ulcer. The ulcer is a small (less than 0.5 cm) focus of epithelial necrosis that may appear as erosion, vesicle or full-thickness epithelial loss. In untreated animals destined to develop the full clinical expression, the ulcer enlarges, deepens, and frequently attracts enough neutrophils to qualify as a corneal abscess. Stromal liquefaction ensues, probably as a result of neutrophil lysis, which is itself initiated by *Moraxella*-derived leukotoxins. By the end of the first week, there is

extensive stromal edema and vascularization extending from the limbus. As with any severe ulcerative keratitis, the subsequent progression or regression of the lesion varies with each case as modifications by therapy, opportunistic bacterial and fungal contamination, trauma, inflammation, and immunity interact. Keratomalacia frequently leads to forward coning of the weakened cornea (keratoconus). In most instances, whether treated or not, the cornea heals by sloughing of necrotic tissue and filling of the defect by granulation tissue. Re-epithelialization may take up to a month, leaving a cornea that is slightly coned and variably scarred. The scarring often is scant and interferes little with vision in spite of the severity of the primary lesion.

Less satisfactory sequelae, while not common in relation to the overall disease prevalence, are still relatively common. Sterile anterior uveal inflammation may result in focal or generalized adherence of iris to cornea (anterior synechia) or lens (posterior synechia). Descemetocele may progress to corneal rupture, which in turn may lead to phthisis bulbi or resolve by sealing with prolapse of the iris. Synechia and staphyloma may lead to impairment of aqueous drainage and thus to the lesions of glaucoma.

6. *Infectious Keratoconjunctivitis of Sheep and Goats*

Epizootics of conjunctivitis and keratitis in sheep and goats share many of the features of the bovine disease: summer prevalence, rapid spread, and exacerbation by dust, sunlight, and flies. Feedlot lambs seem particularly susceptible. Unlike that of bovine keratoconjunctivitis, the range of clinical signs and proposed causes suggests that there may in fact be several different diseases. Many agents including bacteria, mycoplasmas, chlamydiae, and rickettsiae have been suggested as causes, but various mycoplasmas and *Chlamydia psittaci* may be the important agents. The lesions caused by *M. mycoides* var. *capri* in goats and *M. conjunctivae* var. *ovis* in sheep are similar but usually milder than those caused by *Moraxella bovis* in cattle. This is particularly true of goats, in which deep corneal ulceration is uncommon.

Keratoconjunctivitis associated with *Chlamydia psittaci* is usually predominantly conjunctivitis. Initial chemosis and reddening are followed by massive lymphofollicular hyperplasia in bulbar conjunctiva and nictitating membrane. Keratitis may occur, but ulceration is seldom prominent. Animals with conjunctivitis may have concurrent polyarthritis from which chlamydiae can be isolated.

Bibliography

Brown, J. F., and Adkins, T. R. Relationship of feeding activity of face fly to production of keratoconjunctivitis in calves. *Am J Vet Res* **33:** 2551–2555, 1972.

Jones, G. E. *et al.* Mycoplasmas and ovine keratoconjunctivitis. *Vet Rec* **99:** 137–141, 1976.

Kagnoyera G., George, L. W., and Munn, R. Light and electron microscopic changes in cornea of healthy and immunomodulated calves infected with *Moraxella bovis*. *Am J Vet Res* **49:** 386–395, 1988.

Kagonyera, G. M., George, L. W., and Munn, R. Cytopathic effects of *Moraxella bovis* on cultured bovine neutrophils and corneal epithelial cells. *Am J Vet Res* **50:** 10–17, 1989.

Nayar, P. S. G., and Sanders, J. R. Antibodies in lacrimal secretions of cattle naturally or experimentally infected with *Moraxella bovis*. *Can J Comp Med* **39:** 32–40, 1975.

Pedersen, K. B., Froholun, L. O., and Bovre, K. Fimbriation and colony type of *Moraxella bovis* in relation to conjunctival colonization and development of keratoconjunctivitis in cattle. *Acta Pathol Microbiol Scand* **80:** 911–918, 1972.

Pugh, G. W., and Hughes, D. E. Comparison of the virulence of various strains of *Moraxella bovis*. *Can J Comp Med* **34:** 333–340, 1970.

Pugh, G. W. *et al.* Infectious bovine keratoconjunctivitis: Comparison of a fluorescent antibody technique and cultural isolation for the detection of *Moraxella bovis* in eye secretions. *Am J Vet Res* **38:** 1349–1352, 1977.

Pugh, G. W. *et al.* Experimentally induced infectious bovine keratoconjunctivitis: Resistance of vaccinated cattle to homologous and heterologous strains of *Moraxella bovis*. *Am J Vet Res* **37:** 57–60, 1976.

Rogers, D. G., Cheville, N. F., and Pugh, G. W., Jr. Pathogenesis of corneal lesions caused by *Moraxella bovis* in gnotobiotic calves. *Vet Pathol* **24:** 287–295, 1987.

Trotter, S. L. *et al.* Epidemic caprine keratoconjunctivitis: Experimentally induced disease with a pure culture of *Mycoplasma conjunctivae*. *Infect Immunol* **18:** 816–822, 1977.

Vandergaast, N., and Rosenbusch, R. F. Infectious bovine keratoconjunctivitis epizootic associated with area-wide emergence of a new *Moraxella bovis* pilus type. *Am J Vet Res* **50:** 1438–1441, 1989.

Whitley, R. D., and Albert, R. A. Clinical uveitis and polyarthritis associated with *Mycoplasma* species in young goats. *Vet Rec* **115:** 217–218, 1984.

Wilcox, G. E. Infectious bovine keratoconjunctivitis: A review. *Vet Bull* **38:** 349–360, 1968.

Williams, L. W., and Gelatt, K. N. Food animal ophthalmology. *In* "Veterinary Ophthalmology" K.N. Gelatt (ed.), pp. 614–621. Philadelphia, Pennsylvania Lea & Febiger, 1981.

Wilt, G. R., Wu, G., and Bird, C. Characterization of the plasmids of *Moraxella bovis*. *Am J Vet Res* **50:** 1678–1683, 1989.

V. The Lens

The lens is a flattened sphere of epithelial cells suspended in the pupillary aperture by an equatorial row of suspensory zonules radiating from the basement membrane of the nonpigmented ciliary epithelium in the valleys between the ciliary processes and from pars plana. The morphologic reaction of lens to injury is very limited due to the simplicity of its structure and physiology, and its lack of vascularity.

The lens is entirely epithelial. Outermost is a thick, elastic capsule, which is the basement membrane produced by the underlying germinal epithelial cells. The capsule is thickest at the anterior pole and becomes progressively thinner over the posterior half of the lens. The capsule in the neonate is thin, but it thickens progressively throughout life.

Below the capsule is a layer of simple cuboidal lens epithelium, which, in all but fetal globes, is found below

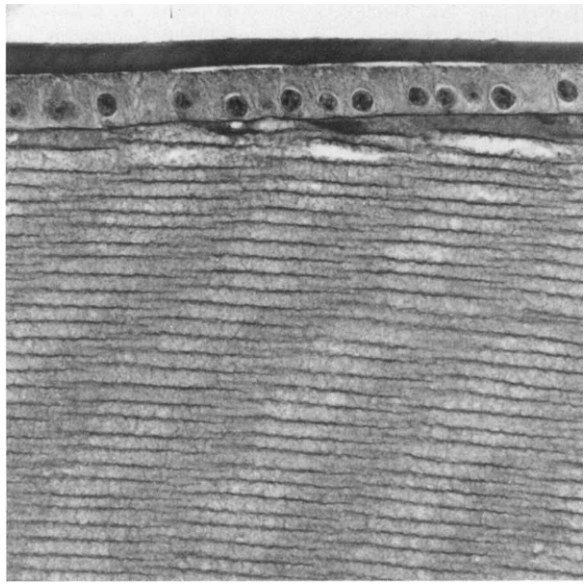

Fig. 4.28 Normal canine lens with characteristic regularity of surface epithelium and lens fibers.

the capsule of only the anterior half of the lens. The apex of these cells faces inward toward the lens nucleus. At the equator, these germinal cells extend into the lens cortex as the nuclear bow, an arc of cells being progressively transformed from cuboidal germinal epithelium to the elongated spindle shape of the mature lens fibers (Fig. 4.28). The bulk of the lens is composed of onionlike layers of elongated epithelial cells anchored to each other by interlocking surface ridges, grooves, and protuberances. These elongated fibers contain no nucleus and few cytoplasmic organelles, relying almost entirely on anaerobic glycolysis for energy. Since the lens cannot shed aging fibers as does skin or intestine, these cells are compacted into the oldest central part of the lens, the nucleus. The continuous accumulation of these old desiccated fibers with altered crystalline protein results in the common but visually insignificant aging change of nuclear sclerosis.

Although in many ways similar to cornea in structure and function, the optical clarity of lens rests not with the regularity of its fibers but in its high percentage of cytoplasmic soluble crystalline protein and paucity of light-scattering nuclei or mitochondria. The lens is about 35% protein, the highest of any tissue, and over 90% of it is the soluble crystalline variety. Insoluble high-molecular-weight protein (albuminoid) is found in the nucleus and cell membranes. Opacity of lens is associated, at least in some cases, with decreasing concentrations of crystalline and increasing albuminoid protein, the latter insoluble in water and optically opaque. Many of the insults that result in degeneration of lens ultimately interfere with its nutrition. Since it is avascular in the postnatal animal, the lens relies entirely on the aqueous for the delivery of nutrients and removal of metabolic wastes. Glaucoma, ocular inflammation, metabolic disorders, and various toxins share the common feature of altering the amount or quality of lenticular nutrition by altering the flow or composition of the aqueous humor.

A. Ectopia Lentis

The only lenticular defects of importance in domestic animals are those affecting location, configuration, and clarity. Those affecting configuration are usually developmental defects and are discussed in earlier sections. Dislocations of the lens may be congenital or acquired, and the latter include spontaneous dislocations and those secondary to trauma and glaucoma. Apparently spontaneous dislocations are encountered most frequently in middle-aged (3–8 years) terrier dogs in which an inherited predisposition to bilateral zonular rupture exists. The pathogenesis of the defect has been best studied in the Tibetan terrier, in which the zonules develop in a dysplastic, reticulate fashion that precedes luxation by several years. Traumatic dislocation is usually via blunt trauma, notably automobile accidents. The dislocation may be partial (subluxation) or complete (luxation), and in the latter instance, the free lens may damage corneal endothelium or vitreous causing edema and liquefaction, respectively. Such lenses may be surgically removed but seldom receive histopathologic examination. Anterior luxation frequently results in glaucoma, perhaps caused by anterior prolapse of the vitreous into the pupil. Lens luxation is inexplicably uncommon in cats. It is seen in middle-aged cats as unilateral and usually anterior luxation. One third of cases occur in eyes with no other observed lesion, while the remainder occur in eyes with preexistent uveitis or glaucoma, or a history of trauma.

Bibliography

Curtis, R. Lens luxation in the dog and cat. *Vet Clin North Am: Small Anim Pract* **20:** 755–773, 1990.

Curtis, R., and Barnett, K. C. Primary lens luxation in the dog. *J Small Anim Pract* **21:** 657–668. 1980.

Martin, C. L. Zonular defects in the dog: A clinical and scanning electron microscopic study. *J Am Anim Hosp Assoc* **14:** 571–579, 1978.

B. Cataract

Cataract is the most common and most important disorder of lens. Cataract means lenticular opacity, and is usually prefixed by adjectives relating to location, maturity, extent, suspected cause and ophthalmoscopic appearance (Fig. 4.29). Of these adjectives, only those of location and, to some extent, maturity are useful in histologic description. The simple structure of the lens results in stereotyped reaction to injury that provides few clues as to pathogenesis. The histology of cataract is the histology of the general pathology of the lens and includes germinal epithelial hyperplasia and metaplasia, hydropic change, fiber necrosis, and occasionally, deposition of calcium salts or cholesterol. Unless permitted by invasion through a capsular

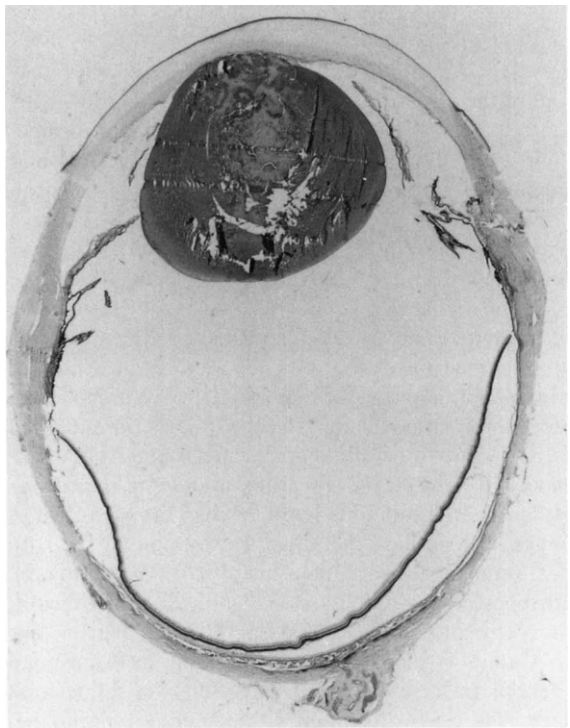

Fig. 4.29 Anterior polar pyramidal cataract. Puppy. Anterior bulging of liquefied lens has destroyed corneal endothelium, resulting in diffuse corneal edema.

tear, inflammation cannot occur within the avascular and totally epithelial lens.

Epithelial hyperplasia or **metaplasia** is the usual histologic counterpart of anterior subcapsular cataract, and is usually seen following focal trauma, or adherence of the iris or of persistent pupillary membranes to the anterior surface of the lens. Initial epithelial degeneration or necrosis is followed by hyperplasia and sometimes by fibrous metaplasia. The resultant epithelial plaque lies just under the anterior lens capsule. The innermost epithelial layer may remain basilar in type rather than fibroblastic. Each epithelial layer, even if metaplastic, secretes a new basement membrane that separates each layer from the adjacent layers. The end result is a focal plaque formed by multiple, sandwiched layers of flattened epithelium and basement membrane at the anterior pole of the lens. Remnants of adherent iris or pupillary membrane, including pigment, may complicate the histologic appearance.

A more common manifestation of epithelial hyperplasia is **migration** from the equator to line the posterior capsule. This reestablishment of the fetal morphology is seen most commonly with any chronic cataract in young animals, whose epithelial cells perhaps retain greater migratory ability. Adjacent cortical fibers are usually degenerate.

Degeneration and subsequent **fragmentation** or **liquefaction** of lens fibers is the most common lesion of cataract. Cataractous fragmentation must be distinguished from the almost unavoidable artifactual fragmentation of fibers that occurs in histologic sections. Degenerate fibers break into pieces that rapidly contract to acquire rounded ends, in contrast to the sharp, jagged ends of artifactually shattered fibers. As fiber fragmentation progresses, the fragments liquefy and assume a spherical shape. These proteinaceous spheres are referred to as **morgagnian globules.** Clefts and protein lakes appear between fibers, presumably the result of complete liquefaction of fibers. Some of the clefts are probably the result of osmotic fluid imbibition by the cataractous lens. The osmosis results from protein denaturation into more numerous, smaller peptides and from degeneration of the capsular epithelium in which resides the Na-K-dependent ATPase osmotic pump critical to normal lens hydration. Abortive efforts at new fiber formation by lens epithelium results in the formation of large, foamy nucleated cells called **bladder cells,** pathognomonic of cataract (Fig. 4.20). In advanced cataracts the degenerate fibers may liquefy to the extent that their low-molecular-weight end products diffuse through the semipermeable capsule, resulting in the spontaneous clearing of the opaque lens typical of the hypermature cataract. Histologically, such lenses consist of a dense, eccentric residual nucleus in a lake of proteinaceous fluid, surrounded by a wrinkled capsule. Deposition of calcium salts is seen rarely. Such hypermature cataracts are often accompanied by a lymphocytic–plasmacytic iridocyclitis, presumably in response to the leaking lens protein (see phacolytic uveitis).

A different picture is seen in lenses in which degeneration is associated with rupture of the capsule, as occurs with ocular trauma. First, massive release of more or less native lens protein at the time of rupture may cause a severe perilenticular nonsuppurative endophthalmitis about 10 days after the initial trauma (see phacoclastic uveitis). Second, the capsular rent permits leukocytes to enter the lens to speed the dissolution of lens fibers. Fibroblastic metaplasia of lens epithelium may result in cartilage or even bone within the lens. Even after total destruction of the lens fibers, the durable capsule will be found somewhere in the anterior or posterior chamber as a curled eosinophilic mass, often encapsulated in fibrous tissue probably derived from surviving lens epithelium or from injured ciliary epithelium. Such remnants distinguish lenticular rupture with subsequent dissolution from true developmental aphakia.

The sequence of histologic change in cataract is the same regardless of cause, and thus diagnosis of cause can be made only in light of patient data or concurrent ocular disease. In dogs, for example, familial cataracts may be congenital or of later onset. Specific examples may typically occur alone or with other ocular lesions, and occur at an age, in a location and with a progression sufficiently characteristic to allow presumptive diagnosis of a breed-specific syndrome. Cataract also occurs secondary to glaucoma, endophthalmitis, ocular trauma, and anterior segment anomalies, and observation of these latter defects permits presumptive diagnosis of the pathogenesis of the accompanying cataract.

Cataract may result from exposure of the lens to a wide variety of physical and chemical insults, such as solar or other irradiation, cold, increased intraocular pressure, toxins, nutritional excesses and deficiencies, nearby inflammation, and direct trauma. The list of potential cataractogenic chemical toxins grows daily and includes food additives, chemotherapeutic agents, and by-products of ocular inflammation. The pathogenesis of the cataract is not determined for more than a few such insults, but a common denominator seems to be the ability to upset the precarious balance between substrate supply and enzymic activity within the almost exclusively anaerobic lens. This imbalance results in degeneration of fibers, accumulation of nonmetabolized substrate, or production of abnormal metabolites. The latter two classes of products may be cytotoxic or osmotically active, thus drawing water into the critically dehydrated lens and causing opacity.

Most cataracts in humans and animals are not identified as being caused by a single insult, but are assumed to represent the result of years of accumulated and perhaps synergistic cataractogenic activity of environmental, dietary, and inborn insults. The majority of cataracts seen in veterinary practice fall into one of three categories: inherited, postinflammatory, and idiopathic. In reality, the large group of inherited cataracts in dogs is of unknown pathogenesis, although extrapolation from knowledge of similar cataracts in rodents and humans suggests inborn errors of lenticular metabolism are at fault. Postinflammatory cataracts result from injury to lenticular epithelium by adjacent inflammation, interference with aqueous production, composition, and flow, and accumulation of toxic bacterial, leukocytic, and plasma by-products in the lenticular environment. Adherence of iris to lens (posterior synechia) inevitably causes a focal subcapsular cataract.

Other than these broad categories, there are a few naturally occurring examples of cataract about which there is some understanding.

Diabetic cataract develops in about 70% of spontaneously diabetic dogs. The opacity is bilateral and begins in the cortex at the equator. Progression to complete cortical opacity usually occurs within a few weeks. The pathogenesis of the cataract has traditionally been ascribed to the excessively high level of glucose within the aqueous. Glucose is normally the major energy source for lens fibers, with most of it used to fuel the Embden–Meyerhof pathway of anaerobic glycolysis. When the rate-limiting enzyme of this pathway, hexokinase, is saturated with glucose, the back-up of glucose is shunted to alternative metabolic pathways. Chief among these is the sorbitol pathway, activated in the rabbit lens by glucose concentrations of greater than 90 mg/dl. In this pathway, the excess glucose is converted by an aldose reductase to the polyalcohol, sorbitol, which is then slowly reduced to a ketose. Because this second reaction is much slower than the first, sorbitol may accumulate to very high concentrations within the lens, and osmotically attracts water even to the point of hydropic cell rupture. Under experimental conditions at least, the early cataract may be reversed if aqueous sugar levels are reduced to normal, but the later cataract is irreversible.

However, osmotic events alone are not enough to explain all of the structural and metabolic changes in sugar-induced cataracts. The efficacy of antioxidants in ameliorating such cataracts, the nature of intralenticular biochemical alterations, and detection of increased intralenticular oxidants all point to some kind of oxidative damage as an additional promoter of cataract.

Galactose-induced cataracts probably have the same complex and incompletely understood pathogenesis as the diabetic cataract and are seen in orphaned kangaroos and wallabies raised on cows' milk, as well as in a host of experimental models. Since marsupial milk is much lower in lactose than is bovine milk, the enzymically ill-equipped neonate develops osmotic diarrhea from undigested lactose and galactose in the intestine, and some excess galactose enters the aqueous humor. The lens, deficient in the enzymes to utilize the galactose by converting it to glucose-6-phosphate for anaerobic glycolysis, shunts the galactose via aldose reductase to its polyalcohol, dulcitol, which acts osmotically as does sorbitol to disrupt lens fibers. Cataract reported in puppies and wolf cubs fed commercial milk replacer, or in kittens on feline milk replacer, has been attributed to deficiency of arginine, although in several case reports the specific dietary error was not identified. Cataract due to **dietary deficiency** of any of several sulfur-containing amino acids, zinc, or vitamin C occurs in farmed fish, and many models of nutritional cataract exist in various laboratory animals.

Various forms of irradiation cause cataract. The lens absorbs most of the ultraviolet and short-wavelength visible blue light that would otherwise damage the retina. At least in humans, the chronic exposure to such irradiation is thought to be important in the pathogenesis of senile cataract. **Sunlight-induced cataract** has been described several times in farmed fish but not yet for other domestic animals as a naturally occurring phenomenon. Absorption of ultraviolet or near-ultraviolet wavelengths by lens epithelium nucleic acids or lenticular aromatic amino acids results in photochemical generation of free radicals and peroxidative damage to numerous structural components of the lens.

A similar pathogenesis probably explains the development of cataract in animals irradiated as part of cancer therapy. In one study, 28% of dogs receiving **megavoltage x-radiation** for nasal carcinoma developed diffuse cortical cataract within 12 months of irradiation. In humans, the risk of cataract is dose related, and reaches virtual certainty with dosages of 800 to 1500 centigray or rads, whereas rodents require at least twice that dosage. The dogs in the study cited received between 3680 and 5000 centigrays. Antioxidants such as vitamin E or C, or hypoxia, are significantly protective against several models of light- or other irradiation-induced cataract, providing further support for the common denominator of oxidative stress in the pathogenesis of such cataracts.

The aminoglycoside antibiotic and anthelmintic **hygro-**

mycin B has been shown to induce posterior cortical and subcapsular cataracts in sows, but not boars, fed the drug continuously for 10 to 14 months. The effect is dose-dependent and perhaps even cumulative. Pigs fed the same therapeutic daily dose, but consuming the drug on an 8-week-on, 8-week-off basis in accordance with the manufacturer's recommendations, do not develop cataracts. The pathogenesis of the cataract is unknown, but a partial inhibition of hygromycin-induced cataracts *in vitro* by addition of vitamin E suggests that peroxidative damage to lens fiber membranes may be important. Deafness in pigs, and also dogs, caused by hygromycin B is discussed with the Ear.

Bibliography

Bhuyan, K. C., and Bhuyan, D. K. Molecular mechanism of cataractogenesis: III. Toxic metabolites of oxygen as initiators of lipid peroxidation and cataract. *Curr Eye Res* **3:** 67–81, 1984.

Glaze, M. B., and Blanchard, G. L. Nutritional cataracts in a Samoyed litter. *J Am Anim Hosp Assoc* **19:** 951–954, 1983.

Martin, C. L., and Chambreau, T. Cataract production in experimentally orphaned puppies fed a commercial replacement for bitch's milk. *J Am Anim Hosp Assoc* **18:** 115–118, 1982.

Poston, H. A. *et al.* The effect of supplemental dietary amino acids, minerals, and vitamins on salmonids fed cataractogenic diets. *Cornell Vet* **67:** 472–509, 1977.

Rathbun, W. B. Biochemistry of the lens and cataractogenesis: Current concepts. *Vet Clin North Am: Small Anim Pract* **10:** 377–398, 1980.

Roberts, S. M. *et al.* Ophthalmic complications following megavoltage irradiation of the nasal and paranasal cavities in dogs. *J Am Vet Med Assoc* **190:** 43–47, 1987.

Varma, S. D. *et al.* Oxidative stress on lens and cataract formation: Role of light and oxygen. *Curr Eye Res* **3:** 35–58, 1984.

Woollard, A. C. S. *et al.* Abnormal redox status without increased lipid peroxidation in sugar cataract. *Diabetes* **39:** 1347–1352, 1990.

VI. The Uvea

The uvea is the vascular tunic of the eye. It is derived from the primitive neural crest mesenchyme surrounding the primary optic cup (only the vascular endothelium is mesodermal). Its differentiation is guided by the retinal pigment epithelium. Anteriorly, the mesenchyme accompanies the infolding of the neurectoderm at the anterior lip of the optic cup to form the stroma of the iris and ciliary processes. That portion of anterior periorbital mesenchyme not accompanying these neurectodermal ingrowths remains to form the ciliary muscle and trabecular meshwork. Posteriorly it forms the choroid and sclera. In all domestic mammals except the pig, the choroid undergoes further differentiation to produce the tapetum lucidum dorsal to the optic disk. Defects in the development of the retinal pigment epithelium (including its cranial specialization as iridic and ciliary epithelium) inevitably result in defective induction or differentiation of the adjacent uvea.

The mature uvea includes iris, ciliary body, and choroid, the last divided into vascular portion and tapetum lucidum. The filtration angle is shared by iris, ciliary body, and sclera. Its diseases are discussed under the heading of glaucoma.

The **iris** is the most anterior portion of the uveal tract. It is a muscular diaphragm separating anterior from posterior chamber, forming the pupil and resting against the anterior face of the lens. The bulk of the iris is stroma of mesenchymal origin, with melanocytes, fibroblasts, and endothelial cells its major constituents. There is neither epithelium nor basement membrane along its anterior face, but rather a single layer of tightly compacted fibrocytes and melanocytes.

The posterior surface of the iris is formed by the double layer of neurectoderm from the anterior infolding of the optic cup. The two layers are heavily pigmented and are apposed apex to apex, with the basal aspect of the posterior epithelium facing the posterior chamber, and separated from it by a basement membrane. The basilar portion of the anterior epithelium, in contrast, is differentiated to form the smooth muscle fibers of the dilator muscle of the iris. These fibers lie along the posterior aspect of the iris stroma immediately adjacent to the epithelium. The constrictor muscle is found deeper within iris stroma but only in the pupillary third to quarter of the iris. The iris epithelium is rather loosely adherent between layers and between adjacent cells of the same layer, so that cystic separation occurs quite commonly. Numerous spaces reminiscent of bile canaliculi lie between adjacent cells and communicate freely with the aqueous humor of the posterior chamber.

The **ciliary body** extends from the posterior iris root to the origin of neurosensory retina. Like iris, it consists of an inner double layer of neuroepithelium and an outer mesenchymal stroma. The epithelial cells are oriented apex to apex and separated from the posterior chamber and vitreous by a basal lamina. Only the outer epithelial layer is pigmented. The ciliary body is divided into an anterior pars plicata and a posterior pars plana, the latter blending with retina at the ora ciliaris retinae. The pars plicata consists of a circumferential ring of villuslike epithelial ingrowths supported by a fibrovascular core, called ciliary processes. External to the ciliary processes the mesenchyme forms a ring of smooth muscle, the ciliary muscle, responsible for putting traction on the lens zonules and effecting the changes in lens shape necessary for visual accommodation. The muscle in domestic animals, particularly ungulates, is poorly developed, and accommodation is thought to be minimal in these species. The lens zonules anchor in the basal lamina of the nonpigmented ciliary epithelium, particularly of the pars plana and within the crypts between ciliary processes.

The **choroid** is the posterior continuation of the stroma of the ciliary body. The posterior continuations of the inner and outer layers of ciliary epithelium are retina and retinal pigment epithelium, respectively, with the transition made rather abruptly at the ora ciliaris retinae. The choroid consists almost entirely of blood vessels and melanocytes, except for the postnatal metaplasia to tapetum

dorsal to the optic disk. The choroid is thinnest peripherally, thickest at the posterior pole, blends indistinctly with sclera externally, and is separated from the retinal pigment epithelium internally by a complex basal lamina called Bruch's membrane.

The **general pathology** of **uvea** includes anomalous or incomplete differentiation, degeneration, inflammation, and neoplasia. Anomalies have been previously discussed, and uveal neoplasms are considered in the section on ocular neoplasia. Uveal degenerations, except as a sequel to uveitis, are poorly documented. **Idiopathic atrophy** of the **iris** is described in Shropshire sheep as a bilateral defect obvious by 1 to 2 years of age. About 25% of the iris is converted to full- or partial-thickness holes. Those of partial thickness are spanned by a posterior bridge of iris epithelium. The eye is otherwise normal except for rudimentary corpora nigra. The pathogenesis of the apparently spontaneous atrophy is unknown. Similar atrophy is seen in middle-aged Siamese cats and in several breeds of small dogs (poodles, Chihuahuas, miniature schnauzers). The pathogenesis is unknown, and there are no published descriptions of the microscopic lesions in dogs or cats.

Multifocal cystic separation of the posterior iris epithelium is common in old dogs, and occasionally may be seen clinically as one or more translucent black cysts attached to the posterior iris or freely floating in the aqueous. Whether the cysts are truly degenerative, or represent residual lesions of fluid exudation from an undetected iritis, is unknown.

A. Uveitis

Uveal inflammation is common and may result from ocular trauma, noxious chemicals, infectious agents, neoplasia, or immunologic events. In addition, corneal injury may cause hyperemia and increased permeability of anterior uveal vessels either by percolation of bacterial toxins or inflammatory mediators into the aqueous, or by stimulation of a vasoactive sensory reflex via the trigeminal nerve. The uvea may be the initial site of inflammation, as in localization of infectious agents, or may become involved as the nearest vascular tissue capable of responding to injury of the lens, cornea, or ocular chambers. Conversely, the uvea seldom undergoes inflammation without affecting adjacent ocular structures.

The vocabulary of uveitis and its sequelae is complex. **Anterior uveitis** describes inflammation of iris and ciliary body. **Posterior uveitis** involves ciliary body and choroid, with panuveitis occasionally used to designate diffuse uveitis. **Chorioretinitis** describes inflammation of choroid and, usually less severely, overlying retina. **Endophthalmitis** is inflammation of uvea, retina, and ocular cavities, with **panophthalmitis** reserved for inflammation that has spread to involve all ocular structures including sclera. The usefulness of such terminology is doubtful when one considers the vascular unity of the uvea and its intimate association with other ocular tissues. Uveal exudation inevitably leads to protein and cellular exudation into the aqueous and vitreous and thus technically is endophthalmitis. Uveal vessels permeate the sclera as a normal anatomic feature and thus provide an easy route for uveal leukocytes to enter the sclera. By convention, the choice of diagnostic classification is strongly influenced by clinical severity, with anterior uveitis the mildest and panophthalmitis the most severe lesion.

Ocular inflammation is further classified as suppurative, granulomatous or nonsuppurative, nongranulomatous. The last is a peculiar historical term in human ophthalmology. It is equivalent to lymphocytic–plasmacytic inflammation and will be so described here. The usefulness of such classification in predicting causes decreases as the lesion ages and as the events of host immune response blend with the initial inflammation. Furthermore, the reaction may differ between anterior and posterior segments, with choroiditis much more commonly lymphocytic than suppurative, despite concurrent anterior uveal suppuration. Specific examples of uveitis are presented later. Discussed here are the features common to uveal inflammation and its sequelae, regardless of cause.

Acute uveitis involves the usual sequence of protein-rich fluid exudation followed by emigration of leukocytes, typically neutrophils. In the iris, the fluid and cells readily percolate through the loose stroma to enter the anterior chamber as the clinically observed aqueous flare and hypopyon, so that large numbers of neutrophils are rarely seen within the iris itself. In ciliary processes there usually is severe stromal edema, perhaps a consequence of the initial inability of the serous exudate to pass through the tight intercellular junctions of the ciliary epithelium. Choroid exhibits the most convincing vascular engorgement as well as edema, with the latter frequently seeping through the retinal pigment epithelium to cause serous retinal separation.

Leukocytes are initially **neutrophils** in uveitis of bacterial origin, such as in the neonatal septicemias of calves, foals, and pigs. Neutrophils also predominate in acute mild neurogenic uveitis associated with corneal epithelial injury and in the acute phase of phacoclastic uveitis. In very mild uveitis they are found marginated along the endothelium of iris and ciliary venules, in perivascular adventitia, adherent to ciliary processes, and in the filtration angle (Fig. 4.30). Neutrophils rapidly degenerate within the aqueous to assume an unsegmented globular morphology. Clumps may adhere to the corneal endothelium as keratic precipitates, settle ventrally within the anterior chamber as hypopyon, or plug the filtration spaces, possibly (but rarely) to cause glaucoma if the plugging is extensive. Fibrin exudation may accompany the acute inflammation, but fibrinolysis is very efficient within the anterior chamber so that glaucoma rarely results.

Nonsuppurative uveitis usually is dominated by lymphocytes and plasma cells. It may occur simply as a chronic form of what was initially a suppurative uveitis, but is more frequently seen as the typical manifestation of immune-mediated uveitis, ocular trauma, viral and mycotic uveitis, phacolytic uveitis, and uveitis accompanying

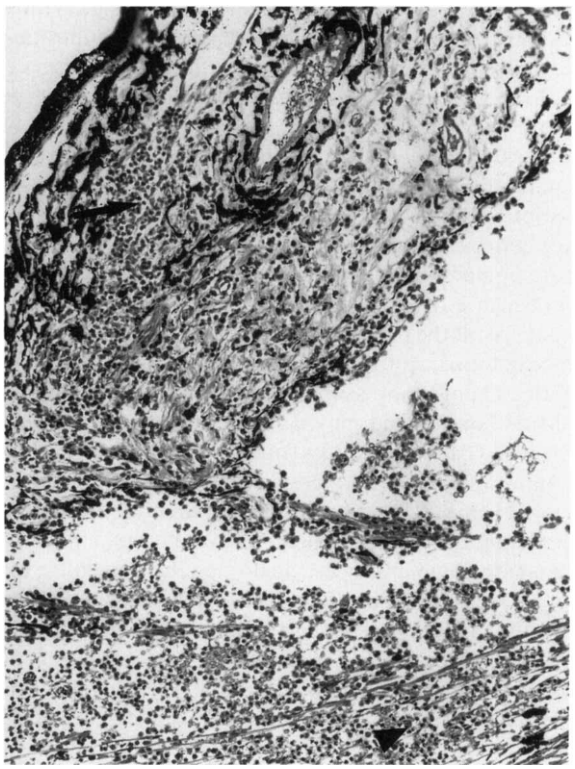

Fig. 4.30 Anterior uveitis. Dog. Leukocytes within stroma of iris (arrow) and peripheral cornea (arrowhead), and within filtration angle.

intraocular neoplasia. Inasmuch as the inflammation in most of these examples is probably of immunologic pathogenesis, it is probably more accurate to consider all nonsuppurative uveitis as immune mediated, with the prefix idiopathic or the name of the inciting antigen. Dogs, cats, and horses are the species most frequently affected, and in these species, the inciting agent is usually unknown.

The eye is an immunologically privileged site, with no resident lymphocytes, no antigen-processing macrophages or dendritic cells, and no lymphatic drainage. These peculiarities, plus the blood–eye barrier created by the tight intercellular junctions of iris endothelium, ciliary nonpigmented epithelium, and retinal pigmented epithelium, fostered the mistaken belief that many intraocular antigens were sufficiently sequestered as to be seen as "nonself" in the event of their release into systemic circulation. The numerous diseases characterized by lymphocytic–plasmacytic uveitis in the absence of an identified infectious agent have thus been broadly grouped as examples of autoimmune reaction to sequestered uveal, lenticular, or retinal antigens.

More recent studies have demonstrated that these supposedly unique and sequestered antigens are neither unique nor completely sequestered. Antigens identical to some of the lenticular or uveal antigens, for example, are found in nonsequestered tissues elsewhere in the body. Antigens inoculated into anterior chamber induce a systemic humoral and T-cell response, clearly pointing to at least some leakiness in the blood–eye barrier. A variety of experiments have lead to the suggestion of a carefully regulated system of ocular immunity, termed **anterior chamber-associated immune deviation.** In this system, intraocular antigens are somehow processed within the eye before draining from the trabecular meshwork into systemic circulation. These antigens, on reaching the spleen, initiate a typical humoral immune response but an atypical cell-mediated immune response. Proliferation of cytotoxic and suppressor T cells is enhanced, but those T cells committed to the production of cytokines as part of delayed hypersensitivity are suppressed. The theoretical result is that when these activated lymphocytes return to the eye, they are only of the types destined to produce the most localized and specific effects on the offending antigen, with the least nonspecific "bystander" injury. As a further safety measure to prevent unnecessarily damaging immune-mediated injury, both uveal tissue and aqueous humor contain cytokines [transforming growth factor β (TGF-β) is one] that inhibit activation of T lymphocytes.

Whatever their type, the splenic lymphocytes reach the eye about 1 week after experimental introduction of antigen into anterior chamber. Typically the lymphocytes are seen as perivascular aggregates in iris stroma, in ciliary body and, less obviously, in choroid and even retina. In long-standing cases (which are most likely to receive histologic examination), the aggregates may be very large and resemble lymphoid follicles (Fig. 4.31). As in other tissues, amplification of the immune response results in recruitment of lymphocytes that are not necessarily specific for the inciting antigen. The polyclonal nature of these lymphocytes is probably important in the typically recurrent nature of uveitis in all species. Once established in the eye, these cells respond to a diverse range of circulating antigens that enter the eye through a blood–eye barrier disrupted by the previous bout of inflammation. It is thus possible, or even probable, that chronic, recurrent uveitis results not from persistence of a single antigen, or repeated exposure to the same antigen, but is a stereotyped ocular response to activation of any one of its many acquired lymphoid populations by a variety of circulating antigens or native ocular antigens.

Granulomatous uveitis is distinguished from simple lymphocytic–plasmacytic uveitis by the conspicuous presence of epithelioid macrophages and, occasionally, giant cells. Ocular localization of some species of dimorphic fungi or of algae, helminths, or mycobacteria may cause granulomatous ophthalmitis, as may lens rupture and the Vogt–Koyanagi–Harada-like syndrome in dogs.

The major significance of uveitis is its effect on adjacent nonuveal tissues. Some effects result from the accumulation of acute exudates or chemical by-products of inflammation, but most result from the later organization of exudates and proliferative events of wound healing within ocular cavities.

Corneal changes include edema and peripheral stromal hyperemia (ciliary flush). The edema results from corneal

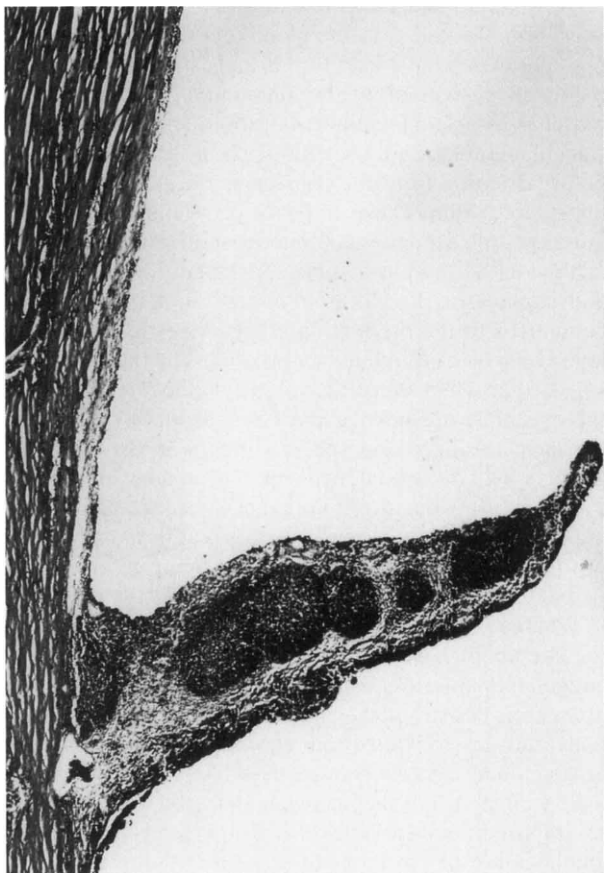

Fig. 4.31 Lymphonodular iritis and secondary glaucoma. Cat. The iridocorneal angle has been dislocated far posterior to the termination of Descemet's membrane (angle recession).

endothelial damage or as part of the reaction of limbic blood vessels to the inflammatory mediators released from the adjacent uvea. In the former instance, damage may be the direct result of the agent causing uveitis, as occurs in infectious canine hepatitis or feline infectious peritonitis. It may also occur as a result of an immune response to endothelial cells containing antigens of these infectious agents, to cross-reaction between microbial and corneal endothelial antigens, or as a nonspecific response to the presence of the chemical by-products of inflammation within the anterior chamber. Similar by-products mediate the acute inflammatory response in the nearby limbic and conjunctival vasculature, leading to edema in the peripheral corneal stroma. Hyperemia of this limbic network also results in the circumferential peripheral corneal stromal hyperemia, resembling a brush border, that is a clinical hallmark of anterior uveitis. In eyes with chronic uveitis, corneal edema may also result from glaucoma or from anterior synechia. Persistent edema may lead to stromal fibrosis, vascularization, bullous keratopathy, and the risk of ulceration. Limbic hyperemia may give way to peripheral corneal stromal vascularization, again presumed to be merely a response to the spillover of angiogenic cytokines from the chronic intraocular inflammation.

The accumulation of fibrin, leukocytes, and erythrocytes in the aqueous may result in plugging of the filtration angle and subsequent glaucoma. The infrequent observation of this sequel suggests either unusual potency of the fibrinolytic system within the aqueous or the inability of exudates to plug more than the most ventral portion of the circumferential angle. Much more common is the organization of inflammatory exudates on the surface of iris or ciliary body. Adherence of iris to lens (**posterior synechia**) is more common than adherence to cornea (**anterior synechia**) because of the normally intimate association of the lens and iris. If the posterior synechia involves the circumference of the iris, the pupillary flow of aqueous is blocked, posterior chamber pressure rises, and the iris bows forward (**iris bombé**) and may actually adhere anteriorly to the cornea. Glaucoma results from pupillary block, peripheral anterior synechia, or both. In severe and prolonged anterior uveitis, there may be development of a fibrovascular membrane on the iris face, which may span the pupil to cause pupillary block (occlusio pupillae) or cover the face of the pectinate ligament to cause neovascular glaucoma (Fig. 4.32). Alternatively, the membrane may contract on the face of the iris resulting in infolding of the pupillary border to adhere to the anterior (**ectropion uveae**) or posterior (**entropion uveae**) iris surface. Atrophy of iris may follow severe and necrotizing inflammation, and some examples can be distinguished from idiopathic and senile atrophy by the observation of residual lesions of the previous uveitis, such as lymphoid aggregates, focal synechiae, and uveal hyalinization.

The ciliary apparatus suffers the same range of chronic lesions as does iris. Deposition of PAS-positive hyaline material along the luminal surface of the ciliary epithelium is particularly frequent in horses. It appears to be depos-

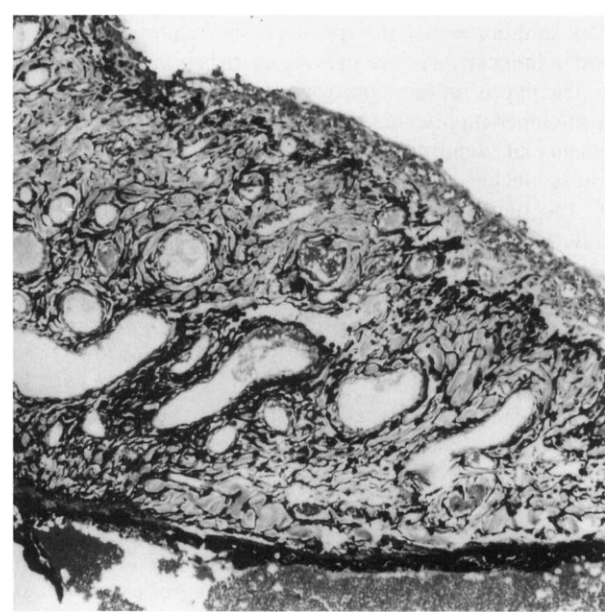

Fig. 4.32 Preiridal fibrovascular membrane.

ited in the cytoplasm of the nonpigmented epithelium, and may represent aberrant basement membrane. It is not fibrin. Organization of exudate within the posterior chamber or vitreous results in a retrolental fibrovascular membrane, called a **cyclitic membrane,** which stretches around the ciliary body and across the back of the lens. Vitreous is almost always liquefied as a result of the severe uveitis, and continued contraction of fibrin in the posterior chamber and vitreous causes a separation of retina. Histologic examination of most cyclitic membranes reveals a fibrovascular retrolental membrane incorporating lens into its anterior face and a folded, degenerate retina in its posterior surface.

The residual lesions of chronic choroiditis include focal lymphoid aggregates and scarring. Tapetum usually remains unaffected. As choroiditis severe enough to evoke these lesions will almost invariably have involved retina and retinal pigment epithelium, the residual scar will involve these structures. Chorioretinal scars are seen as focal fibrous chorioretinal adhesions in place of normal retinal pigment epithelium. Because these scars prevent the involved retina from separating as part of processing artifact, they frequently appear as "spot welds" along an otherwise artifactually detached retina. Retinal pigment epithelium may be hypertrophic or hyperplastic, particularly if retina has been chronically separated by choroidal effusion. The fibroblastlike cells forming the scar may be derived from retinal Müller cells, choroidal fibroblasts, or metaplasia of retinal pigment epithelium, the last being the major source.

Cataract is a common sequel to uveitis, either as a result of uveal adhesions to lens surface, altered aqueous flow with lenticular malnutrition, exposure to injurious inflammatory by-products, or increased aqueous pressure in postinflammatory glaucoma.

Phthisis bulbi describes a hypotonic, shrunken, structurally disorganized eye that is the end stage of severe ophthalmitis. Phthisis is seen most commonly as a sequel to severe prolonged suppurative septic ophthalmitis from corneal perforation. Cornea and sclera are thickened by fibrosis and leukocytic infiltration, and ocular content is barely recognizable. Mineralization and even ossification may occur, but cartilage is absent (unlike that in congenitally dysplastic globes). A shrunken, end-stage eye that contains ocular structures with at least recognizable orientation is properly termed **atrophia bulbi.** The term is seldom used, but atrophia is much more common than true phthisis bulbi.

Bibliography

Bistner, S., Shaw, D., and Riis, R. C. Diseases of the uveal tract (part I). *Compend Cont Ed* **1:** 868–875, 899–906, 1979.

Davidson, M. G. *et al.* Feline anterior uveitis: A study of 53 cases. *J Am Anim Hosp Assoc* **27:** 77–83, 1991.

Peiffer, R. L., Wilcock, B. P., and Yin, H. The pathogenesis and significance of pre-iridal fibrovascular membrane in domestic animals. *Vet Pathol* **27:** 41–45, 1990.

Swanson, J. F. Ocular manifestations of systemic disease in the dog and cat. *Vet Clin North Am: Small Anim Pract* **20:** 849–867, 1990.

1. Immune-Mediated Uveitis

The humoral and cellular events of immunologic reaction may occur within the eye in response to endogenous or exogenous antigen. The normal eye contains no lymphoid tissue and, following initial antigenic challenge, must rely on diffusion of antigen to the spleen before effector lymphocytes enter the eye. The lymphocytes do so as perivascular aggregates throughout the uvea. Subsequent exposure to the sensitizing antigen results in one or several of hypersensitivity reactions I through IV. For reasons previously stated (see anterior chamber-associated immune deviation), it is likely that the prolonged disruption of the blood–eye barrier following any uveitis allows a variety of circulating antigens to contact the polyclonal lymphoid population newly established within the uvea, and perpetuate the uveitis.

There is no clear distinction between immune-mediated uveitis and uveitis traditionally ascribed to a specific causative agent. Except for rapidly progressing bacterial uveitis following hematogenous localization or penetrating injury, virtually all uveitis probably has an immune component superimposed on initial nonspecific inflammation. Even traumatic uveitis probably permits unusually large amounts of endogenous ocular antigens to enter venous drainage and to reach the spleen and other lymphoid tissue. Types III and IV hypersensitivity have been induced in various laboratory animals using tissue-specific antigens of photoreceptor, uveal, lens, and corneal origin. Lens-induced uveitis and an idiopathic uveitis associated with dermal depigmentation in dogs (the so-called Vogt–Koyanagi–Harada syndrome) are naturally occurring examples of uveitis induced by endogenous ocular antigens. Recent demonstration of strong cross-reactivity between leptospiral antigens and equine corneal endothelium serves to further obscure the distinction between infectious and immune-mediated ocular disease.

Included in this section are those diseases that are exclusively or predominantly immune mediated. In general, all are chronic, nonsuppurative, and diffuse affections of the uvea in which the infiltrating leukocytes are predominantly lymphocytes and plasma cells in perivascular collars. Clinically, they are either continuously progressive syndromes or subject to periodic irregular clinical exacerbations and remissions. The histologic lesion is continuously present, and may eventually lead to the formation of uveal lymphoid nodules.

Examples of immune-mediated uveitis should be divided into those in which the antigen is known by culture, morphology, or history, and those of unknown cause. In the former category are many examples of viral, mycotic, protozoan, and helminthic uveitis, postvaccinal uveitis in dogs, and at least some cases of recurrent ophthalmitis in horses. The idiopathic group includes the majority of canine and feline cases. Lens-induced uveitis is a frequent

and special syndrome that is, at least in part, a manifestation of endogenous uveitis.

a. CANINE ADENOVIRUS Infectious canine hepatitis virus (canine adenovirus, type 1) is the best-documented cause of immune-mediated uveitis in domestic animals. The systemic disease is discussed in Volume 2, Chapter 2, Liver and Biliary System. During the acute viral stage of the disease, viral replication within endothelium and stromal phagocytes of the uvea results in a primary mild nonsuppurative uveitis that usually is clinically undetected. Inoculation of field virus into the anterior chamber of dogs and foxes may result in viral inclusion bodies within corneal endothelium and subsequent edema, but edema is not a feature of the active stage of naturally occurring disease. During the convalescent phase of the disease, or 6–7 days after vaccination with a modified live virus, a small percentage of dogs develop anterior uveitis, endothelial damage, and corneal edema that is a manifestation of type III hypersensitivity to persistent viral antigen in which complement fixation attracts neutrophils. The proteases of neutrophils are responsible for the cell injury.

The histologic lesion is bilateral but not usually of equal intensity so that clinically apparent disease may be unilateral. Corneal edema results from diffuse hydropic degeneration of corneal endothelium and secondary stromal edema. In a small percentage of affected dogs, the damage is so persistent as to cause interstitial keratitis and permanent fibrosis. Whether this sequel results from unusually persistent antigen, unusually severe endothelial damage or age-dependent variation in endothelial regenerative ability is unknown. Intranuclear inclusion bodies of adenovirus type may be seen in a few degenerate endothelial cells. There is an accompanying anterior uveitis, with lymphocytes and plasma cells around vessels in iris and ciliary body, in the filtration angle, and adherent to cornea as keratic precipitates. Choroidal involvement is mild or absent. Sequelae such as synechia or angle obstruction with debris are infrequent, occurring in fewer than 5% of affected eyes. In most dogs, whether recovering from natural or vaccine-induced infection, the ocular reaction subsides within 3 to 4 weeks.

b. EQUINE RECURRENT OPHTHALMITIS (PERIODIC OPHTHALMIA) This is a worldwide and important cause of blindness in horses and mules. The blindness results from repeated attacks of anterior uveitis occurring at unpredictable intervals and with increasing severity. With each attack there is increasing involvement of posterior uvea, retina, and optic nerve, and increasingly frequent sequelae of cataract, lens luxation, synechiae, retinal separation, and interstitial keratitis. Despite the frequent observation of posterior synechiae, glaucoma is rarely reported. It is speculated that aqueous drainage in horses relies less on the trabecular meshwork and more on uveal resorption than is true of dogs or cats. The disease may initially be unilateral but eventually affects both eyes. Blindness is usually a late sequel, but may occur early in the disease if exudative choroiditis causes retinal separation.

Gross lesions of the acute disease are typical of anterior uveitis in any species: serous conjunctivitis, chemosis, circumcorneal ciliary hyperemia, corneal edema, and plasmoid aqueous and vitreous, with fibrin and leukocytes in the aqueous. Clinically, such animals are often systemically ill as detected by fever, decreased appetite, and depression. Lacrimation and photophobia are usually marked. Subsequent attacks tend to become increasingly severe, and resolution of the gross lesions between attacks is less complete. Such horses, during the quiescent period, may have one or more of peripheral corneal vascularization with fibrosis and persistent edema; irregular thickening and pigmentation of iris; multiple posterior synechiae; patchy residual uveal pigment on lens capsule; and peripapillary retinal hyperreflectivity suggesting retinal scarring.

The microscopic lesions depend on the stage of the disease and represent a continuum from anterior uveitis to endophthalmitis with retinal scarring, or even phthisis bulbi. The earliest lesion is anterior uveal inflammation that is transiently neutrophilic but rapidly becomes predominantly lymphocytic. Ciliary processes are most obviously affected. Edema, fibrin, and leukocytes distend the stroma, and PAS-positive hyaline material obscures the nonpigmented epithelium (Fig. 4.33). Leukocytes and fibrin lie in the anterior chamber and in the filtration angle. In the eyes of horses with a history of several attacks of uveitis, the exudate in active phases of the disease is almost purely lymphocytic–plasmacytic and is found about vessels of choroid, retina, and optic nerve as well as anterior uvea (Fig. 4.34A). Peripheral corneal vascularization, both from conjunctival and limbic ciliary vessels, becomes increasingly prominent and extends farther toward the center of the cornea (Fig. 4.34B). Edema accompanies the newly formed vessels. The chorioretinitis may be sufficiently exudative to cause multifocal retinal separation. As these severe uveal lesions regress during clinically quiescent periods, they leave behind characteristic residual changes. Relatively early in the disease there is the development of perivascular lymphoid aggregates in iris and ciliary body, which persist and may even form true lymphoid nodules (Fig. 4.34C,D). The ciliary processes may remain thickened by fibrous organization of stromal edema, and a hyaline membrane often seems to cover the ciliary epithelium. This material, in fact, lies within the apical cytoplasm of the nonpigmented ciliary epithelium and may be the histologic counterpart of crystalline protein inclusions seen in this epithelium ultrastructurally. Small blood vessels persist along corneal stromal lamellae, and there is subtle fibrous disorganization of the stroma, the result of previous edema. Peripapillary chorioretinal scarring is seen as focal retinal photoreceptor loss, jumbling of layers, and gliosis. Adjacent retinal pigment epithelium may be hypertrophic or hyperplastic, and a focal cluster of lymphocytes in the nearby choroid is common.

Choroidal vessels are unusually thick-walled due to

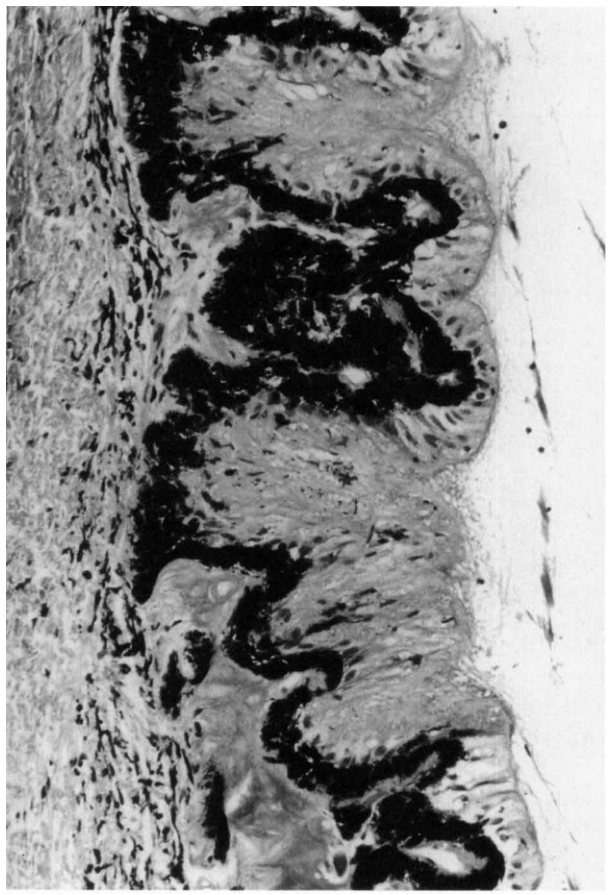

Fig. 4.33 Hyalinization of inner nonpigmented ciliary epithelium. Equine recurrent ophthalmitis.

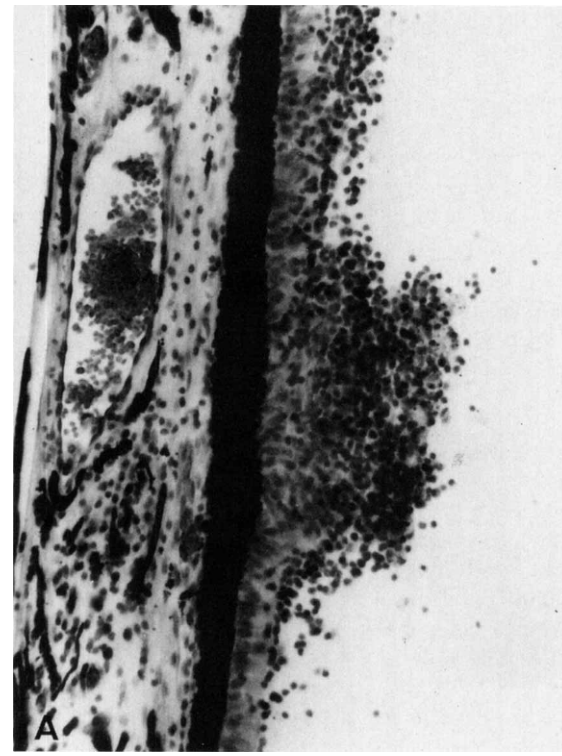

Fig. 4.34A Choroiditis and inflammatory infiltrate of pars plana. Equine recurrent ophthalmitis.

edema or fibrin, the latter probably analogous to the hyalinization described in several reports. Increased vascular permeability persists even in quiescent periods, with loss of the blood–aqueous barrier demonstrated by fluorescein angiography. Whether or not this vascular alteration participates in the perpetuation of the uveitis is unknown, but it is known that such alterations predispose to localization of circulating immune complexes and subsequent type III hypersensitivity-induced inflammation (Auer reaction).

Focal retinal detachments may reattach by fibrous organization of subretinal exudate or may progress to total separation with a barely recognizable retina adherent to posterior lens capsule. Gliosis and lymphocytic aggregates may be found within proximal optic nerve. Scarring in optic disk and adjacent retina often is clinically obvious and may occur in horses with no other lesions of uveitis, leading to speculation that it is not really linked to, or at least not specific for, equine recurrent uveitis. Lesions of such sequelae as cataract, chronic conjunctivitis, and glaucoma are described elsewhere.

The causes and pathogenesis of recurrent equine ophthalmitis have not been intensively studied, in contrast to the abundance of opinion expressed in reviews or texts. The almost universal opinion is that the disease is the result of hypersensitivity to exogenous antigen. The most frequently cited antigens are *Leptospira* and dead microfilariae of *Onchocerca cervicalis*. The recent demonstration of antigenic cross-reaction between equine corneal endothelium and several common leptospiral serovars suggests that accidental autoimmunity may participate in some of the lesions. Cross-reaction with other ocular antigens has not been studied, but the repeated observation that lesion development follows the development of serum or aqueous antibody titers to *Leptospira* makes an immune pathogenesis very likely for this disease syndrome.

There seems little doubt that *Leptospira*, particularly *L. pomona*, can initiate uveitis in horses and in humans. In both species the uveitis develops as a sequel to infection, delayed by weeks or years. The initial suspicion of this association was the observation, as early as 1948, that horses with uveitis frequently had very high serum and aqueous agglutination titers against *L. pomona*. This observation has since been repeatedly confirmed, and has been supported by the observation of uveitis in 22 of 36 eyes of Shetland ponies inoculated subcutaneously with small numbers of *L. pomona*. All ponies underwent subsequent leptospiremia, but none developed ocular lesions until 50 weeks after inoculation. The lesions were typical of anterior uveitis, and six eyes progressed to phthisis bulbi after repeated bouts of uveitis. In 18 eyes there were central retinal scars typical of the naturally occurring disease. Although there seems

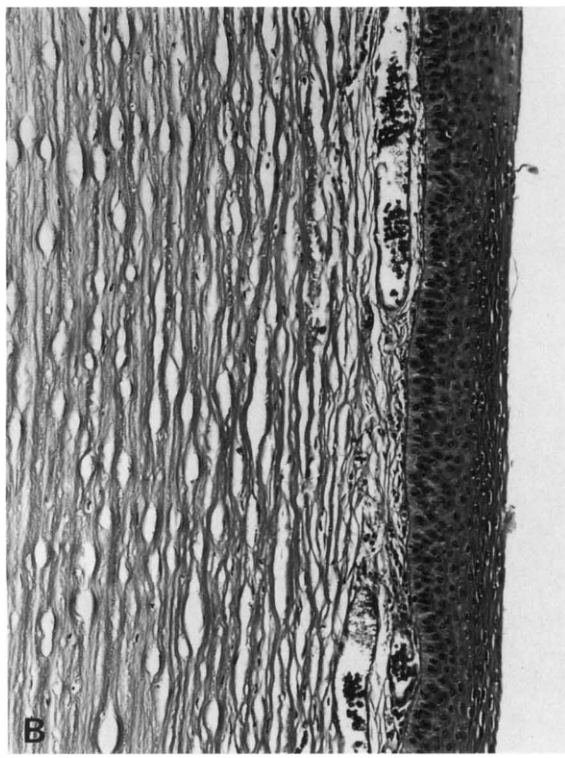

Fig. 4.34B Peripheral corneal stromal vascularization and subtle fibrosis in a horse with equine recurrent ophthalmitis.

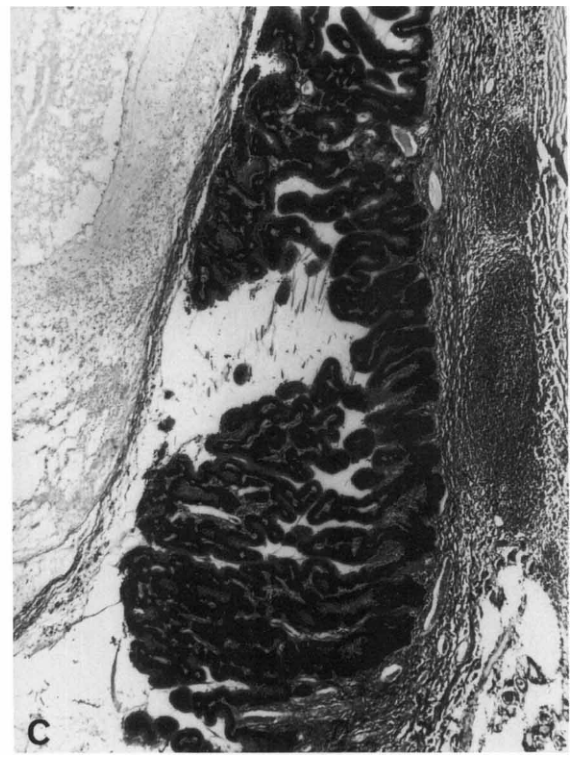

Fig. 4.34C Equine recurrent ophthalmitis. Lymphoid nodules in iris stroma.

little doubt that hypersensitivity to *L. pomona* can cause the syndrome of equine recurrent ophthalmitis, it is unlikely to be the only cause. In a recent survey in Florida, only 1 of 10 horses with uveitis had a positive microagglutination titer against *L. pomona*. Eight had cutaneous onchocerciasis, but that was not significantly different from the overall 60% prevalence of that parasite in the sample population. Typical of the long-standing controversy about this disease is a 1990 survey of horses with uveitis in Virginia and Maryland, in which 52 of 80 affected horses had positive serum titers to one or more leptospiral serovars, and a statistically significant association between uveitis and positive titer was found for the serovars *pomona* and *autumnalis*.

Onchocerca cervicalis infection of the eye is considered briefly with helminthic uveitis. Reaction to dead microfilariae within uveal tissues is considered by some an important cause of equine recurrent uveitis, although the high prevalence of this parasite in the horse population makes such claims difficult to support statistically. The enthusiasm for this pathogenesis may be generated, in part, by the importance of onchocerciasis as a leading cause of blinding keratitis in people.

c. BOVINE MALIGNANT CATARRHAL FEVER-ASSOCIATED UVEITIS The presence of severe uveitis is an important clue in the clinical differentiation of malignant catarrhal fever from other bovine systemic disorders, particularly from mucosal disease. The histologic lesions within the eye resemble those elsewhere in the body: arterial necrosis and perivascular and intramural lymphocytic accumulations. The presence of mitotic figures among the lymphoid cells is distinctive. The arteritis usually is most obvious in the iris, but may be seen affecting arterioles or venules in retina, choroid, meninges of optic nerve, or even peripheral cornea. There is marked corneal edema with a ring of peripheral corneal stromal vascularization, clinically seen as a dark red circumferential brush border of straight vessels in the perilimbal cornea. Blood vessels in the conjunctiva and even in the newly vascularized cornea may be targets for the disease, so that the edema and hemorrhage of vessel injury are added to the nonspecific lesions of conjunctivitis and peripheral keratitis that accompany uveitis of any cause in all species.

Infiltration of lymphocytes among corneal endothelial cells is associated with patchy necrosis of that layer, which may also contribute to the corneal edema (Fig. 4.35). A layer of mononuclear leukocytes enmeshed in fibrin often is adherent to the aqueous face of the corneal endothelium.

Even the very early lesions are lymphocytic. In vessels the first changes involve subendothelial and adventitial lymphocytic and lymphoblastic accumulation, with little necrosis. Despite long-standing speculation for an immune-complex pathogenesis for the vasculitis, proof is lacking. Deposition of immunoglobulin or complement is

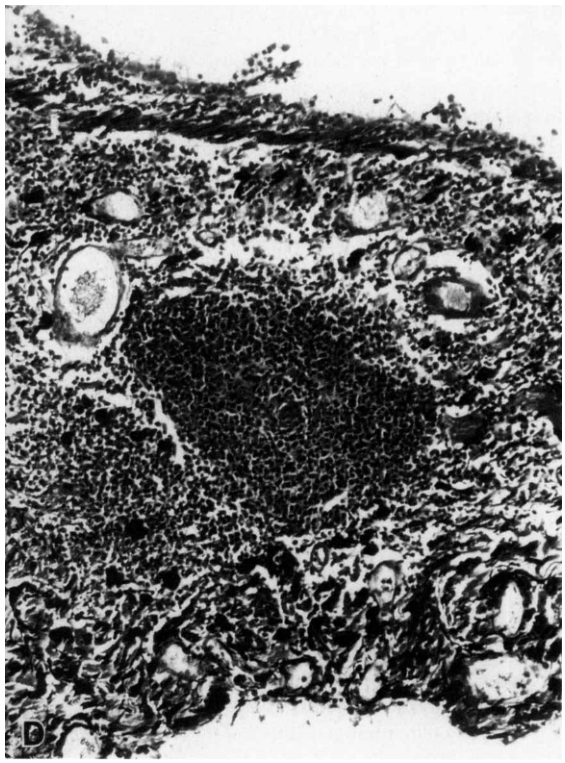

Fig. 4.34D Equine recurrent ophthalmitis. Lymphoid nodules in iris stroma.

not a significant feature of the vascular lesion within the eye, and a T cell-dependent, type IV immune pathogenesis has been suggested.

d. FELINE INFECTIOUS PERITONITIS-ASSOCIATED UVEITIS The coronavirus of feline infectious peritonitis causes diffuse uveitis that is probably immune mediated (see Volume 2, Chapter 4, The Peritoneum). The frequency of ocular lesions is unknown because the eyes are not regularly examined in cats with the disease. Estimates based on clinical examination range from about 10% in an outbreak to 50% of unselected clinical cases. Most cats which die of the disease have ocular involvement as detected by coagulation of aqueous with acidic fixatives (indicating increased aqueous protein). The histologic evidence for inflammation in some eyes may be subtle indeed, and such eyes usually reach postmortem without clinically detected uveitis. Conversely, some cats develop severe uveitis attributed to this virus by clinical, serologic, or histologic evaluation, without concurrent evidence of the disease elsewhere.

The typical histologic lesion, as is the case elsewhere in the body, varies with time and location. The leukocytic infiltration is most extensive in ciliary body and adjacent limbic sclera, and is usually a rather even mixture of neutrophils, lymphocytes, plasma cells, and macrophages. In some eyes the infiltrate is purely histiocytic. The inflammatory cell population often becomes more purely

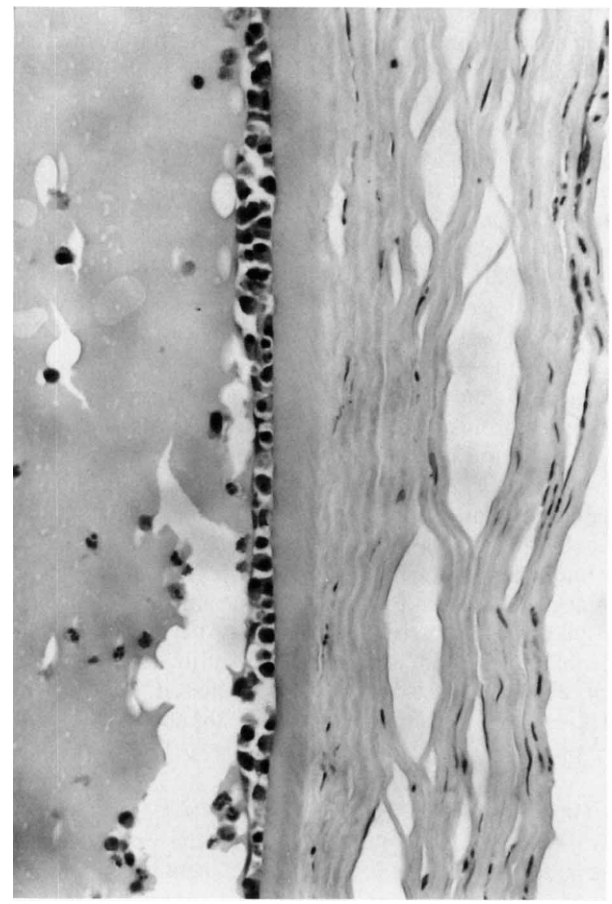

Fig. 4.35 Lymphocytes as part of a presumed immune-mediated endothelialitis obscure the few remaining corneal endothelial cells. Bovine malignant catarrhal fever.

lymphoid in the choroid and more neutrophilic in the anterior chamber. Perivascular lymphocytic–plasmacytic aggregates are common in retrobulbar connective tissue and in the optic nerve sheath, and in the retina. In the retina the accumulations are larger and are more likely to involve a true phlebitis than is the case with the subtle perivascular retinitis that is a frequent and nonspecific accompaniment to most forms of anterior uveitis. Sequelae to the uveitis are rarely seen, either because the cats are in the late stages of the disease when ocular lesions are examined or because euthanasia halts its progression. Retinal separation with serous subretinal exudate is occasionally observed. The presence of large globular accumulations of macrophages and neutrophils adherent to the corneal endothelium (**keratic precipitates**) is an important clinical hallmark of the disease, and is useful histologically as well. Neutrophilic endothelialitis with severe corneal edema may also occur.

e. IDIOPATHIC LYMPHOCYTIC UVEITIS OF DOGS AND CATS Chronic lymphocytic–plasmacytic uveitis is frequent in dogs and cats. Most cases are of unknown cause,

in that affected animals are otherwise healthy, the eye itself contains no visible causal agent, and serologic tests are inconclusive. The last point is the most hotly debated, particularly for cats, in which there is serologic evidence for involvement of toxoplasmosis or feline immunodeficiency virus in the pathogenesis of the uveitis. Other studies still conclude that about 80% of all uveitis in cats is of unknown cause, but many cats had not been tested for antibody to the immunodeficiency virus.

The lesions are similar in dogs and cats. Perivascular accumulations of lymphocytes and plasma cells are seen throughout the uvea and, with less regularity, around small vessels in the retina. Ciliary body tends to have the greatest accumulation. Formation of lymphoid nodules may occur in chronic and severe cases, and for unknown reasons, these are seen much more often in cats than in dogs. The presence of this lymphonodular anterior uveitis is highly correlated with the development of glaucoma in cats but not in dogs (see succeeding sections).

Idiopathic lymphocytic uveitis is presumed to be immune mediated, but the identity of the antigen or antigens is unknown. In dogs the lesion may be confused with the mild uveitis that accompanies maturing cataracts (see Phacolytic Uveitis), while in cats the alternative diagnoses include feline infectious peritonitis, toxoplasmosis, and lymphoma.

f. GRANULOMATOUS UVEITIS IN DOGS (VOGT–KOYANAGI–HARADA SYNDROME) Despite the exotic-sounding name, this disease is relatively frequent in those areas in which the most susceptible breeds (Akitas, Siberian huskies, Samoyeds) are popular. The clinical syndrome of facial dermal depigmentation and severe bilateral uveitis is distinctive, although many dogs examined for the uveitis are not noted to have skin lesions. The canine syndrome closely parallels the human disease, except for the encephalitis that is the least frequent part of the human syndrome and has not been confirmed in dogs. The human disease is most prevalent in Asians; the predilection in dogs for the Japanese Akita is a fascinating but unexplained parallel.

The histologic lesion is a destructive granulomatous endophthalmitis with abundant dispersal of melanin. The melanin-laden retinal pigmented epithelium seems to be especially susceptible. Retinal detachment and destructive granulomatous inflammation are seen in advanced cases. The lesion is distinguished from the more prevalent systemic mycotic diseases by the predilection for pigmented tissues within the eye, the lack of visceral involvement, and the distinctive skin lesions, if they are present (see Chapter 5, The Skin and Appendages).

The pathogenesis of the human disease is thought to involve cell-mediated immune reaction to uveal (or epidermal) melanin.

Bibliography

Bistner, S., and Shaw, D. Uveitis in the horse. *Compend Cont Ed* **2**: S35–S43, 1980.

Bussanich, M. N., Rootman, J., and Dolman, C. L. Granulomatous panuveitis and dermal depigmentation in dogs. *J Am Anim Hosp Assoc* **18**: 131–138, 1982.

Cousins, S. W., and Streilein, J. W. Flow cytometric detection of lymphocyte proliferation in eyes with immunogenic inflammation. *Invest Ophthalmol Vis Sci* **31**: 2111–2122, 1990.

Gwin, R. M. *et al.* Idiopathic uveitis and exudative retinal detachment. *J Am Anim Hosp Assoc* **16**: 163–170, 1980.

Lindley, D. M., Boosinger, T. R., and Cox, N. R. Ocular histopathology of Vogt–Koyanagi–Harada-like syndrome in an Akita dog. *Vet Pathol* **27**: 294–296, 1990.

Liu, S. H., Prendergast, R. A., and Silverstein, A. M. The role of lymphokines in immunogenic uveitis. *Invest Ophthalmol Vis Sci* **24**: 361–367, 1983.

Morter, R. L. *et al.* Experimental equine leptospirosis (*Leptospira pomona*). *Proc 68th Ann Mtg of U.S. Livestock Sanitary Assoc* 147–152, 1964.

Parma, A. E. *et al.* Experimental demonstration of an antigenic relationship between *Leptospira* and equine cornea. *Vet Immunol Immunopathol* **10**: 215–224, 1985.

Peiffer, R. L., Jr., and Wilcock, B. P. Histopathologic study of uveitis in cats: 139 cases (1978–1988). *J Am Vet Med Assoc* **198**: 135–138, 1991.

Roberts, S. R. Etiology of equine periodic ophthalmia. *Am J Ophthalmol* **55**: 1049–1955, 1963.

Schmidt, G. M. *et al.* Equine ocular onchocerciasis: Histopathologic study. *Am J Vet Res* **43**: 1371–1375, 1982.

Streilein, J. W. Anterior chamber associated immune deviation: The privilege of immunity in the eye. *Surv Ophthalmol* **35**: 67–73, 1990.

Whitely, H. E. *et al.* Ocular lesions of bovine malignant catarrhal fever. *Vet Pathol* **22**: 219–225, 1985.

Williams, R. D. *et al.* Experimental chronic uveitis—ophthalmic signs following equine leptospirosis. *Invest Ophthalmol* **10**: 948–954, 1971.

g. LENS-INDUCED UVEITIS Uveitis in response to leakage of lens material is seen in all species, but is most frequent by far in dogs. The term **lens-induced uveitis** encompasses two very different syndromes—phacolytic and phacoclastic uveitis—that differ markedly in clinical severity, in histopathology, and in pathogenesis.

Phacolytic uveitis is a mild lymphocytic–plasmacytic anterior uveitis that occurs in response to the leakage of denatured lens protein through an intact lens capsule, which occurs regularly in the course of maturation of cataracts toward total fiber liquefaction. The inflammation is readily controlled by routine therapy, so the pathologist is likely to encounter this lesion only as an incidental finding in eyes with hypermature cataracts that were enucleated for reasons unrelated to the uveitis. The lesion is identical to that described for idiopathic (immune-mediated) uveitis, except it is always mild. Its pathogenesis is unknown. The lens leaks small denatured lens proteins that are not immunogenic but are, perhaps, direct inflammatory stimulants with lymphocytic chemotactic properties.

Phacoclastic uveitis is, at least histologically, a more complicated disease that follows rupture of a normal lens in an unknown percentage of cases. The rupture is usually from corneal penetration by a thorn, quill, bullet, or cat claw, and thus usually is of the anterior capsule. The

clinical syndrome is distinctive: corneal perforation and mild traumatic uveitis that are successfully managed by conventional therapy, followed by the sudden reappearance of a severe, intractable uveitis 10–14 days after the initial injury. Poor response to medical therapy and the eventual development of glaucoma or phthisis bulbi prompt enucleation, so that phacoclastic uveitis is one of the most prevalent ocular diseases to be submitted for histologic examination.

The macroscopic changes in the bisected globe are diagnostic: the lens is flattened in its anteroposterior dimension, and there frequently is a wedge of opacification extending from the anterior capsule toward the nucleus (Fig. 4.36A). Usually there is posterior synechia, iris bombé, and the various other lesions of any severe uveitis (Fig. 4.36B).

The histologic lesions vary considerably depending on duration and, probably, on the amount of lens protein that escaped through the rupture site. There are often complex lesions that result from a combination of the direct effects of trauma, immunologic reaction to massive release of lens protein, reparative proliferation of metaplastic lens and/or iridociliary epithelium, and possible contributions by corneal wound healing, sepsis, and glaucoma.

The simplest and presumably earliest lesion of phacoclastic uveitis occurs at the site of capsular perforation.

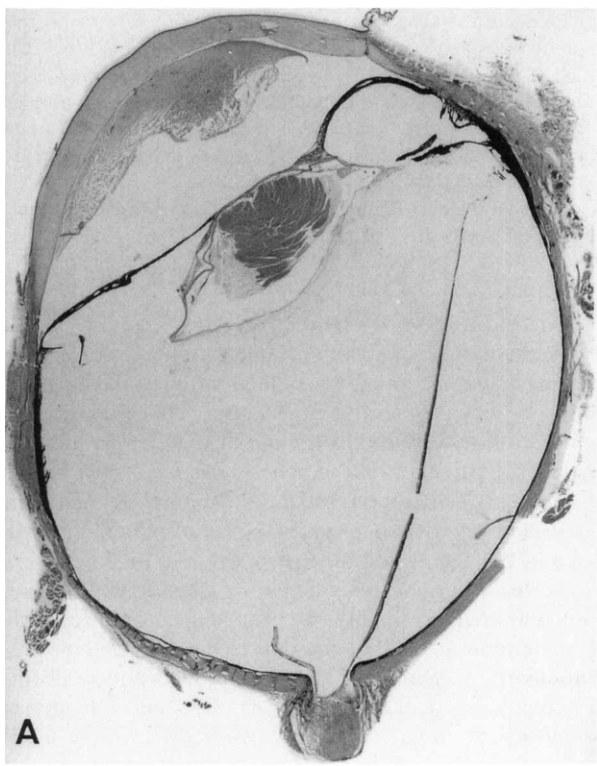

Fig. 4.36A Posterior synechia, iris bombe, and glaucomatous cupping of optic disk following traumatic corneal and lenticular perforation. The anterior–posterior flattening of the liquified lens is typical.

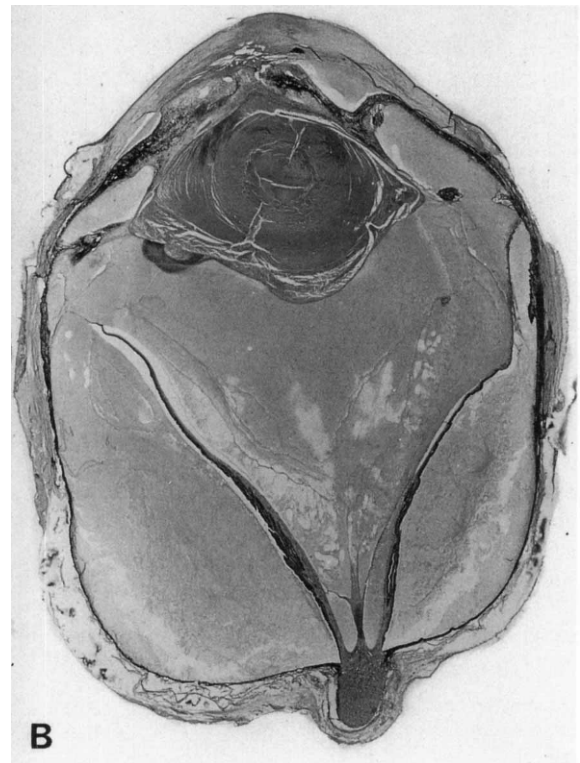

Fig. 4.36B Phacoclastic uveitis with posterior synechiae, iris bombe, and a serous endophthalmitis with complete retinal detachment. Note continuity between transcorneal scar and perilenticular fibroplasia.

The edges of the capsule are retracted and coiled outward, and a wedge of neutrophils and liquified lens material extends from the perforation toward the nucleus. The inflammation outside of the lens is usually distinctly perilenticular and involves a mixture of neutrophils and macrophages in the anterior and posterior chambers, and a lymphocyte-dominated reaction within the uveal stroma.

Older lesions (which predominate in most enucleated globes) are dominated by the perilenticular proliferative changes of wound repair. There is proliferation and fibroblastic metaplasia of lens epithelium adjacent to the perforation, which escapes from the lens to ramify over the lens surface and frequently incorporates lens, ciliary processes, and iris leaves into a large fibrous mass that obstructs aqueous outflow. Metaplasia of ciliary epithelium or recruitment of fibroblasts from uveal stroma may contribute to the proliferation (Fig. 4.37). Many such specimens contain little evidence of inflammation other than the fibroplasia, probably because of very extensive antiinflammatory therapy that is, in hindsight, useless against the proliferative events that doom the eye to glaucoma or phthisis.

Phacoclastic uveitis is an important complication of cataract surgery in which fragments of lens cortex or epithelium may be left in the eye. These initiate the same inflammatory and proliferative reaction as described, and

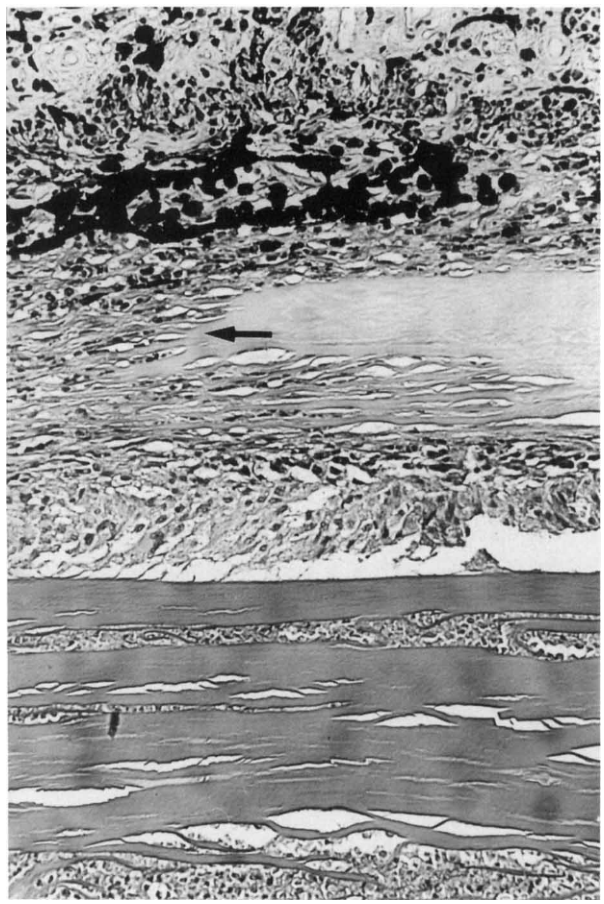

Fig. 4.37 Phacoclastic uveitis. Severed ends of anterior lens capsule (arrow) are fimbriated. Typical fibrous proliferation fuses cataractous lens to the (pigmented) iris.

the complications are as refractory to conventional antiinflammatory therapy as is the naturally occurring disease.

The immune pathogenesis of phacoclastic uveitis has been extensively studied, but with no universally accepted conclusion. The current theory is that the release of massive amounts of lens protein antigen overwhelms the splenic T-cell tolerance to small amounts of lens antigen. Recruitment of lens-sensitized lymphocytes into the perilenticular uvea then initiates both the pyogranulomatous perilenticular inflammation and the proliferative events of healing that, unfortunately, doom the eye. This pathogenesis, if true, explains the typical delay between injury and reaction, and why rapid surgical removal of lens is preventive. It may also explain the unpredictability of phacoclastic uveitis, especially following small perforations in puppies, which seem often to heal uneventfully. Even in adult dogs the disease is unpredictable, so owners' questions about the risk of phacoclastic uveitis as the justification for surgical removal of a perforated lens cannot be answered with certainty. One recent study found lens removal shortly after perforation prevented serious complications in 6 of 7 dogs thus treated, whereas 5 of 6 dogs treated with aggressive medical therapy lost the eye to complications of the uveitis.

Two interesting variations on what is basically a canine scheme are seen in rabbits and cats. Rabbits suffer what appears to be spontaneous lens capsule rupture of a previously normal lens. The response is a well-contained perilenticular granulomatous inflammation very similar to human phacoanaphylactic uveitis. Cats occasionally develop lesions similar to those in dogs, but also develop a unique feline primary intraocular pleomorphic sarcoma that may arise from metaplastic lens epithelium or from other transformed epithelial elements in the reparative reaction (see Feline Primary Ocular Sarcoma).

Bibliography

Davidson, M. G. *et al.* Traumatic anterior lens capsule disruption. *J Am Anim Hosp Assoc* **27**: 410–414, 1991.

Dietz, H. H., Jensen, O. A., and Wissler, J. Lens-induced uveitis in a domestic cat. *Nord Vet Med* **37**: 10–15, 1985.

Fischer, C. A. Lens-induced uveitis. *In* "Comparative Ophthalmic Pathology" R. L. Peiffer, Jr. (ed.), pp. 254–263. Springfield, Illinois, Charles C Thomas, 1983.

Misra, R. N., Rahi, A. H. S., and Morgan, G. Immunopathology of the lens: II. Humoral and cellular immune responses to homologous lens antigens and their roles in ocular inflammation. *Br J Ophthalmol* **61**: 285–296, 1977.

Murphy, J. M. *et al.* Sequelae of extracapsular lens extraction in the normal dog. *J Am Anim Hosp Assoc* **16**: 47–51, 1980.

Paulsen, M. E. *et al.* The effect of lens-induced uveitis on the success of extracapsular cataract extraction: A retrospective study of 65 lens removals in the dog. *J Am Anim Hosp Assoc* **22**: 49–55, 1986.

Rahi, A. H. S., Misra, R. N., and Morgan, G. Immunopathology of the lens: I. Humoral and cellular immune responses to heterologous lens antigens and their roles in ocular inflammation. *Br J Ophthalmol* **61**: 164–176, 1977.

Wilcock, P. B., and Peiffer, R. L., Jr. The pathology of lens-induced uveitis in dogs. *Vet Pathol* **24**: 549–553, 1987.

2. Endophthalmitis

a. BACTERIAL ENDOPHTHALMITIS Bacteria may enter the eye hematogenously or via penetrating wounds. Those arriving hematogenously cause their initial lesion in ciliary body or, less frequently, in choroid. Those arising via penetration usually incite the initial reaction in anterior chamber, particularly if the penetration is via perforation of an ulcerative keratitis. Most are suppurative, and their extent and severity vary with the size of inoculum, virulence of the agent, and host response and its duration.

The list of organisms capable of causing endophthalmitis is long. It is probably true that any bacterium capable of bacteremia or septicemia can cause endophthalmitis. Particularly prominent are the streptococci and coliforms in neonatal septicemia (Fig. 4.38). The failure to detect ocular lesions in such animals is more often the result of the brief, fatal course of the disease than of specific ocular resistance. The ocular lesion may be very mild, better detected by opacification of the plasmoid aqueous in Bouin's or Zenker's fixative than by histologic examination. Histology may reveal only edema of ciliary processes

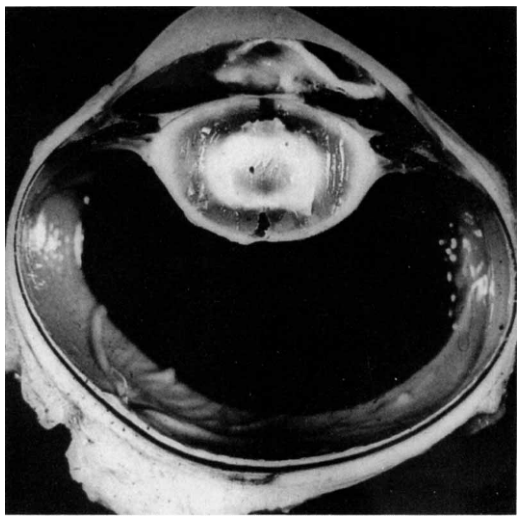

Fig. 4.38 Acute streptococcal ophthalmitis with corneal edema and hypopyon. Calf.

with a few neutrophils along the capillary endothelium or enmeshed in filaments among ciliary processes. The best-known bovine septicemic disease, infectious thrombotic meningoencephalitis, is seen as focal rather than diffuse chorioretinitis.

Exceptions to the generalization that bacterial endophthalmitis is suppurative occur if infection is caused by bacteria which, in other tissues, incite lymphocytic or even granulomatous inflammation. **Ocular tuberculosis** is largely of historical interest. It occurred as part of generalized systemic disease, and the typical tubercles were most numerous in the choroid. *Mycobacterium tuberculosis* var. *bovis* was the usual isolate except in cats, in which the human strain was common (Fig. 4.39). In cats, ocular tuberculosis may also occur as keratoconjunctivitis without uveal involvement.

Brucella canis may cause chronic lymphocytic endophthalmitis that is probably immunologically mediated. Agglutinating titers for *B. canis* antigen in aqueous exceed those of serum, and the ocular lesions are similar to those of equine recurrent ophthalmitis.

Listeria monocytogenes often causes endophthalmitis in association with meningoencephalitis in ruminants (see Chapter 3, The Nervous System). The condition is unilateral, and the pathogenesis is obscure.

Uveitis caused by the rickettsias of **Rocky Mountain spotted fever** and **ehrlichiosis** are discussed under Retinitis.

b. MYCOTIC ENDOPHTHALMITIS Fungi may affect the eye as causes of keratitis, orbital cellulitis, or endophthalmitis. Only rarely do the fungi causing keratitis or orbital infection penetrate the fibrous tunic to cause intraocular disease. However, hematogenous uveal localization is rather common in the course of systemic mycoses caused by *Cryptococcus neoformans* and *Blastomyces dermatitidis* and, less regularly, with *Coccidioides immitis* and *Histoplasma capsulatum*. In immunodeficient animals, one might expect occasionally to detect endophthalmitis as part of generalized disease caused by saprophytic fungi such as *Aspergillus* or *Candida*.

Fig. 4.39 Tuberculous ophthalmitis. Cat. Exudate in vitreous and detaching retina (arrows).

The frequency with which endophthalmitis accompanies systemic mycosis is unknown and probably varies with the specific agent, the species affected, and whether the disease is in an endemic area or is a sporadic occurrence. Hematogenous ocular mycosis is found almost exclusively in dogs, except for cryptococcosis, which is more common in cats. *Blastomyces* and *Cryptococcus* are more likely to invade the eye in the course of generalized infection than are *Coccidioides* or *Histoplasma*, and occurrence in nonendemic areas is strongly linked to prolonged systemic corticosteroid therapy. Involvement is bilateral but not necessarily equal. Blastomycosis, cryptococcosis, and coccidioidomycosis are discussed with the Respiratory System (Volume 2, Chapter 6), and histoplasmosis with the Hematopoietic System (Volume 3, Chapter 2).

Blastomycosis is the most frequently reported cause of intraocular mycosis in dogs. It is rare in cats. Between 20 and 26% of dogs with the systemic disease are blind or have grossly observed ocular lesions, suggesting that intraocular involvement would be recognized more often if histologic examinations were routinely done. The clinical ocular disease is severe diffuse uveitis, frequently with retinal separation.

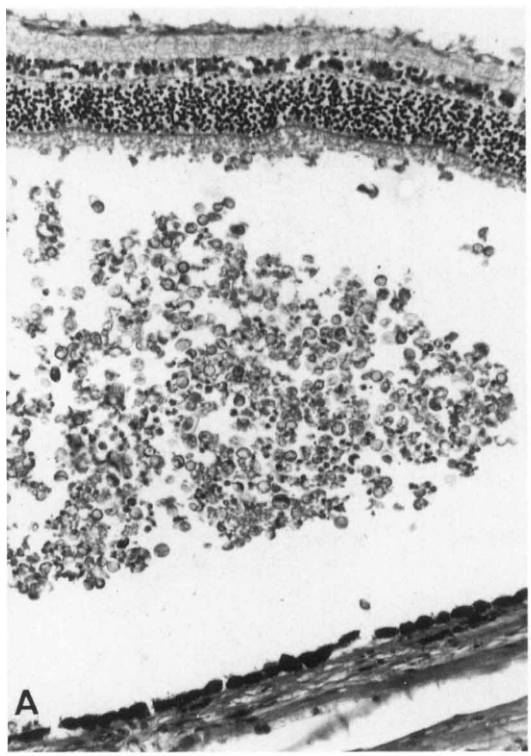

Fig. 4.40A Subretinal exudate containing *Blastomyces dermatitidis*. Dog receiving long-term corticosteroid therapy.

Fig. 4.40B Retinal separation and focal necrotic retinitis. Cat, *Cryptococcus*. Note soap-bubble appearance (arrow) and minimal host reaction.

The histologic appearance is of diffuse pyogranulomatous or granulomatous endophthalmitis with retinitis, exudative retinal separation, and commonly, granulomatous optic neuritis. Choroiditis is often more pronounced than is the anterior uveitis. The greatest accumulation of leukocytes often is in the subretinal space enlarged by exudative retinal detachment. The causative diagnosis depends on the demonstration of the spherical-to-oval, thick-walled yeasts in vitreous aspirates or in the histologic section. They are usually most numerous in the subretinal exudate, but are rare in anterior chamber or in retina itself (Fig. 4.40A). The organisms are free or within macrophages, are 5–20 μm in diameter and show occasional broad-based budding. Extremes in sizes may result in yeasts from 2 to 30 μm in diameter. The eye may, in addition, have the full spectrum of corneal, lenticular, and glaucomatous sequelae, as expected of any severe uveitis. Panophthalmitis with orbital cellulitis is seen in about one third of enucleated globes.

Cryptococcosis is similar to blastomycosis in that the lesions are predominantly within retina, choroid, and optic nerve. However, infection of the eye may arise either hematogenously or by extension from the brain via optic nerves, and lesions are often conspicuously lacking in cellular host reaction. Large collections of poorly stained pleomorphic yeasts, surrounded by wide capsular halos, impart a typical soap-bubble appearance to the histologic lesions (Fig. 4.40B). The yeasts vary in size, but most are 4–40 μm in diameter. Round, oval, and crescentic forms are seen. In some animals, however, a granulomatous reaction mimicking that of blastomycosis can be found. In such lesions the organism typically is scarce.

The frequency with which *Coccidioides immitis* infects the eye appears to be low, ~2%, despite the prevalence of generalized infection in endemic areas. The ocular lesion resembles blastomycosis in that pyogranulomatous reaction occurs around fungal spherules. The reaction is predominantly purulent around newly ruptured spherules, gradually becoming granulomatous as the released endospores mature. The lesion tends to be more destructive than other mycoses, usually spreading to involve sclera and even episclera in a suppurative panophthalmitis.

Histoplasma capsulatum is a common cause of generalized mycosis in dogs but is rare in other domestic species. It has a predilection for lymphoid tissue and other tissues rich in phagocytes such as lung and liver, and perhaps this preference accounts for the paucity of ocular involvement in spontaneous disease. In dogs and cats infiltrative choroiditis or panuveitis occurs and is dominated by plasma cells and by macrophages filled with the organisms. Retinal separation, plasmoid vitreous, and optic neuritis also develop. The reaction tends to target the choroid, and to be less destructive than either blastomycosis or coccidioidomycosis.

Prototheca are colorless saprophytic algae capable of

causing enteric, cutaneous, mammary, or generalized granulomatous disease in a variety of mammalian species. Ocular lesions have been described only in dogs with the disseminated form of the disease. The lesions are bilateral and may vary from lymphocytic–plasmacytic to granulomatous panuveitis with optic neuritis and exudative retinal separation. The host response is usually quite mild. The lesions resemble ocular mycosis, particularly cryptococcosis, and are distinguished only by the observation of the pleomorphic algae. In histologic section, the algae are free or within phagocytes. The organisms are spherical to oval, from 2 to 20 μm in diameter with a refractile, PAS-positive and argyrophilic cellulosic cell wall. Each cell consists of granular, weakly basophilic cytoplasm surrounding a central nucleus. *Prototheca* produces by asexual multiple fission, so that multiple daughter cells form within a single cell wall. One or two cycles of nuclear division without cytoplasmic cleavage may produce transient multinucleated cells before eventual cytoplasmic division results in up to eight daughter cells. Each daughter cell acquires a capsule, resulting in a parent cell crisscrossed by septations that represent the cell walls of maturing daughter cells. Rupture of the parent cell wall releases the unicellular autospores. Collapsed, crumpled, and seemingly empty cell walls are visible in histologic section. There is no budding as with *Blastomyces* and *Cryptococcus*.

Those canine isolates that were definitively identified were *P. zopfii*. An enteric route of entry is probable inasmuch as necrotic enteritis is a feature of the disease (see Volume 2, Chapter 1, The Alimentary System). Immunodeficiency may be prerequisite for dissemination of the organism. Lesions are found in many visceral organs, skin, and lymph nodes in most cases. The reaction is granulomatous but is usually minimal in comparison to the large number of organisms.

c. PROTOZOAN ENDOPHTHALMITIS While ocular lesions have been reported in infections caused by protozoa of the genera *Toxoplasma, Leishmania, Encephalitozoon, Besnoitia* and *Trypanosoma*, only *Toxoplasma* specifically causes intraocular lesions, although some cases so diagnosed may have been caused by *Neospora*. Most of the others cause keratoconjunctivitis that occasionally extends to anterior or generalized uveitis in which the causal agent may be found. The exception is *Encephalitozoon* that may induce periarteritis within the uvea and retina as it does elsewhere.

Toxoplasmosis affecting the eye is, as elsewhere, much more frequently suspected than proven, and clinical diagnoses greatly outnumber those confirmed by histopathology. The histologic lesion is usually in retina, uvea, or extraocular muscles, and varies from focal, acute coagulative necrosis to granulomatous or lymphocyte-rich inflammation. The organisms are seen most easily as intracellular pseudocysts during acute disease or as true cysts during remission. The more noxious merozoites are found only with difficulty as 7- to 9-μm crescentic, basophilic bodies within phagocytes, or free amid necrotic debris.

The histologic changes of ocular toxoplasmosis have received various interpretations, and valid differences probably exist between species and between individuals of differing immune status. In humans, the disseminated disease is usually congenital, and the ocular lesion is multifocal necrotic retinitis, in which free or encysted *Toxoplasma gondii* are found. There may be lymphocytes and plasma cells in adjacent choroid. In human adults, the ocular lesion is predominantly a lymphocytic–plasmacytic choroiditis, suggesting that the pathogenesis is related more to host immune response to the previously encountered, ubiquitous antigen than it is to local infection.

Lesions analogous to human congenital toxoplasmosis occur in young cats as multiple foci of retinal necrosis. Choroiditis may be present and is lymphocytic-plasmacytic, and anterior uveitis is seen in only 20–30% of such cases. Much more common than this classical retinochoroiditis, however, is lymphocytic–plasmacytic anterior uveitis with serologic evidence for active *Toxoplasma* infection. The role of toxoplasmosis in feline anterior uveitis is controversial. Retrospective histologic studies list the majority of such cases as idiopathic and are presumed to be immune mediated, with antigen or antigens unknown. In the several large published studies, there has not been a single case confirmed by observation of merozoites or cysts in the eye; even serologic evidence in these studies pointed to toxoplasmosis in only 1–2% of cases. In contrast, one study reported evidence of anterior uveal production of toxoplasma-specific antibody in 32 of 69 cats with anterior uveitis, and another report confirmed that anterior uveitis is indeed the most frequent manifestation of toxoplasmosis in cats, seen in 60% of cats with confirmed toxoplasmosis. Nonetheless, evidence remains less than conclusive about the role of *T. gondii* in the prevalent and enigmatic syndrome of anterior uveitis in this species. It may be that the local production of *Toxoplasma* antibody in cats with uveitis is merely the result of nonspecific recruitment of *Toxoplasma*-sensitized lymphocytes into the chronically inflamed uvea, and that lymphoid aggregates in such eyes are producing a whole range of antibody quite irrelevant to the original cause of the uveitis.

The situation in other species is not clear, but the prevalence of ocular lesions seems quite low. Lymphocytic cyclitis and multifocal necrotic retinitis are most frequently described and are usually seen together. Multifocal choroiditis, not necessarily adjacent to retinal lesions, is lymphocytic-plasmacytic in most species but granulomatous in sheep. A more common lesion is severe myonecrosis in extraocular muscles associated with free and encysted *Toxoplasma*. Toxoplasmosis is discussed in more detail in the Alimentary System (Volume 2, Chapter 1).

d. PARASITIC ENDOPHTHALMITIS Many parasites are found incidentally in the eye, including echinococcosis in primates and cysticercosis in swine, multifocal ischemic chorioretinitis and optic neuritis in elk caused by occlusive

vasculitis due to microfilariae of *Elaeophora schneideri*, and uveitis associated with fortuitous localization of larvae of *Toxocara canis* or other ascarids, *Angiostrongylus vasorum*, *Dirofilaria immitis*, and *Onchocerca cervicalis*. In addition, adults of *Setaria* spp. are occasionally found within the eye of horses. The long threadlike worms are seen floating within the aqueous, and the uveitis that results seems to be the result of mechanical irritation. The only specific intraocular parasitism is seen with the lens fluke of fish (*Diplostomum spathaceum*), which, after penetrating the skin, seeks the lens with remarkable speed and specificity. The principal lesion is cataract induced by the intralenticular presence of hundreds of larvae awaiting ingestion by fish-eating birds for completion of their life cycle, but infected fish may have larvae arrested in many other ocular or extraocular locations.

Chronic mild anterior uveitis is reported to accompany ectopic localization of immature *Dirofilaria immitis* within aqueous and vitreous cavities of dog eyes. Pathological studies are sparse, but endophthalmitis is reported in which anterior synechiae, subretinal exudate, and early cyclitic membrane may accompany the numerous vitreal and subretinal larval nematodes.

Ocular onchocerciasis affects humans and horses. The human disease is endemic in Africa and Central America and is one of the most frequent causes of blindness in the world. The microfilariae of the causal agent, *Onchocerca volvulus*, are transmitted by *Simulium* spp. flies to affect the skin, eyelids, and corneas of children and young adults. The microfilariae are found throughout the eye, but the lesion of greatest visual significance is diffuse sclerosing superficial stromal keratitis complicated by anterior uveitis with synechiae and eventual glaucoma.

Equine onchocerciasis has some similarities. The parasite, *O. cervicalis*, is of worldwide distribution, and surveys from the United States of America document the prevalence of dermal infection in horses as varying from 48 to 96%. About one half of the infected horses have microfilariae in conjunctiva or sclera. The microfilariae enter the eye only incidentally in the migration from the ligamentum nuchae to the subcutis. The ocular sites of greatest concentration are the peripheral cornea and the lamina propria of the bulbar conjunctiva near the limbus. The microfilariae in the cornea are associated with a superficial stromal keratitis resembling the disease of man, albeit much milder. Some of the horses also have anterior uveitis typical of equine recurrent ophthalmitis, prompting theories that *Onchocerca* is one cause of this disease. The microfilariae can be recovered from the conjunctiva and eyelids of horses with uveitis, keratoconjunctivitis, and eyelid depigmentation, but are recovered with equal frequency from horses with no ocular disease and no microscopic reaction to the worms.

Ocular manifestations of **visceral larva migrans** in humans are associated with larvae of *Toxocara canis* or, perhaps more frequently, of the raccoon roundworm *Baylisascaris procyonis*. The unilateral granulomatous fundic lesions are caused by a single wandering larva, and are relatively common in children but have rarely been described in nonhuman subjects, despite the rather common occurrence of ascarid-induced granulomas in canine kidneys, lungs, or livers. The paucity of reports may not reflect the actual prevalence of disease in specific canine populations. One large survey of working sheepdogs in New Zealand recorded a 39% prevalence of lesions attributed to visceral larva migrans, contrasted to a 6% prevalence in similar dogs living in urban environments. The active lesions were lymphocytic and granulomatous uveitis, nonsuppurative retinitis, and peripapillary nontapetal retinal necrosis. Inactive lesions involved choreoretinal scars and multifocal chronic retinal separations in dogs older than 3 years. Larvae most compatible with *Toxocara canis* were seen in sections of some acutely affected eyes. The high prevalence in these dogs was tentatively ascribed to the feeding of uncooked frozen mutton that may have contained *T. canis* larvae as part of a dog–sheep–dog life cycle. A report of similar lesions in Border collies in the United States was associated with the feeding of raw pork.

Ocular disease may also result from the intraocular migration of fly larvae. This syndrome, termed *internal ophthalmomyiasis*, is discussed with diseases of conjunctiva.

Bibliography

Bistner, S., Shaw, D., and Riis, R. C. Diseases of the uveal tract (part III). *Compend Cont Ed* **2:** 46–53, 1980.

Buyukmihci, N. C., and Moore, P. F. Microscopic lesions of spontaneous ocular blastomycosis in dogs. *J Comp Pathol* **97:** 321–328, 1987.

Buyukmihci, N., Rubin, L. F., and DePaoli, A. Protothecosis with ocular involvement in a dog. *J Am Vet Med Assoc* **167:** 158–161, 1975.

Carlton, W. W., and Austin, L. Ocular protothecosis in a dog. *Vet Pathol* **10:** 274–280, 1973.

Chandler, F. W., Kaplan, W., and Ajello, L. "Histopathology of Mycotic Diseases." Chicago, Illinois, Year Book Medical Publishers, 1980.

English, R. V. *et al.* Intraocular disease associated with feline immunodeficiency virus infection in cats. *J Am Vet Med Assoc* **196:** 1116–1119, 1990.

Flamm, H., and Zehetbauer, G. Die Listeriose des Auges im Tierversuch. *Graefe's Arch Ophthalmol* **158:** 122–135, 1956.

Gwin, R. M. *et al.* Ocular lesions associated with *Brucella canis* infection in a dog. *J Am Anim Hosp Assoc* **16:** 607–610, 1980.

Hughes, P. L., Dubielzig, R. R., and Kazacos, K. R. Multifocal retinitis in New Zealand sheep dogs. *Vet Pathol* **24:** 22–27, 1987.

Johnson, B. W. *et al.* Retinitis and intraocular larval migration in a group of border collies. *J Am Anim Hosp Assoc* **25:** 623–629, 1989.

Migaki, G. *et al.* Canine protothecosis: Review of the literature and report of an additional case. *J Am Vet Med Assoc* **181:** 794–797, 1982.

Piper, R. C., Cole, C. R., and Shadduck, J. A. Natural and experimental ocular toxoplasmosis in animals. *Am J Ophthalmol* **69:** 662–668, 1970.

Trevino, G. S. Canine blastomycosis with ocular involvement. *Pathol Vet* **3:** 651–658, 1966.

Vainisi, S. J., and Campbell, L. H. Ocular toxoplasmosis in cats. *J Am Vet Med Assoc* **154:** 141–152, 1969.
Van Kruiningen, H. J., Garner, F. M., and Schiefer, B. Protothecosis in a dog. *Pathol Vet* **6:** 348–354, 1969.
Wilder, H. C. Nematode endophthalmitis. *Trans Amer Acad Ophthalmol Oto-laryngol* **55:** 99–109, 1950.

B. Glaucoma

Glaucoma is a pathophysiologic state characterized by prolonged increase in intraocular pressure. Although such increases of pressure may theoretically result from increased production or decreased removal of aqueous, only the latter is known to occur. The lesions in glaucomatous eyes include those related to the pathogenesis of the glaucoma and those resulting from the glaucoma itself. Glaucoma occurs commonly in dogs, less commonly in cats, occasionally in horses, and rarely in other species. Because most affected eyes eventually require enucleation, glaucoma is one of the most frequent ocular conditions examined histologically.

The lesion predisposing to glaucoma may be the result of antecedent ocular disease, particularly anterior uveal inflammation with posterior or anterior synechiae. Such cases are termed secondary glaucoma. Primary glaucoma describes those cases without evidence of prior ocular disease and, in practical terms, is synonymous with malformation of the filtration angle. Primary glaucoma is seen almost exclusively in dogs and vies with neoplasia as the most frequent cause of glaucoma in dogs.

Because the pathogenesis of glaucoma so frequently involves developmental or acquired distortion of the filtration angle, a description of that structure is appropriate here.

The **filtration apparatus** is a series of mesenchymal sieves that occupies the iridocorneal angle, and extends circumferentially around the globe. These sieves appear to form by rarefaction of the same mesenchyme that forms iris stroma, and its rarefaction continues (at least in carnivores) for several weeks after birth. This area of perforated mesenchyme is the ciliary cleft, bordered externally by sclera, posteriorly by the muscles of the ciliary body, and internally by the iris stroma. Its anterior border is the **pectinate ligament,** which is visible clinically as a series of cobweblike branching cords (carnivores) or a fenestrated sheet (ungulates) stretching from the termination of Descemet's membrane to the anterior portion of the iris root. They consist of collagenous cords covered by a very thin endothelium, with a thin intervening layer of basement membranelike material. The endothelium is continuous with the corneal endothelium, and the collagenous core is continuous with corneal stroma.

Aqueous humor percolating through the pectinate ligament into the ciliary cleft must then pass through mesenchymal sieves consisting of collagenous cords covered by phagocytic and pinocytotic endothelium, called the **trabecular meshwork.** The large, open network of cords occupying most of the ciliary cleft is the uveal trabecular meshwork, and external to it is a more compressed network called the corneoscleral trabecular meshwork. Ordinarily, aqueous humor produced by the ciliary processes passes through the pupil, through the pectinate ligament, and then through the uveal and corneoscleral trabecular meshworks en route to the scleral venous plexus that will return the aqueous to the systemic circulation. Improper development or acquired obstruction of any part of this drainage pathway may result in glaucoma, but one must remember that the ciliary cleft extends 360° around the iridocorneal angle. Blockage of most of it is required for the development of glaucoma, and this assessment is virtually impossible with two-dimensional histologic examination. It is quite common to encounter dog eyes with maldeveloped filtration angles in both portions contained in a histologic section, yet with no evidence of glaucoma. Examination of the circumference of the angle with a dissecting microscope or scanning electron microscope in such cases often reveals the maldevelopment to be segmental and thus not a cause for glaucoma.

Differences exist among species in the finer details of angle structure and in the degree to which alternative routes of aqueous outflow are utilized (Fig. 4.41A,B). The horse, for example, has very thick pectinate fibers, an inconspicuous corneoscleral trabecular meshwork and

Fig. 4.41A Normal canine filtration angle showing fenestrated pectinate ligament inserting at the termination of Descemet's membrane. Large vessels are part of scleral venous plexus.

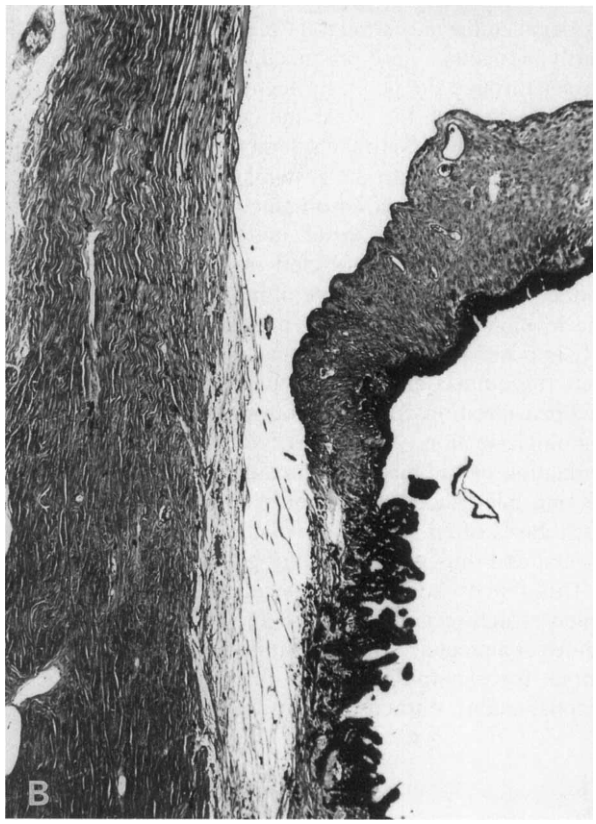

Fig. 4.41B Normal feline filtration angle.

scleral venous plexus, and alternative routes of aqueous outflow (into iris stroma or caudally through ciliary muscle into choroid) that are probably much more important than similar routes in dogs or cats. In contrast, the cat has extremely delicate pectinate fibers, a very large, open ciliary cleft, a conspicuous scleral venous plexus, and minimal (about 3% of aqueous outflow) reliance on alternative outflow pathways (Fig. 4.41B). In dogs alternative drainage routes account for 15 to 25% of all outflow. The existence of these alternative routes may explain the absence of glaucoma in some eyes (especially in horses) in which the angle changes would ordinarily have resulted in glaucoma, and may even explain the presence of glaucoma in eyes with apparently normal angles but lesions affecting portions of these other potential drainage routes.

Primary glaucoma is most frequently encountered in dogs. Although theoretically primary glaucoma may have no visible angle lesion (which is frequently the case in humans), in dogs there is almost always a readily detected maldevelopment. The one exception is primary open-angle glaucoma in beagle dogs, in which there is no visible antecedent lesion. The broad term **goniodysgenesis** encompasses all developmental defects of the filtration angle, of which two types account for most canine cases. The most prevalent is continuation of mature iris stroma across the trabecular meshwork to insert into the termination of Descemet's membrane. Some consider this an example of dysplasia of pectinate ligament, and the term **imperforate pectinate ligament** is widely used. The band usually is much broader than pectinate ligament, no matter how poorly perforated, but the term seems well entrenched. It is seen as a breed-related and thus presumably inherited defect in Bouvier des Flandres, Basset hounds, American cocker spaniels, Dandie Dinmont terriers, Siberian huskies, Samoyeds, and numerous other breeds. The defect, and the resultant glaucoma, are occasionally seen in mixed-breed dogs. The dysplasia is usually bilateral but not necessarily of equal extent, so that the glaucoma often is initially present only in one eye. The prevalence of the iridopectinate dysplasia is much higher than the prevalence of glaucoma, and even in dogs with very extensive dysplasia that should seemingly eliminate almost all aqueous drainage, the onset of glaucoma is not until several years of age. Age-related changes in outflow resistance in alternative routes of aqueous outflow have been postulated as the explanation, but no proof exists.

The second major type of goniodysgenesis is seen as an apparent arrest in the maturation of the trabecular meshwork so that the ciliary cleft is filled with dense tissue resembling primitive anterior uveal mesenchyme (Fig. 4.13A,B). This may occur in conjunction with iris hypoplasia or anterior chamber cleavage syndromes, but it may exist as an isolated defect.

Secondary glaucoma occurs most commonly as the result of peripheral anterior synechiae, with the root of the iris effectively sealing the filtration angle. The synechiae may result from iris bombé, from expanding neoplasia behind or within the iris, or from primary adhesion of an inflamed iris to the cornea. Because the iris does not normally contact the cornea, anterior synechia by the last mechanism is frequent only as a consequence of corneal perforation, in which case the iris flows forward to seal the defect and may then adhere diffusely to the corneal endothelium (Fig. 4.42A). Other causes of secondary glaucoma include occlusion of the trabecular meshwork by preiridal fibrovascular membrane, inflammatory debris, or tumor cells. Lens luxation may precipitate glaucoma by allowing vitreous to occlude the pupil, by stimulating anterior uveitis, or by trapping iris against cornea. Rarely, lens swelling with cataract (intumescent cataract) seems to occlude the pupil. In small terrier dogs with an inherited tendency to luxation, there is an unusually high prevalence of glaucoma. Removal of lens prior to the onset of glaucoma prevents the expected glaucoma, seemingly establishing the causal role of the luxation. Posterior synechiae may also occlude the pupil (particularly as part of phacoclastic uveitis), but posterior synechiae usually cause glaucoma via iris bombé and thus a circumferential peripheral anterior synechia.

There are substantial differences among species in what mechanisms of glaucoma predominate. In **dogs,** goniodysgenesis, posterior synechiae with iris bombé, anterior uveal melanoma, and anterior lens luxation are the leading causes. In **cats,** diffuse iris melanoma and chronic idiopathic anterior uveitis (by an unknown mechanism) are

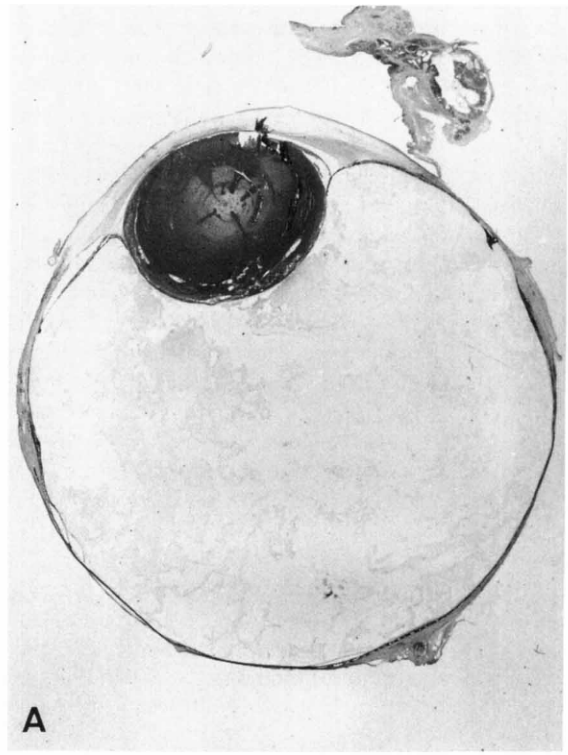

Fig. 4.42A Glaucoma caused by swelling of cataractous lens (intumescent cataract) and resultant functional anterior synechia. Dog. Note thin sclera typical of buphthalmos secondary to glaucoma.

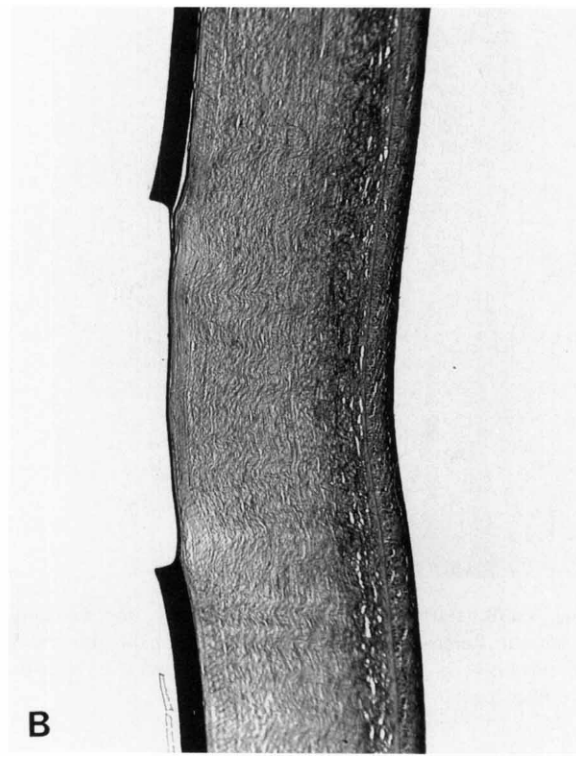

Fig. 4.42B Focal break in Descemet's membrane (corneal stria) commonly seen in horses and dogs with glaucoma.

the only prevalent causes of glaucoma, with posterior synechiae very uncommon. In **horses,** the presence of preiridal fibrovascular membranes across the pectinate face (neovascular glaucoma) is the most frequent cause, although the stimulus for the membrane development is unknown in most reported cases. In those horses with glaucoma in which the membrane had not apparently crossed the pectinate ligament, the glaucoma may have been caused by obstruction of alternative (i.e., iridal) routes of aqueous outflow, which are assumed to be more important in horses than in dogs or cats.

Lesions that develop as a result of glaucoma vary with the duration and severity of the glaucoma and the distensibility of the globe, and affect virtually all parts of the globe. Enlargement of the globe **buphthalmos** or **megaloglobus**) occurs most readily in young animals or in those species with thin scleras such as cats and laboratory animals. In cornea, increased aqueous pressure forces fluid into the corneal stroma resulting in diffuse edema and eventual fibrosis and vascularization. If buphthalmos occurs, corneal stretching results in rents in Descemet's membrane, visible clinically as corneal striae (Fig. 4.42B). These are relatively most frequent in horses and least prevalent in cats with glaucoma. Failure of lids to cover the enlarged globe permits corneal desiccation and eventual ulceration with all its sequelae. Cataract is usual, presumably the result of stagnation of aqueous and subsequent lens malnutrition. Iris and ciliary body undergo bland atrophy, most obvious as thinning and flattening of ciliary processes. Collapse of the ciliary cleft and trabecular meshwork itself is frequent and makes evaluation of these structures for possible goniodysgenesis very difficult. Increased prominence of PAS-positive material in linear arrays resembling posterior migration of Descemet's membrane is probably

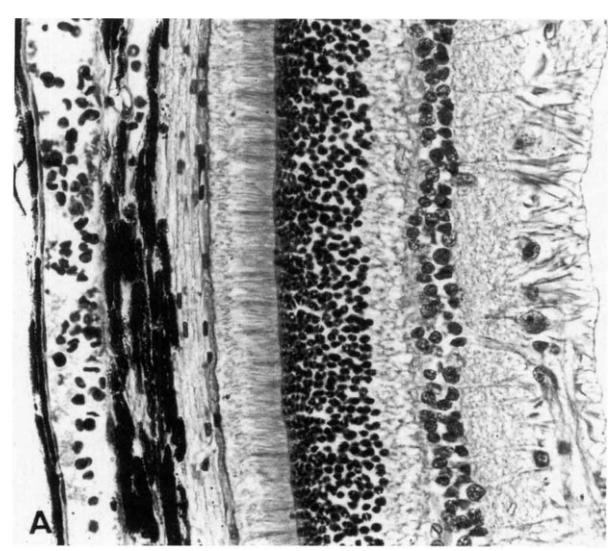

Fig. 4.43A Normal canine retina overlying tapetum lucidum.

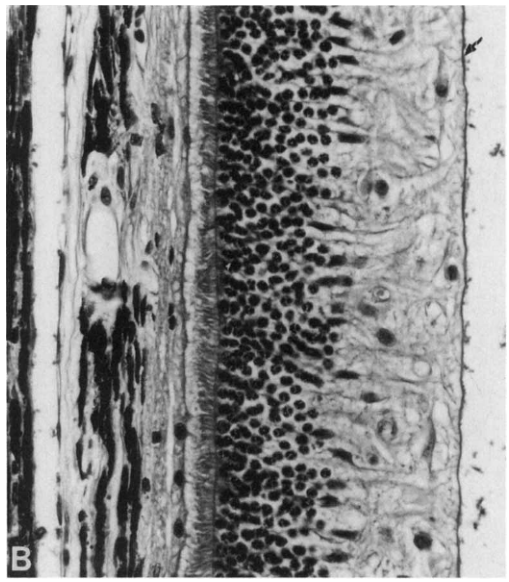

Fig. 4.43B Early glaucomatous retinopathy, dog. Ganglion cells absent. Remnant of inner nuclear layer remains. Inner limiting membrane is abnormally prominent (arrow) over atrophic nerve fiber layer.

a response of the endothelium covering the trabecular beams to the glaucoma, but its possible primary role in the pathogenesis of glaucoma has not been adequately investigated.

The retinal lesion is characteristic and is the most reliable method of diagnosis of glaucoma based solely on histologic criteria. Atrophy begins in nerve fiber and ganglion cell layers, making glaucoma the only naturally occurring cause of inner retinal atrophy other than the rare instances of traumatic or neoplastic disruption of optic nerve (Fig. 4.43A,B). Loss of nerve fibers unmasks the normally inconspicuous Müller fibers, a lesion that may be more easily seen and more confidently interpreted than the loss of the nerve fibers or ganglion cells themselves (Fig. 4.44). This is particularly true in cats, in which the ganglion cells persist with considerable tenacity under circumstances that would, in dogs, have progressed to a very obvious atrophy. With increasing duration or severity, the inner nuclear layer and its axons and dendrites also atrophy, resulting in thinning of the inner nuclear layer and the blending of this layer with the outer nuclear layer as the plexiform layers (the axons and dendrites of the nuclear layer cells) rarefy.

Eventually the retina exists only as a thin glial scar with scattered remnants of outer nuclear layer and melanin-laden phagocytes derived from retinal pigmented epithelium. The retina overlying tapetum is less severely affected than nontapetal retina. Excavation ("cupping") of the optic disk is a pathognomonic lesion when present, but its absence does not rule out the diagnosis. It occurs by two mechanisms, either (or both) of which may explain the cupping in an individual eye. Particularly in animals with

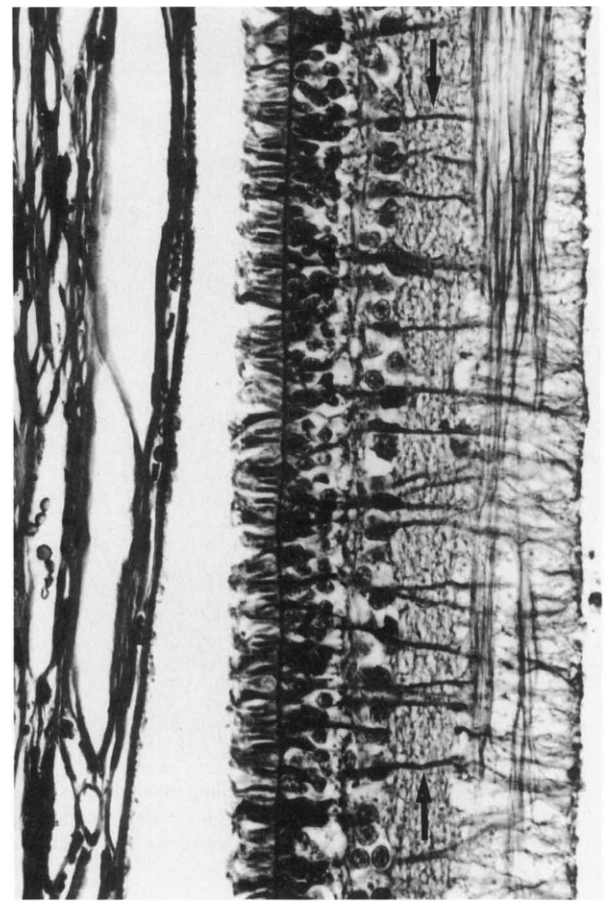

Fig. 4.44 Glaucomatous retinal atrophy. Ganglion cells are absent, inner nuclear layer is sparse, and Müller's fibers (arrows) unduly obvious due to loss of nerve fiber layer.

a thin sclera and lamina cribrosa, the elevation of pressure may cause rapid posterior bowing of the lamina, resulting in visible cupping without apparent nerve atrophy. This is frequently seen in cats and rabbits, but not in ungulates with their thick, rigid lamina. In all species, cupping also occurs by axonal loss from the optic nerve. It has been suggested that the posterior bowing of the lamina cribrosa contributes to the later atrophy of nerve by mechanical pinching of axons or blood vessels as they pass through the distorted lamina (Fig. 4.45A,B). This cupping is distinguished from coloboma by the absence of dysplastic neurectoderm lining the defect and the presence of inner retinal atrophy. The pathogenesis of the retinal and optic disk atrophy is controversial. Either pressure-induced retinal ischemia or interference with axoplasmic flow in the axons of the ganglion cells en route to the optic nerve may be responsible. Why the dorsal (tapetal) retina is more resistant is unknown.

Bibliography

Bedford, P. G. C. The clinical and pathological features of canine glaucoma. *Vet Rec* **108:** 53–58, 1980.

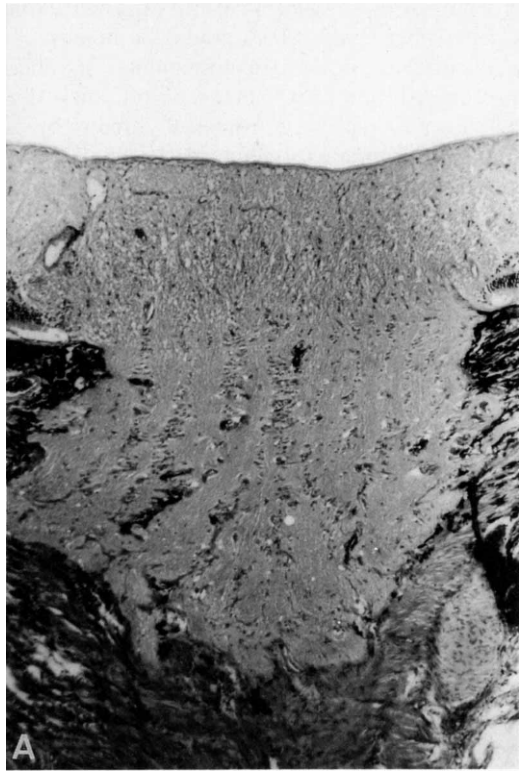

Fig. 4.45A Normal canine optic disk.

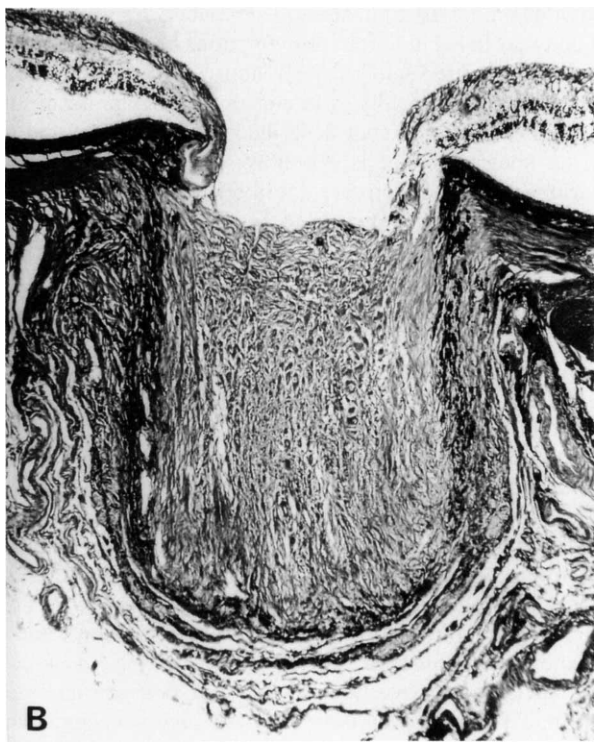

Fig. 4.45B Cupping of optic disk and rarefaction of the nerve. Chronic glaucoma.

Brooks, D. E. Glaucoma in the dog and cat. *Vet Clin North Am: Small Anim Pract* **20:** 775–797, 1990.

De Geest, J. P. *et al.* The morphology of the equine iridocorneal angle: A light and scanning electron microscopic study. *Eq Vet J* **10:** 30–37, 1990.

Martin, C. L. The pathology of glaucoma. *In* "Comparative Ophthalmic Pathology" R. L. Peiffer (ed.), pp. 137–169. Springfield, Illinois, Charles C Thomas, 1983.

Quigley, H. A., and Addicks, E. M. Chronic experimental glaucoma in primates. II. Effect of extended intraocular pressure elevation on optic nerve head and axonal transport. *Invest Ophthalmol* **19:** 137–152, 1980.

Smelser, G. K., and Azanics, V. The development of the trabecular meshwork in primate eyes. *Am J Ophthalmol* **71:** 366–385, 1971.

Smith, P. J., Samuelson, D. A., and Brooks, D. E. Aqueous drainage patterns in the equine eye: Scanning electron microscopy of corrosion cast. *J Morphol* **198:** 33–42, 1988.

van der Sinde-Sipman, J. S. Dysplasia of the pectinate ligament and primary glaucoma in the Bouvier des Flandres dog. *Vet Pathol* **24:** 201–206, 1987.

Wilcock, B. P., Brooks, D. E., and Latimer, C. A. Glaucoma in horses. *Vet Pathol* **28:** 74–78, 1991.

Wilcock, B. P., Peiffer, R. L., Jr., and Davidson, M. G. The causes of glaucoma in cats. *Vet Pathol* **27:** 35–40, 1990

VII. The Retina

When involution of the primary optic vesicle brings into apposition the anterior and posterior poles, the anterior (innermost) neurectodermal layer undergoes mitotic replication and subsequent specialization to form the nine layers of the neurosensory retina. The outermost neurectoderm remains as a relatively unspecialized simple cuboidal layer, the retinal pigment epithelium. Although it is traditionally considered the tenth retinal layer, its structure, function, and reaction to injury are unlike those of neurosensory retina, and it is best discussed separately. In this discussion, retina refers only to the neurosensory retina.

In the fixed, bisected globe, the retina is seen as a thin, opaque membrane lining the posterior half of the globe between vitreous and choroid. It joins the darkly pigmented pars plana of the ciliary body at an abrupt transitional point called the **ora ciliaris retinae.** In all but the best-preserved specimens, the retina is separated artifactually from the retinal pigment epithelium and adjacent choroid, remaining adherent only at the ora ciliaris and at the optic disk.

Histologically, the neurosensory retina begins abruptly at the ora ciliaris as a multilayered continuation of the inner layer of the ciliary epithelium. In dogs and sometimes in horses, the layers here are poorly defined and photoreceptors, sparse. The peripheral retina is only about half the thickness (100 μm) and has half the photoreceptor density (250,000/mm^3) of the central retina, with fewer nuclear and plexiform elements and a thin innermost nerve fiber layer.

The retina consists of three structural components: neurons, glia, and vasculature. The neurons are the functional elements and transmit the photoactivated electrical im-

pulse from photoreceptor process to occipital cortex. The photoreceptor is the *raison d'être* of the entire globe. It is a sensory, apical cytoplasmic process of the neurons forming the outer nuclear layer. These processes, called rods or cones, based on their shape and ultrastructural composition, extend from the outer nuclear layer toward the choroid. They are enveloped by a glycosaminoglycan interphotoreceptor matrix, and interdigitate with apical processes of the retinal pigment epithelium, but no actual adhesions exist between the two layers. Within the outer segment of the photoreceptors are stacks of collapsed, disklike spheres which contain the photoactive chemicals. The disks within rod outer segments are constantly produced basally and shed apically at the rate of 80 to 100 disks per day, with an outer segment turnover time of 6 days in dogs. Effete disk debris is engulfed and degraded by the retinal pigment epithelium. Such turnover has not been demonstrated in the outer segment of cones, which have stacks of lamellae formed by infoldings of the plasma membrane. In addition, cones appear to be of many different types within a single retina. It is probably the ratio of different cones sensitive to different wavelengths of light that permits the visual cortex to discriminate color. In general, fish, amphibia, reptiles, and birds have excellent color discrimination. Ungulates can distinguish yellows, blues, and, variably, green and red. Carnivores have very limited color perception as far as can be determined.

Other retinal layers are best described in terms of function. The photoelectric stimulus originating in the photoreceptor outer segment is transmitted through the outer nuclear layer and along the axons of the photoreceptor nuclei to the bipolar and horizontal neurons of the inner nuclear layer. The accumulation of outer nuclear layer axons and inner nuclear layer dendrites forms the outer synaptic or plexiform layer. The inner nuclear layer contains the nuclei of the bipolar, horizontal, amacrine, and glial (Müller) cells. The bipolar cells receive impulses from the photoreceptors and relay them to ganglion cells. The bipolar cells also stimulate the horizontal cells, which transmit the impulse horizontally to excite adjacent bipolar cells. Amacrine cells counterbalance the bipolar cells in that their stimulation releases an inhibitor of ganglion cell excitation. The glial cells are primarily structural support cells, whose processes traverse the retina to form the retinal scaffold, and their anterior and posterior terminations fuse to form the inner and outer limiting membranes. The axons of the bipolar and amacrine cells, dendrites of ganglion and horizontal cells, and glial processes form the thick, inner synaptic or plexiform layer. The ganglion cell layer is the thinnest and innermost of the neuronal layers. Large, granular neurons form a single and often sparse layer, supplemented by a few astrocytes, that become bilayered in the area centralis to accommodate the marked increase in photoreceptor density. The density of ganglion cells predicts, in a general way, visual acuity. They are most closely packed in animals requiring fine visual discrimination (most birds, predatory fish, many reptiles). In contrast, they are sparse in ungulates, who do not feed by sight, but who flee at anything that moves. Their axons form the nerve fiber layer, which gradually increases in thickness toward the optic disk. In most animals, the fibers are not myelinated until they reach the optic disk. The nerve fiber layer is separated from the vitreous by an internal limiting membrane formed by the terminations of the Müller fibers and a true basal lamina.

The organization of the retinal vasculature is an important variable in ophthalmoscopic examination, both because vascular abnormalities are frequent signposts of disease and because normal species variation can erroneously be diagnosed as disease. Carnivores, ruminants, and swine have large venules and smaller arterioles radiating from the optic disk to peripheral retina. The horse has about 60 thin, short vessels extending from the disk for about 5.0 mm into surrounding retina. In dogs and cats, the major vessels lie within the deep half of the nerve fiber layer and the ganglion cell layer. In ruminants and pigs, the vessels are very superficial and bulge into the vitreous, covered only by a thin layer of nerve fibers and basal lamina. The retinal vessels form an end-artery circulation which supplies the inner layers of the retina. The photoreceptors and outer nuclear layers are avascular and receive nutrients primarily by diffusion from choroid. Such dependence cannot be absolute (except in horses) because degeneration of these outer layers is surprisingly slow (weeks to months) following retinal separation. In contrast, occlusion of a retinal vessel results in focal infarction of the inner retina within less than 1 hour.

The blood vessels also participate in the blood–eye barrier similar to that already described for uvea. The tight endothelial junctions and junctions between adjacent retinal pigmented epithelial cells conspire to create a retina that is immunologically isolated from nonocular tissues in a manner similar to that described for uvea. Like that in uvea, such a barrier is probably not absolute, and the various retinal antigens are not likely to be totally sequestered or absolutely unique to retina. Saline extracts of retina yield the retinal S antigen, and the interphotoreceptor retinoid-binding protein is another antigen that may be important in the initiation or perpetuation of degenerative (see sudden acquired retinal degeneration in Section VII,B,1) or inflammatory retinopathies.

The retinal pigmented epithelium extends from the ora ciliaris to optic disk as the posterior continuation of the outer layer of ciliary epithelium. It forms a simple cuboidal epithelial layer that is separated from the choroid by a complex basal lamina, Bruch's membrane. The apical border interdigitates with the photoreceptors, with an average of about 30 photoreceptors contacting a single pigment epithelial cell, but forms no junctional complexes. The inclusion of the adjective "pigmented" is somewhat a misnomer in domestic species except the pig, inasmuch as the epithelium overlying the tapetum contains no cytoplasmic pigment granules. This seemingly insignificant layer plays a major role in embryologic induction of the eye as previously described, and also plays a crucial role in the nurturing of the photoreceptors throughout life. The

pigment epithelium engulfs and degrades obsolete rod and cone outer segments, absorbs light to protect photoreceptors, synthesizes and degrades part of the glycosaminoglycan matrix enveloping photoreceptor outer segments, and participates in the vitamin A–rhodopsin cycle. Which of these functions are most essential for photoreceptor health is still unclear.

The ocular fundus is a clinical term describing those ophthalmoscopically visible portions of the posterior globe, excluding vitreous. The fundus is commonly divided into dorsal tapetal and ventral nontapetal fundus, with the optic disk usually at the junction of the two. Retina, although almost transparent, does absorb some incident and reflected light to somewhat dull the fundus reflection ophthalmoscopically. Areas of retinal atrophy absorb less light and are seen as areas of increased tapetal reflectivity. Pre- or subretinal exudates, conversely, increase light absorption and are seen as focal fundic opacities. Developmental or acquired absence of tapetum allows black choroidal pigment to be seen. More severe choroidal lesions may be seen as red choroidal vasculature or even pink sclera obscured by variable amounts of residual pigment. Particularly in dogs, cats, and horses, selective breeding has made hypoplastic variations in amount and pigmentation of choroid and tapetum normal for particular breed or color varieties.

The **general pathology** of **retina** is often said to resemble that of brain. While this is undoubtedly true, inasmuch as retina is merely an extension of the brain, the prevalence of such lesions as malacia, nonsuppurative perivascular cuffing, and proliferative microgliosis within the retina is very low compared to the brain. Although no actual data are published, most animals with encephalitis do not, in fact, have concurrent retinitis. Retinal inflammation is most often the result of spread from choroid or across the vitreous from anterior uvea. Degenerations are much more common than inflammations and are not usually accompanied by inflammatory reaction. The mature mammalian retina has no capacity for regeneration of entire neural cells, although photoreceptor outer segments and glia may be replaced if destroyed in the course of degenerative or inflammatory disease. Even the fetal retina has poor regenerative capacity, as evidenced by the prevalence of retinal dysplasia following prenatal or neonatal retinal injury. Retinal repair is by proliferation of inner layer astrocytes, which eventually form a dense glial scar. Occasionally the astrocytes proliferate along the vitreal face of the retina, forming a preretinal fibroglial membrane. Similar subretinal membranes are seen with chronic detachments and originate from retinal pigment epithelium or Müller cells. The retinal pigment epithelium retains mitotic ability. When injured, these cells respond with hypertrophy, hyperplasia, and fibrous metaplasia. The presence of pigment in the neuroretina is frequent in instances of retinal atrophy, most probably derived from migration of retinal pigmented epithelial cells into the adjacent retina.

Autolytic changes are visible within retina within 30 min of death and within a few hours are of sufficient magnitude to interfere with the diagnosis of retinal degenerations. The earliest histologic change is pyknosis of a few nuclei in outer and inner nuclear layers, and loss of uniform density of the photoreceptor layer. Progressive dissolution of the photoreceptor outer segments results in retinal separation. Nuclear layer pyknosis and ganglion cell chromatolysis are widespread within 4 to 6 hr. By 12 hr, the retinal separation is complete, and the extensively folded retina, with autolytic photoreceptors, may mimic genuine retinal separation. The extensive pyknosis within both nuclear layers distinguishes the two, being absent in antemortem separation (see the following for other criteria). By 18 hr after death, the retina is represented by a barely separable bilayer of pyknotic nuclei suspended in a pale, eosinophilic foamy matrix representing fragmented nerve fiber and plexiform layers.

Bibliography

Barrie, K. N., and Gelatt, K. N. Diseases of the canine posterior segment: The ocular fundus. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 480–484. Philadelphia, Pennsylvania Lea & Febiger, 1981.

Bellhorn, R. W., Murphy, C. J., and Thirkill, C. E. Anti-retinal immunoglobulins in canine ocular diseases. *Sem Vet Med Surg (Small Anim)* **3:** 28–32, 1988.

Buyukmihci, N., and Aguirre, G. Rod disc turnover in the dog. *Invest Ophthalmol* **15:** 579–584, 1976.

Donovan, A. The postnatal development of the cat retina. *Exp Eye Res* **5:** 249–254, 1966.

Young, R. W., and Bok, D. Participation of the retinal pigment epithelium in the rod outer segment renewal process. *J Cell Biol* **42:** 392–403, 1969.

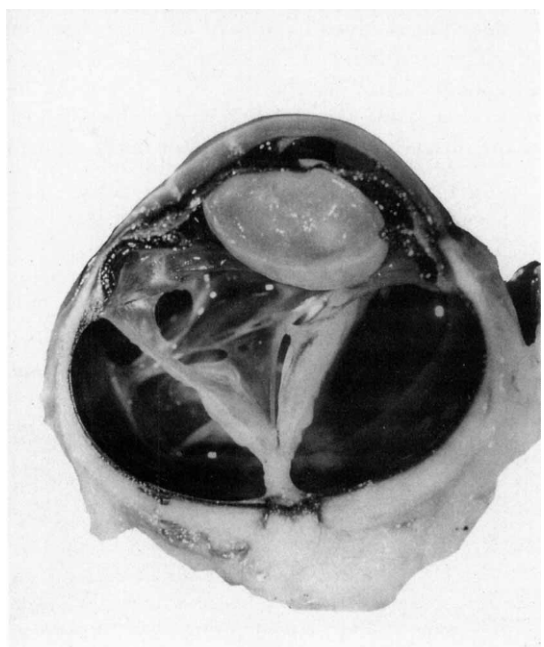

Fig. 4.46 Healed ophthalmitis with retinal detachment, synechia, and displacement of lens.

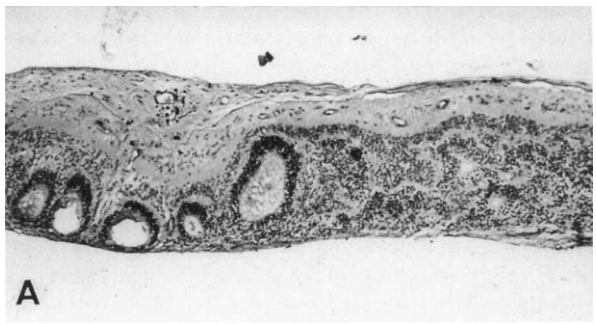

Fig. 4.47A Cystic degeneration and gliosis in spontaneously detached retina. Dog.

A. Retinal Separation

The retina is firmly attached in the globe only at the ora ciliaris and at optic disk. When the retina separates, it does so by cleaving photoreceptors from their interdigitations with the retinal pigment epithelium. Separation may occur as the result of accumulation of inflammatory exudates (Fig. 4.46), transudates, tumor cells, or helminths between pigment epithelium and photoreceptors, by contraction of a cyclitic membrane, or by leakage of liquefied vitreous through retinal tears. Such tears may result from orbital trauma or from progression of peripheral cystic retinal degeneration (Fig. 4.47A). The latter is relatively common in humans but not in domestic animals, despite the frequent occurrence of microcystoid retinal degeneration in the peripheral retina of dogs (Fig. 4.47B) and, less often, of horses.

The diagnosis of retinal separation in fixed specimens is complicated by the ease with which retinal separation can be induced by delayed fixation or improper handling of globes. The credibility of the diagnosis is greatly enhanced by the presence of subretinal exudates or cyclitic membranes (Fig. 4.48), but in their absence, the diagnosis rests on the observation of photoreceptor outer segment

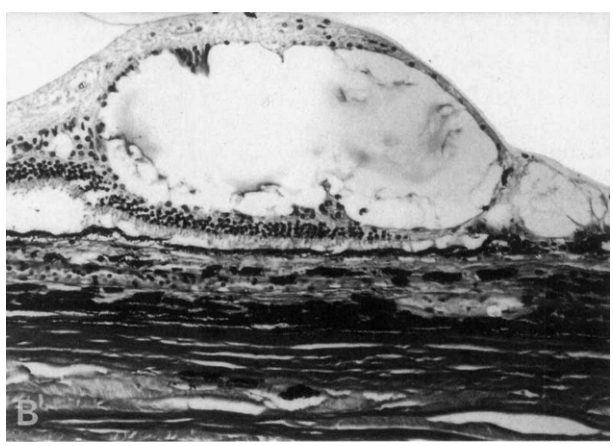

Fig. 4.47B Peripheral microcystoid retinal degeneration. Dog. Such change is very common and of no apparent functional significance.

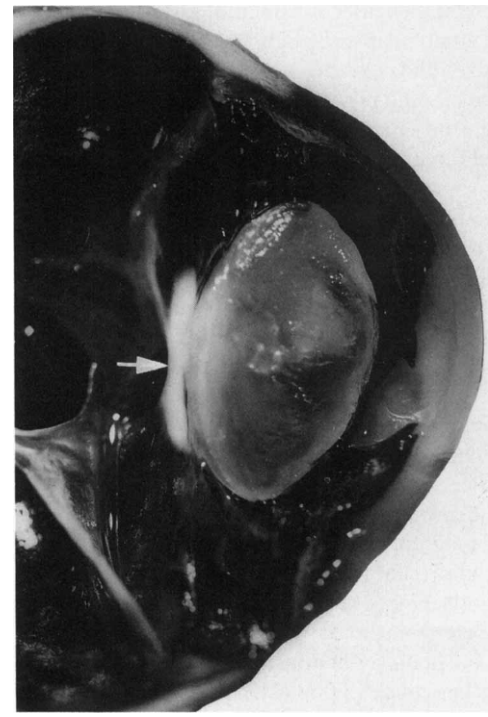

Fig. 4.48 Healed ophthalmitis. Ox. Cyclitic membrane (arrow) behind lens.

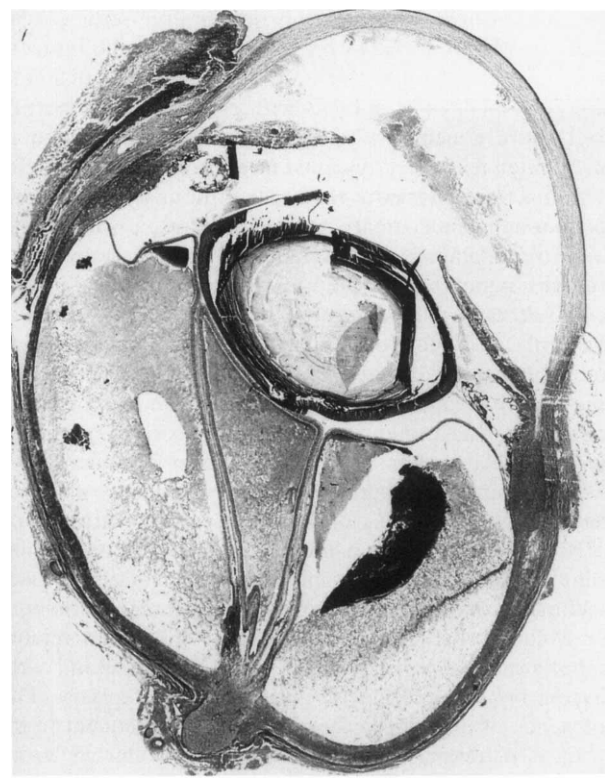

Fig. 4.49 Complete retinal exudative separation. Dog with metastatic choroidal melanoma.

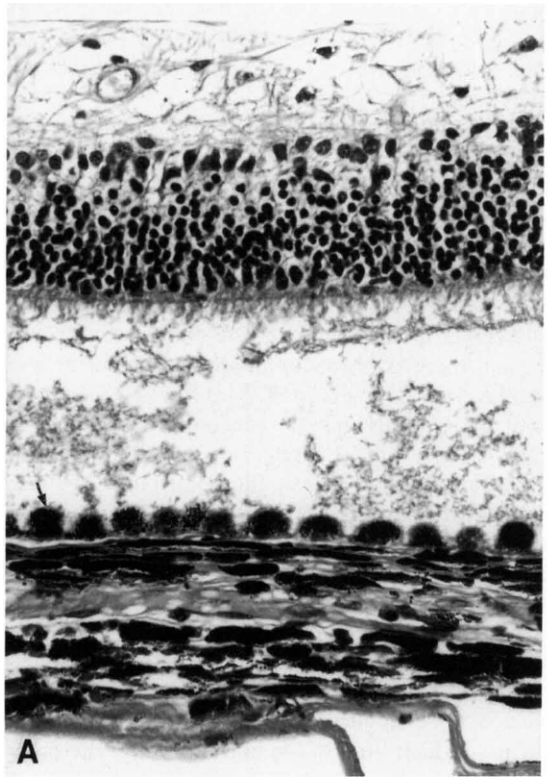

Fig. 4.50A Serous retinal separation. Dog. Hypertrophic retinal pigment epithelium; photoreceptors atrophic; loss of nuclei from inner and outer nuclear layers. Blending of nuclear layers due to atrophy of outer plexiform layer.

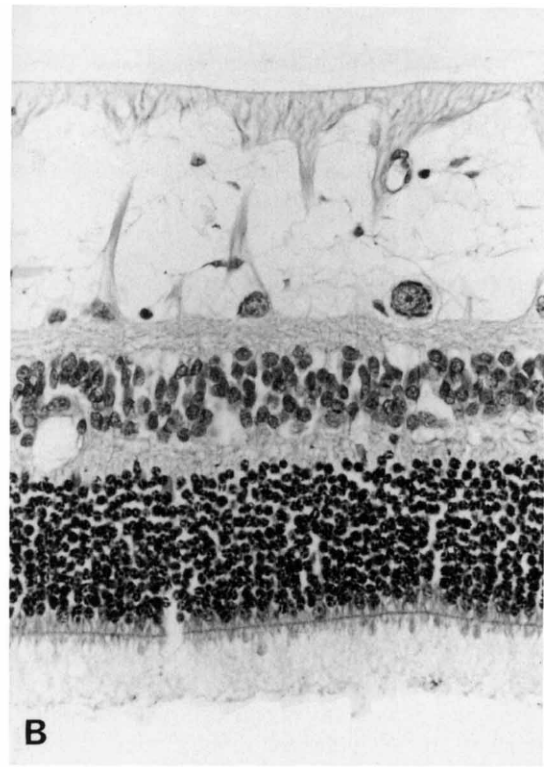

Fig. 4.50B Prolonged retinal separation with retinal edema and photoreceptor degeneration. Radial Müller's cell fibers anchor nerve fiber layer to ganglion cell layer. Retinal outer limiting membrane is prominent because of photoreceptor loss.

degeneration, hypertrophy and hyperplasia of pigmented epithelium, and the development of marked edema in inner nuclear, ganglion cell and inner plexiform layers (Figs. 4.49, 4.50A,B). **Hypertrophy** of the **retinal pigmented epithelium** is the most rapid change, occurring within a few hours after separation. The edematous changes are visible with the light microscope as early as 3 days following experimentally induced separation in owl monkeys. Coalescence of the edema creates a virtual cleavage of inner from outer retina, called **retinoschisis.** The cleavage is spanned by the radial Müller fibers, which seem the only anchor holding retina together. **Photoreceptor degeneration** is slower to appear under the light microscope, with loss of outer segments (probably the most subtle change that can be unequivocally diagnosed with routine light microscopy) visible by about 14 days. Inner segments and the cell bodies of the outer nuclear layer are almost unaffected and may remain so for months, suggesting that their maintenance is not so intimately linked to the pigment epithelium as is the case with the outer segments. This temporal hierarchy of change permits reasonably accurate aging of retinal separations, sometimes a necessary or at least interesting assessment in eyes enucleated after numerous clinical examinations or manipulation. The outer retinal lesions are apparently not ischemic, inasmuch as there is very little necrosis and no similarity to the lesion induced by retinal artery occlusion. Perhaps the outer layers can survive by diffusion of oxygen and nutrients from the subretinal fluid or from vascularized inner layers, and indeed the speed of photoreceptor atrophy varies with the height of the separation. An exception is seen in horses, inasmuch as the horse retina depends almost entirely on choroidal diffusion for oxygenation. Separation in this species results in rapid, full-thickness retinal infarction. A very frequent lesion in horses is focal, linear, or multifocal chorioretinal glial scarring with pigment migration and fibrous metaplasia of pigment epithelium, a lesion which is probably a healed infarct following traumatic separation or thromboembolic disease.

Bibliography

Aaberg, T. M., and Machemer, R. Correlation of naturally occurring detachments with long-term retinal detachment in the owl monkey. *Am J Ophthalmol* **69:** 640–650, 1970.

Anderson, D. H. *et al.* The onset of pigment epithelial proliferation after retinal detachment. *Invest Ophthalmol Vis Sci* **21:** 10–19, 1981.

Anderson, D. H. *et al.* Retinal detachment in the cat: The pigment epithelial–photoreceptor interface. *Invest Ophthalmol Vis Sci* **24:** 906–926, 1983.

Anderson, D. H. *et al.* Morphological recovery in the reattached retinal. *Invest Ophthalmol Vis Sci* **27:** 168–183, 1986.

Erickson, P. A. *et al.* Retinal detachment in the cat: The outer

nuclear and outer plexiform layers. *Invest Ophthalmol Vis Sci* **24:** 927–942, 1983.

Machemer, R. Experimental retinal detachment in the owl monkey. II. Histology of retina and pigment epithelium. *Am J Ophthalmol* **66:** 396–410, 1968.

Machemer, R., and Lagua, H. Pigment epithelium proliferation in retinal detachment (massive periretinal proliferation). *Am J Ophthalmol* **80:** 1–23, 1975.

B. Retinal Degeneration

Retinal degeneration, more commonly called retinal atrophy, may result from senile change, nutritional deficiency, metabolic disorder, or injury caused by infectious, chemical, or physical agents. With the exception of the previously described glaucomatous retinal atrophy, virtually all are initially degenerations of photoreceptor outer segments or of retinal pigmented epithelium, and many retinal atrophies of different pathogenesis have similar histologic appearance. The similarities become even stronger as the lesions progress to the severity usually encountered in enucleated eyes from clinically affected animals. Nonetheless, it is useful to review the subject and to discuss the differences between some of the best-studied examples of naturally occurring retinal atrophies. Most frequent are the inherited retinopathies of dogs, grouped under the name **progressive retinal atrophy.** Less common are retinal degenerations caused by deficiencies of taurine, vitamin E, or vitamin A, by excessive visible light, or by several toxic or metabolic diseases.

1. Inherited Retinal Atrophies in Dogs

Progressive retinal atrophy describes, admittedly with some inaccuracies, a large group of bilateral retinal diseases in dogs. They share the clinical features of being bilateral, progressing to blindness and being unassociated with inflammatory or other ocular disease. More than 100 breeds have been identified as affected, although there is little published information as to the prevalence within various breeds. All thus far studied are inherited as an autosomal recessive trait. Some are juvenile onset degenerations that result from a congenital biochemical defect and are thus properly termed **photoreceptor dysplasias.** Photoreceptors never reach proper ultrastructural or physiologic maturity, and affected dogs may be blind by a year or two of age. Irish setters, collies, Norwegian elkhounds, and miniature schnauzers are the best-studied breeds that are affected, each with slightly different clinical expression and biochemical abnormality. Some initially affect only rods, but most affect both rods and cones. Alaskan malamute dogs have what seems to be a purely cone dysplasia, leaving dogs visually impaired in daylight but with good night (i.e., rod-dependent) vision.

A quite separate group of diseases are currently considered to be true degenerations, in that photoreceptor development seems normal. It may be, however, that even these inherited atrophies will be shown to have a developmental biochemical defect. The trend to date has been to reclassify more and more degenerations as dysplasias, in parallel with the use of more sensitive investigative techniques.

All of these different diseases may have significant differences in pathogenesis, but by the time the eyes are removed from impaired or totally blind dogs, the histologic and ultrastructural lesions are similar. At this stage, the old name of **progressive retinal atrophy** continues to be used as a catch-all. The light-microscopic lesion is degeneration of photoreceptors beginning dorsolateral to the optic disk. Over months or years the photoreceptor loss extends, and there is secondary atrophy of nuclear and plexiform layers of retina (Fig. 4.51). Eventually, in dogs permitted to live long enough, the retina remains as a poorly cellular glial scar. Despite the many similarities in clinical and histologic features, the importance of these retinopathies in the study of retinal disease in general warrants some more-detailed explanation of the best-described variants.

Retinal atrophy in Irish setters is described as rod–cone dysplasia, inherited as a simple autosomal recessive trait. Dogs homozygous for the defect have arrested differentiation of the rod external segments. Cones are less affected. The defect is detected ultrastructurally as early as 16 days after birth, at which time in the normal retina, the outer rod segments should be developing adjacent to the pigment epithelium. Arrested development is followed by degeneration of inner rod segments, so that there is diffuse loss of all rod photoreceptors by 12 weeks of age. This is followed by loss of cones and of outer nuclear layer. By the time

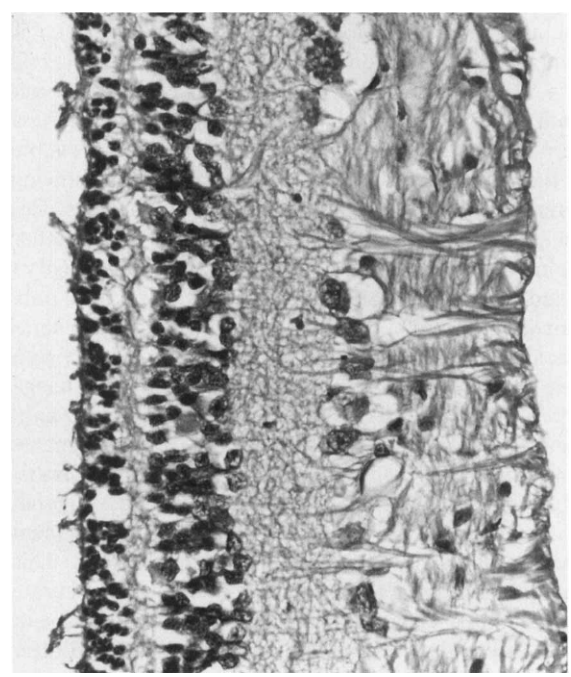

Fig. 4.51 Progressive retinal atrophy. English cocker spaniel. Diffuse atrophy of photoreceptors and outer nuclear layer.

the dog is about 1 year of age, there is diffuse atrophy of the outer nuclear layer, and the inner nuclear layer is in direct contact with the pigment epithelium. The inner retinal layers are unaffected. Dogs show visual deficits in dim light as early as 6 weeks of age and are usually blind by 1 year. The biochemical defect is a marked deficiency of the phosphodiesterase responsible for the continuous hydrolysis of cyclic guanine monophosphate within outer segments. While the function of the enzyme in this site is not fully understood, the resultant excess of cyclic guanine monophosphate (cGMP) is toxic to photoreceptors *in vitro*, and is known to cause arrested development or degeneration of rod outer segments *in vivo*. In the Irish setter, the substrate levels are about 10 times higher in affected than in control dogs, and the elevation precedes morphologic change in the photoreceptors. There are other biochemical retinal abnormalities (in rhodopsin and in membrane lipids), but it is not known whether they are primary abnormalities or merely effects of the cGMP phosphodiesterase deficiency. The basic defect is in the gene encoding the outer segment-specific phosphodiesterase.

Rough collies have a very similar rod–cone dysplasia, also inherited as an autosomal recessive tract. The progression of the lesion is slightly slower than that in Irish setters, but the biochemical defects are virtually identical. In neither instance is it clear how photoreceptor death leads to death of all the outer nuclear layer neurons.

Retinal atrophy in Norwegian elkhounds resembles that of the Irish setter in most respects. Onset of visual deficits in dim light is early, progression to blindness is only slightly less rapid, and the histologic retinal lesion in blind dogs is almost identical to that in setters. Ultrastructurally and biochemically, however, the two diseases are distinct. In elkhounds the primary lesion is restricted to rods and is not associated with elevated cGMP. The rods are not halted in their development but develop imperfectly. There is disorientation of lamellar disks and eventual disintegration. Light microscopic lesions appear at about 6 months of age and progress to complete photoreceptor loss by 1 to 2 years. Atrophy progresses to affect outer nuclear, outer plexiform, and inner nuclear layers. Eventually the retina, as in any of the canine familial retinopathies, may remain only as a thin glial scar with disorganized neuronal clumps. A second type of rod–cone dysplasia exists in this breed, with rapid progression to blindness by 12 to 18 months of age. Photoreceptor growth is erratic and apparently uncoordinated, but there is also dysplasia of rod and cone axonal synaptic junctions in the outer plexiform layer, which results in greatly reduced transmission of impulses from the photoreceptors.

Retinal atrophy in miniature poodles is classified as a true degeneration, in that photoreceptor differentiation seems to be normal until 6 to 9 weeks of age. After this time, and progressing at an unpredictable rate, there is disk disorganization and plasma membrane fragmentation in rod outer segments, visible as early as 15 weeks of age in the retina adjacent to the optic nerve. Peripheral retina is unaffected at this early stage, but by several years of age, the entire retina is affected. Cones are affected in a similar but milder fashion later in the disease course. The reason for the fragmentation is unknown, but it is known that affected dogs have abnormally slow outer segment turnover (about 40% of normal) prior to any observed structural change. Affected poodles have evidence for decreased rate of incorporation of docosahexanoic acid, the major long-chain structural membrane fatty acid, into rod outer segments. It may be that the decreased disk turnover permits older membranes to unduly persist and to be peroxidatively damaged *in situ*. The histologic lesion is identical to that of Irish setters or Norwegian elkhounds. Cataracts are present in many poodles with retinal atrophy. Because of wide variation in disease progression, dogs may not be noticed to have dim-light deficiencies until middle, or even old, age.

Retinal atrophy in Alaskan malamute dogs is a progressive cone dysplasia, inherited as a simple recessive trait. Although now rare because of elimination by selective breeding, it remains an interesting example of specific cone dysfunction. Affected dogs are noticed to have poor vision in bright light as early as 8 weeks of age. Night vision is, and remains, clinically normal, as does the ophthalmoscopic appearance of affected eyes. The ultrastructural lesion is disorganization and loss of cones, with rods normal. Adult dogs have no cone outer segments, and atrophic inner segments, but no change in rods or outer nuclear layer.

Central progressive retinal atrophy of dogs (pigmented epithelial dystrophy) denotes a peculiar lesion in retinal pigment epithelium of dogs that apparently results from defective intracellular phagocytosis of shed photoreceptor outer segments. Normal pigment epithelium engulfs and enzymatically degrades this material, resulting in a gradual buildup of intracellular lipopigments throughout life. In dogs with this pigment epithelial dystrophy, membrane peroxidation is excessive, and lipopigments accumulate to excess. Associated with the pigmentary accumulation, the epithelial cells hypertrophy. Photoreceptor outer segments adjacent to hypertrophic pigment epithelium degenerate. As the lesion progresses, hypertrophy and hyperplasia of epithelium give rise to dysplastic pigmented cell clumps. Within such clusters there may be an eosinophilic, hyaline, periodic acid-Schiff positive concretion resembling drusen. This material, rather frequent in ophthalmic specimens from humans with a variety of degenerative retinal or choroidal diseases, is a concretion of excess basal lamina produced by the pigment epithelium. The eventual histologic lesion in affected dogs is a monolayer of hypertrophic, lipochrome-rich pigment epithelial cells with multifocal hyperplastic clumps. Retina has atrophy of photoreceptors and outer nuclear layer, and some irregular gliosis. Pigment-laden cells may invade the retina.

The disease is sporadic and of unpredictable clinical

progression. The prevalence is, for example, much higher in Great Britain than in North America, where it is rare. Retrieving and herding dogs are most frequently affected. The ophthalmoscopic lesion of irregular black mottling begins near the optic disk and may progress to generalized pigment mottling interspersed with the increased reflectivity of atrophic retina. The mode of transmission is unknown. An interesting speculation, based on morphologic similarities, is that the disease represents a defect in vitamin E metabolism within pigment epithelium.

Sudden acquired retinal degeneration is an enigmatic, rapidly progressing photoreceptor degeneration that is histologically identical to the inherited progressive retinal atrophies. Blindness occurs very rapidly (over a period of a few days to a few weeks). Affected dogs are adult or even elderly, and the disease can affect any breed or crossbreed. The fundoscopic lesion is bilaterally symmetrical and diffuse across the retina, but histologic studies of the early lesions are very few. The cause is unknown, but the presence of the retinal disease is linked to systemic signs of polyuria, polydipsia, and elevated serum cholesterol and alkaline phosphatase. Some, but not even the majority, of the affected dogs have adrenal cortical hyperfunction. How this malfunction causes the irreversible retinopathy, if indeed it does, is unknown. One small study demonstrated circulating, complement-fixing antibody to retinal S-antigen and interphotoreceptor retinoid-binding protein, raising the possibility that the disease is a cytotoxic autoimmune phenomenon.

2. Inherited Retinopathies in Cats

Inherited retinal dysplasias and degenerations have been reported in a variety of cat breeds, but only in the Abyssinian breed has the syndrome been adequately studied. In this breed there are two different diseases: early-onset rod–cone dysplasia and late-onset retinal degeneration affecting rods much sooner than cones. The early-onset dysplasia is inherited as an autosomal dominant trait. It is histologically and ultrastructurally similar to the disease in Irish setter dogs, and a similar defect in the activity of cGMP phosphodiesterase has been reported. Affected cats are blind by a few months of age.

The late-onset retinal degeneration is inherited as an autosomal recessive, and affected cats progress slowly to blindness by 5 to 10 years of age. The earliest structural changes are in rod outer segments in peripheral retina, with jumbling of the rod disks and patchy blunting of the photoreceptors themselves. Only after many years is there histologically detected diffuse photoreceptor loss. A much more prevalent feline retinopathy, caused by a deficiency of dietary taurine, is discussed later.

3. Inherited Night Blindness in Horses

This poorly documented disease affects the Appaloosa breed and is probably inherited, and is seen as night blindness with daylight vision that is usually, but not always, normal. No structural lesion is seen in retinas of affected horses, and functional studies point to a defect in intraretinal synaptic transmission in outer plexiform or inner nuclear layers rather than a defect in photoreceptors.

Bibliography

Aguirre, G. Inherited retinal degeneration in the dog. *Trans Am Acad Ophthalmol Otolaryngol* **81:** 667–676, 1976.

Aguirre, G. D., and Rubin, L. F. Pathology of hemeralopia in the Alaskan malamute dog. *Invest Ophthalmol* **13:** 231–235, 1974.

Aguirre, G. D., and Rubin, L. F. Rod–cone dysplasia (progressive retinal atrophy) in Irish setters. *J Am Vet Med Assoc* **166:** 157–164, 1975.

Aguirre, G. *et al.* Rod-cone dysplasia in Irish setters: A defect in cyclic GMP metabolism in visual cells. *Science* **201:** 1133–1134, 1978.

Barnett, K. C. Canine retinopathies—I. History and review of the literature. *J Small Anim Pract* **6:** 41–55, 1965.

Buyukmihci, N., Aguirre, G., and Marshall, M. Retinal degenerations in the dog. II. Development of the retina in rod–cone dysplasia. *Exp Eye Res* **30:** 575–591, 1980.

Chader, G. J. Animal mutants of hereditary retinal degeneration: General considerations and studies on defects in cyclic nucleotide metabolism. *Prog Vet Comp Ophthalmol* **1:** 109–126, 1991.

Cogan, D. G., and Kuwabara, T. Photoreceptive abiotrophy of the retina in the elkhound. *Pathol Vet* **2:** 101–128, 1965.

Goldman, A. I., and O'Brien, P. J. Phagocytosis in the retinal pigment epithelium of the RCS rat. *Science* **201:** 1023–1025, 1978.

Liu, Y. P. *et al.* Involvement of cyclic GMP phosphodiesterase activator in an hereditary retinal degeneration. *Nature* **280:** 62–64, 1979.

Lolley, R. N., and Farber, D. B. A proposed link between debris accumulation, guanosine 3′-5′ cyclic monophosphate changes and photoreceptor cell degeneration in retinas of RCS rats. *Exp Eye Res* **22:** 477–486, 1976.

Millichamp, N. J. Retinal degeneration in the dog and cat. *Vet Clin North Am: Small Anim Pract* **20:** 799–836, 1990.

Parry, H. B. Degeneration of the dog retina. VI. Central progressive atrophy with pigment epithelial dystrophy. *Br J Ophthalmol* **38:** 653–668, 1954.

West-Hyde, L., and Buyukmihci, N. Photoreceptor degeneration in a family of cats. *J Am Vet Med Assoc* **181:** 243–247, 1982.

Witzel, D. A. *et al.* Night blindness in the Appaloosa: Sibling occurrence. *J Am Anim Hosp Assoc* **13:** 383–386, 1977.

4. Light-Induced Retinal Degeneration

Light of various wavelengths has a variety of injurious effects on cornea, lens, or retina that vary with the wavelength, duration, and intensity of the light. The effects also vary with a large but poorly understood group of animal variables that include ocular pigmentation, habitat, previous experience with photoperiod, nutrition, body temperature, age and, most obviously, species. The wavelength of light has the greatest effect; short wavelengths in the ultraviolet and blue range (up to about 475 nm) have the greatest energy per photon and are the most damaging. Fortunately, most of these wavelengths are absorbed by cornea and lens, so that their lethal effects on retina are seldom seen. They may cause corneal epithelial injury or cataract, although these effects are apparently rare in domestic animals (see Section V,B, Cataract).

In humans, accidental exposure to light from arc weld-

ing, solar eclipses, or ophthalmic examination or operating equipment (including lasers) creates the potential for rapid injury from mechanical disruption or heat. Although such damage is certainly possible in other animals, most naturally occurring lesions result from the additive effects of much less intense ultraviolet and short-wavelength visible light because of unnatural photoperiods. Animals with poorly pigmented eyes, and those adapted for nocturnal vision, are most susceptible. Susceptibility also increases with age and with temperature.

The initial lesion is disruption of rod outer-segment disks, with eventual destruction of all photoreceptors and their nuclei. Because the lesion is identical to most inherited, nutritional, and toxic retinopathies, the diagnosis is made on the circumstantial evidence of abnormally bright light, abnormally long light photoperiod, or a rapid change in photoperiod. Most instances occur with rodents or fish kept in continuous fluorescent light. Albino rodents or deepwater fish are, predictably, the most susceptible.

The mechanism by which visible light of moderate intensity damages the retina is still incompletely understood, and different experimental models give rise to different theories. Most studies use blue light in the 400- to 475-nm range which, unlike shorter ultraviolet wavelengths, is not filtered out by cornea or lens. The most popular theory is that of light-induced oxidation of the very abundant polyunsaturated long-chain fatty acids of the rod disks, with the generation of free radicals to then cause cell membrane damage. This theory gains support from studies showing a protective effect by vitamin C or E, and enhanced injury under conditions of retinal hyperoxia.

5. Nutritional Retinopathy

Nutritional causes of retinal degeneration include deficiencies of vitamins C, A, or E, and the amino acid, taurine. Retinal atrophy and cataracts have been seen in fish with a dietary deficiency of vitamin C. The lesions were thought to be light induced, with the fish unusually susceptible because of the deficiency in the antioxidant effects of the vitamin. The ocular lesions of vitamin E deficiency resemble those of retinal pigment epithelial dystrophy and were referred to briefly under that heading. Pups fed severely deficient diets develop night blindness within about 6 weeks, and an extinguished electroretinogram suggestive of diffuse photoreceptor damage. These last two effects are not seen in naturally occurring central retinal atrophy. Retinopathy has been described only in primates and dogs fed rations deliberately and severely deficient in vitamin E. Lipofuscin, seen as eosinophilic cytoplasmic inclusions, accumulated to excess in the pigment epithelium, and was followed by hypertrophy of the pigment epithelium and degeneration of photoreceptor outer segments. Eventually there were full-thickness central retinal atrophy and some small foci of retinal separation.

a. HYPOVITAMINOSIS A Retinopathy caused by hypovitaminosis A is seldom encountered except in growing cattle or swine kept in confinement and fed a ration deficient in the vitamin over months or years. Grains other than corn (maize) are very poor sources of vitamin A, and the level in corn falls markedly with prolonged storage. Green pasture is very rich in carotene, which is converted to vitamin A by intestinal epithelium. Hay that is excessively dry, leached by rain, cut late in the year, or stored for prolonged periods is a much less adequate source, but in most pastured animals the liver reserves are sufficient to prevent clinical signs of deficiency for at least 6 months and often up to 2 years. Young, rapidly growing animals have greater requirements and smaller stores of the vitamin and are thus more susceptible than adults.

Hypovitaminosis A affects bone remodeling and causes epithelial cell atrophy and defects in synthesis of rhodopsin. Ocular lesions can result from each of these three defects.

As previously discussed, maternal deficiency of vitamin A causes blindness in offspring due to defective remodeling of optic nerve foraminae and subsequent ischemic or pressure atrophy of the nerve. In piglets, there may be massive ocular dysplasia and such anomalies as cleft palate, skeletal deformities, hydrocephalus, epidermal cysts, genital hypoplasia, and anomalous hearts. Optic nerve atrophy is preceded by optic disk swelling (papilledema) and followed by atrophy of nerve fiber and ganglion cell layers. This sequence of events may occur if very young animals are on deficient diets, with the optic nerve changes being caused in part by stenosis of optic foramen and in part by increased cerebrospinal fluid pressure that itself results from atrophy and metaplasia of arachnoid villi. The papilledema precedes optic nerve necrosis and is reversible. The corneal lesions of hypovitaminosis A have received scant attention and are seldom seen in natural outbreaks.

The acquired ocular effect of hypovitaminosis A involves photoreceptor outer segments. The ophthalmoscopic lesion is multifocal retinal atrophy and scarring in animals with slow or absent pupillary light reflex and apparent blindness. The histologic lesion is patchy-to-diffuse photoreceptor atrophy, which first affects the rod outer segments. Night blindness is thus the initial complaint and is often the chief complaint about a deficient herd. Eventually the atrophy affects all photoreceptors and their nuclei, and may progress to full-thickness atrophy with scarring. The lesions have been produced in all domestic species on specially formulated diets, but naturally occurring retinal lesions are almost restricted to cattle with chronic deficiencies.

The pathogenesis of the photoreceptor atrophy demonstrates the structure:function interdependence of retinal cells. Vitamin A is converted to retinene and then to the glycoprotein rhodopsin. Rhodopsin is stored as a component of the lamellar disks of the outer segment. Light initiates a physicochemical change in rhodopsin, resulting in a cascade of events culminating in the hyperpolarization of the outer segment membrane. The resultant electrical impulse is transmitted to bipolar cells, ganglion cells, and then to brain. The deficiency of vitamin A necessarily

results in a deficiency of rhodopsin. The corresponding ultrastructural lesion is swelling, then fragmentation of lamellar disks that can be reversed by therapy with vitamin A unless inner segments have also been affected. Regeneration simulates normal development and requires about 2 weeks to rebuild outer segments completely. Vitamin A is discussed further with Bones and Joints in Chapter 1.

b. TAURINE-DEFICIENCY RETINOPATHY Retinal degeneration caused by taurine deficiency is seen only in cats, although taurine is the predominant free amino acid in the retina of other species. Among domestic mammals, only the cat seems unable to synthesize taurine from cysteine in amounts adequate for retinal function. Taurine is considered a dietary essential for cats, and its deficiency results in a characteristic central retinal atrophy and in cardiomyopathy (see Volume 3, Chapter 1, The Cardiovascular System).

The ocular lesion of taurine deficiency was first detected in cats fed semipurified diets in which casein was the only protein. After several months, such cats developed focal retinal atrophy adjacent to the optic disk, which progressed to generalized retinal atrophy. Supplementation with taurine halted but did not reverse the lesion, presumably because photoreceptor nuclei or inner segments already had been damaged. The naturally occurring disease of cats, called **feline central retinal degeneration,** is described in a variety of breeds. The lesion is bilateral, dorsolateral to the optic disk, and is usually unassociated with visual impairment. The histologic lesion is photoreceptor degeneration, initially targeting cone outer segments but eventually affecting rods as well. The rods of the peripheral retina are the last to degenerate. Taurine also seems essential for membrane integrity of the tapetal reflective rodlets, so that dissolution of the membrane surrounding these crystalline intracytoplasmic inclusions is another characteristic lesion. Some of the cases of idiopathic central atrophy are associated with the feeding of dry dog food, which is low in taurine. Most, if not all, examples of feline central retinal atrophy are probably due to taurine deficiency.

Less clear is the association of taurine deficiency with diffuse retinal atrophy in cats (Fig. 4.52). Familial atrophy occurs in Abyssinian and Persian cats, but most cases are of unknown cause. Continued deficiency of taurine leads to diffuse retinal atrophy and thus might be responsible. Many cases of central atrophy remain static for years, perhaps as the permanent scar of a temporary dietary deficiency.

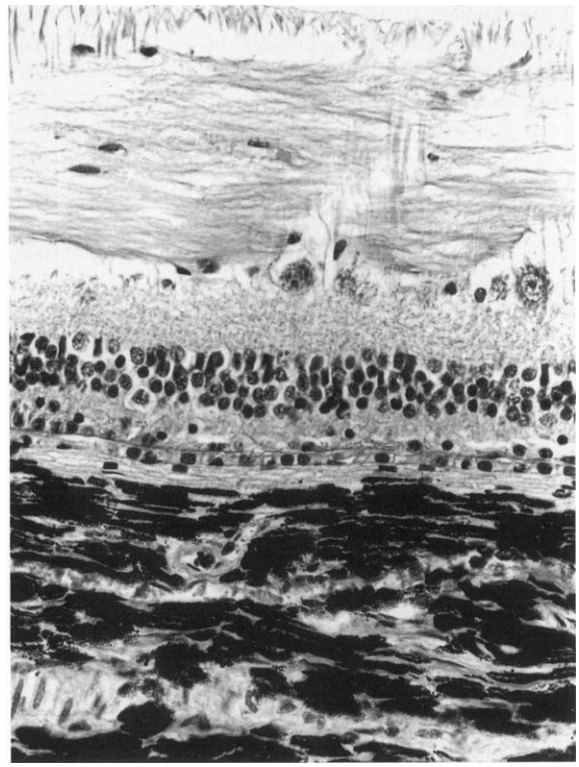

Fig. 4.52 Idiopathic diffuse retinal atrophy. Cat. Note complete atrophy of photoreceptors and depletion of outer nuclear layer.

6. Toxic Retinopathies

Experimental toxic retinopathies have been caused by many chemicals and toxic plants, but only a few toxic plants cause important diseases of domestic animals.

Bracken fern (*Pteridium aquilinum*) causes a progressive retinal degeneration in sheep in several areas of Great Britain. The common name bright blindness refers to pupillary dilation and tapetal hyperreflectivity of the severely affected sheep. The disease has been seen only in flocks grazing hills rich in bracken fern, and has been reproduced by prolonged feeding of the fern to sheep. A similar syndrome has been noted in cattle during long-term exposure to the fern. The lesion is usually seen in middle-aged or older sheep as bilateral and initially central tapetal hyperreflectivity. Diffuse involvement follows. The histologic lesion is nonspecific, consisting of photoreceptor outer segment degeneration progressing to depletion of all retinal layers.

Blindness is one of the features of intoxication with **locoweed,** *Astragalus* and *Oxytropis* spp., in the United States of America, darling pea, *Swainsona* spp., and blind grass, *Stypandra* spp. in Australia, and selenium indicator plants worldwide.

Astragalus and *Swainsona* cause a neurovisceral lysosomal storage disease analogous to genetically transmitted mannosidosis (see Chapter 3, The Nervous System). All members of the genus *Swainsona* contain an indolizidine alkaloid, swainsonine, that is a potent inhibitor of lysosomal mannosidase. At least some *Astragalus* spp. contain a similar alkaloid. Chronic ingestion of the plant occurs in cattle, sheep, and horses forced to eat the plants on dry pastures where nothing more palatable is available. Affected animals develop behavioral abnormalities and defects of gait and vision. The histologic lesion consists of widespread cytoplasmic vacuolation in most organs due

to the intralysosomal accumulation of mannose-rich oligosaccharides. Onset of clinical signs may require several months of heavy *Swainsona* ingestion, but ultrastructural vacuolation is seen within a few days. The ocular lesion is, as elsewhere in the central nervous system, vacuolation of neuronal cytoplasm and, later, axonal degeneration. The vacuolation is readily reversible on cessation of ingestion of the plant and seems not to be the lesion responsible for clinical signs. The axonal degeneration is not reversible and is probably the more important lesion. Whether blindness is retinal or central in origin is unknown.

Poisoning with *Stypandra* spp. occurs in sheep and goats on dry pastures in southwestern Australia. The plant is among the first to reappear after autumn rains end the drought, and is eaten if nothing better is available. Acute intoxication is frequently fatal. Animals surviving the acute stage become blind and ataxic. In retina there is diffuse photoreceptor atrophy and patchy hyperplasia of retinal pigment epithelium. Axonal degeneration is found within the optic nerve and elsewhere within the central nervous system.

The colloquial term blind staggers refers to chronic intoxication of sheep and cattle with plants known to accumulate organic selenium selectively. Affected animals wander aimlessly, become weak and ataxic and are finally paralyzed prior to death. There is some question as to whether blindness is genuine or merely the result of stupor. Ocular lesions are not described. The syndrome of blind staggers does not occur in experimental selenium toxicity, and it is possible that the syndrome is of much more complex pathogenesis than simple selenium toxicity. Plants of the genera *Astragalus* and *Oxytropis* are selenium accumulators as well as sources of swainsoninelike alkaloids.

7. Miscellaneous Retinopathies

Retinal lesions are found in a number of metabolic disorders and systemic states. Best known among these is diabetes mellitus, but retinal lesions are found also in any of the neuronal storage diseases, coagulation disorders, anemia, disseminated intravascular coagulation, hyperviscosity syndrome, and hypertension, and following excessive exposure to oxygen or light.

Diabetes mellitus is the major cause of blindness in humans in North America. The cause of the blindness is chorioretinal vascular disease with subsequent retinal degeneration. The characteristic lesions are seen only in patients with diabetes of 10 to 15 years' duration. Even though virtually all chronic diabetics develop some retinal lesions, less than 10% become blind. Blindness is strongly predictive of the development of fatal diabetic nephropathy. Lesion development is not prevented by insulin replacement. Other ocular lesions include cataract, rubeosis iridis, and glycogen-induced vacuolation of iris epithelium and massive thickening of the ciliary basal lamina. The corneal epithelium may be unduly fragile, and tear production may be reduced.

The retinal lesion in humans is mostly the result of microvascular disease. Loss of retinal pericytes, development of microaneurysms, thickening of capillary basal lamina, and retinal hemorrhages constitute the early, degenerative phase of the retinopathy. This is followed by a proliferative phase in which more capillary aneurysms, arteriolar–venular shunts, and neovascularization occur as the presumed responses to retinal ischemia. The neovascularization is initially bland and confined to retina, but later there is extension into preretinal vitreous with accompanying fibroplasia (retinitis proliferans). Hemorrhages and hyalinized collections of leaked plasma are common in the retina.

In nonprimates, the naturally occurring retinopathy is seen only in dogs and, even then, infrequently. This low frequency may be due to the fact that affected dogs do not live long enough for the retinal disease to develop. In dogs deliberately made diabetic and kept for up to 6 years, microvascular lesions typical of human diabetes occur. Pericyte loss is accompanied by capillary aneurysms, reactive endothelial proliferation, and perivascular plasmoid exudates or hemorrhages.

Retinal hemorrhages are seen in a variety of primary clotting disorders, in thrombocytopenia of any cause, and in degenerative or inflammatory vascular disorders. Massive hemorrhage may occur from completely separated retinas. The best-known examples in veterinary medicine are multifocal hemorrhage from vessels damaged in the course of thrombotic meningoencephalitis of cattle, and with Rocky Mountain spotted fever or ehrlichiosis of dogs. Apparently unique to cats is multifocal retinal hemorrhage observed in severe anemia. The lesions heal with scarring if the cat survives the anemia, suggesting that the hemorrhage is only the most visible manifestation of multifocal and probably ischemic retinopathy. Similar retinal atrophy, but without hemorrhage, has been seen in horses following massive but sublethal blood loss as in surgery or from nasal hemorrhage subsequent to severe cranial trauma. Affected eyes have multifocal retinal atrophy and hyperpigmentation. Similar lesions may also result from focal retinal separation (which causes infarction in horses), or from thromboembolic consequences of bacteremia. Retinal hemorrhage, and sometimes retinal infarcts, occur in an unknown percentage of animals with disseminated intravascular coagulation of any pathogenesis. Horses seem particularly susceptible, perhaps because of their poorly vascularized retina (Fig. 4.53). Rarely, retinal infarcts are caused by neoplastic emboli.

Senile retinopathy is characterized by microcystoid degeneration, which is very common in dogs from middle age onward (Fig. 4.47B). A similar lesion is found occasionally in horses. The lesion affects peripheral retina adjacent to ora ciliaris and for a variable distance medially. There is formation of small cystic spaces within inner nuclear and plexiform layers, fusion of inner and outer nuclear layers, pigment cell accumulation and haphazard atrophy and mingling of nuclei in a manner simulating peripheral retinal dysplasia. If the cysts rupture to the vitreal face, the retina external to the cyst is seen as an

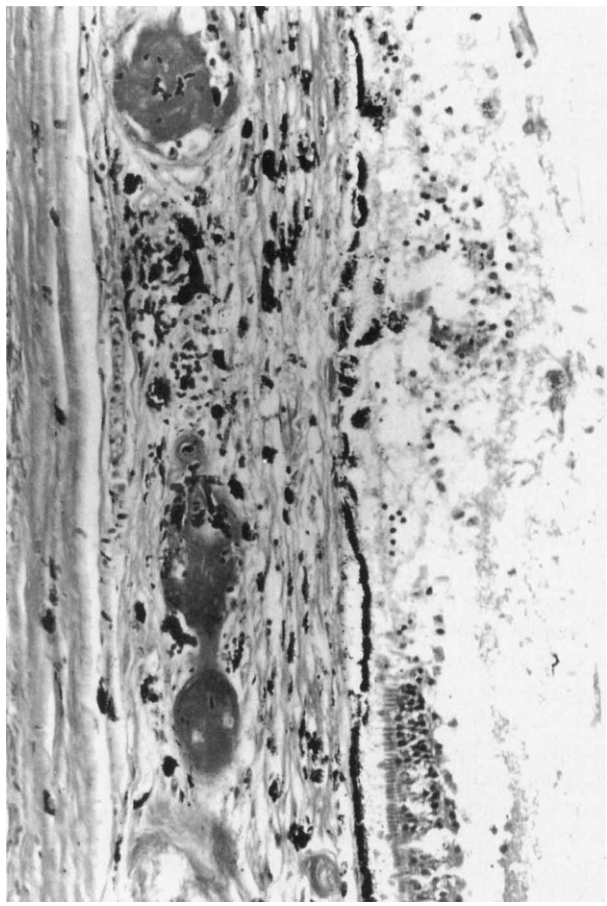

Fig. 4.53 Choroidal thrombosis and vasculitis. Horse. Idiopathic purpura hemorrhagica. Note infarction of adjacent retina.

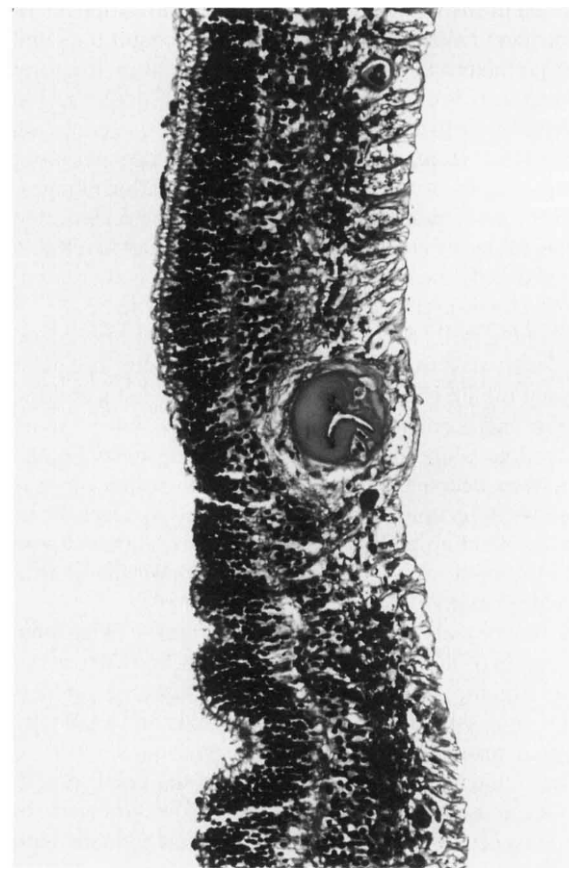

Fig. 4.54 Hypertensive retinopathy, dog. Hyalinized, thick-walled retinal arteriole and focal retinal degeneration.

atrophic hole. Such holes are foci of extreme retinal thinning, so that only the external limiting membrane separates vitreous from pigment epithelium. The pigment epithelium and choroid are usually normal, but they too may show atrophy and fibrosis. Intermingling of cysts and holes in peripheral retina is common. Complete breaks are uncommon and do not usually lead to retinal separation as occurs in humans.

Multifocal coalescing peripheral retinal atrophy is very frequent in very old dogs and horses, and is of no apparent visual importance.

Hypertensive retinopathy is in most cases associated with chronic renal failure. At least 60% of dogs with chronic renal failure are hypertensive. Dogs and cats are most frequently affected.

The macroscopic ocular lesions include retinal or preretinal hemorrhage, retinal edema, and retinal detachment. The histologic lesions are primarily in retinal and choroidal vessels, which have lesions varying from fibrinoid necrosis of tunica media to medial hypertrophy with adventitial fibrosis. Changes that are probably secondary to vessel damage include localized retinal necrosis, exudative retinal separation with resultant atrophy of photoreceptors and hypertrophy of retinal pigmented epithelium, and intraretinal hemosiderin deposition (Fig. 4.54). Vascular lesions and associated necrosis may also occur in anterior uvea. Eyes that are eventually enucleated or obtained at necropsy may have a variety of other lesions that probably occur secondary to chronic retinal detachment and chronic intraocular hemorrhage. Most notable among these is preiridal fibrovascular membrane and its resultant hyphema or neovascular glaucoma.

The early lesions, likely to be seen only under experimental conditions, are the result of exaggerated autoregulatory vasoconstriction in response to the systemic hypertension. Sustained vasoconstriction leads to ischemic necrosis of the deprived retina or choroid, as well as necrosis of vascular endothelium distal to the constricted precapillary sphincters. The histologic consequences are focal retinal necrosis, and leakage of plasma or even erythrocytes through damaged endothelium. This leakage causes intramural fibrinoid change in the vessels and edema or hemorrhage in adjacent retina.

Many of the neuronal storage diseases cause retinal lesions identical to those in the brain. The list of those with described ocular lesions probably reflects those in which the eyes have been examined rather than a true

reflection of those diseases in which ocular lesions do, or do not, occur. Those interested should consult a useful, referenced table in the text by Slatter.

Bibliography

Aguirre, G. D. Retinal degeneration associated with the feeding of dog food to cats. *J Am Vet Med Assoc* **172:** 791–796, 1978.

Andersen, A. C., and Hart, G. H. Histological changes in the retina of the vitamin A-deficient horse. *Am J Vet Res* **4:** 307–317, 1943.

Bellhorn, R. W., Aguirre, G. D., and Bellhorn, M. B. Feline central retinal degeneration. *Invest Ophthalmol* **13:** 608–616, 1974.

Bradley, R., Terlecki, S., and Clegg, F. G. The pathology of a retinal degeneration in Friesian cows. *J Comp Pathol* **92:** 69–83, 1982.

Dorling, P. R., Huxtable, C. R., and Vogel, P. Lysosomal storage in *Swainsona* spp. toxicosis: An induced mannosidosis. *Neuropathol Appl Neurobiol* **4:** 285–295, 1978.

Gwin, R. M. *et al.* Hypertensive retinopathy associated with hypothyroidism, hypercholesterolemia, and renal failure in a dog. *J Am Anim Hosp Assoc* **14:** 200–209, 1978.

Ham, W. T. *et al.* The nature of retinal radiation damage: Dependence on wavelength, power level, and exposure time. *Vision Res* **20:** 1105–1111, 1980.

Hayes, K. C., Carey, R. E., and Schmidt, S. Y. Retinal degeneration associated with taurine deficiency in the cat. *Science* **188:** 949–951, 1975.

Huxtable, C. R., and Dorling, P. R. Swainsonine-induced mannosidosis. *Am J Pathol* **107:** 124–126, 1982.

Kremer, I. *et al.* Oxygen-induced retinopathy in newborn kittens. *Invest Ophthalmol Vis Sci* **28:** 126–130, 1987.

Lanum, J. The damaging effects of light on the retina. Empirical findings, theoretical and practical implications. *Surv Ophthalmol* **22:** 221–249, 1978.

Lerman, S. Light-induced changes in ocular tissues. *In* "Clinical Light Damage to the Eye" D. Miller (ed.), Chapter 10, pp. 183–215. New York, Springer-Verlag, 1987.

Michels, M., and Sternberg, P., Jr. Operating microscope-induced retinal phototoxicity: Pathophysiology, clinical manifestations, and prevention. *Surv Ophthalmol* **34:** 237–252, 1990.

Noell, W. K. Possible mechanisms of photoreceptor damage by light in mammalian eyes. *Vision Res* **20:** 1163–1171, 1980.

Riis, R. C. *et al.* Vitamin E deficiency retinopathy in dogs. *Am J Vet Res* **42:** 74–86, 1981.

Schaller, J. P. *et al.* Induction of retinal degeneration in cats by methylnitrosourea and ketamine hydrochloride. *Vet Pathol* **18:** 239–247, 1981.

Schmidt, S. Y., Berson, E. L., and Hayes, K. C. Retinal degeneration in cats fed casein. I. Taurine deficiency. *Invest Ophthalmol* **15:** 47–52, 1976.

Slatter, D. "Fundamentals of Veterinary Ophthalmology," 2nd Ed., Philadelphia, Pennsylvania, W. B. Saunders, 1990.

Toole, D. O., Miller, G. K., and Hazel, S. Bilateral retinal microangiopathy in a dog with diabetes mellitus and hypoadrenocorticism. *Vet Pathol* **21:** 120–121, 1984.

Tulsiani, D. R. P., Harris, T. M., and Touster, O. Swainsonine inhibits the biosynthesis of complex glycoproteins by inhibition of Golgi mannosidase II. *J Biol Chem* **257:** 7936–7939, 1982.

Van Donkersgoed, J., and Clark, E. G. Blindness caused by hypovitaminosis A in feedlot cattle. *Can Vet J* **29:** 925–927, 1988.

Van Kampen, K. R., and James, L. R. Ophthalmic lesions in locoweed poisoning of cattle, sheep, and horses. *Am J Vet Res* **32:** 1293–1295, 1971.

Zuclich, J. A. Ultraviolet induced damage in the primate cornea and retina. *Curr Eye Res* **3:** 27–34, 1984.

C. Retinitis

Retinitis as the sole ocular lesion is rare but may occur in animals with neurotropic virus infections, with toxoplasmosis, and with thrombotic meningoencephalitis of cattle (Fig. 4.55). In the latter disease, however, it is more usual to find the typical thrombotic, inflammatory lesions in choroid as well as retina. Their character is identical to the lesions in the brain. The multifocal chorioretinal scars expected as sequelae are seldom seen, perhaps because cattle with neurologic and ocular lesions almost inevitably die. The prevalence of the ocular lesion, useful as an aid in the clinical diagnosis, is estimated at 30 to 50% in animals with the septicemic form of the disease, and as high as 65% in experimentally infected calves.

Multifocal viral retinitis with the same histologic features as the respective brain lesions occurs in animals with scrapie, hog cholera, rabies, Teschen disease, Borna disease, pseudorabies in pigs, and canine distemper. Undoubtedly the list is incomplete. The ocular lesions associated with canine distemper will be described here because

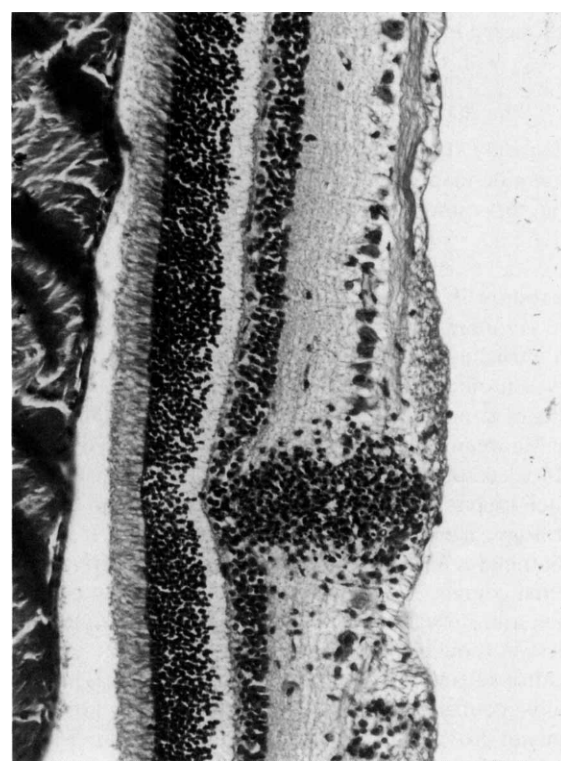

Fig. 4.55 Focal destructive retinitis. *Haemophilus somnus.* Steer.

it is a classic example of inflammatory and postinflammatory retinopathy of viral etiology; canine distemper is discussed with the Respiratory System (Volume 2, Chapter 6).

1. Canine Distemper

Retinal and optic nerve lesions occur in most dogs with naturally occurring distemper. The lesions most often are degenerative rather than inflammatory, although some of the degenerative changes may have been sites of inflammation earlier in the disease course.

Acute lymphocytic–plasmacytic chorioretinitis and optic neuritis are found in about 25% of dogs submitted for laboratory confirmation of the disease. Random perivascular cuffing, edema, focal exudative retinal separation, and hypertrophy of retinal pigment epithelium are present. Eosinophilic intranuclear inclusion bodies occur in ganglion cells or astrocytes in 30 to 40% of the cases, which is the only etiologically specific change in what is an otherwise nonspecific picture shared by many systemic infections.

The more prevalent lesions are multiple random foci of retinal degeneration and scarring. These usually affect the full thickness of retina and are most likely sequelae to the previous undetected retinitis. Such foci often contain numerous melanin-laden cells, probably derived from migration of adjacent, injured retinal pigment epithelium. Occasionally only the outer nuclear layer and photoreceptors are missing, probably a sequel to focal exudative retinal detachment.

Optic nerve lesions of one type or another are present in all dogs with ocular lesions. Nonsuppurative neuritis, astrocytic scarring, and demyelination similar to that in brain are the three most frequent changes. In those dogs suffering only the demyelinating disease, the ocular lesions may be inapparent, or there may be demyelination of optic nerve and ganglion cell degeneration.

2. Tick-Transmitted Infections

Infection with the tick-transmitted rickettsial agents of Rocky Mountain spotted fever (*Rickettsia rickettsii*) or canine ehrlichiosis (*Ehrlichia canis*) cause ocular lesions in dogs. The clinical and histologic ocular lesions are virtually identical and occur in a high percentage (80% for Rocky Mountain spotted fever) of dogs with active infection. Most of the lesions result from injury to vascular endothelium parasitized by the rickettsiae, and multifocal hemorrhage, edema, and vascular necrosis occur in all parts of the eye. Multifocal retinal hemorrhage, perivascular retinal edema, and necrosis of endothelium in retinal venules and arterioles are the characteristic retinal changes. Although often listed along with other agents as a cause of anterior uveitis or endophthalmitis, most naturally occurring infections have clinical signs attributable only to the vascular injury rather than a genuine uveal inflammation. There is one report of unusually severe uveitis occurring 14–28 days after experimental infection with *Rickettsia rickettsii*, following the disappearance of all other signs of the acute systemic disease. Dogs thus affected had a neutrophilic and lymphocytic destructive vasculitis, assumed to represent a type III immune reaction to parasitized endothelium.

Bibliography

Barnett, K. C., and Palmer, A. C. Retinopathy in sheep affected with natural scrapie. *Res Vet Sci* **12:** 383–385, 1971.

Davidson, M. G. *et al.* Ocular manifestations of Rocky Mountain spotted fever in dogs. *J Am Vet Med Assoc* **194:** 777–781, 1989.

Dukes, T. W. The ocular lesions in thromboembolic meningoencephalitis (ITEME) of cattle. *Can Vet J* **12:** 180–182, 1971.

Jubb, K. V., Saunders, L. Z., and Coates, H. V. The intraocular lesions of canine distemper. *J Comp Pathol* **67:** 21–29, 1957.

VIII. Optic Nerve

The optic nerve is a white fiber tract of brain formed by the outgrowth of ganglion cell axons from the eye through sievelike perforations in posterior polar sclera, called the **lamina cribrosa.** The axons travel within a preformed neurectodermal tube formed by the primary optic stalk to reach the optic chiasm and then the lateral geniculate body. The neurectoderm lining the optic stalk induces the surrounding mesenchyme to form the three meningeal layers, similar to and continuous with those of brain itself. Later differentiation of neurectoderm produces the astrocytes and oligodendroglia that, together with the ganglion cell, axons, and fibrovascular septa from pia mater, form the substance of the optic nerve. The optic disk is the intraocular portion of the nerve and is the only portion available to ophthalmoscopic examination. It is formed by the convergence of ganglion cell axons prior to their exit via the lamina cribrosa. The axons of the nerve fiber layer are unmyelinated, and at what point (relative to lamina cribrosa) the axons become myelinated determines the ophthalmoscopic appearance of the optic disk. Histologically, the disk is unmyelinated in most domestic species except the dog, contains abundant glia, and may have a small paracentral excavation—the physiologic cup—from which Bergmeister's papilla originates. A few pigmented cells are commonly seen, as are small neuroblastic clusters, both probably minor anomalies of retinal differentiation but of no significance.

There is considerable variation in the normal histology of the optic nerve among animals of different species and ages. Optic disk myelination has already been mentioned. The lamina cribrosa is formed by heavy fibrous trabeculae in horses, dogs, and cattle and is therefore more obvious than in cats and laboratory animals. Fibrous septa within the nerve are prominent in cattle and horses, and their similarity to the axons in hematoxylin and eosin sections may mask a pathologic paucity of nerve fibers. The fibrous tissue reportedly increases with age.

The general pathology of optic nerve shares features of both retinal and neural disease. Because it is in direct continuity with both structures via its axons, and with brain via the perineural cerebrospinal fluid, it is common

that optic nerve be affected by diseases of either retina or brain. Thus optic neuritis is expected in at least a proportion of animals suffering with inflammation of retina or neural white matter, and optic nerve atrophy inevitably follows loss of ganglion cells. Fortuitous hematogenous localization of infectious agents or tumor cells may occur in optic nerve as anywhere else.

Papilledema is hydropic swelling of the optic disk. It may result from extraocular events that cause an increase in cerebrospinal fluid pressure within the optic nerve or from local vascular leakage. The former is usually associated with retrobulbar tissue masses, but is also seen with intracranial neoplasms and with hypovitaminosis A. Ocular hypotony may cause optic disk edema as a result of decreased tissue hydrostatic pressure. Serous inflammation within the nerve also results in papilledema. Papilledema is a common clinical diagnosis that rarely is available for histologic examination.

Optic neuritis is a term sometimes used rather broadly to describe both inflammatory and degenerative diseases of the nerve. Optic neuritis is seen clinically as swelling, hyperemia, and focal hemorrhage within the optic disk. Affected animals, usually dogs or horses, are blind when the lesion is bilateral. Although described as a clinical entity not associated with other ocular lesions, histopathologic confirmation is lacking. Optic neuritis may, of course, accompany any case of retinitis or endophthalmitis.

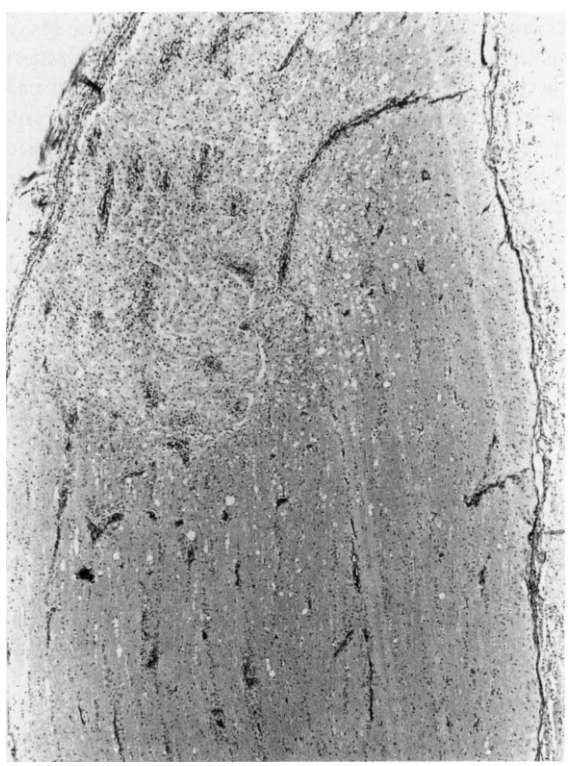

Fig. 4.56 Axonal degeneration in the retrobulbar, intraorbital optic nerve. Dog, 11 days after being struck by a car.

The pattern of inflammation within the nerve may provide clues as to the pathogenesis of the neuritis. Perineuritis, or optic nerve leptomeningitis, is typical of meningeal spread of bacterial meningitis from the brain. Toxoplasmosis and cryptococcosis frequently cause multifocal and nonselective lesions within the extraocular nerve, as does canine distemper. Optic neuritis originating as endophthalmitis is usually restricted to the optic disk. Feline infectious peritonitis is frequently associated with perineuritis and optic neuritis in which the mononuclear aggregates are around blood vessels in the meninges and in the extensions of the meninges into the nerve.

Chronic optic neuritis, like its counterpart in the brain, is characterized by focal gliosis, astrocytic scarring, and secondary axonal degeneration. The loss of axons may be partially masked by the increased prominence of glia and pial septa.

Degeneration of the optic nerve is part of optic neuritis, glaucoma, and chronic, severe retinal atrophy of any cause. Initiation of gliosis and fibrosis may eventually make the chronic degenerative lesion indistinguishable from that of chronic inflammation. The most frequently diagnosed example is that following trauma to one or both nerves in dogs or cats struck by cars (Fig. 4.56). The gross lesion may be avulsion or contusion. Injury to the nerve may be instantaneous, as caused by tearing or complete severance, or may result from vascular injury with slightly delayed ischemic necrosis. In severed nerves, there is disintegration of the distal axons back to the lateral geniculate body. The proximal portion of each affected axon dies back to the ganglion cell, which eventually also dies. The inner nuclear layer remains unaffected, a useful criterion to distinguish traumatic, "die back," ganglion cell atrophy from that of glaucoma.

Degeneration of optic nerve also occurs in calves deficient in vitamin A, and in ruminants ingesting male fern or hexachlorophene. Ingestion of male fern, *Dryopteris*, on pasture or as a taenicidal extract causes papilledema and subsequent optic nerve demyelination when ingested in large amounts. Retina may be unaffected early, but ganglion cell atrophy occurs eventually. Hexachlorophene administered to calves or sheep as an anthelmintic causes edema and then atrophy and gliosis of optic nerve.

Proliferative optic neuropathy is an unusual lesion of horses. Anecdotal descriptions are numerous, but histologic descriptions are few. The lesion is a raised, gray mass on the surface of the optic disk, unassociated with visual deficit. The mass is composed of spherical mononuclear cells with hyperchromatic, eccentric nuclei and foamy eosinophilic cytoplasm (Fig. 4.57). Some of these cells are also found within extraocular optic nerve. The cytoplasmic content may be stored lipid, but its origin is not known. The described lesion bears much resemblance to the proliferation of myelin-laden macrophages that occurs in and on optic nerves injured by trauma or ischemia. Also, the distinction between the proliferative optic neuropathy and gliomas or granular cell tumors described in various reports is unclear.

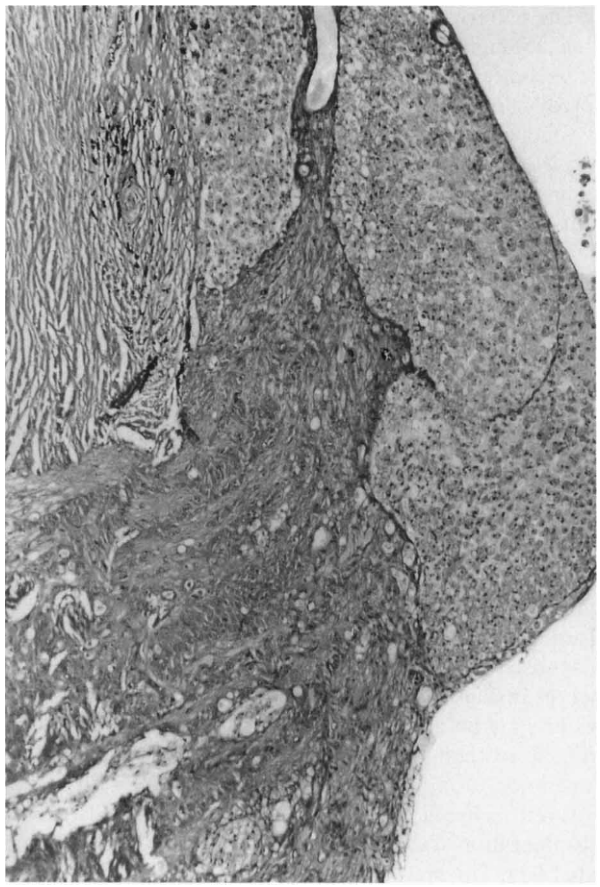

Fig. 4.57 Equine proliferative optic neuropathy. The identity of the foamy cells is much debated.

Bibliography

Bistner, S. *et al.* Neuroepithelial tumor of the optic nerve in a horse. *Cornell Vet* **73:** 30–40, 1983.

Gelatt, K. N. *et al.* Optic disc astrocytoma in a horse. *Can Vet J* **12:** 53–55, 1971.

Nafe, L. A., and Carter, J. D. Canine optic neuritis. *Compend Cont Ed* **3:** 978–984, 1981.

Saunders, L. Z., and Rubin. L.F. "Ophthalmic Pathology of Animals." Basel, Switzerland, Karger, 1975.

Saunders, L. Z., Bistner, S. I., and Rubin, L. F. Proliferative optic neuropathy in horses. *Vet Pathol* **9:** 368–378, 1972.

Vestre, W. A., Turner, T. A., and Carlton, W. W. Proliferative optic neuropathy in a horse. *J Am Vet Med Assoc* **181:** 490–491, 1982.

IX. The Sclera

The limbus marks the transition from the avascular, nonpigmented, and very orderly cornea to the vascularized, pigmented, and interwoven fibrous tissue that identifies sclera. The sclera forms the posterior two thirds of the fibrous tunic of the eye, blending with choroid on its inner aspect and orbital fascia exteriorly. Its thickness increases with age and varies considerably among domestic species. In cattle and horses, it is thickest at the posterior pole (2.2 mm in cattle and 1.3 mm in horses) and thinnest at the orbital equator (1.0 mm in cattle, about 0.5 mm in horses). In dogs and cats, it is much thinner, about 0.3 mm at the posterior pole and 0.1 mm at the equator, varying somewhat with age and globe size. In carnivores, however, there is a circumferential ring of thickened (1 mm) sclera at the limbus, in which is buried the venous plexus receiving aqueous drainage. The sclera is perforated by numerous vessels and nerves, the most notable of which are the optic nerve and limbic scleral venous plexus.

The optic nerve fibers exit the globe through extensive scleral fenestrations called the lamina cribrosa. Diseases of the sclera are few in comparison to diseases of other ocular structures. Most are inflammatory and arise by extension from within the globe or from orbital cellulitis. The efficiency with which the sclera resists inflammatory spread is evidenced by the infrequency of panophthalmitis as opposed to endophthalmitis, and the even greater infrequency of intraocular involvement resulting from orbital inflammation. When the sclera is involved in inflammatory disease originating within the eye, its initial involvement is seen histologically as leukocytes in perivascular adventitia, which is in direct communication with the choroid. A similar phenomenon is seen in scleral extension of choroidal neoplasms, in which collars of tumor cells surround scleral vessels but show little inclination to infiltrate directly into scleral connective tissue.

Nodular fasciitis (nodular granulomatous episcleritis) is the most prevalent primarily scleral disease of dogs. It occurs rarely in cats. It is the proliferative, nodular lesion of the limbus that has been variously termed nodular fasciitis, nodular scleritis or episcleritis, fibrous histiocytoma, proliferative keratoconjunctivitis, conjunctival granuloma, and collie granuloma. The various names reflect the spectrum of clinical presentations of this lesion. The variations are treated as a single entity, nodular fasciitis, in this discussion.

The usual macroscopic lesion is a firm, painless, moveable, nodular swelling, 0.5–1.0 cm in diameter, below the bulbar conjunctiva at, or just posterior to, the limbus. Infiltrative extension of the mass into the peripheral corneal stroma is accompanied by edema and vascularization (Fig. 4.58A). Although the temporal limbus unilaterally is the most frequent site for initial occurrence, other common locations include third eyelid and elsewhere along the limbus. Third eyelid involvement is often bilateral and occurs almost exclusively in rough collies. Limbic and nictitans involvement may occur in the same dog and even in the same eye.

Ocular nodular fasciitis behaves as would a locally infiltrative neoplasm. Extension is usually into peripheral corneal stroma and posteriorly into sclera, episclera, and Tenon's capsule. The tissue of origin of this lesion is unresolved. Fibrous tissue of sclera, episclera, and Tenon's capsule have all been suggested. Lesions involving the third eyelid, or the rare case of palpebral subconjunctival origin, probably originate from the fascia native to

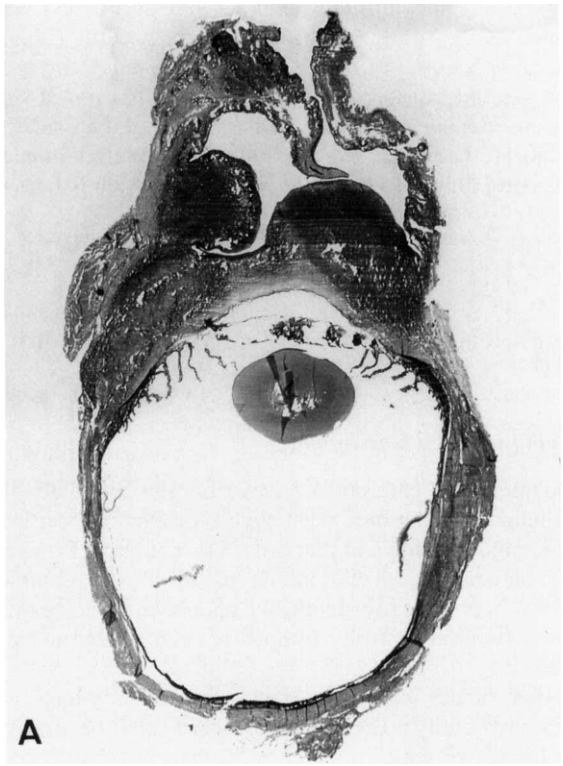

Fig. 4.58A Nodular fasciitis. Dog. Infiltrative scleral mass of 2 years' duration.

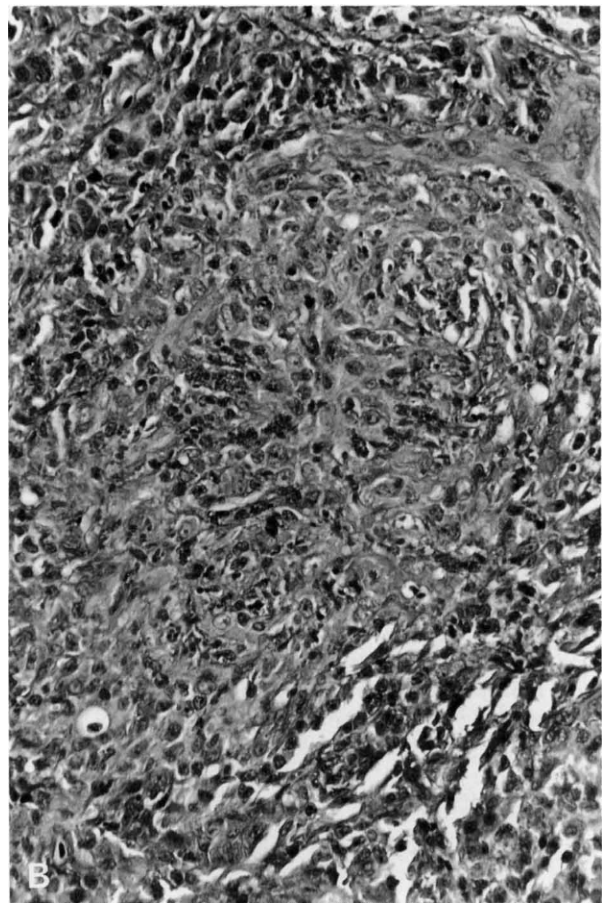

Fig. 4.58B Higher magnification, nodular fasciitis.

those structures. Histologic examination distinguishes this lesion from extension of intraocular tumors or the rare scleral sarcomas. Occasionally, infiltration of therapeutically refractory fasciitis is so extensive, both into cornea and sclera, as to require enucleation.

Histologically, the lesion is a proliferative, nonencapsulated mixture of neocapillaries, spindle cells, and mononuclear leukocytes (Fig. 4.58B). The spindle cells may be fibroblasts, histiocytes, or a mixture of both. The spindle cells are haphazardly arranged and, despite a fibrous appearance to the section, surprisingly little collagen is demonstrated by special stains except in coarse septa that may dissect the mass into irregular lobules. Reticulin, however, is abundant. The mononuclear leukocytes are found loosely throughout the mass but are usually most numerous near its periphery. When present in cornea, the above cell mixture affects stroma but spares the epithelium and an adjacent zone of subepithelial stroma.

Necrotizing scleritis is a rare lesion seen in dogs as a poorly delineated inflammatory and proliferative lesion of anterior sclera. The disease incites much more inflammatory reaction, as measured by clinical criteria, than does nodular fasciitis. The lesion consists of coalescing scleral granulomas centered around remnants of denatured, refractile collagen. Eosinophils sometimes are seen in the centers as well. Some cases have diffuse granulomatous inflammation rather than discrete granulomas. The lesion tends to slowly spread circumferentially and posteriorly to involve the entire sclera, and involvement of uvea and even retina with granulomas eventually occurs. Bilateral involvement is usual, but not necessarily at the same time. Response to antiinflammatory therapy is poor. No etiologic agent has been seen.

X. The Orbit

Diseases of the orbit are few and relatively uncommon in domestic animals except for those resulting from trauma. Systemic diseases of bone, muscle, blood vessels, and nerves may incidentally affect orbital components. Orbital fat fluctuates with nutritional status, contributing to the enophthalmos of malnourished animals. Ordinarily, however, orbital disease arises by extension of inflammatory lesions from the mouth, paranasal sinuses, or from penetrating wounds through periorbital soft tissue. Extension from intraocular inflammation is surprisingly rare, a tribute to the barrier offered by the sclera. Conversely, orbital disease rarely invades the globe. Metastatic orbital neoplasia is rare except for lymphoma of cattle and of cats. While theoretically the orbit may suffer from primary neoplasia of any of the bony or soft tissues within it, such

occurrences are rare. Of these, ill-defined spindle-cell sarcomas and lacrimal gland tumors in dogs are the most common (see Ocular Neoplasia).

Orbital cellulitis is the commonly used term to describe pyogenic orbital inflammation. The cause is usually bacterial, and the pathogenesis involves extension from nearby inflammation of paranasal sinuses, molar tooth socket, or periorbital soft tissue. Only rarely does uncontrolled endophthalmitis spread through the sclera into the orbit. Bacteremic localization within the orbit, while presumably occurring as do such localizations elsewhere, is seldom detected except perhaps for *Streptococcus equi* infection in young horses.

Orbital inflammation most frequently results from penetrating foreign bodies, whether by direct penetration or particle migration from conjunctival sac or pharynx. Horses seem particularly prone. Aberrant localization by nematode parasites (*Dirofilaria immitis, Ancylostoma caninum*) or *Diptera* larvae is reported.

Bibliography

Gwin, R. M., Gelatt, K. N., and Peiffer, R. L. Ophthalmic nodular fasciitis in the dog. *J Am Vet Med Assoc* **170:** 611–614, 1977.

Smith, J. S., Bistner, S., and Riis, R. Infiltrative corneal lesions resembling fibrous histiocytoma: Clinical and pathologic findings in six dogs and one cat. *J Am Vet Med Assoc* **169:** 722–726, 1976.

XI. Ocular Neoplasia

Although the eye is the site of a wide range of primary and metastatic neoplasms, only a few are of sufficient prevalence or importance to justify discussion here. Metastatic ocular neoplasia is reported rather infrequently but it is common when sought. Multicentric lymphoma in cats, dogs, and cattle regularly involves the eye, although in cattle the retrobulbar tissue is preferred over the eye itself. Carcinomas are reported more frequently than sarcomas, and this probably reflects the greater prevalence and metastatic potential of carcinomas. Uveal vessels are the usual sites of lodgement, and ocular disease may result from vessel occlusion, or from inflammation in response to tumor antigen, or to necrosis of either tumor or damaged host tissue. Hyphema is more common in eyes with tumor-induced uveitis than with uveitis of other causes and is therefore a diagnostically useful sign.

Primary ocular tumors may arise from the eyelids and adnexa, from optic nerve, or from the globe. Those of the globe may originate from any of the tissues, but only those from uveal melanoblasts and neurectoderm are anything other than rare. Most primary intraocular tumors are benign in terms of histologic appearance or potential for metastasis. Dogs and cats are frequently affected, but primary intraocular neoplasms are inexplicably rare in other domestic species.

The most important primary ocular neoplasms are squamous cell carcinoma, meibomian adenoma, melanoma, and ciliary adenoma. Other tumors are uncommon.

Bibliography

Blodi, F. C., and Ramsey, F. K. Ocular tumors in domestic animals. *Am J Ophthalmol* **64:** 627–633, 1967.

Dubielzig, R. R. Ocular neoplasia in small animals. *Vet Clin North Am: Small Anim Pract* **20:** 837–848, 1990.

Gwin, R. M., Gelatt, K. N., and Williams, L. W. Ophthalmic neoplasms in the dog. *J Am Anim Hosp Assoc* **18:** 853–866, 1982.

Lavach, J. D., and Severin, G. A. Neoplasia of the equine eye, adnexa and orbit: A review of 68 cases. *J Am Vet Med Assoc* **170:** 202–203, 1977.

Williams, L. W., Gelatt, K. N., and Gwin, R. M. Ophthalmic neoplasms in the cat. *J Am Anim Hosp Assoc* **17:** 999–1008, 1981.

A. Squamous Cell Carcinoma

Squamous cell carcinoma arises from the conjunctival epithelium of the limbus, third eyelid, or eyelid in cattle, horses, cats, and dogs, in that order of frequency. Bovine ocular squamous cell carcinoma is the most common and most economically significant neoplasm of domestic animals. Its relative rarity in dogs is peculiar and unexplained.

Bovine ocular squamous cell carcinoma, which is largely restricted to the Hereford breed, also occurs in other breeds of cattle, as well as Indian water buffalo, sheep, and cattalo (Fig. 4.59). It has a prevalence shown to be related directly to exposure to ultraviolet radiation, and less directly to lack of pigment in lids and conjunctiva. Nevertheless, variation in prevalence in different lines of Herefords in the same district has led to speculation that other genetic factors within the breed may influence susceptibility. The question has been further widened by demonstration of papillomaviruses in some of the papillomatous precursor lesions which eventually transform into squamous cell carcinoma. Similar papillomaviruses, as well as being the causative agents of cutaneous warts, have been demonstrated in bovine alimentary papillomas in Scotland, and viral DNA persists in the squamous cell

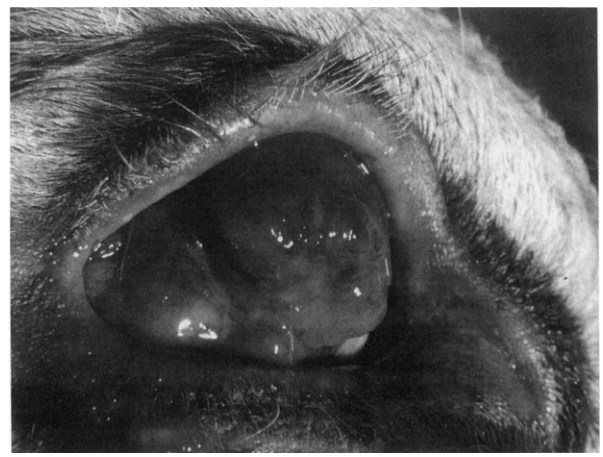

Fig. 4.59 Squamous cell carcinoma. Ox.

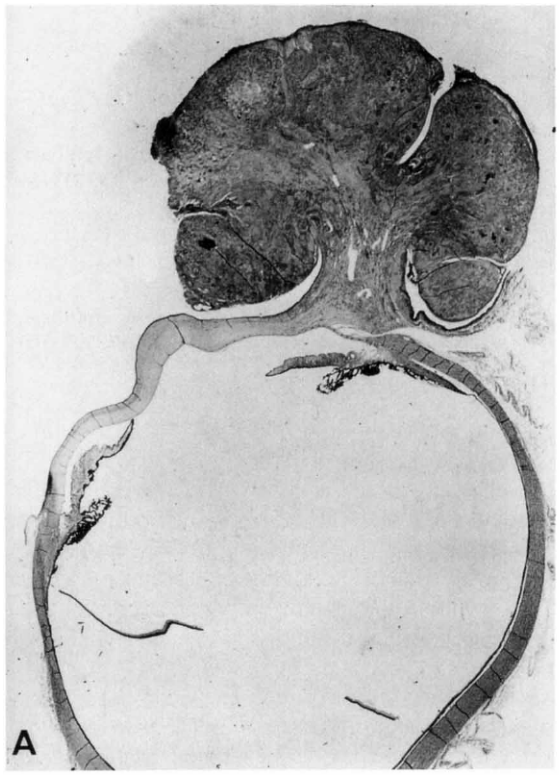

Fig. 4.60A Squamous papilloma of corneoscleral junction. Ox.

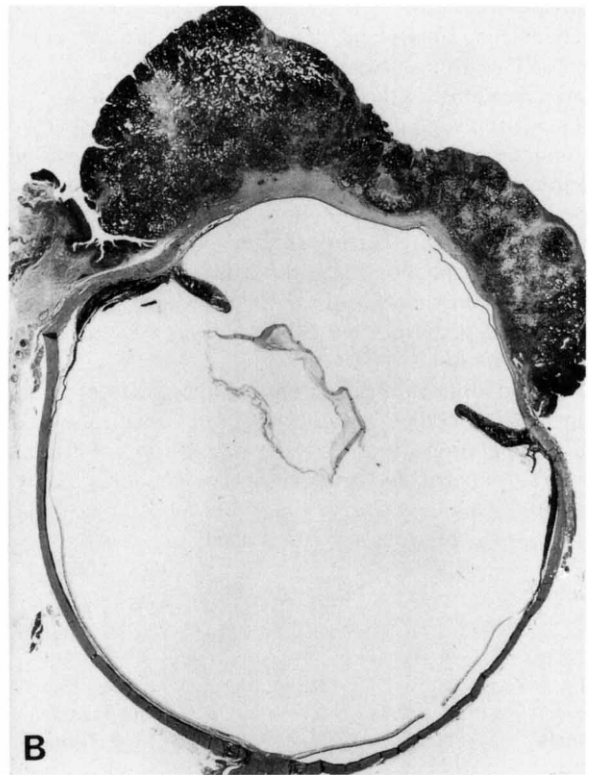

Fig. 4.60B Squamous cell carcinoma arising from bulbar conjunctiva.

carcinomas which arise from these papillomas in cattle grazing pastures that contain bracken fern. It remains to be determined whether or not there is any relationship between a viral component of the ocular carcinoma and the fact that in many cases the tumor regresses after immunotherapy. At least at the moment, no viral particle or viral genome has been consistently demonstrated in ocular squamous cell carcinomas in any species. Environmental co-carcinogens such as those in bracken have not yet been implicated in the induction of ocular tumors.

The tumor in all species develops through a series of premalignant stages, called epidermal plaques and papillomas, before proceeding over months or years to carcinoma *in situ* and to invasive carcinoma (Figs. 4.59, 4.60A,B). Spontaneous regression of the precancerous lesions may occur with an estimated frequency of 25 to 50%. At least in cattle, plaques are much more common (about 6:1) than papillomas or outright carcinomas. The epidermal plaque is characterized by marked acanthosis, with variable presence of keratinization, dyskeratosis, and epidermal downgrowth into the subconjuctival connective tissue. Invasion through basal layer or basement membrane is not seen. Papilloma also involves acanthosis but, in addition, there is marked para- and hyperkeratosis with papillary projections supported by a vascularized connective tissue core. Papillomas may be up to 3.0 cm in diameter, pedunculated or sessile, and are often ulcerated. Carcinoma *in situ* arises by focal or multifocal transformation of increasingly dysplastic cell nests in the deep layers of plaques or papillomas. Fully developed carcinoma has squamous cell invasion across the basement membrane. Tumor invasion is almost always accompanied by an intense lymphocytic–plasmacytic infiltration, presumably the host response to tumor antigen. It is assumed that this response is responsible for regression of some of the precursor lesions, although spontaneous regression of fully developed carcinoma is rare. Stimulation of immune-mediated rejection by intra lesional inoculation of antigenic tumor extracts or nonspecific lymphocyte stimulants induces partial or total regression of small tumors.

Histologically, ocular squamous cell carcinoma resembles similar tumors in other sites and ranges from well-differentiated carcinomas with keratin pearl formation to anaplastic carcinomas with marked nuclear size variation and mononuclear tumor giant cells. Metastatic or invasive potential has not been correlated with histologic criteria, but there is a correlation between site of origin and subsequent behavior. Most surveys in cattle identify the bulbar conjunctiva of the limbus as the most frequent site of origin, estimated at about 70% of all occurrences. Some surveys consider nictitating membrane as next most frequent, with palpebral conjunctiva of the true eyelid as third. Other reports claim nictitans origin to be uncommon and eyelid tumors to be as common as those of limbic origin. Tumors probably do not arise from cornea unless

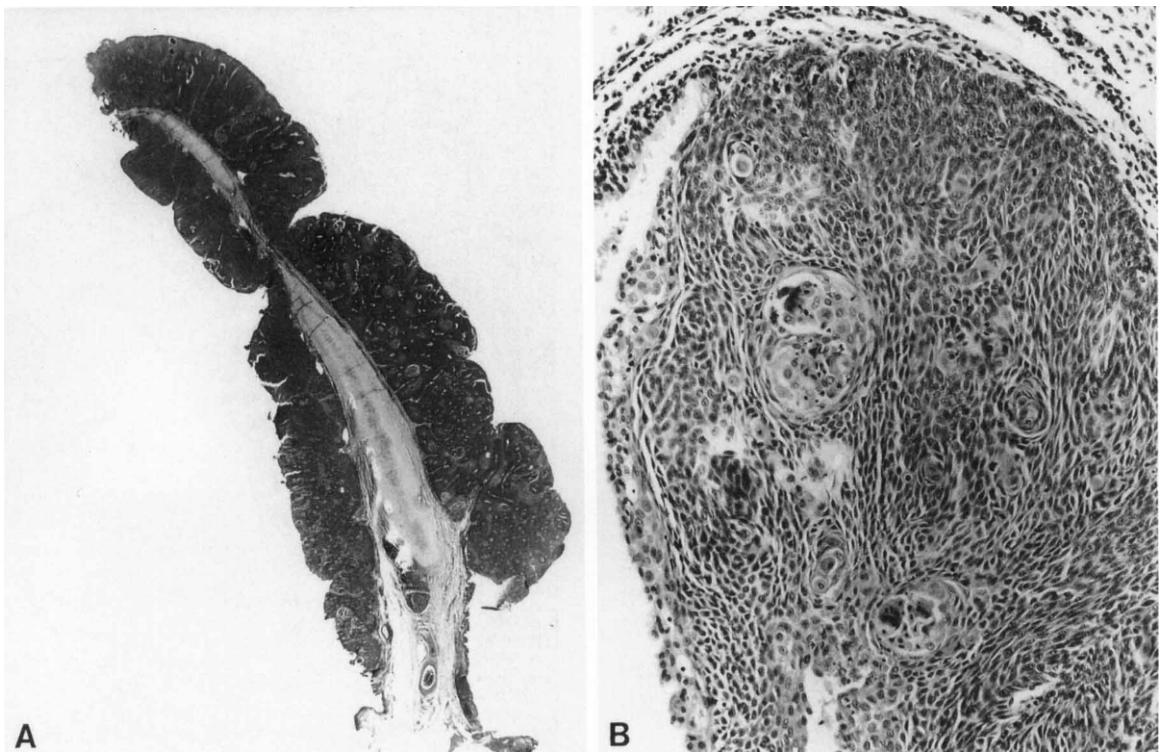

Fig. 4.61 (A) Early squamous cell carcinoma involving conjunctiva of nictitating membrane. Horse. (B) Histology of (A). Disorderly and defective maturation, premature keratinization, and invasion across the basement membrane.

it has previously been vascularized. Tumors arising at the limbus are confronted by the dense and poorly vascularized connective tissue of sclera and peripheral cornea, which retards metastasis to extraocular sites. Invasion of corneal stroma, sclera, and anterior chamber occurs slowly. Tumors arising from the nictitans extend to the root of the membrane and then to the cartilage and bone of the orbit and internal nares. Metastasis probably will eventually occur in all instances, with parotid lymph node the initial site. Wide dissemination to thoracic and abdominal organs has been reported and is probably limited only by the limited longevity of the animal.

Squamous cell carcinoma of the **equine** eye is much less thoroughly documented but is quite common. In contrast to cattle, the preferred site is the edge of the third eyelid, followed by limbic bulbar conjunctiva (Fig. 4.61). Bilateral involvement is seen in 15 to 20%. All breeds may be affected, and the mean age of affected horses is about 9 years. The same range of precancerous lesions occurs in horses as in cattle. Prognosis is strongly influenced by therapy, but the untreated neoplasm is slow to metastasize, and even then, it is usually only to local lymph nodes. Retrospective studies document 10–15% of equine ocular squamous cell carcinomas to have regional or distant spread, but the data do not consider duration of the disease prior to therapy (Fig. 4.62).

In **cats,** ocular squamous cell carcinoma most frequently affects the skin or palpebral conjunctiva of the eyelids. White cats are particularly susceptible, and squamous cell carcinomas in these animals may occur simultaneously or sequentially on eyelids, ear pinnae, nose, and lips. The early lesion is one of sunlight-induced epithelial necrosis, and even the early neoplasm may be ulcerated and inflamed to a degree that may mask its neoplastic character and delay appropriate therapy. Growth tends to be circumferential around the lid margins, resulting in a palpebral fissure bordered by a thickened, red, and ulcerated tumor.

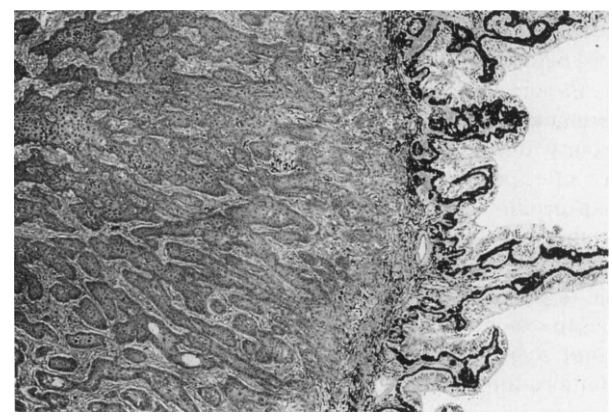

Fig. 4.62 Scleral squamous cell carcinoma has grown inward to approach ciliary processes, an unusual behavior for these normally exophytic tumors. Horse.

Metastasis to local lymph nodes occurs late in the course of the disease.

Squamous cell carcinoma in **dogs** infrequently involves the eye. Proliferative eyelid or conjunctival growths in dogs are much more likely to be meibomian adenomas, viral papillomas, or nodular fasciitis. In one study of 202 canine eyelid neoplasms, squamous cell carcinoma accounted for only 2% of lesions. Precancerous changes probably occur but, in contrast to cattle and horses, eyelid papillomas in dogs are usually benign and nonprogressive lesions.

Bibliography

Anderson, D. E., and Badzioch, M. Association between solar radiation and ocular squamous cell carcinoma in cattle. *Am J Vet Res* **52:** 784–787, 1991.

Anson, M. A., Benfield, D. A., and McAdaragh, J. P. Bovine herpes virus-5 (DN-599) antigens in cells derived from bovine ocular squamous cell carcinoma. *Can J Comp Med* **46:** 334–337, 1982.

Atluru, D., Johnson, D. W., and Muscoplat, C. C. Tumor-associated antigens of bovine cancer eye. *Vet Immunol Immunopathol* **3:** 279–286, 1982.

Dugan, S. J. *et al.* Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma: 147 cases (1978–1988). *J Am Vet Med Assoc* **198:** 298–303, 1991.

Russell, W. O., Wynne, E. S., and Loquvam, G. S. Studies on bovine ocular squamous cell carcinoma (cancer eye). I. Pathological anatomy and historical review. *Cancer* **9:** 1–52, 1956.

Spradbrow, P. B., and Hoffman, D. Bovine ocular squamous cell carcinoma. *Vet Bull* **50:** 449–459, 1980.

Williams, L. W., and Gelatt, K. N. Ocular squamous cell carcinoma. *In* "Veterinary Ophthalmology" K. N. Gelatt (ed.), pp. 622–632. Philadelphia, Pennsylvania, Lea & Febiger, 1981.

B. Meibomian Adenoma

Meibomian adenoma is the most common ocular neoplasm of dogs, accounting for at least 50% of eyelid tumors. It is comparable in most respects to sebaceous adenomas found elsewhere in the skin, and many authors have abandoned the name, meibomian adenoma, in favor of the latter term. However, these tumors are specifically of meibomian gland and not of other eyelid sebaceous glands and regularly have histologic features that are infrequently seen in their cutaneous counterparts. In the eyelid tumors, the lobules of foamy, eosinophilic sebaceous cells are surrounded by basal (reserve) cells that are regularly a prominent part of the tumor (Fig. 4.63). In many instances, the basal cell component is so prominent as to cause diagnosis to be made of basal cell tumor with sebaceous differentiation or even sebaceous adenocarcinoma. None metastasizes, and even the so-called carcinomas show little inclination for invasive growth. Other distinctive features are the regular occurrence of squamous metaplasia appropriate to sebaceous gland ducts, and a marked lymphocytic–plasmacytic infiltrate within the stroma between tumor lobules and around the tumor margins, and

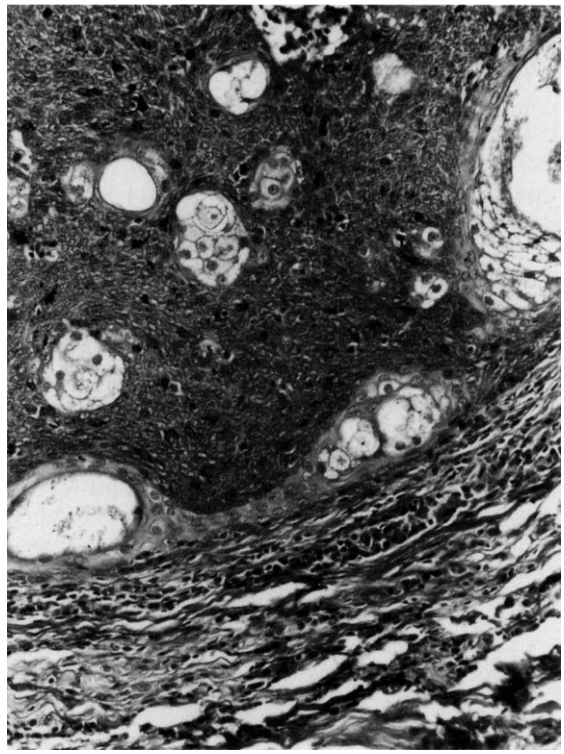

Fig. 4.63 Meibomian adenoma. Dog. Note sebaceous cells, basal (reserve) cells, melanin, abundant mononuclear leukocytic infiltration.

localized granulomatous response (chalazion) to leaking secretion. The basal cells in many of these tumors are heavily pigmented, with mature melanocytes interspersed with the basal cells and melanophages prominent in the stroma.

C. Other Adnexal and Conjunctival Tumors

A wide range of neoplasms has been reported to occasionally affect the conjunctiva or adnexa of domestic animals. Other than meibomian adenoma, squamous cell carcinoma, or papilloma (previously described) or melanoma (to be described) in their respective species, all are uncommon to rare.

Hemangiomas and hemangiosarcomas occur anywhere in the conjunctiva, most frequently on the perilimbal bulbar conjunctiva of dogs and horses. They resemble vascular tumors elsewhere, although some of the canine tumors occur in the very superficial plexus adjacent to a hyperplastic conjunctival epithelium, and have been called angiokeratomas. Their behavior is the same as that of hemangioma. Malignant variants seem more prevalent in horses, where more than half of the reported cases are solid hemangiosarcomas with a very aggressive local infiltration and, usually, distant metastasis. There is much speculation, but no proof, that sunlight is important in their causation.

Adenocarcinoma of the gland of the third eyelid occurs as a nodular swelling in very old dogs (mean age 11.5 years). They are locally infiltrative, recur after attempted resection, but are cured by complete removal of the third eyelid. Only chronically neglected cases metastasize to lung after a very protracted local expansion. Histologically these are tubular carcinomas with abundant squamous metaplasia. They should not be confused with the prominence of the gland that occurs with prolapse of the gland (cherry eye) or with lymphocytic interstitial adenitis.

Lymphoma may have several ocular manifestations, the most frequent of which are diffuse uveal metastases as part of generalized lymphoma in dogs or cats, or as retrobulbar tumor in cattle. It may occasionally occur as a conjunctival disease as part of generalized lymphoma or as a mucocutaneous manifestation of epitheliotrophic lymphoma. There are several reports of conjunctival or third eyelid lymphoma occurring in horses as an apparently isolated lesion cured by local excision.

Bibliography

George, C., and Summers, B. A. Angiokeratoma: A benign vascular tumor of the dog. *J Small Anim Pract* **31:** 390–392, 1990.

Glaze, M. B. *et al.* A case of equine adnexal lymphosarcoma. *Eq Vet J* **10:** 83–84, 1990.

Håkanson, N., Shively, J. N., and Merideth, R. E. Granuloma formation following subconjunctival injection of triamcinolone in two dogs. *J Am Anim Hosp Assoc* **27:** 89–92, 1991.

Hargis, A. M., Lee, A. C., and Thomassen, R. W. Tumor and tumorlike lesions of perilimbal conjunctiva in laboratory dogs. *J Am Vet Med Assoc* **173:** 1185–1190, 1978.

Krehbiel, J. D., and Langham, R. F. Eyelid neoplasms of dogs. *Am J Vet Res* **36:** 115–119, 1975.

Moore, P. F., Hacker, D. V., and Buyukmihci, N. C. Ocular angiosarcoma in the horse: Morphological and immunohistochemical studies. *Vet Pathol* **23:** 240–244, 1986.

Roberts, S. M., Severin, G. A., and Lavach, J. D. Prevalence and treatment of palpebral neoplasms in the dog: 200 cases (1975–1983). *J Am Vet Med Assoc* **189:** 1355–1359, 1986.

Wilcock, B. P., and Peiffer, R. L. Adenocarcinoma of the gland of the third eyelid in seven dogs. *J Am Vet Med Assoc* **193:** 1549–1550, 1988.

D. Melanotic Tumors

Our understanding of the biology of primary ocular melanomas in animals has suffered greatly from the premature assumption that they are similar to the much-studied human ocular melanomas, and for many years the descriptions and prognoses reflected the human experience. Perhaps because of this error, a great many enucleated globes were available for histologic evaluation, inadvertently allowing the flurry of retrospective studies that eventually established ocular melanomas in dogs and cats as distinct entities quite different in structure and behavior from the human neoplasms.

Primary melanomas of the eye or adnexa are common in dogs and cats, rare in horses, and almost nonexistent in other domestic species. Even in dogs and cats, the prevalence and behavior of the various types of ocular melanomas differ markedly, so that generalizations must be studiously avoided.

1. Canine Ocular Melanomas

In **dogs,** melanomas arise in the skin of the lid margin, in conjunctiva, in anterior uvea, in the pigmented line demarcating the limbus, and in the choroid (Fig. 4.64A,B). The tumors arising in each location represent a distinct biologic group with a natural behavior and therapeutic protocol quite different from melanomas arising at one of the other sites.

Melanomas of the haired skin of the lid margin are the second most prevalent eyelid tumor in dogs. They are rare in this site in other species. They are almost invariably benign and closely resemble benign melanomas elsewhere in the skin.

Melanomas arising in the conjunctiva are very infrequent compared to all other ocular melanomas. The few case reports do not allow for generalizations about behavior, but they often are histologically and behaviorally malignant. Their relationship to eyelid melanoma seems analogous to those of the lip, where melanomas of the haired exterior lip are benign like most skin melanomas, and those of the mucous membrane of the inside of the lip are malignant like those elsewhere in the mouth. Conjunctival melanomas may appear as well-pigmented tumors of bland, plump melanocytes with little anisokaryosis or mitotic activity, but often are poorly melanotic and have invasive clusters of angular epithelioid cells with marked anisocytosis and numerous mitotic figures. Local recurrence and spread after excision is frequent, and metastasis to lung has been reported.

Limbal (epibulbar) melanoma is a histologically and behaviorally benign tumor of the melanocytes normally found in an oblique line that demarcates the junction of corneal stroma with sclera at the limbus. The tumor is composed of large plump melanocytes with a central nucleus and abundant cytoplasmic pigment. Mitotic figures are absent, and nuclear variation is minimal. The tumor grows outward as a protruding spherical nodule, hence the alternative name of epibulbar melanoma. There may be nodular expansion into peripheral cornea, but virtually never into the uvea or anterior chamber. Tumors with similar clinical and histologic appearance that do invade the globe should be assumed to have originated as anterior uveal melanomas, and the scleral extension of such tumors along the adventitia of the scleral venous plexus merely mimics the outflow of many other materials from within the eye.

Anterior uveal melanomas (melanocytomas) of dogs is the most frequent intraocular tumor in that species. It is topographically, histologically, and behaviorally unrelated to human epithelioid ocular melanomas, to which it was long compared. The typical tumor arises from melanocytes of the iris root or adjacent ciliary body, and is composed of variable proportions of lightly pigmented spindle cells and heavily pigmented plump melanocytes identical

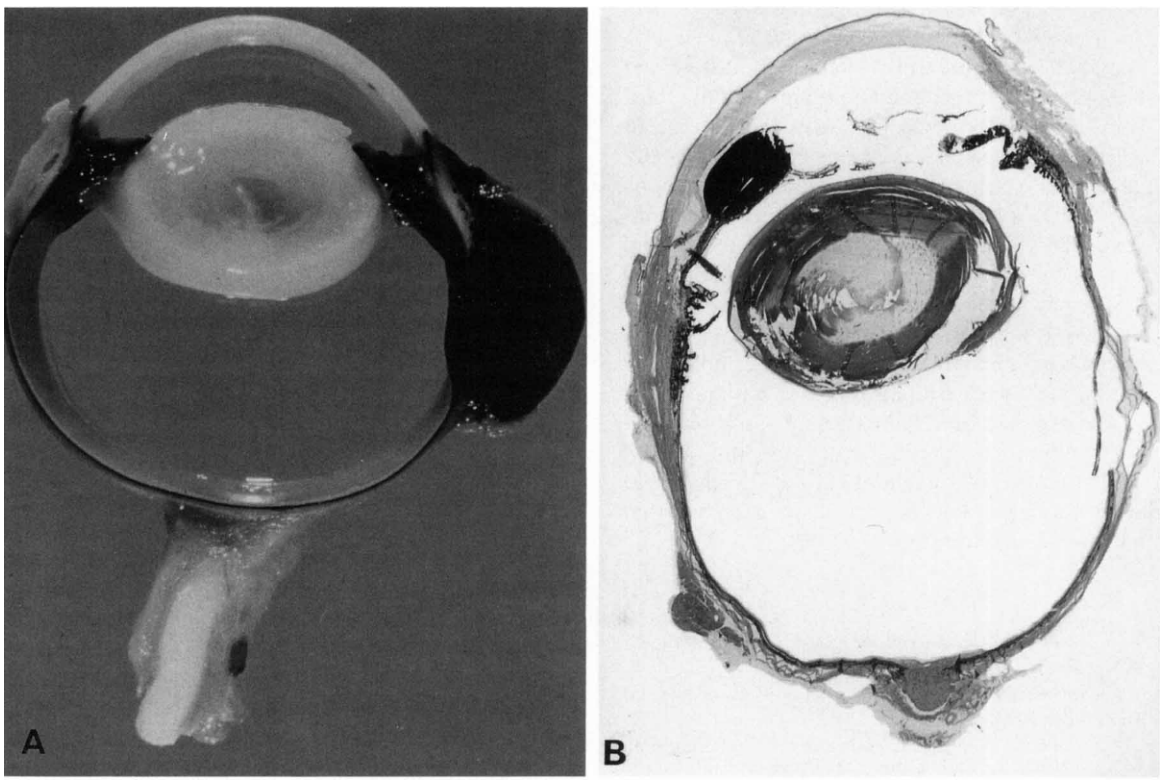

Fig. 4.64 (A) Ciliary melanoma at the limbus, which resembles an epibulbar melanoma grossly. (B) Benign iris melanoma (nevus), dog iris.

to those of limbal melanomas. The spindle cells are assumed to be the proliferative population, and the plump cells probably represent the mature, end-stage melanocyte with a storehouse of cytoplasmic pigment.

The diagnosis itself presents no problem, but offering an accurate prognosis is more complex. About 15% of all canine anterior uveal melanomas are histologically malignant, and one third of these have been confirmed to be behaviorally malignant by virtue of extraocular metastases. The overall prevalence of behavioral malignancy is thus about 5%, and this small group can be predicted by mitotic index. Histologically malignant tumors are dominated by the spindle cells rather than the plump cells, are more lightly pigmented, have much more anisokaryosis and more mitotic figures than the benign tumors. Of these, mitotic index is the most reliable predictor of behavior. Benign tumors have virtually no mitotic figures. Those confirmed as behaviorally malignant have a mitotic index of 3 or more (usually much more!).

Even benign melanomas are significant to the eye, spreading transclerally and circumferentially within the globe. Glaucoma from occlusion of ciliary cleft is seen in about half the dogs presented for enucleation, and is probably the eventual fate of all eyes with this neoplasm. Uveitis from tumor necrosis or hyphema from tumor-induced uveal neovascularization are other frequent accompaniments.

Clinically insignificant **iris nevi or freckles** occur in dogs as nonprogressive pigmented spots. Their only significance is to cause premature and unnecessary enucleation. Histologically, the lesions are well circumscribed clusters of bland melanocytes adjacent to the anterior border layer of the iris.

Choroidal melanomas account for about 80% of all human ocular melanomas, but are rare in dogs. The few reported were discovered as incidental findings on fundoscopic examination, and grew very slowly. They seem very similar to the benign melanomas of limbus or anterior uvea: well-pigmented, cytologically bland, and cause clinical signs only by their slow expansion into adjacent sensitive tissues. In the case of choroidal melanomas, such expansion results in localized retinal detachment and tumor infiltration of overlying retina or adjacent optic nerve. One of five dogs in one report became blind because of complete retinal separation from the choroid.

2. Feline Ocular Melanomas

Ocular melanomas in cats are very different from their canine counterparts. Cats very rarely have eyelid or conjunctival melanomas, paralleling the paucity of melanomas reported in other cutaneous or mucous membrane sites in this species. The few reported conjunctival melanomas have been histologically and behaviorally very malignant. Limbal melanomas, histologically and behaviorally identical to those in dogs, are occasionally seen. The major presentation, however, is of diffuse iris thickening and

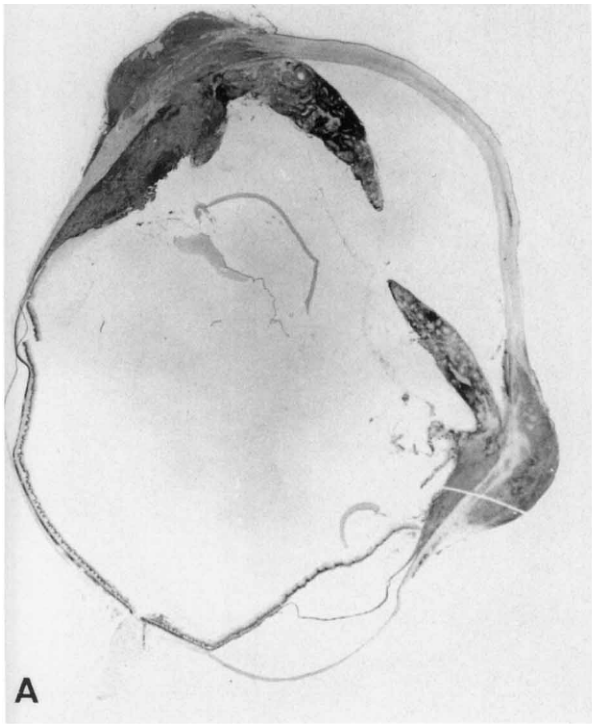

Fig. 4.65A Diffuse iris melanoma. Cat. The scleral infiltration is a grim prognostic sign in this species.

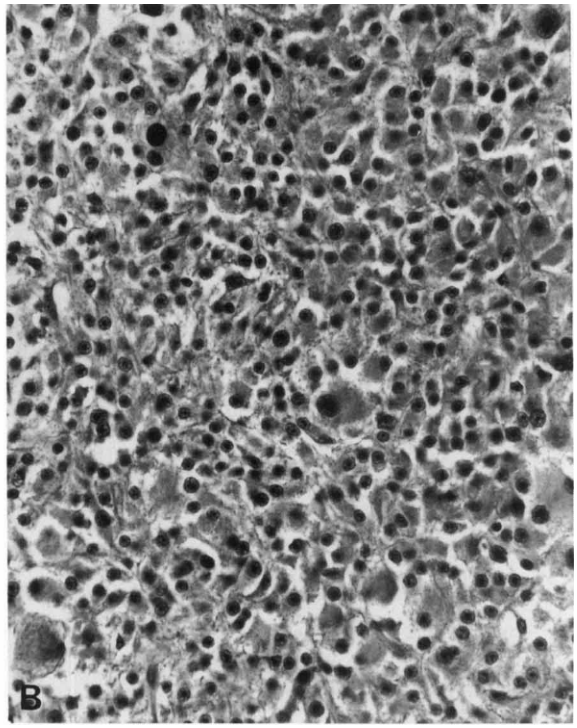

Fig. 4.65B Pleomorphic round cells. Iris melanoma. Cat. Pigmentation is light and mononuclear giant cells are conspicuous.

glaucoma—clinical findings typical of the diffuse iris melanoma unique to cats (Fig. 4.65A). Only rarely does one encounter a well-pigmented, plump-cell melanoma analogous to the common canine uveal melanoma.

The **diffuse iris melanoma** was at first considered an interesting but benign lesion causing diffuse thickening and hyperpigmentation of the iris. Subsequent retrospective studies have been unanimous in documenting a 50 to 60% metastatic rate. Because cats seem even more elusive than dogs in terms of follow-up studies, the actual number of cases with good postoperative data is small, and considerable debate persists among ophthalmologists about the real rate of metastasis of these tumors.

Histologically, these tumors diffusely infiltrate the stroma of the iris, the ciliary cleft, and then the overlying sclera, peripheral cornea, and ciliary body. They are notoriously pleomorphic, and are apt to be misdiagnosed by those pathologists not aware of this disease. Tumor cells vary from spindle-shaped cells to multinucleated epithelioid cells (Fig. 4.65B). Pigmentation often is light, and the cytoplasm may be foamy and eosinophilic. Balloon cells with foamy cytoplasm and very distinct cell boundaries are frequent in some tumors. The accurate prediction of tumor behavior is compromised, in all published studies, by the low percentage of affected cats available for follow-up. Metastasis has been correlated with large tumor size, intrascleral spread, and mitotic index.

Like dogs, cats have focal-to-coalescing hyperpigmentation of the anterior iris stroma. Some cases, as in dogs, are nonprogressive and harmless. Others seem slowly to coalesce and thicken, at which time they are indistinguishable from the most benign variants of diffuse iris melanoma.

3. Equine Ocular Melanomas

If one excludes the chance occurrence of gray-horse skin melanomas on the eyelid, primary ocular melanomas in horses are rare. Almost all reported cases have been in gray horses, many quite young (younger than 8 years). Most involve anterior uvea and are histologically similar to the benign uveal melanomas of dogs. None has metastasized.

There are two reports of benign limbal melanomas in horses, histologically similar to those in dogs.

Bibliography

Acland, G. M. *et al.* Diffuse iris melanoma in cats. *J Am Vet Med Assoc* **176:** 52–56, 1980.

Barnett, K. C., and Platt, H. Intraocular melanomata in the horse. *Eq Vet J* **10:** 76–82, 1990.

Belkin, P. V. Malignant melanoma of the bulbar conjunctiva in a dog. *Vet Med Small Anim Clin* **70:** 957–958, 1975.

Cook, C. S. *et al.* Malignant melanoma of the conjunctiva in a cat. *J Am Vet Med Assoc* **5:** 505–506, 1985.

Duncan, D. E., and Peiffer, R. L. Morphology and prognostic indicators of anterior uveal melanomas in cats. *Prog Vet Comp Ophthalmol* **1:** 25–32, 1991.

Gelatt, K. N., Johnson, K. A., and Peiffer, R. L. Primary iridal

pigmented masses in three dogs. *J Am Anim Hosp Assoc* **15:** 339–344, 1979.
Harling, D. E. *et al.* Feline limbal melanoma: Four cases. *J Am Anim Hosp Assoc* **22:** 795–802, 1986.
Hirst, L. W., and Jabs, D. A. Benign epibulbar melanocytoma in a horse. *J Am Vet Med Assoc* **183:** 33–334, 1983.
Hogan, R. N., and Albert, D. M. Does retinoblastoma occur in animals? *Prog Vet Comp Opthalmol* **1:** 73–82, 1991.
Patnaik, A. K., and Mooney, S. Feline melanoma: A comparative study of ocular, oral, and dermal neoplasms. *Vet Pathol* **25:** 105–112, 1988.
Peiffer, R. L. The differential diagnosis of pigmented ocular lesions in the dog and cat. *Calif Vet* **5:** 14–18, 1981.
Saunders, L. Z., and Barron, C. N. Primary pigmented intraocular tumors in animals. *Cancer Res* **18:** 234–245, 1958.
Schäffer, E. H., and Funke, K. Das primär-intraokulare maligne melanom bei hund und katze. (Primary malignant ocular melanoma in dogs and cats). *Tierärztl Praxis* **13:** 343–359, 1985.
Wilcock, B. P., and Peiffer, R. L., Jr. Morphology and behavior of primary ocular melanomas in 91 dogs. *Vet Pathol* **23:** 418–424, 1986.

E. Tumors of Ocular Neurectoderm

These tumors include adenoma and carcinoma of mature ciliary epithelium and medulloepithelioma and retinoblastoma from embryonic neurectoderm. The prevalence of these neoplasms is second to that of anterior uveal melanomas, although it is perhaps underestimated because the most common examples are small, slowly expansive ciliary adenomas that are unlikely to cause clinical signs. They are relatively common in dogs, rare in cats, and virtually unknown in other species except for medulloepitheliomas in horses.

Ciliary adenoma is the most common of this group (Fig. 4.66A,B). It is a well-differentiated papillary or tubular adenoma arising from the nonpigmented inner layer of ciliary epithelium. Most originate from the pars plicata, but occasionally the histologic evidence points to origin from posterior iris epithelium. The tumor cells resemble mature ciliary epithelium and usually have very little associated stroma. Nuclei are basilar, regular, and are surrounded by eosinophilic cytoplasm (Fig. 4.67A). The tumor cells are not pigmented, although melanophages are occasionally seen within tumor stroma. They make an abundance of basal lamina oriented, as in normal ciliary epithelium, toward the inside of the eye. Its abundance, easily seen with periodic acid-Schiff reagent, is useful in distinguishing ciliary tumors from carcinomas metastatic to the eye. Examples which have little tubular or papillary organization, or have locally invasive growth, have traditionally been called **ciliary carcinomas.** Metastasis is exceedingly rare, so there seems little point in debating the histological criteria that justify the appellation of malignancy.

Even small ciliary body tumors may cause hyphema or glaucoma. This paradox, unexplained by tumor mass or by particularly abundant tumor vasculature, is attributed to this tumor's strong propensity to induce preiridal fibrovascular membranes (Fig. 4.67B). Ciliary body tumors are

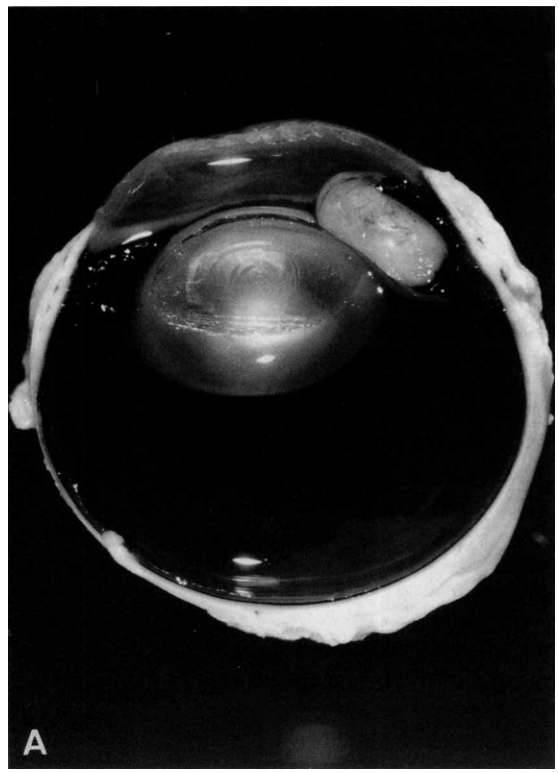

Fig. 4.66A Ciliary adenoma. Dog.

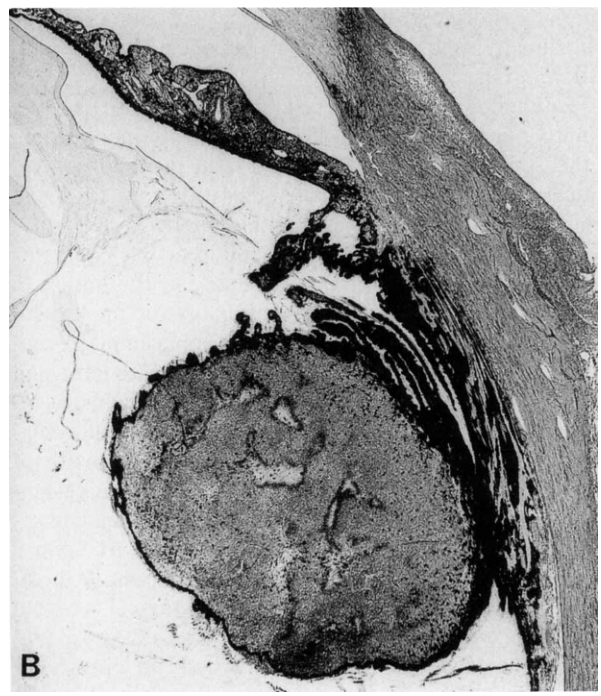

Fig. 4.66B Ciliary adenoma. Dog.

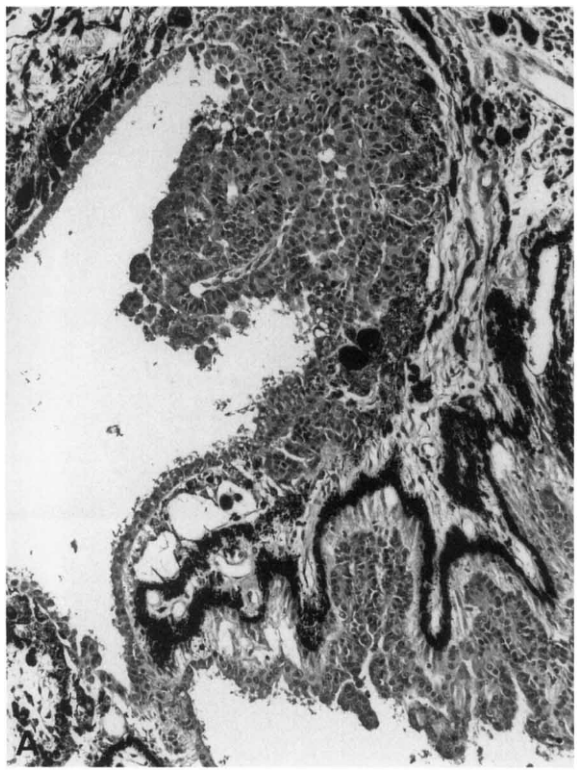

Fig. 4.67A Ciliary adenoma. Dog. Note well-differentiated tubular proliferation.

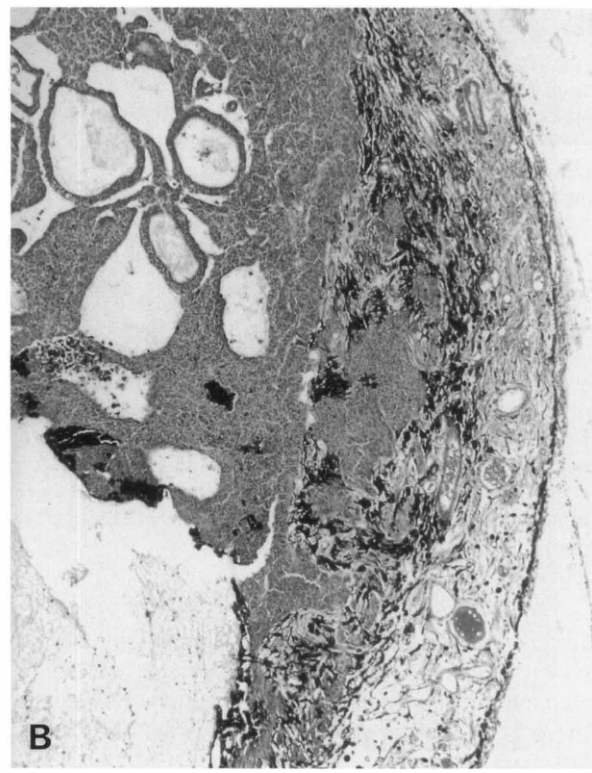

Fig. 4.67B Ciliary adenoma. Dog. Note accompanying preiridal vascular membrane.

more likely to induce such neovascularization than is any other ocular disease. Large tumors may, of course, induce glaucoma by such mechanisms as pupillary block or infiltration of ciliary cleft.

Medulloepitheliomas and retinoblastomas arise from the primitive neurectoderm of the optic cup. Retinoblastoma is the second most frequent neoplasm of children, yet critical review of the veterinary literature fails to reveal a single acceptable diagnosis of this tumor. Conversely, medulloepitheliomas are rare in children, but examples have been observed in animals, mainly in the horse, in which these rare neoplasms are probably the most common primary intraocular tumor. The neoplasm may originate from any portion of embryonic neurectoderm and may show differentiation into any neurectodermal derivative; retina, ciliary epithelium, vitreous, or neuroglia (Fig. 4.68A,B). The typical neoplasm is a loose network of branching cords of small basophilic neuroblasts resembling those of embryonic retina. Mitotic figures are numerous. The cords have definite polarity: they rest upon a basement membrane analogous to the inner limiting membrane of retina, and some have adjoining apical terminal bars analogous to outer limiting membrane. A typical feature is the clustering of neuroblasts around an empty central lumen defined by the terminal bars, creating a true rosette (Fig. 4.69). The basilar portion of the rosette or cord faces a hyaluronic acid-rich myxoid matrix analogous to the vitreous. This histologic feature may be found in only a few foci within a huge mass that is otherwise composed of poorly differentiated, neuroblastlike cells, and has abundant necrosis. Many tumors also contain foci of cartilage, skeletal muscle, or brain tissue and are classified as teratoid medulloepitheliomas. Metastases are not recorded.

Bibliography

Bellhorn, R. W. Ciliary body adenocarcinoma in the dog. *J Am Vet Med Assoc* **159:** 1124–1128, 1971.

Broughton, W. L., and Zimmerman, L. E. A clinicopathologic study of 56 cases of intraocular medulloepitheliomas. *Am J Ophthalmol* **85:** 407–418, 1978.

Eagle, R. C., Font, R. L., and Swerczek, T. W. Malignant medulloepithelioma of the optic nerve in a horse. *Vet Pathol* **15:** 488–494, 1978.

Lahav, M. *et al.* Malignant teratoid medulloepithelioma in a dog. *Vet Pathol* **13:** 11–16, 1976.

Langloss, J. M., Zimmerman, L. E., and Krehbiel, J. D. Malignant intraocular teratoid medulloepithelioma in three dogs. *Vet Pathol* **13:** 343–352, 1976.

Wilcock, B., and Williams, M. M. Malignant intraocular medulloepithelioma in a dog. *J Am Anim Hosp Assoc* **16:** 617–619, 1980.

F. Feline Posttraumatic Sarcoma

This syndrome seems unique to cats. As the name implies, eyes subjected to trauma, especially penetrating

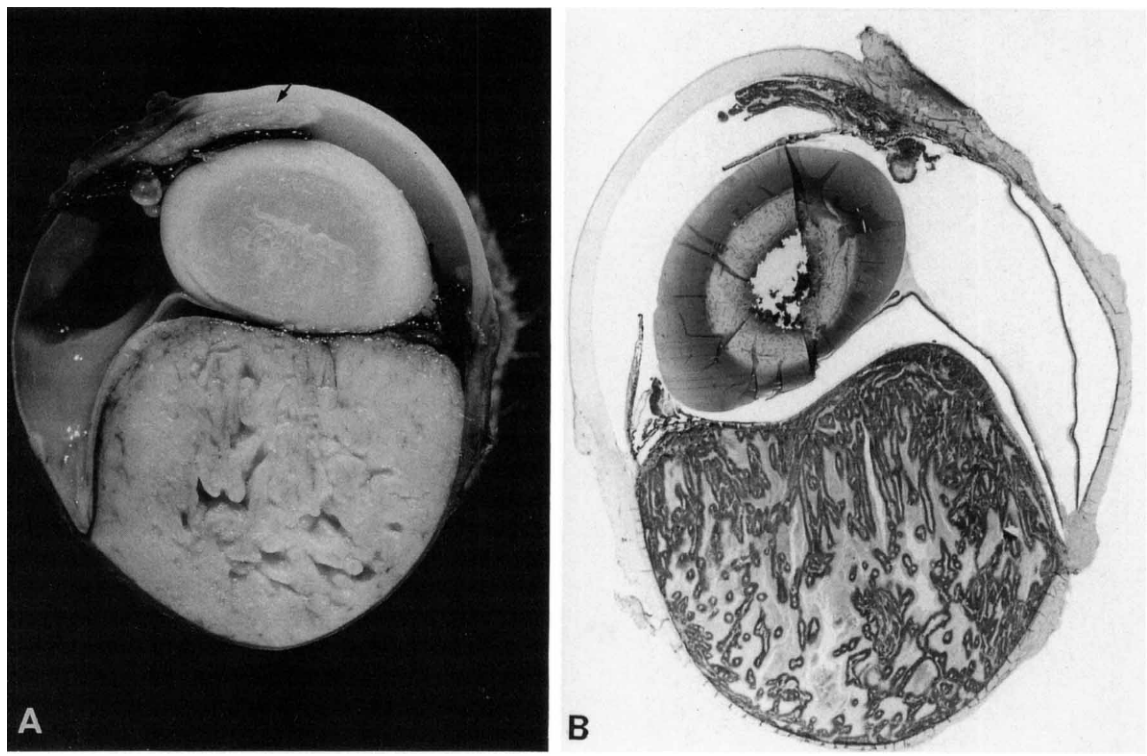

Fig. 4.68 Medulloepithelioma. Dog. (A) The main tumor lies between choroid and retinal pigment epithelium. There is also tumor in anterior chamber (arrow). (B) Histologic section of (A). Note tubular latticework of the tumor.

injury, are prone to develop pleomorphic spindle cell sarcomas that destroy the globe and have substantial risk of metastasis. The interval between injury and observed tumor varies from 5 months to 11 years. Those skeptical about claiming such neoplasia to be the result of an injury 10 years previously prefer to call these tumors primary ocular sarcomas, although such lag times are common in experimental models of carcinogenesis. The risk for injured eyes to develop sarcoma is unknown. Almost all recorded cases have perforated lenses, leading to speculation that these tumors represent malignant transformation of the perilenticular fibroplasia and epithelial metaplasia that characterizes phacoclastic uveitis in all species. Of relevance to ocular surgeons is the development of sarcomas in cat eyes receiving prosthetic implants, presumably viewed by the eye as yet another form of trauma.

The tumor itself varies from fibrosarcoma to osteosarcoma to giant-cell tumor, varying even within the same eye. The tumor tends to line the inside of the eye, and then extend via scleral venous plexus or optic nerve to involve the orbit. Most cases are presented with advanced disease, and follow-up data to document the prevalence of metastasis are scant. Available evidence uniformly documents a metastatic prevalence of at least 60%.

Bibliography

Dubielzig, R. R. *et al.* Clinical and morphologic features of posttraumatic ocular sarcomas in cats. *Vet Pathol* **27:** 62–65, 1990.

Peiffer, R. L., Monticello, T., and Bouldin, T. W. Primary ocular sarcomas in the cat. *J Small Anim Pract* **29:** 105–116, 1988.

G. Optic Nerve Tumors

Although the optic nerve and adjacent retina can presumably develop all of the neoplasms of the central nervous system (excepting those from tissues like ependyma that are not present in the eye), documented examples are few indeed. Most are reported as individual case reports prior to the era of immunohistochemical markers that would have permitted more precise classification.

Primitive neuroepithelial tumors of optic nerve are occasionally seen in young dogs and in horses. They are composed of nests, cords, and rosettelike structures formed by small hyperchromatic neuroblastic cells with a very high mitotic index. Very rapid spread throughout the orbit and into brain occurs in affected dogs and in the one published equine case.

Spindle cell tumors, considered by some to be optic nerve meningiomas or neurofibrosarcomas, will be considered.

H. Orbital Neoplasms

Tumors may be primary within the orbit or arise by extension from adjacent structures or by hematogenous localization. They usually produce deviation or protru-

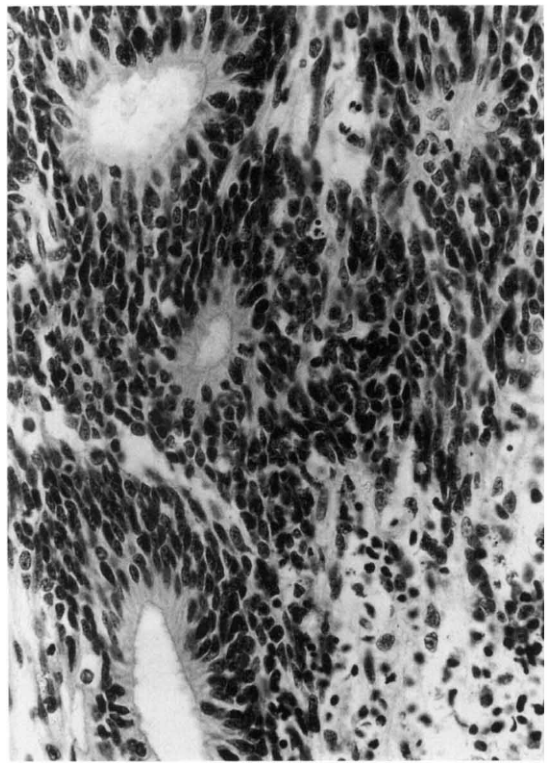

Fig. 4.69 Medulloepithelioma. Dog. Note rosette with rudimentary formation of retinal outer limiting membrane and photoreceptors.

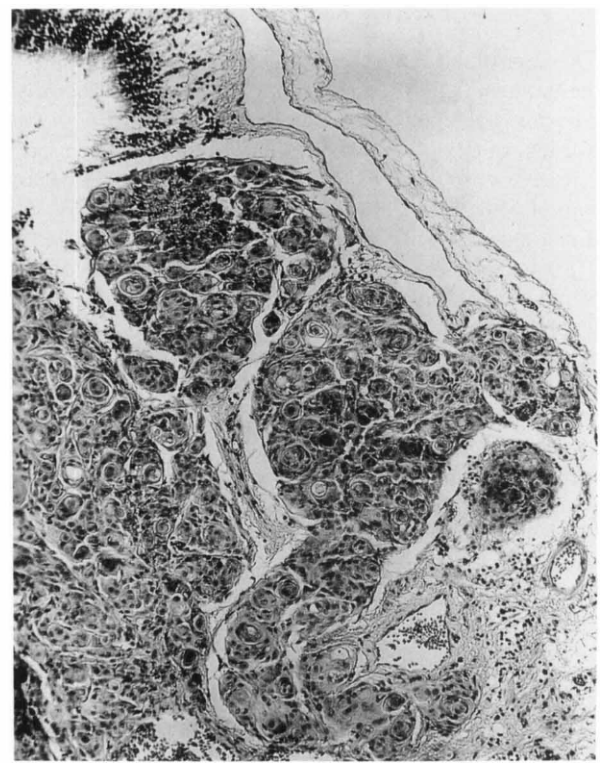

Fig. 4.70 Meningioma of optic nerve invading eye. Dog.

sion of the globe with secondary desiccation keratoconjunctivitis. In dogs, sarcomas and carcinomas are of almost equal prevalence, and primary orbital tumors are approximately equal in frequency to those arising by extension from nose, mouth, or distant sites. Of the primary orbital tumors, sarcomas are much more prevalent than epithelial tumors. The sarcomas are a bewildering array of locally infiltrative spindle cell tumors of unknown origin, with the abundance of diagnoses probably reflecting the diversity of pathologists' opinions rather than actual proof of histologic identity (Fig. 4.70). Metastasis is rare, but their infiltrative growth habit in this difficult site makes eventual elective euthanasia a frequent outcome. One tumor that does have a distinctive appearance is multilobular osteoma arising from the bones of the orbit, identical in appearance and behavior to this tumor elsewhere in the canine skull.

Most primary epithelial tumors of the canine orbit are lacrimal adenocarcinomas, which are locally invasive, recur after attempted resection, but are not noted to metastasize in what usually is a brief postoperative follow-up period. Tumors infiltrating the orbit from the nearby zygomatic salivary gland are similar histologically and behaviorally.

In other species, metastatic lymphoma is the only significant orbital tumor.

THE EAR

I. General Considerations

Diseases of the ear of domestic animals are of small interest to most veterinary pathologists. Of the three broad categories—defects of hearing, otitis media, and otitis externa—only otitis media in farm animals regularly receives some attention, but even that is usually restricted to macroscopic examination at necropsy. Otitis externa is almost exclusively the realm of the clinical practitioner, although hyperplasia of chronically inflamed epithelium within the external ear canal may simulate neoplasia and be submitted for histologic interpretation. Disorders of hearing certainly occur in domestic animals, but their prominence in the medical literature is the result more of their usefulness as models for human deafness than of their intrinsic importance in animals. The growing availability of equipment for evaluation of hearing may, however, see a resurgence of interest in deafness in specific breeds or colors of dogs and cats. The tedious task of preparing adequate sections of the cochlea and labyrinth when related to the relative importance or prevalence of the diseases makes examination of the inner ear a rare event in most veterinary institutions. The gross and microscopic anatomy of the ear in the various species is reviewed in specialized texts, and the appropriate references are included in the bibliography.

II. External Ear: Otitis Externa

Diseases of the external ear may be a local manifestation of generalized skin disease or may specifically affect the ear because of some anatomic or physiologic peculiarity. Disorders of skin that only incidentally affect the ear are discussed with diseases of the Skin and Appendages (Chapter 5).

Ear-tip necrosis may result from frostbite, cold-agglutinin disease, ergot poisoning, thrombosis during the course of septicemia, or from trauma inflicted by the animal itself or cannibalistic herdmates. Particularly in pigs, the prevalence of atrophic and misshapen ears may be quite high in individual herds. This usually results from septicemia, sarcoptic mange, or cannibalism. In some instances, however, no such history can be elicited, and a syndrome of infectious ear necrosis has been proposed. Culture of ears showing marginal lesions results in isolation of a variety of bacterial agents, and claims for a primary bacterial etiology are not convincing. The one that comes closest is the spirochete *Borrelia suilla*. It usually acts as an opportunistic contaminant of abraded skin in pigs, giving rise to localized (usually ear margins) or generalized ulcerative dermatitis.

Auricular hematoma occurs as a consequence of trauma, usually from excessive head shaking by dogs with otitis externa. Dogs and pigs with pendulous ears are particularly prone to hematoma formation, but cats are occasionally affected as well. Hematomas usually develop on the concave side of the pinna and are initially fluctuant but become firm as the hematoma (or blood-contaminated seroma) organizes. As it is converted to granulation tissue by fibroblastic and capillary ingrowth, the lesions become hard. Subsequent fibroblastic contraction may result in disfigurement of the pinna.

The location of the initial damage is unclear. Subcutaneous and subperichondrial sites are suggested but a predominantly intrachondral location seems most likely. The cartilage plate of the pinna is cleaved by a longitudinal fracture and then by the hemorrhage. Granulation tissue forms at the interface of blood and cartilage, and the lesion is eventually converted to a fibrous scar. Late in the reparative process, regeneration of cartilage occurs adjacent to perichondrium or the ruptured edge of the cartilage. The intrachondral location of the hematomas is thought to be the result of rupture of vessels as they pass through minute foraminae in the cartilage plate. The conventional view that the initial lesion results from shear forces or outright trauma caused by head shaking has recently been challenged by one study of 40 dogs and 20 cats with auricular hematoma. No association with ear configuration or otitis externa was found, but most affected animals had serum and local tissue changes interpreted as evidence for a lupuslike autoimmune disease. The link between this proposed pathogenesis and the observation of the early cartilaginous fractures and hemorrhages was not made.

Dermatologic disease of the ear pinna may be part of a generalized skin disorder, but a few diseases seem unique to the ear. Pigs with chronic sarcoptic mange may have gross lesions only on the ears, consisting of reddening, crusting, and thickening of the pinna. Short-haired dogs with pendulous ears (dachshunds, pointers, bloodhounds) are predisposed to a chronic dermatitis of the ear margin, variously termed marginal auricular dermatosis or ear margin seborrhea. The gross lesion is a multifocal, greasy, gray, nodular encrustation that may coalesce to cause thickening of the entire ear margin. The histologic lesion resembles that of seborrhea elsewhere with hyperkeratosis, acanthosis, and a mild superficial perivascular dermatitis in which mononuclear leukocytes predominate.

Chronic ulcerative dermatitis of the ear margin of white cats (feline solar dermatitis) is discussed below as a premalignant lesion under squamous cell carcinoma, as is a similar disease of sheep.

Alopecia of the pinna occurs in dogs and in Siamese cats. In dogs, the alopecia appears gradually and progresses slowly. In cats the lesion may wax and wane at irregular intervals throughout life. Microscopically there is bland pilosebaceous atrophy resembling endocrine alopecia, but the precise cause is unknown.

Pinnal vasculitis is surprisingly frequent and resembles the lesion of cutaneous vasculitis elsewhere. In its mildest form, it may cause only pilosebaceous atrophy and thus may mimic the lesions of idiopathic pinnal alopecia when examined clinically.

Otitis externa is a very common disorder in dogs and cats, and is probably equally common in goats. In dogs, the pathogenesis is complex, while in cats and goats, the ear mite is by far the major initiating factor. Otitis externa in dogs is most prevalent in breeds with pendulous ears or with abundant hair within the ear canal, which implies that inadequate circulation of air and entrapment of moisture are important predispositions to the disease. Foreign bodies, usually foxtail or grass awns, may be important mechanical irritants, creating a breach for microbial infection, but since otitis is common in city dogs, other factors apparently are involved. The role of microorganisms in the pathogenesis of otitis externa is, as elsewhere, intimately linked to environmental circumstances that permit their uncontrolled proliferation. The bacteria and fungi cultured from diseased ears almost invariably are members of the normal aural flora. *Staphylococcus* spp., *Pseudomonas* spp., *Proteus* spp., and the yeast *Malassezia pachydermatis* (syn. *Pityrosporum canis*) are cultured much more frequently or in greater numbers from ears with otitis than from normal ears, but this may relate as much to their resistance to antibiotic treatment as to their causative role. The lipid-rich environment of the ear canal favors the lipophilic *Malassezia*, which is the best candidate for a primary pathogen in the causation of canine otitis externa, inasmuch as it frequently is the only pathogen isolated, and affected ears improve dramatically with antifungal therapy.

Otitis externa in species other than dogs is closely correlated to infestation with **ear mites**, and even in dogs, acariasis is an important cause of otitis.

Otodectes cyanotis is the ear mite of carnivores. The importance of the mite in initiating otitis externa is not entirely clear because the ear canal, once inflamed, becomes an environment unsuitable for the mites and thus gives rise to misleadingly low estimates of the prevalence of ear mites in dogs with otitis. As few as five mites can initiate otitis externa in dogs, with bacterial and mycotic opportunists rapidly masking the role of mites in the development of the lesion. Estimates vary from 2 to 50% prevalence of mites in dogs with otitis externa.

In cats, the role of mites is firmly established. In contrast to dogs, all cats have erect and sparsely-haired pinnae, and the role of ear carriage and hair is negligible. There is a poor correlation between the number of mites, the severity of inflammation in the external meatus, and clinical signs.

The mites are obligate parasites, spending their entire 3- to 4-week life cycle on the host. Transmission between animals of the same or different species readily occurs, and spread of the mites from their preferred aural niche to paws as the animal scratches, or tail as it sleeps with tail curled to touch the ear, is occasionally seen.

The mechanism by which the mites initiate otitis is controversial. Some maintain that the mites feed only on epithelial debris, while others claim that the mites pierce the epithelium and ingest blood and lymph. The latter claim is supported by the demonstration of host-specific serum components within the mites, but such components could exist in exudates, and should not be considered proof of penetrating feeding behavior.

The variation in the number of mites necessary to cause clinically obvious otitis, the species variation, and some tenuous age resistance to disease (if not infection) suggest an allergic basis for the otitis. Most cats, and perhaps dogs, probably are infected with mites at some time. They may react to subsequent minor infection with immune-mediated inflammation of a severity not predicted by the small number of mites within the ear canal.

Psoroptes cuniculi is the ear mite of rabbits that also affects goats, horses, and deer. Its prevalence among domestic animals seems to be greatest in goats, ranging from about 20 to 80%. Careful examination may be required to find the mites. Clinical signs in goats, if present at all, are usually mild, consisting of ear twitching and head shaking. The ear canal of goats is the best site for isolation of several pathogenic *Mycoplasma* species in clinically normal animals. The same mycoplasmas were isolated from ear mites (*P. cuniculi* or *Raillietia caprae*) of infected goats, fueling speculation that the mites are important vectors of the mycoplasmas in endemic herds. Similar coexistence of ear mites and mycoplasmas has been observed in cattle, but identification of the bacteria within the mites was not reported.

Psoroptes cuniculi may be quite common in horses (20% of horses in one Australian report), but it is unclear how frequently it causes clinical signs. Head shaking and resentment of handling of the ears are the usual signs.

Raillietia auris, the ear mite of cattle, occurs in most areas of the world. Infection may be common but is rarely of clinical significance. Manifestations of disease may follow extension of the otitis externa through the tympanum, and affected animals show head tilt and circling due to otitis interna.

Otobius megnini, the spinose ear tick, is parasitic on domestic ruminants, pigs, horses, and dogs, and cats in restricted geographic areas. Infestation may be so heavy that the ear canals are full of ticks, making diagnosis easy. In light infestations, they occur deep in the folds of the ear, at the bottom of the external meatus. Only the larvae and nymphs are parasitic. The larvae attach themselves to the skin below the hairline and, biting through the skin, suck lymph until they are engorged. The parasites irritate the external auditory meatus, and the ensuing exudate may completely fill it. In addition, secondary bacterial infection may occur in the inflamed areas around the bite wounds, and this infection may extend downward and cause otitis media. The microscopic appearance of the ear in this infestation has not been described.

Otitis externa is a nonspecific lesion. The relationship between type of exudate and causative agent has not been critically evaluated. The initial macroscopic lesion is hyperemia of the external auditory meatus followed by accumulation of serum, cerumen, leukocytes, and epithelial debris. A predominance of leukocytes tends to produce a suppurative exudate, whereas cerumen yields a dry, dark brown, crumbly accumulation.

The histopathology of otitis externa varies with the duration of the inflammation and is rather typical inflammation of any epithelial surfaces. Only chronic lesions are likely to be seen by the pathologist. Such specimens show epidermal hyperplasia with acanthosis, atrophy of hair follicles, hyperkeratosis, and parakeratosis. Crusts of inflammatory debris adhere to the epithelial surface. Ulceration may be present, particularly if *Pseudomonas* is predominant and *Malassezia* yeasts may be seen in the surface keratin or debris. The dermis contains numerous lymphocytes, plasma cells, mast cells, and neutrophils, the latter usually within dilated venules or adjacent to ulcers. Neutrophils are very sparse in mite-induced otitis. In very chronic and severe examples, dermal fibrosis is marked, and ossification may occur. A feature of chronic otitis externa is increased production of cerumen. Histologically there is hyperplasia of the normally very large sebaceous glands and cystic hyperplasia of the coiled, tubular, apocrine ceruminous glands, which are distended by eosinophilic cerumen. The combination of epithelial hyperplasia, glandular hyperplasia, and stromal fibroplasia may create proliferative lesions that occlude the ear canal and simulate neoplasia.

Bibliography

Cook, R. W. Ear mites (*Raillietia manfredi* and *Psoroptes cuniculi*) in goats in New South Wales. *Aust Vet J* **57:** 72–75, 1981.

Cottew, G. S. Mycoplasmas in ears. *Aust Vet J* **62:** 420, 1985.

Cottew, G. S., and Yeats, F. R. Mycoplasmas and mites in the ears of clinically normal goats. *Aust Vet J* **59:** 77–81, 1982.

Dubielzig, R. R., Wilson, J. W., and Seireg, A. A. Pathogenesis of canine aural hematomas. *J Am Vet Med Assoc* **8:** 873–876, 1984.

Fernando, S. D. A. Certain histopathologic features of the external auditory meatus of the cat and dog with otitis externa. *Am J Vet Res* **28:** 278–282, 1967.

Gedek, B. *et al.* The role of *Pityrosporum pachydermatis* in otitis externa of dogs: Evaluation of a treatment with miconazole. *Vet Rec* **104:** 138–140, 1979.

Kowalski, J. J. The microbial environment of the ear canal in health and disease. *Vet Clin North Am: Small Anim Pract* **18:** 743–754, 1988.

Kuwahara, J. Canine and feline aural hematoma: Clinical, experimental, and clinicopathologic observations. *Am J Vet Res* **47:** 2300–2308, 1986.

Larsen, S. Intrachondral rupture and hematoma formation in the external ear of dogs. *Pathol Vet* **5:** 442–450, 1968.

Littlejohn, A. I. Psoroptic mange in the goat. *Vet Rec* **82:** 148–155, 1968.

Menzies, G. C. The cattle ear mite, *Raillietia auris* (Leidy, 1872) in Texas. *J Parasitol* **43:** 200, 1957.

Powell, M. B. *et al.* Reaginic hypersensitivity in *Otodectes cynotis* infection of cats and mode of mite feeding. *Am J Vet Res* **41:** 877–882, 1980.

van der Gaag, I. The pathology of the external ear canal in dogs and cats. *Vet Q* **8:** 307–327, 1986.

Weisbroth, S. H. *et al.* Immunopathology of naturally occurring otodectic otoacariasis in the domestic cat. *J Am Vet Med Assoc* **165:** 1088–1093, 1974.

Williams, J. F., and Williams, C. S. F. Psoroptic ear mites in dairy goats. *J Am Vet Med Assoc* **173:** 1582–1583, 1978.

III. Middle Ear: Otitis Media

Otitis media is inflammation of the tympanic cavity within the temporal bone. Its cause is almost always bacterial, the organisms reaching the poorly drained cavity via the Eustachian tube or following perforation of the tympanum. In swine and lambs, the infection usually ascends from the pharynx via the Eustachian tube. In dogs and cats, chronic otitis externa is the major predisposition, although the tympanum is quite resistant to inflammatory lysis. There are insufficient cases recorded in other species to permit generalization. In all species there is circumstantial evidence for hematogenous localization of infection in the middle and inner ear, perhaps occurring most often in pigs.

Otitis media as a clinically obvious entity is most frequent in feeder pigs. The infection is usually unilateral and associated with hemolytic streptococci. The clinical signs of head tilt, circling, and ataxia suggest involvement of the inner ear in most instances. Otitis media in swine may occur as small epizootics involving a dozen or more pigs. The basis for the clustering of the disease is unproven, but its sporadic association with atrophic rhinitis suggests spread from the upper respiratory tract. In lambs, the lesion is usually clinically undetected and unilateral, and often occurs in association with pneumonia. *Pasteurella hemolytica* is the usual isolate from both ear and lung. Bottle feeding also increases the prevalence of otitis media in lambs.

Regardless of the route of entry, the lesion and its progression are similar. The epithelium lining the tympanic cavity is hyperemic, edematous, and may be ulcerated. Neutrophils exuding from the reactive vessels under the epithelium enter the tympanic cavity, joining the initially serous or serofibrinous exudate to make it progressively more purulent. Exudate may temporarily drain into the pharynx via the Eustachian tube, which is soon sealed by inflammatory swelling of its epithelium. In severe infections, the exudate escapes via inflammatory lysis of the tympanum or, rarely, the bone on the ventral floor of the tympanic bulla. Chronic inflammations are characterized by inspissation of exudate, lysis of the ossicles, and occasionally, the tympanum, and spread to inner ear and brain stem.

Bibliography

Jensen, R. *et al.* Middle ear infection in feedlot lambs. *J Am Vet Med Assoc* **181:** 805–807, 1982.

Macleod, N. S. M., Wiener, G., and Barlow, R. M. Factors involved in middle ear infection (otitis media) in lambs. *Vet Rec* **91:** 360–362, 1972.

Olson, L. D. Gross and microscopic lesions of middle and inner ear infections in swine. *Am J Vet Res* **42:** 1433–1440, 1982.

IV. Inner Ear

A. Otitis Interna

Otitis interna is almost always the result of infection spreading from the middle ear. The inflammation is usually of bacterial origin and thus suppurative. Ascension via the eighth nerve is relatively frequent and results in focal suppurative meningitis or encephalitis in the region of the pons. The usual clinical syndrome is vestibular dysfunction, described in a subsequent section.

B. Deafness

Deafness is difficult to assess in animals, and its diagnosis by simply observing behavioral abnormalities is almost impossible unless the animal is totally and bilaterally deaf. The recent introduction of electrodiagnostic tests has identified a higher prevalence of deafness, especially in dogs, than was suspected. Conductive deafness results from interference with the conduction of sound to the sensory end organ (of Corti) by diseases of external or middle ear. Alternatively, **sensorineural deafness** results from maldevelopment or degeneration of the sensory organ, eighth nerve, or auditory pathways within the brain. The last is very unusual and, because of the multitude of possible pathways, is seen only in massive destructive lesions with their neurologic signs overshadowing the hearing loss. Nerve deafness usually involves the organ of Corti, and is by far the most prevalent type of deafness encountered in animals by virtue of hereditary deafness in several breeds of dogs, and in dogs or cats with color-dilution anomalies. Conductive deafness may result from oblitera-

tion of the external auditory meatus by chronic proliferative inflammation or tumor, from inflammatory or traumatic rupture of the tympanum, or from entrapment of the ossicles in exudates or granulation tissue. Rarely there is destruction of the middle or inner ears by osteomyelitis or neoplasia.

The anatomy of the auditory apparatus is complex. The sensory fibers of the eighth cranial nerve terminate at the base of sensory hair cells within the organ of Corti, the latter a sensory specialization of the epithelium lining the cochlear duct. Excitation of the hair cells results from pulsations within the endolymph fluid that fills the entire membranous labyrinth, including cochlear duct. The precise mechanism of such excitation remains unknown. Sound waves in the environment reach the endolymph via the tympanum and ossicles. Vibration of the tympanum is transmitted to the ossicles, and vibration of the ossicles causes vibration of the oval window which separates the foot plate of the stapes from the endolymph. Any lesion that interferes with vibration of the tympanum or ossicle interferes with the establishment of fluid waves within the endolymph. Traumatic fracture of ossicles, rupture of tympanum, or dampening of vibration by exudates within middle ear can do this.

1. Hereditary Cochleosaccular Degeneration

Hereditary deafness in association with incomplete pigmentation of hair coat and uvea is seen in cats, dogs, mink, and mice. Incompletely documented examples exist in other domestic species. The pigmentary defect is not true albinism but is white spotting or merling, the distinction being the absence of melanocytes in white areas in the latter instance and functionally defective melanocytes in the former. In some instances the hearing defect is associated with inheritance of the merling gene. All homozygotes and many of the heterozygotes are deaf and have some degree of iris heterochromia. In other instances there is heterochromia iridis but no apparent coat color dilution (Dalmatian dogs), while in others, both eyes and coat are phenotypically normal. Even when the coat color is white, as in deaf bull terriers, the genetic basis for the white coat and the associated deafness need not be the merling gene. Out of this confusing picture one should rescue the concept that color-dilute animals have ocular heterochromia and deafness much more frequently than normal animals, but that other genetic bases for deafness also exist. Ocular anomalies and deafness commonly are encountered in the same animal, probably the result of the inductive influence of pigmentation on both organs. For example, all white cats with blue irises are deaf, as are many Dalmatian dogs with iris heterochromia. Several dog breeds, particularly Dalmatians and English setters, have a prevalence of early-onset deafness in excess of that predictable from their prevalence in the overall canine population. Prominent also are merle dogs such as Australian shepherds, Australian blue heelers, old English sheepdogs, and Great Danes.

The fully developed lesion of cochleosaccular degeneration is atrophy of the sensory and supporting cells of the organ of Corti and the saccular macula, collapse of the dorsal or lateral walls of the cochlear and saccular membranous labyrinth, and secondary degeneration of the neurons within the spiral ganglion. The osseous portion of the labyrinth is unaffected, as is the vestibular portion of the inner ear. With minor variations, all cases in dogs and cats are similar. Initial structure and function are normal, but there is failure to achieve normal maturation and, subsequently, degeneration occurs.

The carnivore ear is completely developed at birth and continues to mature for 2 (organ of Corti) to 4 (stria vascularis) weeks. Thereafter, the epithelial lining of the cochlear duct is incapable of mitotic regeneration. In white kittens, the ear is morphologically and physiologically normal at birth but shows arrested development as early as 1 week of age. At this time there is inward sagging of the free dorsolateral wall of the cochlear duct (Reissner's membrane) and saccule, and hydropic change in the stria vascularis. The degeneration within the organ of Corti and adjacent nutritive stria vascularis is so rapid that there is no consensus as to the initial or causal lesion. It may be that degeneration of the stria vascularis results in ischemic degeneration of the avascular organ of Corti, or there may be a primary defect within the sensory cells themselves resulting from an inborn metabolic error.

2. Senile Deafness

Many animals become hard of hearing as they reach old age. This phenomenon, called presbyacusis, is more frequently observed in old dogs because dogs tend to be kept well into their advanced years and because hearing loss is more readily noticed in them than in other species. In humans the loss of hearing is progressive from about the fortieth year of life and particularly affects hearing of high tones. The cause seems to be inherent age-related degeneration of the epithelial tissues within the cochlea and of the spiral ganglion, a process that may be accelerated by excessive noise, arteriosclerosis, and nutritional factors. The essential lesions are atrophy of all epithelial structures within the cochlear duct and the associated auditory nerves, as well as neuronal atrophy within the spiral ganglion. Occasionally, the major lesion is atrophy within the stria vascularis or the basal membrane supporting the organ of Corti.

Presbyacusis in animals has been studied in guinea pigs, rats, mice, dogs, and cats. Degeneration of the hair cells in the organ of Corti and loss of neurons from the spiral ganglion are the common denominators in all such instances, and presumably is the aging change common to all mammalian species. Stria vascularis atrophy has not been seen in these animals.

3. Acoustic and Chemical Ototoxicity

Noise, either as a sudden loud noise or as moderate but prolonged environmental background, causes degeneration of the sensory hair cells within the organ of Corti. Loud noise causes hair cell necrosis and even outright

disruption of the organ of Corti or Reissner's membrane by mechanical trauma, mediated via fluid waves within the endolymph that must be the otic equivalent of tidal waves. Environmental noise is frequently an occupational hazard. The eventual lesion is hair cell necrosis, but whether this results from repeated sublethal microtrauma by noise peaks or by interference with hair cell metabolism is not known. That animals are susceptible to such trauma is well established in experimental models, but investigation of naturally occurring examples is not reported.

The list of chemicals that are ototoxic is very long, and is even longer if idiosyncratic drug injury is included. Only a few major examples likely to be encountered in veterinary practice are included here.

Aminoglycoside antibiotics (gentamicin, streptomycin, kanamycin, neomycin, and others) are all nephrotoxic and ototoxic in proportion to their blood levels and duration of administration. Overdosing, or administration to animals with decreased renal function, markedly increases the risk of toxic injury to the inner ear. Clinical signs of vestibular dysfunction precede evidence of hearing impairment. The initial lesion affecting hearing is degeneration of the apical portion of cochlear hair cells. The earliest visible lesion is mitochondrial swelling and increased number of myelin figures. The early lesion is reversible but later becomes permanent, presumably as mitochondrial swelling leads to structural disintegration of cellular respiratory enzymes and cell death. Cats are particularly susceptible, and vestibular toxicity (defects of posture, balance, and gait) precedes clinical evidence of hearing loss. Ordinarily, these signs appear only after several weeks of aminoglycoside therapy.

The **diuretics** furosemide, bumetanide, and ethacrynic acid are chemically related, and all are ototoxic to dogs and cats. Other domestic species have not been tested. Electrophysiologic evidence of hearing impairment occurs within a few hours of even a single high dose but is unaccompanied by structural changes within the cochlea. The exception is ethacrynic acid intoxication, in which edema of the stria vascularis is seen ultrastructurally. There is a corresponding alteration in the composition of the endolymph produced by the stria. The hearing impairment, which occurs frequently in humans receiving therapeutic doses of the drugs, is assumed to result from structural or physiologic lesions in the hair cells nourished by this abnormal endolymph.

Acetylsalicylic acid (aspirin) and its derivatives are ototoxic for humans and several laboratory animal models, but no structural lesion has yet been detected.

The antibacterial–anthelmintic agent, **hygromycin B,** as well as causing cataracts in swine (see the Eye) also causes permanent deafness in dogs if therapeutic dosages are given. The drug is not approved for use in dogs. Deafness is reported occasionally in swine receiving the medication in excess of recommended levels. Histologic descriptions of cochlear lesions are not available.

The antiseptic combination of chlorhexidine and cetrimide (Savlon) is a widely used antiseptic that occasionally is used to cleanse the external ear canal. If used in dogs or cats with a ruptured typanic membrane, this solution is toxic to both vestibular and cochlear cells, although the clinical signs in affected animals are primarily vestibular.

4. Other Causes of Deafness

Deafness is reported in humans with various storage diseases, but few animal counterparts have been studied for this specific defect. Goats with β-mannosidosis have deformed ear pinnae, bony exostoses within the tympanic cavity, and deforming accumulation of oligosaccharides within lysosomes of many tissues of middle and inner ear. Epithelial and mesothelial cells of Reissner's membrane, most structural cells of the organ of Corti, and cochlear neurons of the spiral ganglion are all affected, even at a few days of age.

C. Vestibular Dysfunction

Vestibular dysfunction is characterized by head tilt and falling toward the affected side, ataxia without weakness, and nystagmus. Clinical signs are most obvious with unilateral disease. The lesion may be in brain or in the vestibular apparatus, or both. Animals with vestibular dysfunction caused by brain lesions, as in listeriosis or canine distemper, usually show other signs of neurologic dysfunction. Since vestibular signs are more readily detected than is partial hearing loss, mild lesions of the inner ear are more frequently associated with vestibular abnormalities than with hearing deficits.

The causes of peripheral vestibular disease are the same as those causing deafness: uncontrolled otitis media, trauma, invasive neoplasia, and a number of drugs. Congenital vestibular disease has been reported in several dog breeds, but no morphologic observations were given. Nonspecific destruction of part or all of the vestibular apparatus as a sequel to otitis media is by far the most common cause of labyrinthitis in all species.

Idiopathic vestibular disease occurs in old dogs and in cats of any age. In old dogs it is often mistakenly diagnosed as an acute cerebrovascular accident (stroke), but there is no demonstrable brain lesion in such dogs, and most have rapid, spontaneous remission of clinical signs unless prevented by premature euthanasia. No histologic examination of the labyrinth has been reported. An equally mysterious acute vestibular dysfunction affects cats of any age. Recovery usually occurs over a few days to weeks. No lesions are reported.

Bibliography

Bedford, P. G. C. Congenital vestibular disease in the English cocker spaniel. *Vet Rec* **105:** 530–531, 1979.

Blauch, B., and Martin, C. L. A vestibular syndrome in aged dogs. *J Am Anim Hosp Assoc* **10:** 37–40, 1974.

Braniš, M., and Burda, H. Inner ear structure in the deaf and normally hearing Dalmatian dog. *J Comp Pathol* **95:** 295–299, 1985.

Brown, R. D. *et al.* Comparative acute ototoxicity of intravenous

bumetanide and furosemide in the pure-bred beagle. *Toxicol Appl Pharmacol* **48:** 157–169, 1979.
Coleman, J. W. Hair cell loss as a function of age in the normal cochlea of the guinea pig. *Acta Otolaryngol* **82:** 33–40, 1976.
Deol, M. S. The relationship between abnormalities of pigmentation and of the inner ear. *Proc R Soc Lond* **175:** 201–217, 1970.
Gallé, H. G., and Vanker-van Haagen, A. J. Ototoxicity of the antiseptic combination chlorhexidine/cetrimide (Savlon): Effects on equilibrium and hearing. *Vet Q* **8:** 56–60, 1986.
Hayes, H. M. *et al.* Canine congenital deafness: Epidemiologic study of 272 cases. *J Am Anim Hosp Assoc* **17:** 473–476, 1981.
Igarashi, M. *et al.* Inner ear anomalies in dogs. *Arch Otorhinolaryngol* **81:** 249–255, 1972.
Knowles, K. *et al.* Reduction of spiral ganglion neurons in the aging canine with hearing loss. *J Vet Med A* **36:** 188–199, 1989.
Liberman, M. C., and Kiang, N. Y. S. Acoustic trauma in cats. Cochlear pathology and auditory-nerve activity. *Acta Otolaryngol (Suppl)* **358:** 1–63, 1978.
Mair, I. W. S. Hereditary cochleosaccular degeneration. *In* "Spontaneous Animal Models of Human Disease" E. H. Andrews, B. C. Ward, and N. H. Altman (eds.), Vol. 1, pp. 86–88. New York, Academic Press, 1979.
Mair, I. W. S. Hereditary deafness in the Dalmatian dog. *Arch Otorhinolaryngol* **212:** 1–14, 1976.
Quick, C. A. Chemical and drug effects on inner ear. *In* "Otolaryngology" M. M. Paparella and D. A. Shumrick (eds.), Vol. 2, pp. 391–406. Philadelphia, Pennsylvania, Saunders, 1973.
Render, J. A., Lovell, K. L., and Jones, M. Z. Otic pathology of caprine β-mannosidosis. *Vet Pathol* **25:** 437–442, 1988.
Watson, A. D. J., and Burnett, D. C. Hygromycin B and deaf dogs. *Aust Vet J* **66:** 302–303, 1989.
Wilkes, M. K., and Palmer, A. C. Congenital deafness in dobermans. *Vet Rec* **118:** 218–219, 1986.
Wright, Ch. G. Neural damage in the guinea pig cochlea after noise exposure. A light microscopic study. *Acta Otolaryngol* **82:** 82–94, 1976.

V. Neoplasms and Similar Lesions

Neoplasms of the ear include those capable of affecting skin elsewhere, as well as primary tumors of ceruminous glands and, very rarely, tumors of Eustachian or auditory epithelium and of cranial nerves. Inflammatory polyps are included in this section because of their gross resemblance to neoplasia.

Squamous cell carcinoma is by far the most important skin tumor affecting the ear, although the predilection of canine histiocytoma for the ear pinna probably makes it the most frequent tumor affecting the pinna. Squamous cell carcinoma of the ear occurs commonly in white cats, with a frequency more than 10 times that of nonwhite cats, and in sheep in sunny climates. In cats, the tumor has a long precancerous phase consisting of erythematous, ulcerative dermatitis of the ear margin, known as feline solar or actinic dermatitis because of its association with exposure to sunlight. Other sparsely haired areas, such as nose, lips, and eyelids, may be affected. Histologically, the lesion consists of multifocal coalescing epidermal necrosis overlying a diffuse superficial dermal infiltrate of lymphocytes and plasma cells. The lesion waxes and wanes with the intensity of sunlight. Epidermal hyperplasia proceeds to dysplasia, carcinoma *in situ*, and invasive squamous cell carcinoma in a manner analogous to bovine ocular squamous cell carcimona. The lesion is bilateral but not necessarily of synchronous progression. The progression to invasive neoplasia usually occurs over 3 or 4 years. Metastasis is a late occurrence and prevented (at least in the case of ears) by amputation. Rarely, squamous cell carcinoma occurs within the external ear canal or even within the tympanic cavity of the middle ear. Local infiltration results in damage to the seventh cranial nerve with resultant signs of vestibular dysfunction and facial paralysis.

Neoplasms of the ceruminous glands occur in dogs and cats. The tumors are very similar to those of apocrine sweat glands. The ceruminous glands are modified sweat glands within the deep portion of the external auditory meatus. Tumors are relatively more prevalent in cats than in dogs, and in both species they tend to occur in very old animals. In dogs most are benign, but in cats about half are histologically malignant. The adenomas are smooth, nodular, or pedunculated masses seldom exceeding 1.0 cm in diameter. The epithelium overlying the tumor is intact unless there is concurrent otitis externa. Ceruminous gland tumors cannot be distinguished in the live animal from cystic dilatation with epithelial hyperplasia typical of chronic otitis externa. Carcinomas may occasionally invade from the auditory meatus into the region of the parotid salivary gland or into bone, and when very anaplastic, may be confused with salivary carcinoma. The diagnosis of carcinoma usually is based on histologic criteria of anaplasia and local invasiveness rather than on behavioral evidence of metastasis.

Histologically, adenomas are well-differentiated tubular and cystic growths. The epithelial cells are cuboidal and eosinophilic. They may be flattened when the tubular or acinar lumen is dilated. The most typical feature is the presence within lumina of deeply eosinophilic or orange, colloidlike secretion typical of cerumen. Mixed ceruminous tumors analogous to mixed apocrine sweat glands or mammary tumors occur infrequently. Carcinomas do not differ markedly from adenomas but have less secretion and more cellular anaplasia, and show invasion by tumor cells into an abundant fibrous stroma rich in mononuclear leukocytes. Mixed tumors with cartilage and bone are described.

As expected, a variety of other neoplasms have been described in the external ear canal or tympanic cavity of dogs and cats. All would seem to be rare, and no prognostic statements are justified by the small numbers. In one small series in dogs, eight of eleven middle ear neoplasms originated in the external ear and perforated the tympanic membrane. Two were papillary adenomas formed by ciliated columnar epithelium and goblet cells, thought to have arisen from the epithelium of the dorsal portion of the tympanic cavity. The final case was an anaplastic carcinoma of unknown origin involving oropharynx and ear.

Paraganglioma and fibroma in dogs, and fibrosarcoma in cats, are represented by single case reports.

Inflammatory polyps are observed in dogs and more frequently in cats with clinical signs of head shaking, head tilt, ataxia, or nystagmus. These may be the most common "tumor" of the feline ear canal. In cats, the lesion is a loose mass of connective tissue containing numerous small blood vessels and mononuclear leukocytes, covered by epithelium that may be either stratified, nonkeratinized squamous, or simple to bilayered ciliated columnar. Often the ciliated epithelium is found only focally, but nonetheless it is the characteristic feature distinguishing this lesion from nonspecific proliferations of glands and connective tissue seen in many cases of chronic otitis externa. The presence of this ciliated epithelium is used to support theories that such polyps originate from the Eustachian tube, but only rarely has that opinion been confirmed by careful dissection. An alternative origin could be from ciliated epithelium of the tympanic cavity itself. Some of these polyps are grotesque, protruding from outer ear, hanging into the oropharynx, or even protruding through the nose. A familial occurrence has been seen in Abyssinian and Himalayan kittens, further confusing the debate about the cause of these distinctive lesions.

Under the umbrella of inflammatory polyp fall many of the tumorlike proliferations excised from the external ear canal of dogs (rarely cats) with chronic otitis externa. The lesion consists of variable proportions of hyperplastic surface epithelium, hyperplastic or dysplastic sebaceous and ceruminous glands, fibroplasia, and leukocytes. The rupture of the glands often adds the lesions of sterile foreign body periadenitis to the chronic inflammation associated with the bacteria, yeast, or foreign bodies causing the initial otitis itself.

Another nodular lesion, clinically resembling neoplasia, is the dentigerous cyst of heterotopic polyodontia in foals, seen as a draining nodule on the anterior aspect of the base of the pinna.

Bibliography

Bradley, R. L. *et al.* Nasopharyngeal and middle ear polypoid masses in five cats. *Vet Surg* **14:** 141–145, 1985.

Harvey, C. E., and Goldschmidt, M. H. Inflammatory polypoid growths in the ear canal of cats. *J Small Anim Pract* **19:** 669–677, 1978.

Indrieri, R. J., and Taylor, R. F. Vestibular dysfunction caused by squamous cell carcinoma involving the middle ear and inner ear in two cats. *J Am Vet Med Assoc* **184:** 471–473, 1984.

Legendre, A. M., and Krahwinkel, D. J., Jr. Feline ear tumors. *J Am Anim Hosp Assoc* **17:** 1035–1037, 1981.

Little, C. J. L., Pearson, G. R., and Lane, J. G. Neoplasia involving the middle ear cavity of dogs. *Vet Rec* **124:** 54–57, 1989.

Patnaik, A. K., and Birchard, S. J. Canine paraganglioma: A case report. *J Small Anim Pract* **26:** 681–687, 1985.

Pulley, L. T., and Stannard, A. A. Tumors of skin and soft tissue. *In* "Tumors in Domestic Animals" 2nd Ed., J. E. Moulton (ed.), pp. 58–59. Berkeley, California, University of California Press, 1978.

Rogers, K. S. Tumors of the ear canal. *Vet Clin North Am: Small Anim Pract* **18:** 859–868, 1988.

Stanton, M. E. *et al.* Pharyngeal polyps in two feline siblings. *J Am Vet Med Assoc* **186:** 1311–1313, 1985.

Stone, E. A., Goldschmidt, M. H., and Littman, M. P. Squamous cell carcinoma of the middle ear in a cat. *J Small Anim Pract* **24:** 647–651, 1983.