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.

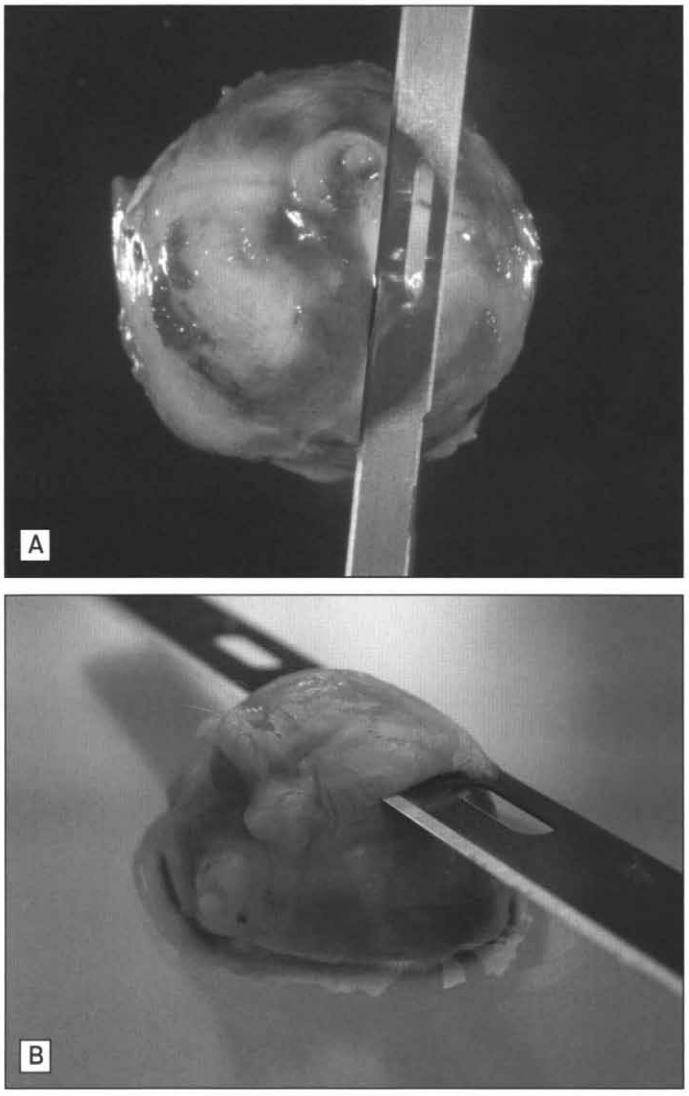

Figure 4.1 A. Trimming a fixed eye. The first incision is made from back to front, perpendicular to the posterior ciliary artery and just adjacent to the optic nerve. **B.** The second cut, made from front to back to avoid detaching the retina, is parallel to the first and far enough to the periphery to miss the lens.

perhaps the single biggest contributor to sections of poor quality. *The optimal cutting instrument is a new disposable microtome blade.* For small globes less than about 1 cm in diameter, an ordinary consumer razor blade is perfectly adequate.

Because there is no easily accessible instruction manual on how to obtain a good histologic section, those details are included here.

- The fixed globe, free of extraocular muscles and eyelids, is opened by a smooth sagittal incision beginning adjacent to the optic nerve and ending with the cornea.
- The correct 6:00–12:00 orientation, needed to capture tapetal and nontapetal fundus, is insured by making the incision at right angles to the orientation of the posterior ciliary artery (Fig. 4.1A).
- The open globe is then inspected for macroscopic lesions.
- A second cut, parallel to the first, is made from the cornea backward through the retina (Fig. 4.1B).
- That second cut should be far enough to the periphery to leave the already-bisected lens undisturbed (for a second cut through the lens will surely dislocate it).
- The resulting slab should be lifted carefully into a thick processing cassette or a tissue bag.
- Even though the piece of tissue is as much as 1 cm thick, it is hollow and thus presents no difficulty in terms of automated tissue embedding procedures.

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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 stepwise induction and interdependence of the various parts of the developing eye. Without proper consideration of ocular embryology, any discussion of the lesions found in anomalous eyes threatens to be just a catologue of observations rather than a roadmap to understanding that such lesions are all predictable results of a relatively small number of possible 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 continues to develop for about 6 weeks postnatally, whereas that of ruminants and horses is mature at birth. Thus, something like retinal dysplasia is necessarily an in utero event in ungulates, but may be in response to early postnatal injury in carnivores.

Review of ocular organogenesis

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

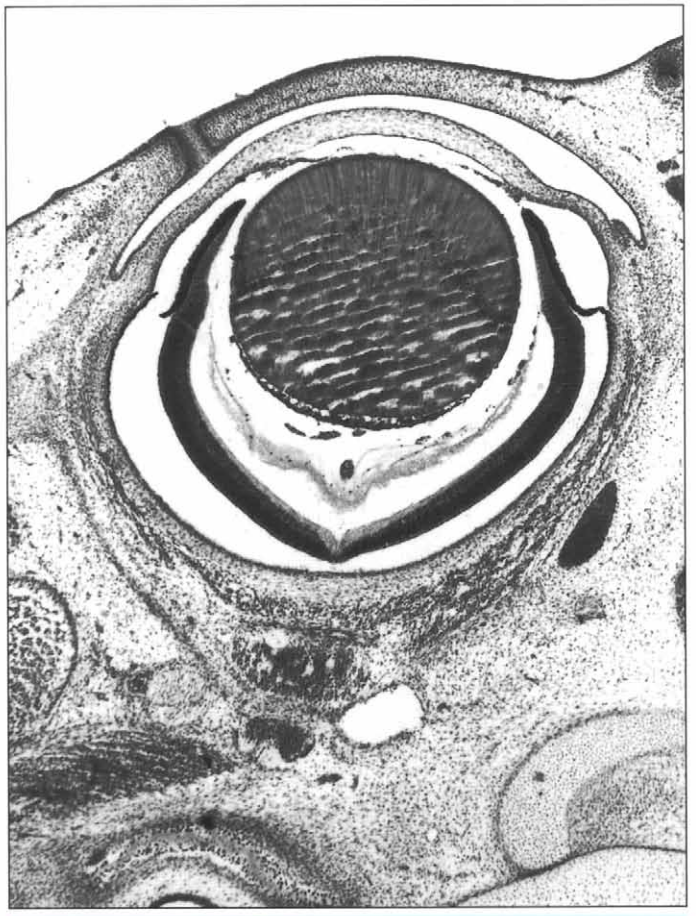

Figure 4.2 Canine embryo at 34 days gestation. Lids fused, cornea fully formed. Large lens surrounded by complete vascular tunic derived posteriorly from hyaloid artery and anteriorly from the future pupillary membrane. Iris not yet formed.

apposition of primary optic vesicle to overlying surface ectoderm induces a focal ectodermal thickening, the *lens placode*. The placode grows to form a primitive *lens vesicle*. It is the developing lens that 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, which will form the vascular and fibrous tunics of the eye (iris and ciliary body stroma, corneal stroma and endothelium, choroid and sclera) under the induction of the differentiating neuroectoderm (Fig. 4.2). *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.

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Defective organogenesis

Failure of the eye to attain even the stage of optic cup is 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.

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 (Fig. 4.3). There is frequently some remnant of lens, a finding that 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.

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 is 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

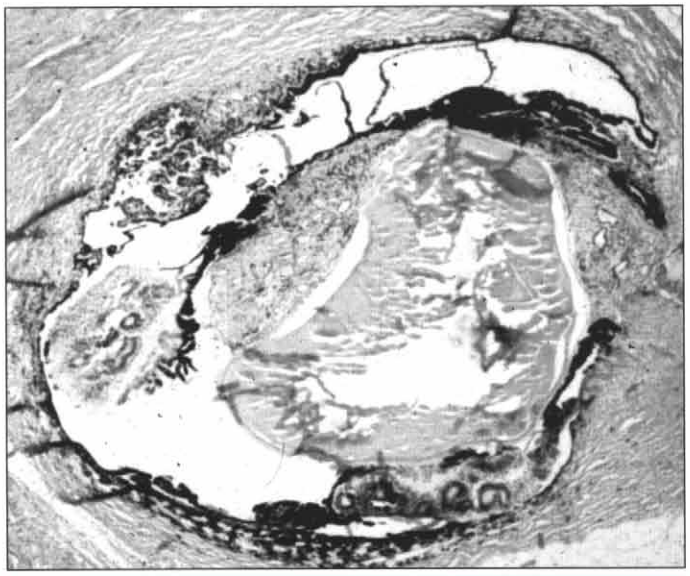

Figure 4.3 Secondary microphthalmia. The ciliary processes tend to be highly conserved even in the most disorganized globes.

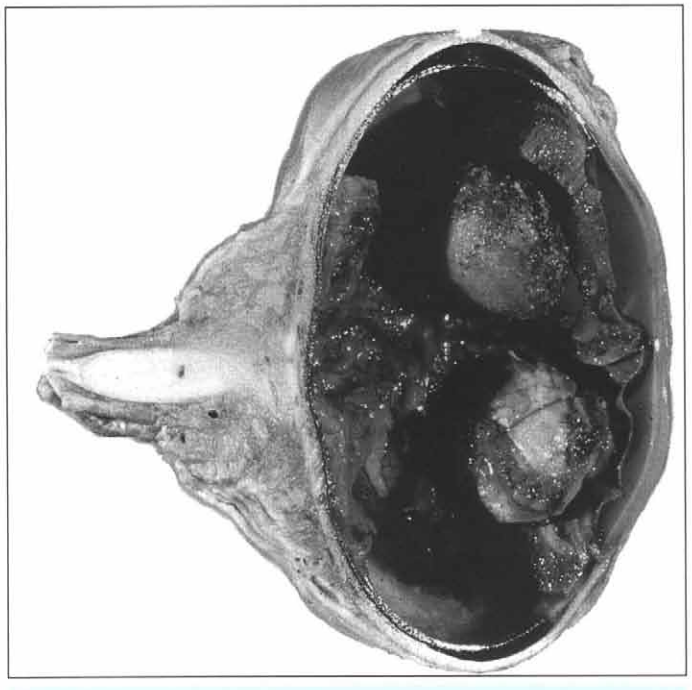

Figure 4.4 Globe from typical "cyclopian" calf. Duplication of lens and pupil indicates **synophthalmos** rather than true cyclopia.

vessels, and are thus more properly considered *incomplete separation or early fusion (synophthalmos)* (Fig. 4.4). 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.

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

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 invagination of the optic vesicle to form the optic cup. *Persistence of the primary optic vesicle is seen as a cystic eye* (Fig. 4.5), consisting of a scleral sheet lined by neurectoderm of variable neurosensory and pigmentary differentiation. The absence of lens and of bilayered iridociliary epithelium distinguishes 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.* 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.

Coloboma

The mildest and latest defect in organogenesis results from failure of complete fusion of the lips of the optic (embryonic) fissure, a slit-like 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 notch-like defect of the caudal pole at, or just ventral to, the optic disk. Its exact location can vary substantially. It is lined by an outpouching of dysplastic neurectoderm. If the defect is sufficiently large, the outpouching of neurectoderm induces a similar bulge in the sclera, termed **scleral ectasia** (Fig. 4.6). Occasionally such ectasias are so large as to form a retrobulbar cyst as large as the globe itself (Fig. 4.7). 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 and permits definitive

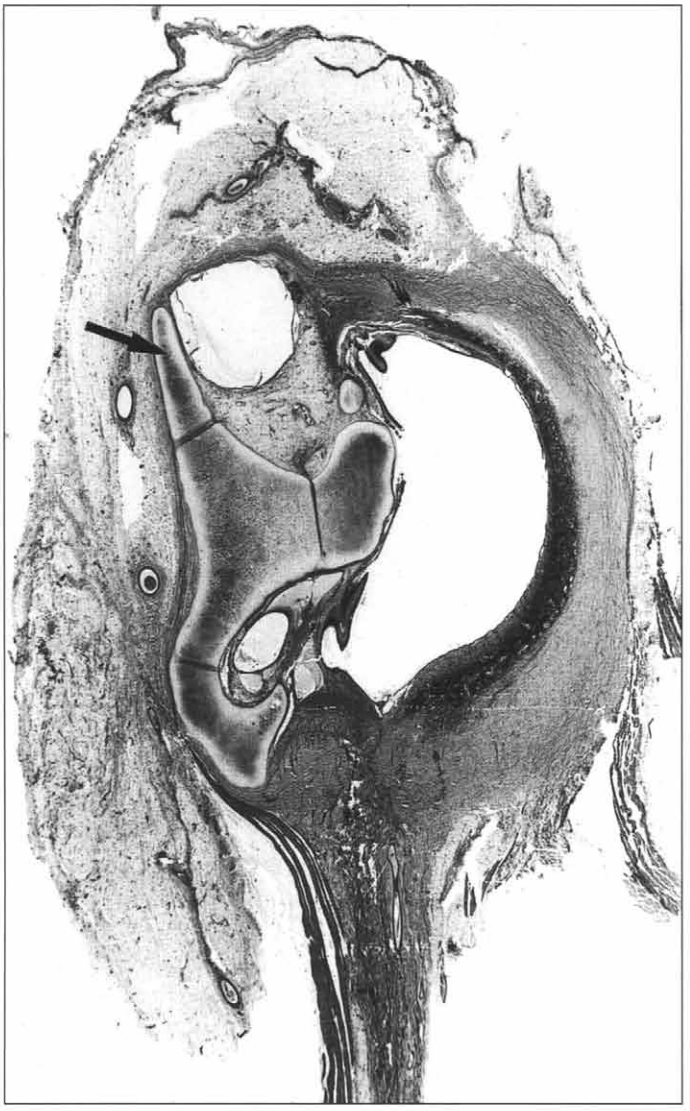

Figure 4.5 Severe **microphthalmos** in a foal. There is no lens, no apparent attempt at invagination, and no neurosensory retinal differentiation. Persistence of the cavity of the optic vesicle qualifies this as a cystic eye. Cartilage plate (arrow) is probably an analog of the third eyelid.

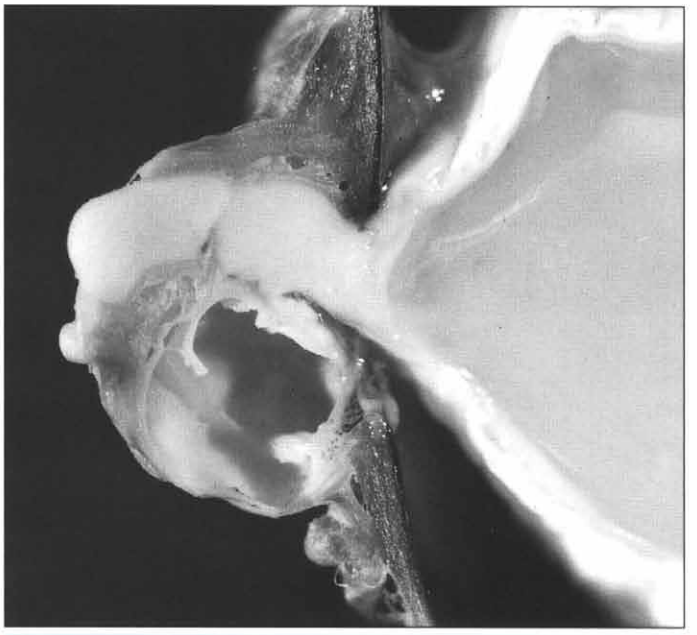

Figure 4.6 Coloboma adjacent to the optic disk, accompanied by retinal separation. Collie eye anomaly.

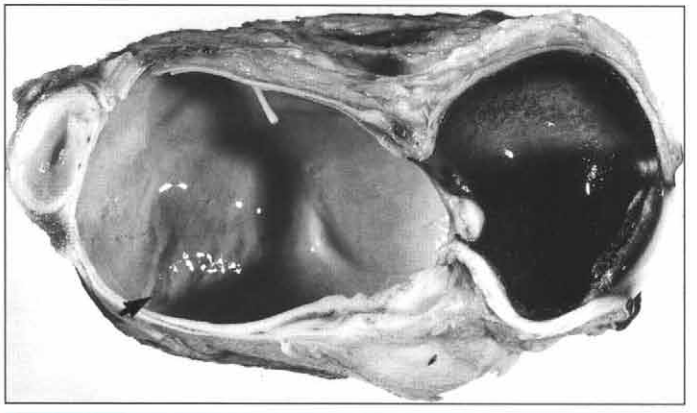

Figure 4.7 Retrobulbar cyst (arrow) formed by coloboma and massive scleral ectasia in a calf. The globe is small and the retina is completely separated.

identification of the retrobulbar cyst as being a **coloboma** (absence or defect of some ocular tissue) in terms of pathogenesis (Fig. 4.8).

Colobomas occur in all domestic species, but are especially frequent in Collie dogs as one manifestation of the Collie eye anomaly. In Collies, they usually arise within or just adjacent to the optic disk. They appear to arise as focal defects in maturation and/or induction of sclera and choroid by the retinal pigment epithelium (RPE) that is forming from the outer layer of the optic cup. Because the exact location of the embryonic fissure is somewhat variable, it is difficult to determine how many examples of coloboma are the result of delayed closure of that normal embryologic structure, and how many represent some more fundamental defect in the proper interaction of RPE and the developing periocular mesenchyme destined to form choroid and sclera. Proper maturation of the RPE, and in particular the normal acquisition of pigmentation, appears to be critical to the induction of normal mesenchymal migration and maturation. Its failure results in such varied anomalies as choroidal hypoplasia, segmental or diffuse iris and ciliary hypoplasia (known clinically as **iris coloboma**), and even microphthalmia. Because of its frequent association with the merle dilution defect in the coat color of dogs, the general syndrome is known as *merle ocular dysgenesis*. It is similar, but not identical, to Collie eye anomaly. The same defect occurs, with much less frequency, in color-dilute (incompletely albinotic) horses, cattle, non-merle dogs, and cats. A similar pathogenesis and spectrum of lesions, not proven to be associated with color dilution, occurs in Collie eye anomaly (see later). 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.

Defective differentiation

Subsequent to formation of the optic cup, ocular differentiation involves continued differentiation of neurectoderm into retinal and

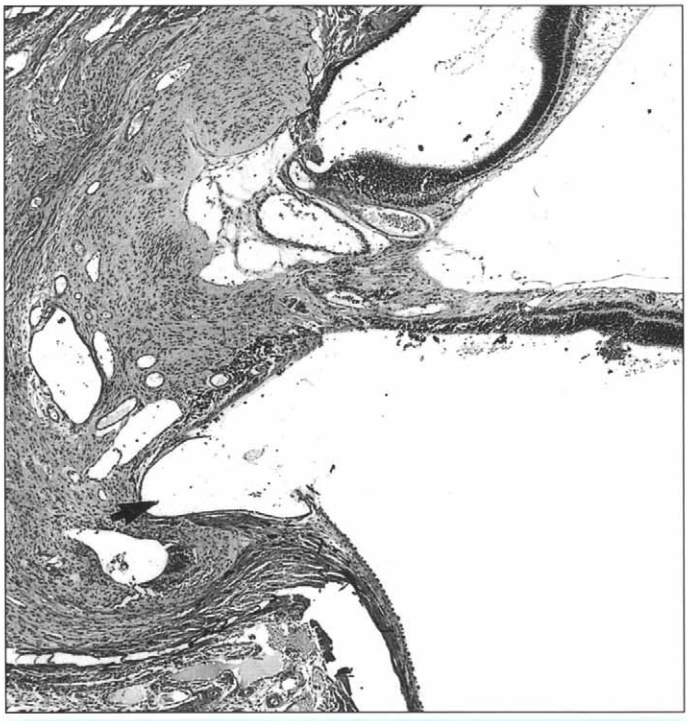

Figure 4.8 Coloboma (arrow) at the optic disk in a Collie pup with Collie eye anomaly. Dysplastic neurectoderm lines the defect and attempts to form sensory retina.

uveal neuroepithelium, and induction of primitive periocular neural crest mesenchyme to form the sclera and uvea. 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.

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 provides no understanding of the fundamental pathogenesis of the anomaly. *Here we will organize these "later" anomalies (occurring after the stage of optic cup formation) on the basis of the presumed pathogenesis: defective migration, proliferation, or remodeling of ocular mesenchyme, defective maturation of neurectoderm, and defective development of ectoderm.*

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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, one or more waves of mesenchymal invasion form corneal endothelium, corneal stroma, and the anterior half of the transient perilenticular vascular network, including the pupillary membrane. The posterior half of this perilenticular vascular tunic is formed by invasion of mesodermal endothelial cell precursors and supporting perivascular mesenchyme through the optic fissure to form the extensive but transient *hyaloid artery system* (see Fig. 4.2). Another mesenchymal wave accompanies the ingrowth of the neurectoderm at the anterior lip of the optic cup to form the iris stroma, although it is unclear which layer acts as the primary inducer. 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 6–8 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, incomplete atrophy of the tunica vasculosa lentis or hyaloid artery system, or incomplete remodeling of the filtration angle to cause primary glaucoma.

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. Other anomalies linked to the choroidal hypoplasia/hypopigmentation include optic nerve coloboma, microphthalmia, and (with the merle ocular dysgenesis) cataract and segmental iris hypoplasia. Some degree of retinal dysplasia is also common. At least in theory, all of these defects are predictable outcomes of improper mesenchymal induction by a defective, inadequately pigmented retinal pigment epithelium. Even in otherwise normal (nonwhite) animals with a blue iris, there is usually hypoplasia of the tapetum and choroid.

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, optic nerve 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. 4.9). 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 (so-called *retinal disinsertion*) may also occur, leaving the folded retina on the floor of the globe (Fig. 4.10).

The fundamental histologic lesion found in all affected eyes is choroidal hypoplasia. It is always diffuse, despite ophthalmoscopic observation of a lesion that may appear only to be focal within the dorsal temporal quadrant of the fundus. The choroid is thin and poorly pigmented, and the tapetum is thinner than normal or even absent (Fig. 4.11A, 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, age-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.

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 in 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 similar growth imbalance, but in the opposite direction, that causes retinal separation in about 10% of eyes with this syndrome. In this situation, a retina that is too small attempts to stretch from optic disk to ora ciliaris by the shortest route, rather than following the curvature of the scleral shell.

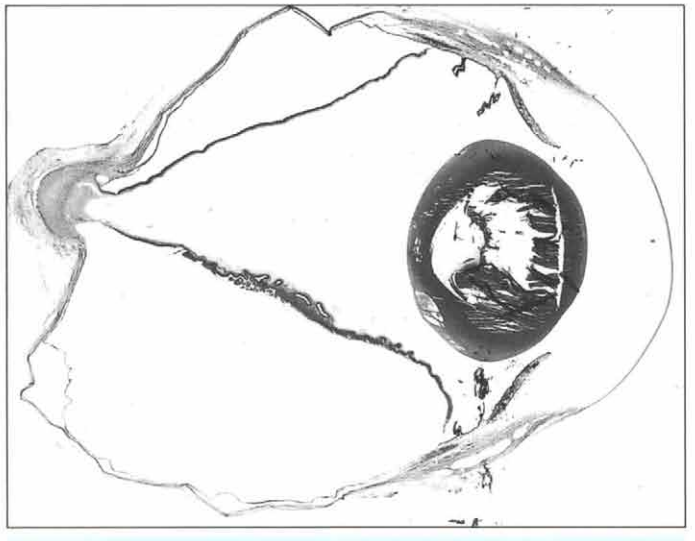


Figure 4.9 Retinal separation in Collie eye anomaly. There is coloboma at the optic disk. Choroid and sclera are thin. Retinal folding does not constitute dysplasia.

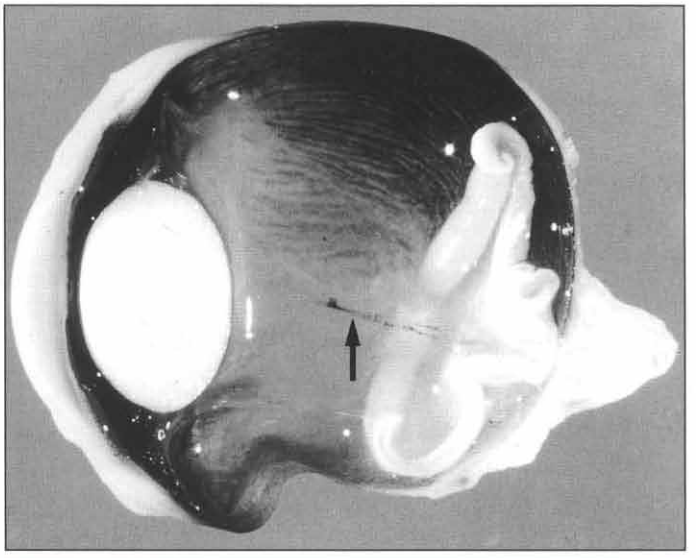


Figure 4.10 Retinal separation from ora ciliaris in Collie eye anomaly. Note hypopigmented choroid and prominent hyaloid artery (arrow).

Focal fibroblastic metaplasia and mineralization are 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.

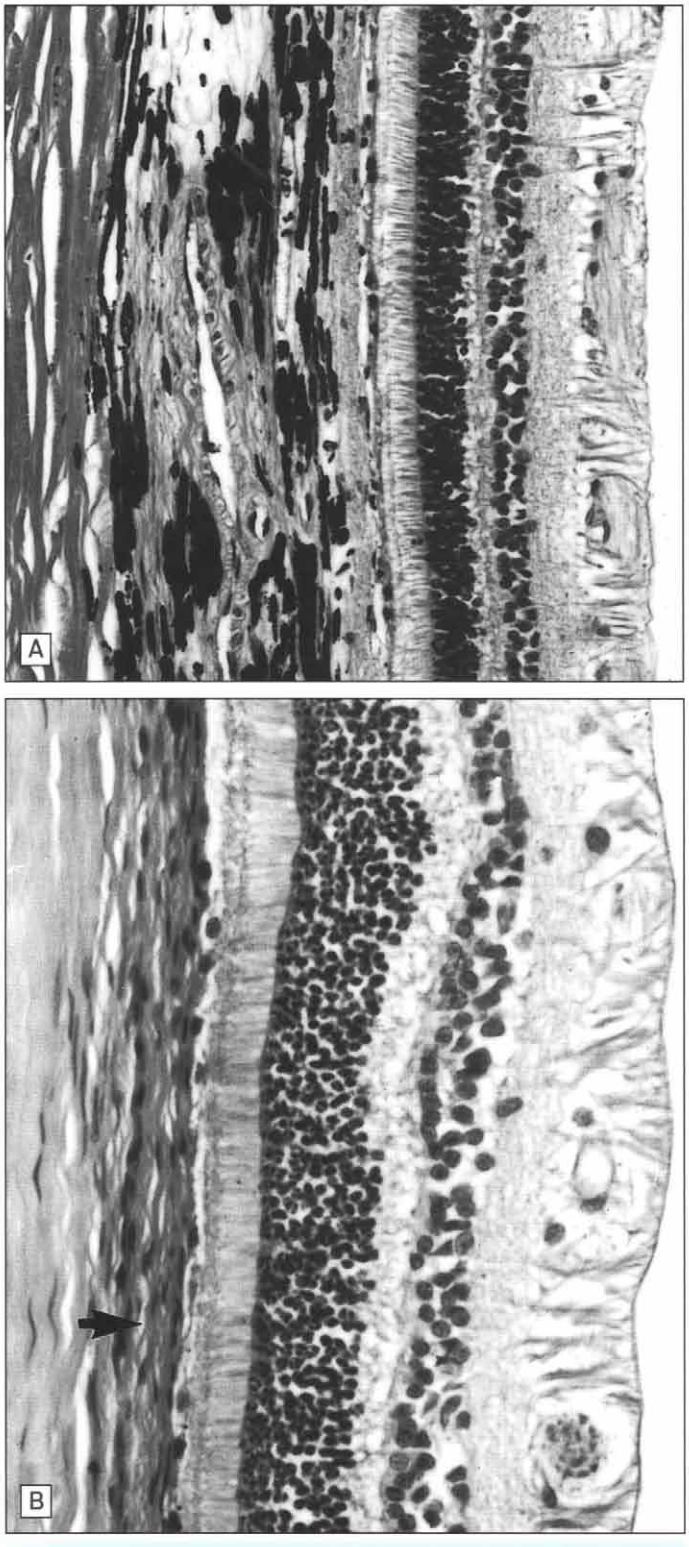


Figure 4.11 A. Normal posterior pole of the globe of a 13-week-old puppy. Tapetum present but thin (normal for puppy). Choroidal thickness approximates that of retina. **B.** Posterior pole just dorsal to the optic disk of a 13-week-old Collie with **Collie eye anomaly**. Tapetum is absent. Choroid (arrow) is severely hypoplastic.

The earliest lesion of this anomaly is defective differentiation of primitive retinal pigment epithelium to form rosette-like 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 the 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 initial induction.

Another manifestation of mesenchymal maldevelopment in Collie eye anomaly, rarely noted clinically, 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 later in life (8–20 weeks) when puppies are examined ophthalmoscopically, it is presumed that they reflect only a minor delay in mesenchymal remodelling.

Defects primarily in anterior chamber 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 subsequent migration of mesenchyme destined to form the 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. 4.12A). The trabecular meshwork within the filtration angles may be malformed, but the ciliary apparatus is usually normal. The lens often is cataractous (Fig. 4.12B) and sometimes ectopic or hypoplastic. Glaucoma has been described as a sequel in horses (but not in other species), but it should be an expected sequel in severely affected eyes in any species because of the inevitable concurrent trabecular hypoplasia (Fig 4.12A).

Hypopigmentation of the iris may be unilateral or bilateral. When the loss of pigment is patchy in one or both irises, it is known as *heterochromia iridis*. The pigmentation may be diffusely absent in the iris stroma but present in the posterior iris epithelium (*subalbinotic*), or absent in both stroma and epithelium (*true albinism*). The iris is normal except for absence of visible pigment granules in the cytoplasm of otherwise normal stromal melanocytes and epithelial cells. Tapetum and, less reliably, choroid of affected eyes usually are hypoplastic as well as poorly pigmented.

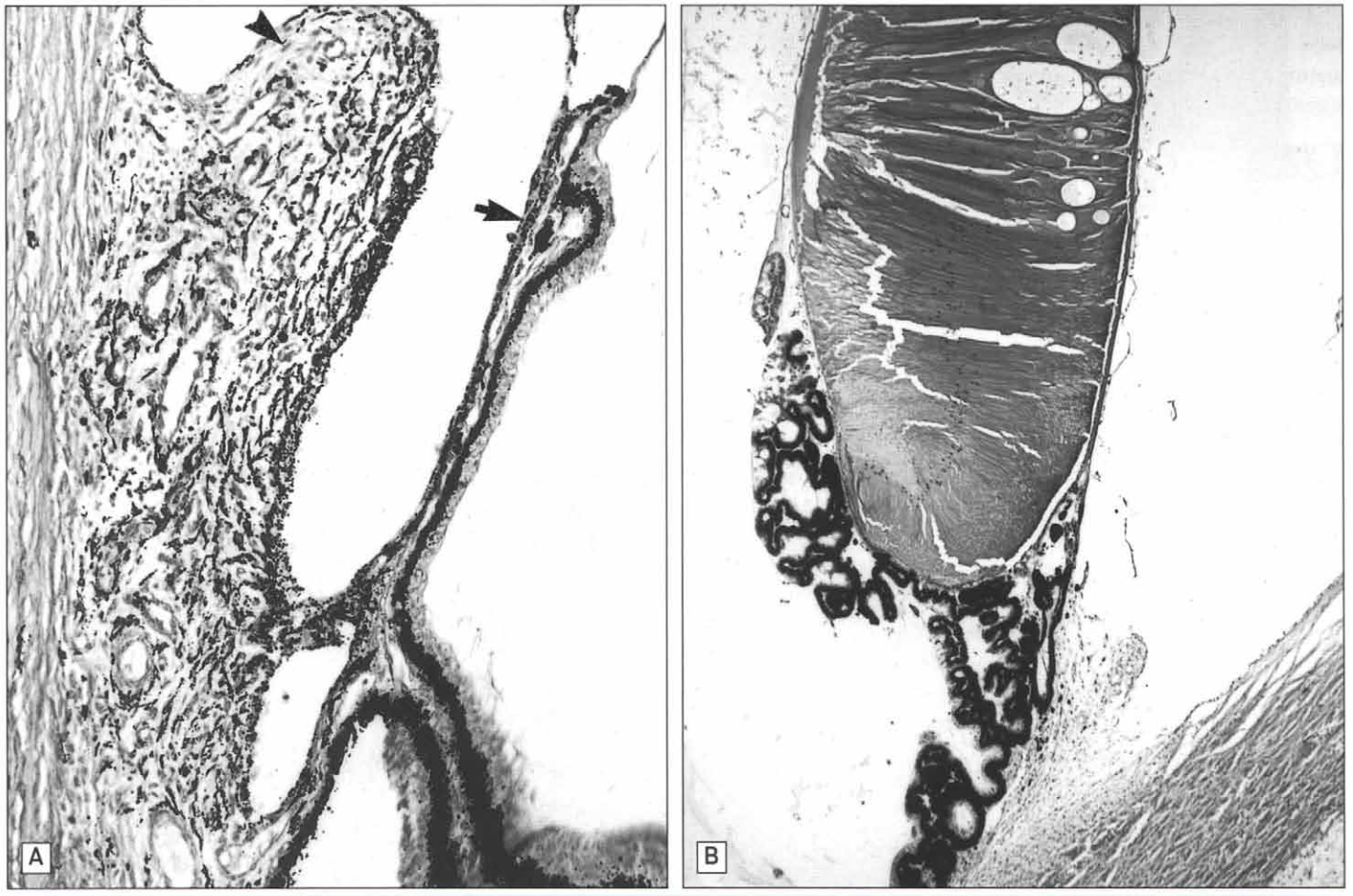
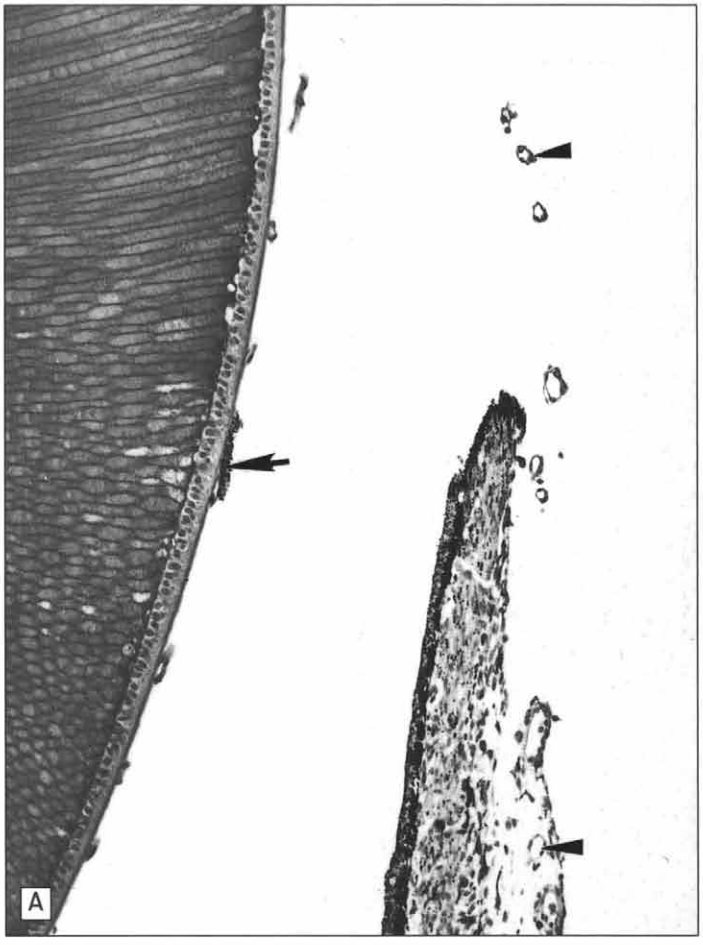


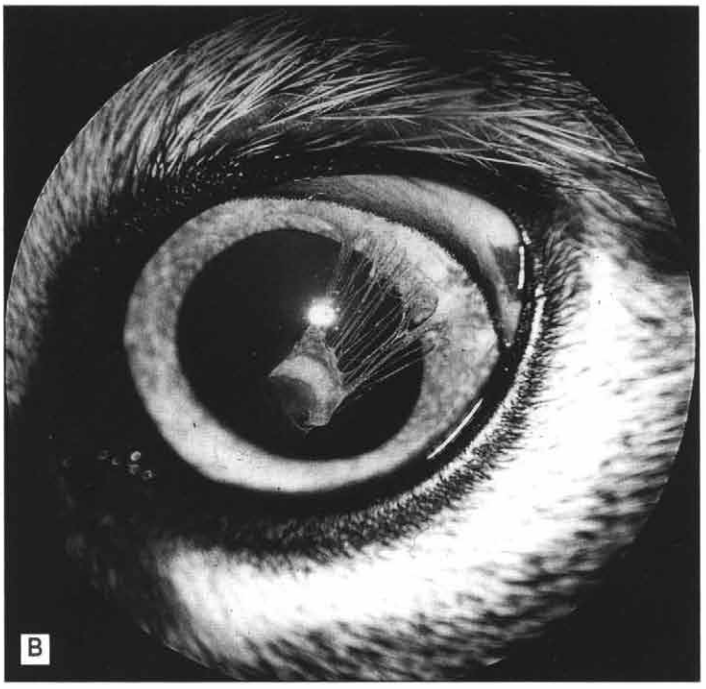
Figure 4.12 A. Iris hypoplasia (arrowhead) with hypoplasia of the trabecular meshwork in a dog. The ciliary processes (arrow) have developed normally. **B. Iris hypoplasia**, congenital cataract and dysplasia of ciliary processes in a piglet; one of three affected. The adherence of ciliary processes to the lens represents an arrest in remodeling rather than improper development.

Incomplete atrophy of the anterior chamber mesenchyme is relatively common in dogs and occurs occasionally in other domestic species. During organogenesis, waves of mesenchyme migrate between the surface ectoderm and the anterior rim of the optic cup. Some of the ingrowing mesenchyme forms corneal endothelium and stroma, while other portions of mesenchyme form the iris stroma and trabecular meshwork. Some of that mesenchyme occupies the anterior chamber and, as it matures, it forms a fibrovascular sheet stretching across the face of the lens and developing iris, known as the *pupillary membrane*. Its vascular component creates the anterior portion of an embryonic perilenticular vascular plexus, known as the *tunica vasculosa lentis*. Both the pupillary membrane and the tunica vasculosa lentis normally disappear late in gestation or in the early postnatal period. Failure of this anterior chamber fibrovascular mesenchyme to atrophy results in the very common anomaly of **persistent pupillary membrane** (persistence of the tunica vasculosa lentis alone is discussed later).

Atrophy of the pupillary membrane 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, thread-like 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. 4.13A). 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. 4.13B). Because the normal pupillary membrane never contacts the cornea, strands of pupillary membrane that extend from iris to cornea are considered to be minor versions of anterior segment dysgenesis (see below).

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 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





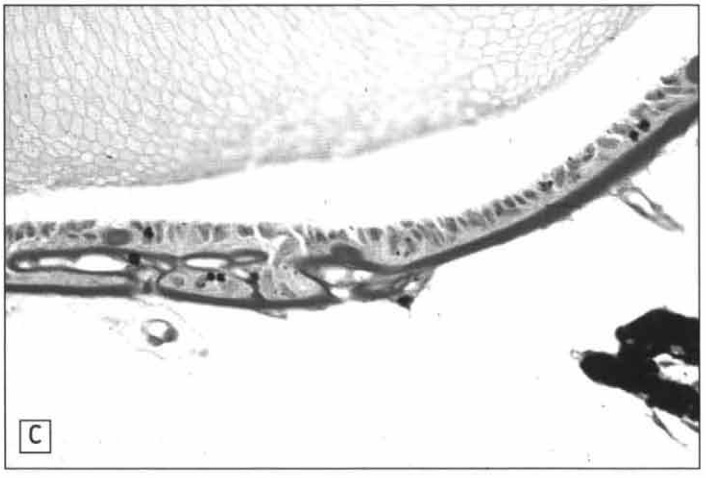


Figure 4.13 Persistent pupillary membrane. A. Persistence of the **anterior tunica vasculosa lentis** (arrow) and **pupillary membrane** (arrowheads), the latter continuous with the iris stromal vessels. **B. Central crescent insertion** of the persistent pupillary membrane in a dog is on the anterior pole of the lens, where it has induced a focal cataract. **C. Dysplastic development** of the anterior lens capsule as a consequence of adherence of persistent pupillary membrane.

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* (Fig. 4.13C). Some would classify this latter, more severe form of persistent pupillary membrane as a mild version of anterior segment dysgenesis (see below).

Much less common than persistent pupillary membrane are those defects grouped under the general category of **anterior segment dysgenesis** (or **anterior segment cleavage syndrome**). This group includes multiple anomalies of cornea, lens, and anterior uvea that stem from disordered development of anterior segment mesenchyme and/or improper separation of the developing lens from the overlying corneal mesenchyme. Such eyes are commonly microphthalmic and usually have microphakia, cataract, and congenital corneal opacities at sites of congenital anterior synechiae. The most severe cases have fusion of iris with corneal stroma without observed corneal endothelium or Descemet's membrane (forming a so-called "internal corneal ulcer"), and thus have no detectable anterior chamber (Fig. 4.14). *Most examples in dogs and cats probably result from perinatal corneal perforation from trauma or from progression of suppurative bacterial keratoconjunctivitis (ophthalmia neonatorum).* The

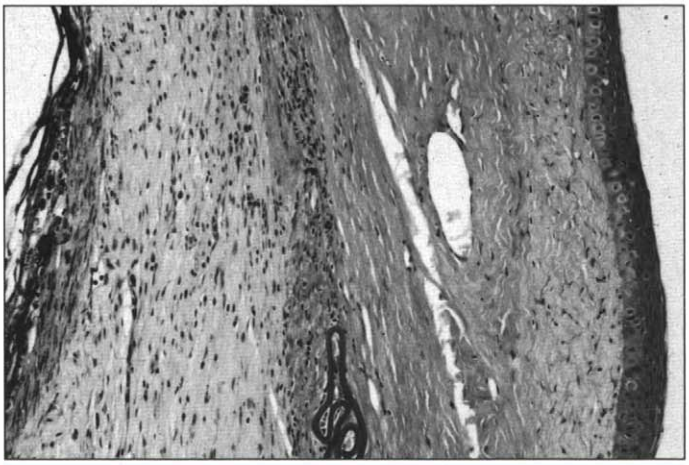


Figure 4.14 Anterior segment dysgenesis. Improper remodeling of anterior segment mesenchyme results in failure of formation of the anterior chamber. The iris is then fused to the cornea.

result is iris prolapse and incorporation of the iris into the developing cornea resulting in obliteration of the anterior chamber. Since the globe of dogs and cats continues to develop for many weeks after birth, this is yet another example of how difficult it can be to precisely distinguish idiopathic developmental disorders from those resulting from postnatal traumatic or inflammatory diseases.

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, or from inadequate posterior migration of the iris root. The defect is much more common in dogs than any other species. In the most severe cases, the trabecular meshwork may appear as a solid mesenchymal mass indistinguishable from the adjacent iris stroma (Fig. 4.15A). This rare lesion, known us *trabecular hypoplasia*, is a cause for truly congenital glaucoma. It is often accompanied by iris hypoplasia. Much more commonly, the error in remodeling is less profound and the lesion is seen as an imperforate or inadequately perforated mesenchymal sheet separating anterior chamber from a relatively normal trabecular meshwork (Fig. 4.15B). The only lesion may thus be a pectinate ligament that is thicker, more heavily pigmented and less fenestrated than normal. This has sometimes been referred to as *"pectinate ligament dysplasia."* (For a more complete discussion, see Glaucoma.)

Clinically noted ocular features of **bovine Marfan syndrome**, which are similar to human Marfan syndrome, are ectopia lentis, microspherophakia, and myopia. The human disease is caused by mutations in the fibrillin-1 gene; affected cattle have abnormal fibrillin metabolism. Eyes of affected cattle are characterized by megaloglobus, increased circumlental distance, asymmetrical ciliary processes, intact but fragile zonular fibers, and ectopia lentis. Affected animals have moderately hypoplastic ciliary bodies, compact filtration angles, and long thin irises with decreased fibrous stroma.

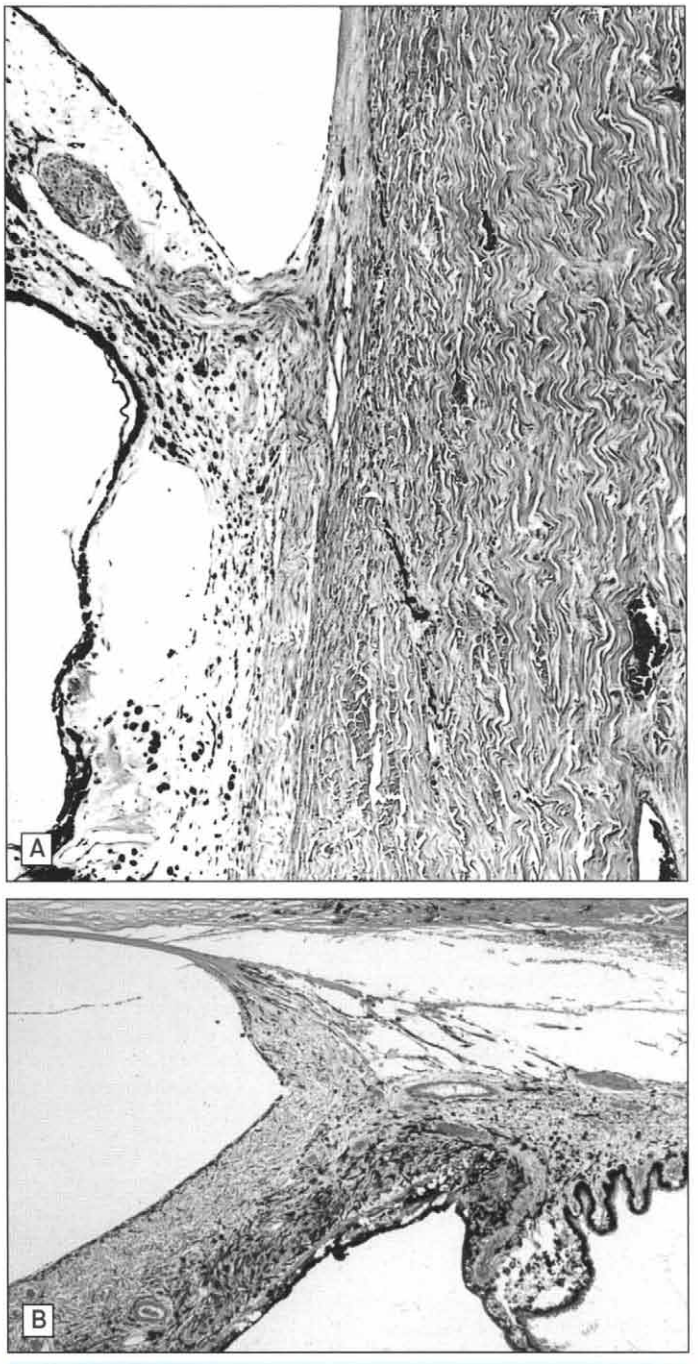


Figure 4.15 A. Goniodysgenesis. A primitive example (**trabecular hypoplasia**) with little maturation of the embryonic mesenchyme destined to form pectinate ligament and trabecular meshwork. **B.** A solid sheet of mesenchyme extends from the termination of Descemet's membrane into the iris stroma, with no obvious pectinate ligament. Other portions of the trabecular meshwork are relatively normal.

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. There is a tendency in clinical literature to group all of these defects under the umbrella of **persistent hyperplastic primary vitreous**, but histologically there is quite a wide range in the nature of the defect. Only the most severe qualify as true persistent hyperplastic primary vitreous.

The hyaloid artery and its branches are formed from mesenchyme and pre-endothelial mesoderm that enter the optic cup through the optic fissure prior to its closure. The vessel traverses the optic cup from optic disk to lens, where it ramifies over the posterior lens surface (posterior tunica vasculosa lentis). It joins with the vascular portion of the pupillary membrane (anterior tunica vasculosa lentis) 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 that extends from optic disk for a few millimeters into the vitreous (Fig. 4.16). In calves up to about 2 months of age, the vestigial hyaloid system may still contain blood. In carnivores, it is the pupillary membrane that normally persists for several weeks postnatally. Bloodless remnants of the anterior termination of the hyaloid artery on the posterior lens capsule are known as *Mittendorf's dot*; it is a harmless anomaly, 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 (**posterior tunica vasculosa lentis**). The normal tissue is a combination of blood vessels and

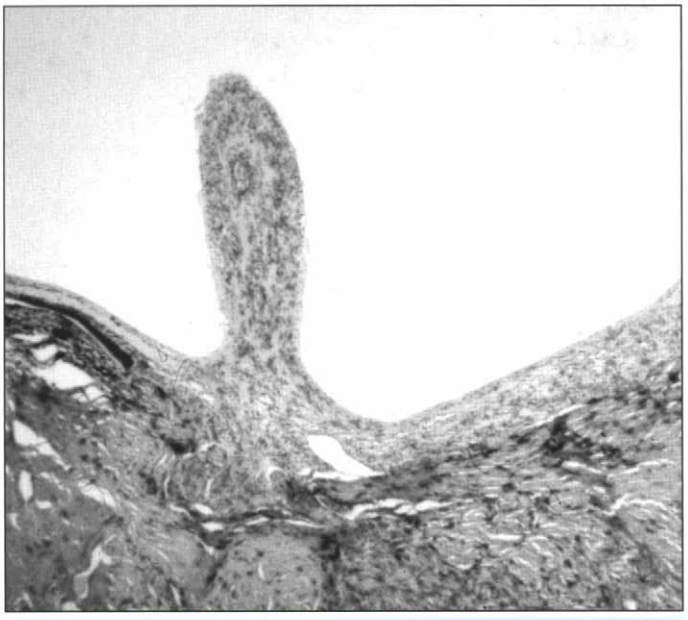
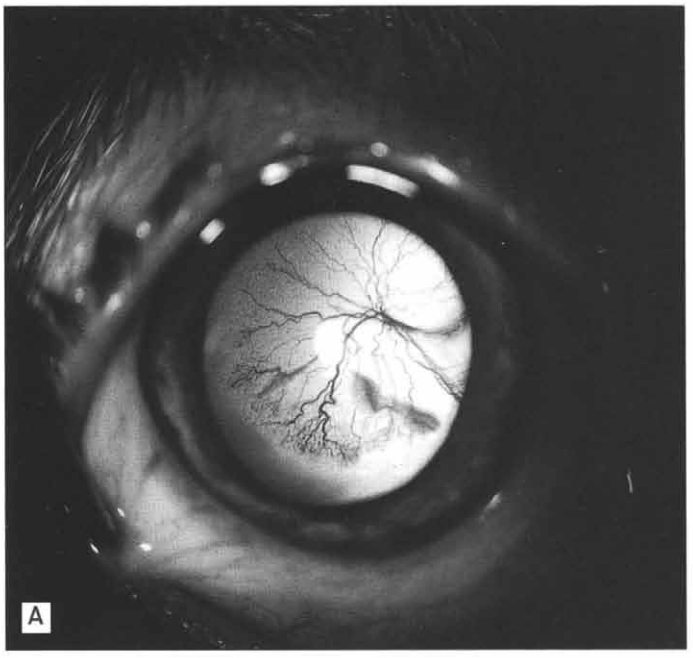


Figure 4.16 Bergmeister's papilla, the minimal histologic presentation of persistent hyaloid artery.



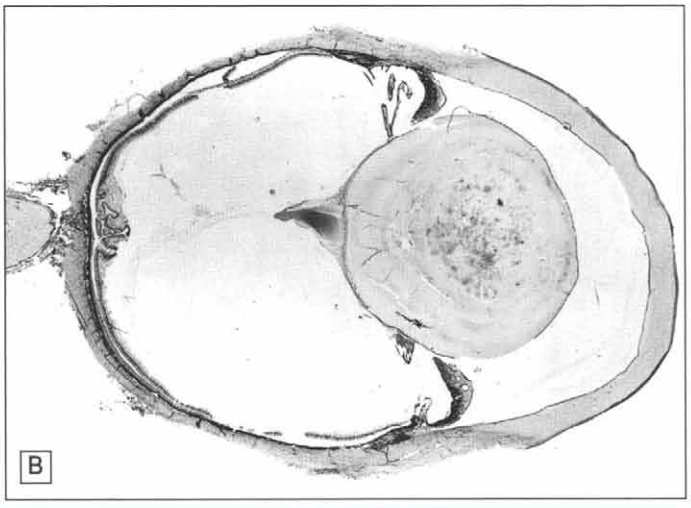


Figure 4.17 A. Persistence of hyaloid artery and posterior tunica vasculosa lentis in a dog. Posterior polar cataract is the almost inevitable consequence, as seen here. **B. Persistent hyperplastic primary vitreous**. A fibrocartilaginous plaque adheres to an elongated lens (lenticonus) and extends to the posterior pole. Retina is dysplastic near the optic disk, and the ciliary processes have not retracted from the lens capsule.

perivascular mesenchyme. Surrounding the hyaloid system is some primitive collagen, poorly characterized extracellular matrix, and a few macrophages. The combination of blood vessels and surrounding stroma is known as the *primary vitreous*. At least theoretically, *anomalous retention of the hyaloid artery and/or primary vitreous could therefore be separated into distinct entities of persistent hyaloid, persistent posterior tunica vasculosa lentis, persistent primary vitreous, and persistent hyperplastic primary vitreous*. Of these, the one most frequently reported (perhaps just because it is the most spectacular and significant) is **persistent hyperplastic primary vitreous**. In people, this rare anomaly is typically unilateral and is accompanied by microphthalmos, microphakia, retinal detachment, shallow anterior chamber, and embryonic filtration angles. The many reports of this anomaly in dogs have described a unilateral or bilateral retrolental vascular or fibrovascular network, usually without any other reported anomalies other than the expected posterior polar cataract. Such lesions are better described as *persistent posterior tunica vasculosa lentis*. In Doberman Pinschers, Bouviers and Staffordshire Bull Terriers, the classification as hyperplastic primary vitreous is more credible. In these breeds, 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. 4.17 A, B). 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. The one report of two cases in cats was not supported by histopathology and its correct classification remains unknown.

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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.*

Retinal dysplasia

Retinal dysplasia *is a general term denoting abnormal retinal differentiation characterized by jumbling of retinal layers and by glial proliferation.* In clinical practice, the term has been used incautiously to include genuine retinal dysplasia, postnecrotic retinal scarring of the developing retina, and retinal folding. Genuine retinal dysplasia results from failure of proper apposition of the two layers of the optic cup or from failure of proper induction by an inherently defective retinal pigment epithelium. Those examples clinically classified as retinal dysplasia that reflect disordered wound healing of developing retina, or just folding of retina that is otherwise perfectly formed, should not be considered examples of true retinal dysplasia. While there is no formal agreement on the issue, it seems most logical to divide so-called retinal dysplasia into three different categories: *retinal folds* within an otherwise normal retina, *postnecrotic dysplastic retinal wound healing*, and rare *"true" retinal dysplasia* that is a sequel to some fundamental developmental error in retinal induction or maturation.

Those examples of retinal dysplasia in which the only abnormality is **retinal folding** are by far the most common, and are seen primarily in dogs. The anatomic 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 most severe examples occur in dogs with retinal nonattachment. These have extensively folded retinas since the distance to be traversed from optic disk to ora ciliaris in a straight line is shorter than the convex route taken by attached retina, and redundant retina is therefore obliged to fold upon itself. Less severe examples, which are seen much more frequently and in the greatest variety of breeds, probably reflect inequity in growth rate between the retina and the outer layer of the optic cup (choroid and sclera). *The most common example is probably seen in Collie eye anomaly and in American Cocker Spaniels*, in which the defect may be transient. Presumably, the folds become flattened and disappear as continued choroidal and scleral growth eventually create a globe that can accommodate the retina. At least in Collies (and other related breeds with syndromes similar to Collie eye anomaly), *the retinal lesion is probably secondary to defective RPE.* Since the other defects of choroidal/scleral formation and maturation are attributed to faulty induction by a defective RPE, it is reasonable to attribute the retinal folding to the same mechanism (Fig 4.18).

A histologically similar retinal folding that may not depend on retinal:scleral growth imbalance is seen in English Springer Spaniels. 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.

Retinal dysplasia as a sequel to **retinal necrosis** can occur as a sequel to a wide variety of viral and physical-chemical insults to the embryonic eye; 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 postnatal injury in

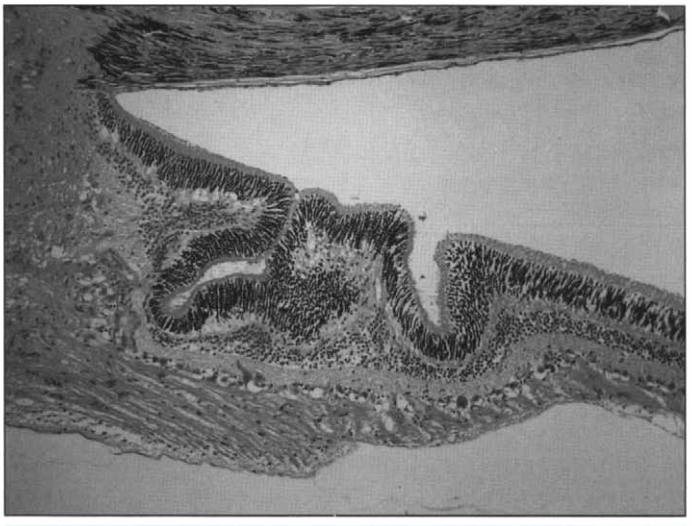

Figure 4.18 Retinal folding, presumably as a result of retinal redundancy that may eventually self-correct as the scleral shell grows to accommodate the retina. Retinal histologic organization is normal, distinguishing this from true retinal dysplasia.

puppies and kittens to produce retinal maldevelopment. Retinal maturation is most rapid in central (peripapillary) retina and progressively less towards 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 viral 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. 4.19A, B). Disorganization of nuclear layers and rosette formation are seen as in other types of dysplasia.

Infection of calves with *Bovine viral diarrhea virus* between 79 and 150 days gestation 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 differentiating and exhibit a combination of the above atrophy and scarring as well as abortive regeneration and arrested differentiation. Retinal pigment epithelium in most examples (*Bluetongue virus* 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. 4.19C). 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 panleukopenia virus* 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 upon published information.

Experimental irradiation of neonatal puppies (and, presumably, kittens) results in retinal necrosis and scarring virtually indistinguishable from postviral retinal dysplasia.

True retinal dysplasia, not associated with exogenous infection or teratogen, is rare. *It 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 1–3 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 (and, as mentioned above, should not be considered true dysplasia if no additional lesions are present). 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.

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

Optic nerve hypoplasia

Hypoplasia is the most common anomaly of the optic nerve. The defect may be 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 glaucomatous, viral, toxic, genetic, or idiopathic retinal disease (Fig. 4.20). 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 in any species. Histologic examination of affected eyes reveals few if any ganglion cells and a thin and moth-eaten nerve fiber layer.

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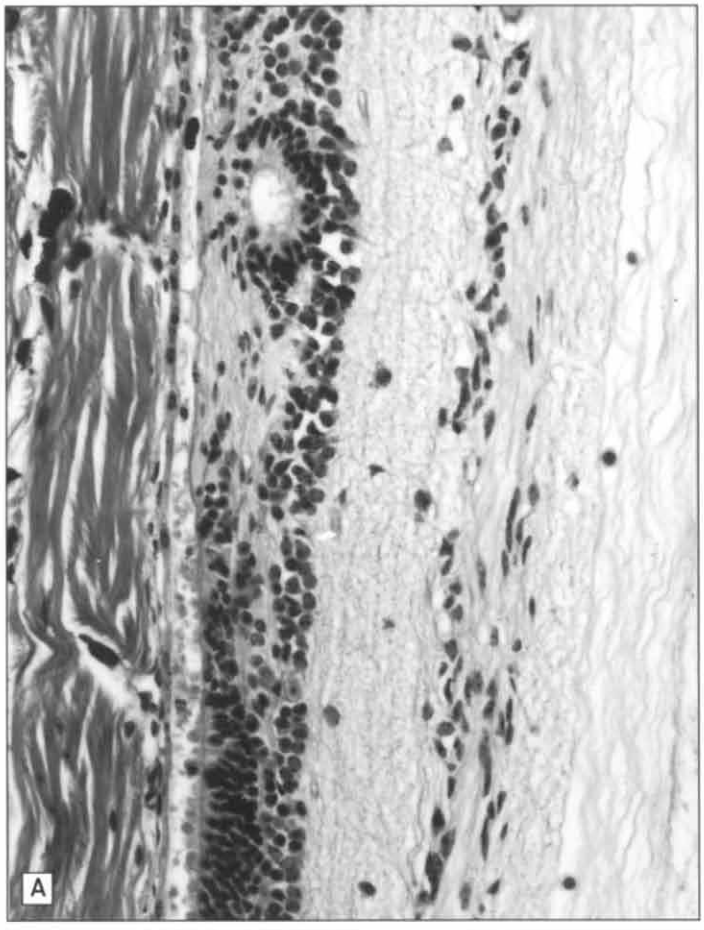

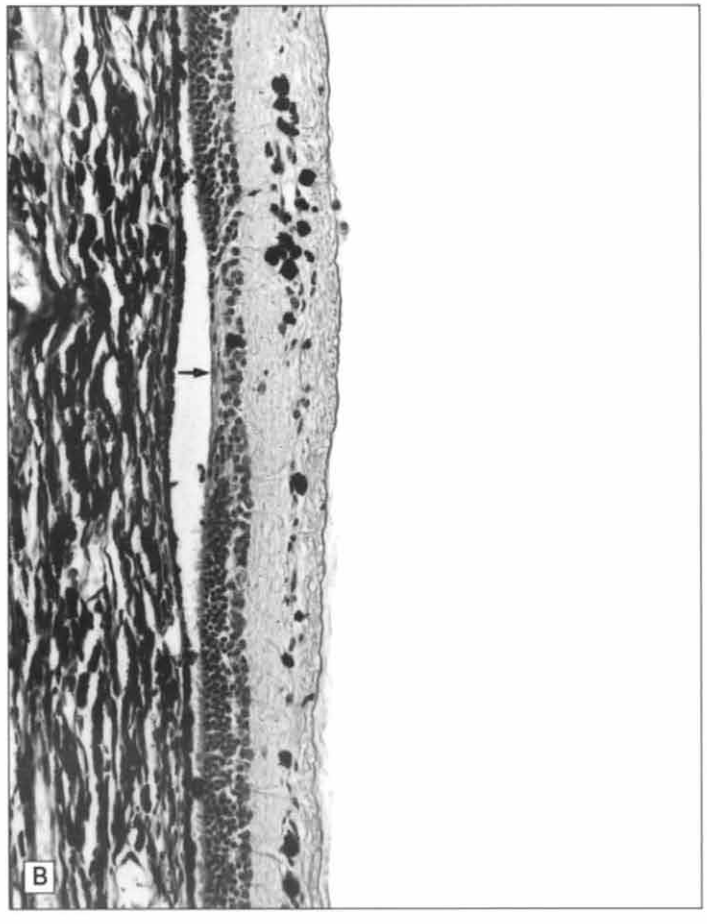

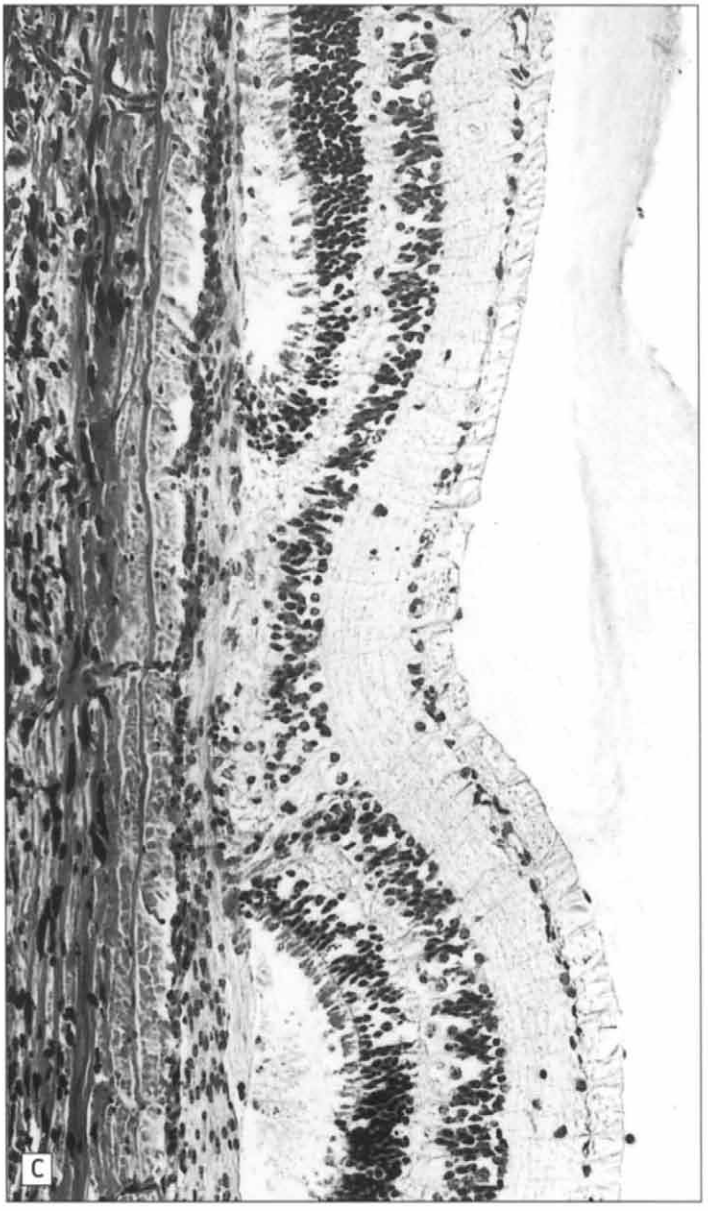

Figure 4.19 A. Postnecrotic retinal "dysplasia" due to *Bovine viral diarrhea virus* infection of a calf. Focal retinal scar with loss of outer nuclear layer and photoreceptors. Abortive regeneration with small rosette. Blending of inner and outer nuclear layers. Note lack of ganglion cells. **B.** Pigment-laden cells from retinal pigment epithelium have migrated into ganglion cell layer, in a calf with BVDV infection. **Post-necrotic scar** (arrow) with loss of photoreceptors and outer nuclear layer. **C. Focal chorioretinal scar** with loss of outer nuclear layer and fibrous metaplasia of adjacent retinal pigment epithelium, in a calf with prenatal BVDV infection.

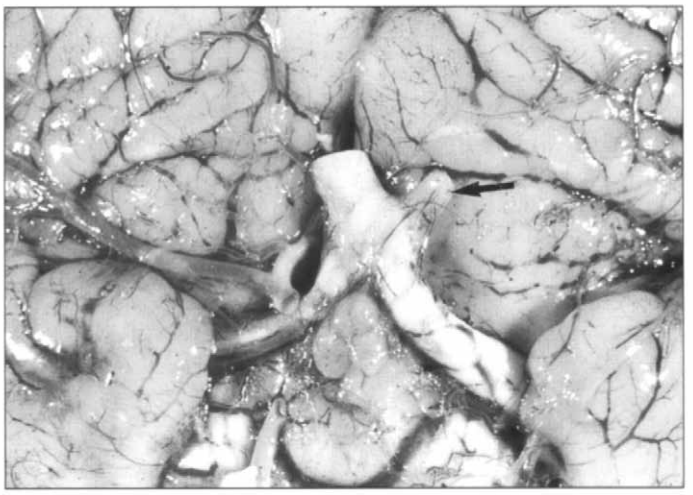

Figure 4.20 Optic chiasm in a foal with unilateral secondary (degenerative) microphthalmos. **Small left optic nerve** (arrow) due to prenatal atrophy following ganglion cell destruction.

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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 the extraocular 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, while 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.

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 skin-like 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. 4.21A, 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 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.

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. Many examples are part of a more widespread anterior segment dysgenesis (see under Defects primarily in anterior chamber mesenchyme).

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, PAS-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 2–3-week-old puppies whose eyes are otherwise normal and thus unavailable for histologic examination.

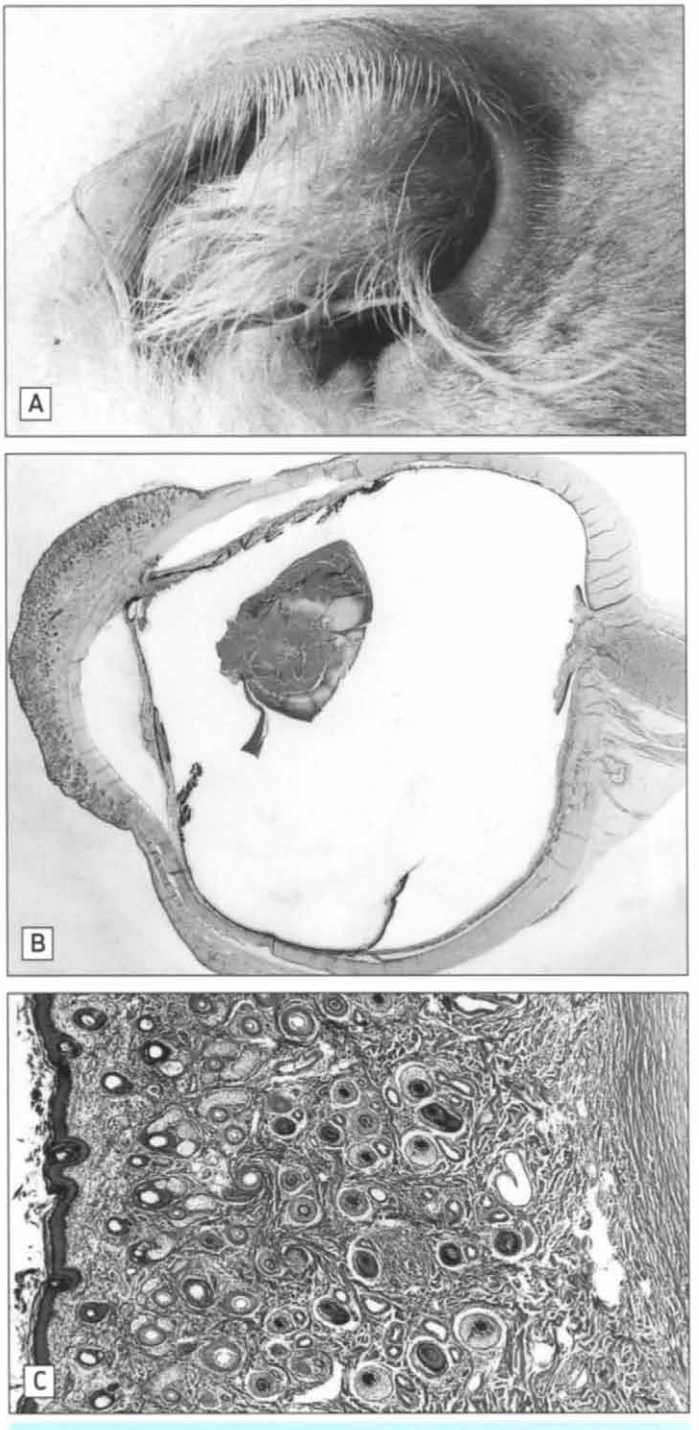

Figure 4.21 Corneal dermoid in a calf. **A.** Notch-like defect in lower lid is a coloboma. **B.** Anterior rupture of lens capsule with well-organized anterior synechia, probably from foreign-body perforation. **C. Corneal dermoid** in a calf; same eye as in (**A**) and (**B**). Development approaches that of normal skin. Note abrupt transition to dense regular corneal stroma at deep margin of the dermoid.

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 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 canine 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. 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 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.

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 *Bovine viral diarrhea virus*.

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 acquired cataract, and is discussed later. It may be nuclear, cortical or capsular, focal or diffuse, stationary or progressive depending upon the timing and pathogenesis of the original injury.

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Ocular adnexa

The adnexa include eyelids, nictitating membrane, 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.

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.

Blepharitis is *inflammation of the eyelid. Ordinarily, it refers to inflammation of the haired skin that covers the outer surface of the eyelid.* Diseases primarily affecting the palpebral conjunctiva that lines the bulbar surface of the eyelid would ordinarily be classified as conjunctivitis and are considered later. The diseases of the eyelid skin are, in general, exactly the same as diseases of skin elsewhere, and

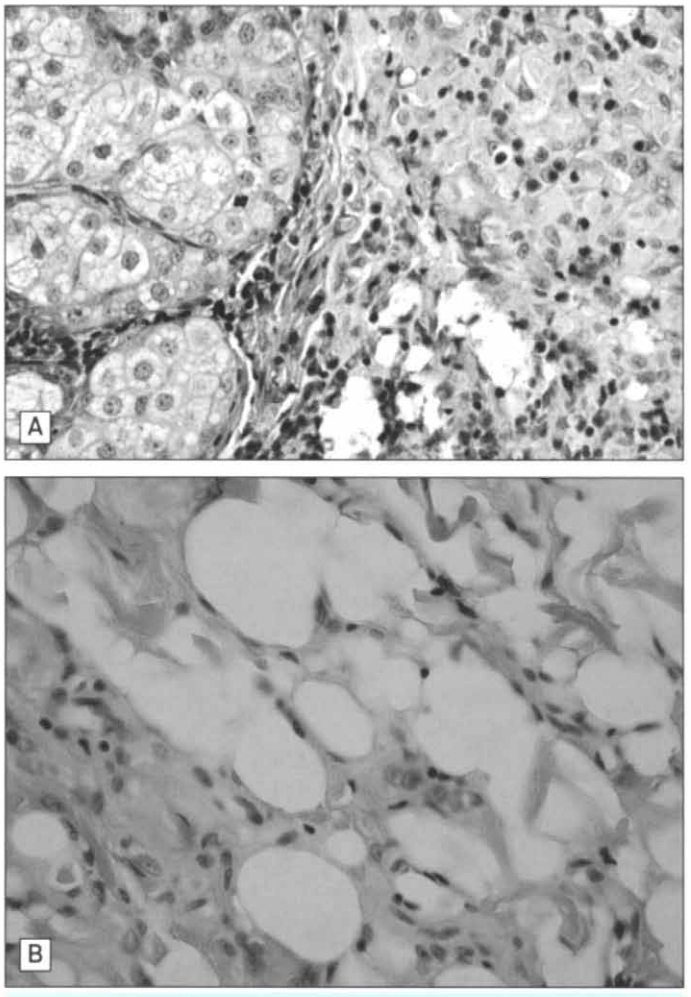

Figure 4.22 Chalazion. A. Leaking Meibomian gland or, more often, Meibomian adenoma surrounded by foamy macrophages. **B.** In this variant (particularly common in cats), the leaking secretion forms **lipid lakes** with a relatively inconspicuous granulomatous reaction.

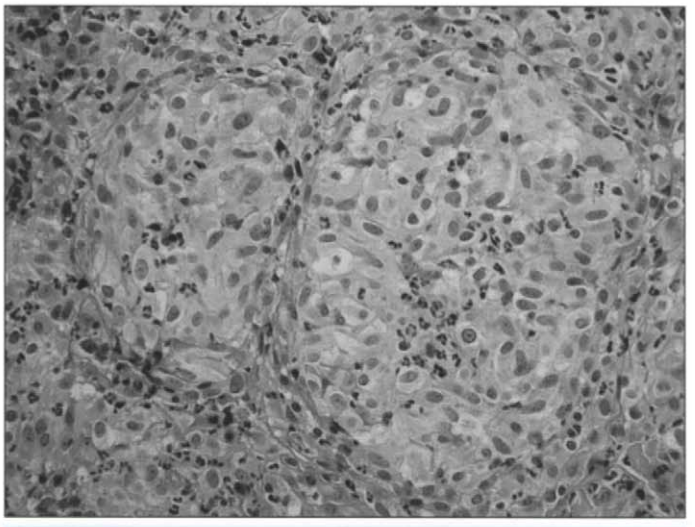

Figure 4.23 Granulomatous marginal blepharitis. Granulomas form around clear lipid vacuoles, sometimes with neutrophils. The location along the palpebral surface of the eyelid margin is critical to the diagnosis.

are thus not considered here in any detail. Inflammatory lesions more or less unique to eyelid include hordeolum, chalazion, and idiopathic granulomatous marginal blepharitis.

External hordeolum or **stye** is *suppurative adenitis of the adnexal glands of Zeis or Moll.* **Internal hordeolum** is *suppurative inflammation of the Meibomian gland.*

Chalazion is *sterile granulomatous inflammation in response to the leakage of Meibomian secretion into the surrounding dermis.* While it can theoretically occur in response to any type of injury to the Meibomian gland, almost all cases are found adjacent to Meibomian adenomas. The histologic lesion is distinctive and comes in two forms that may occur independently or in conjunction with one another. The more common is an accumulation of large foamy macrophages and multinucleated cells around the abnormal Meibomian gland. The macrophages contain distinctive refractile intracellular slender elongated crystals that have a bright silvery-white appearance when examined with polarized light. Alternatively, the reaction may consist of a mixture of these macrophages and lakes of free lipid. In routine sections, these appear as clear empty spaces that could be confused with dilated lymphatics (Fig. 4.22A, B). This latter variant was originally described in cats as idiopathic lipogranulomatous conjunctivitis (see below), but current opinion is that it is just a feline version of chalazion.

Idiopathic granulomatous marginal blepharitis is a uniquely canine lesion. The macroscopic lesion varies from a single nodule to a series of coalescing nodules that create virtually diffuse thickening of one or both eyelid margins. *The histologic lesion is a coalescence of suppurating granulomas in the subconjunctival tissue of the eyelid margin, without any proven association with adnexal structures and without any identifiable etiologic agent.* The granulomas often form around a clear central lipid vacuole, with or without neutrophils at the interface between the vacuole and the surrounding macrophages (Fig. 4.23). The lesion bears considerable similarity to cutaneous sterile pyogranuloma syndrome and other idiopathic granulomatous panniculitis syndromes, all of which are equally mysterious in terms of pathogenesis. *The lesions differ from those of chalazion in that the latter does not form discrete granulomas, does not involve neutrophils, and is always found adjacent to Meibomian glands.*

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 demonstrated viral cause, are assumed to represent autoimmune lacrimal adenitis. The analogous lesion in people 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 though 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.

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 conjunctiva. Goblet cells increase in number from the lid margin to the fornix, but ordinarily are absent in that portion of conjunctiva that extends from the fornix to the corneoscleral junction (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 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 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. Although characteristic of a number of etiologically specific conjunctival diseases, *lymphoid hyperplasia 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*. Because conjunctival biopsy is rarely performed until all therapeutic measures have failed, it is rare to identify an etiologic agent associated with conjunctivitis. The etiologic significance of bacterial, fungal, and even viral agents should be considered very carefully in light of the normal bacterial flora, and the high prevalence of conjunctival carriage of several viral agents in clinically normal animals. 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 viral diarrhea, malignant catarrhal fever, classical swine fever, 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 particularly prominent are discussed here.

Infectious bovine rhinotracheitis (IBR) is usually accompanied by serous to purulent conjunctivitis, which can be confused clinically with *infectious bovine keratoconjunctivitis* ('pinkeye') caused by *Moraxella bovis* (discussed below). However, corneal involvement with IBR 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 *Bovine herpesvirus 1* into the conjunctival sac, and represent hyperplastic lymphoid aggregates. Overlying conjunctiva may be ulcerated and the defect filled with fibrin. IBR is discussed in Vol. 2, Respiratory system; Vol. 2, Alimentary system; Vol. 3, Female genital system.

In contrast to the situation in dogs, most cases of conjunctivitis in *cats* are probably caused by infectious agents. The agents incriminated include mycoplasma, chlamydia, or herpesvirus. The diagnosis is usually made based upon clinical characteristics, the presence of other clinical signs, and demonstration of the infectious agent via PCR or culture. Histologic lesions are not etiologically specific, and demonstration of the specific infectious agent in histology or cytology samples (even with the aid of immunofluorescence) becomes progressively more difficult as the lesions age.

Felid herpesvirus 1 causes a combination of conjunctivitis, keratitis, and upper respiratory disease when it first infects young cats, but it may cause conjunctivitis alone as a recurring infection in older cats that had recovered from the initial disease.

Mycoplasma felis and *M. gatae* have been reported to cause conjunctivitis unassociated with other signs in immunosuppressed cats, but instillation of organisms into the conjunctival sac of healthy cats without prior corticosteroid administration does not cause disease. In addition, many of the cats with putative mycoplasma conjunctivitis have had concurrent infection with herpesvirus or with chlamydia. It is likely that the mycoplasma, which is a member of the normal feline conjunctival flora, acts as a medically significant opportunist rather than as a primary pathogen. 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.

Chlamydophila psittaci usually causes unilateral conjunctivitis in cats of any age, without any other associated disease. The conjunctivitis is initially neutrophilic, but rapidly becomes a nonspecific mixed infection with subepithelial neutrophils, macrophages, lymphocytes, and plasma cells. Early in the disease (between days 7 and 14), typical intracytoplasmic inclusion bodies can be seen, and their

detection is enhanced by immunofluorescent staining. Because the clinical signs are characteristic and disease is easily treated with tetracycline, histologic assessment is rarely required. In cases that are resistant to therapy, the disease is usually chronic and histologically nonspecific by the time biopsy is eventually done.

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 worldwide. 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 species most commonly associated with conjunctivitis in domestic animals are *T. lacrymalis* in horses; *T. rhodesi, T. gulosa, T. skrjabini* in ruminants; *T. callipaeda* in carnivores and humans; and *T. californiensis* in many species including dog, cat, bear, coyote, deer, and man. Female worms are viviparous, and larvae free in lacrimal secretions are consumed by flies of the genus *Musca* in which they develop for 15–30 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 a 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 eosinophilic and granulomatous inflammation surrounding live or dead larvae and eosinophils (Fig. 4.24).

Ocular onchocerciasis results in the formation of granulomas and suppurating granulomas around fragmented or viable adult filarids within the sclera and subconjunctival lamina propria of dogs. Dogs are considered abnormal hosts for this parasite, which is much more commonly found in horses, cattle, and other ungulates. In horses, the infection causes a more diffuse eosinophilic and granulomatous conjunctivitis and peripheral stromal keratitis with a character similar to that in skin. Adults and microfilariae can be identified within the reaction.

Ophthalmomyiasis

A syndrome of periocular and even intraocular invasion by *fly larvae* occurs in various species including man. 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 that 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.

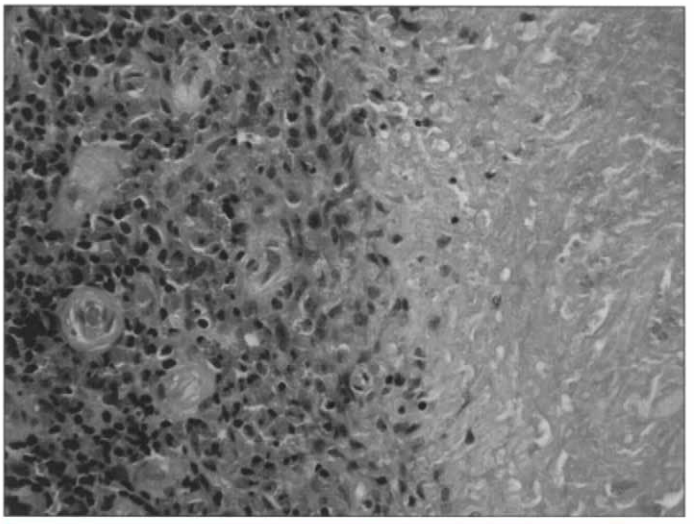

Figure 4.24 Conjunctival habronemiasis. Only rarely would fragments of larvae be detected within the center of these eosinophil-rich granulomas.

The ocular lesions vary from *transient mild conjunctivitis to 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 the 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 people. 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 the 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.

Ophthalmomyiasis interna anterior has also been reported in a cat in association with infection with a first instar larva of ***Cuterebra*** spp. Severe anterior uveitis resolved after prompt surgical removal of the larva, but retinal degeneration and blindness ensued.

Immune-mediated conjunctivitis

Presumed allergic conjunctivitis occurs in all species but is most likely to be investigated in dogs (most examples of conjunctivitis in cats are assumed to have an infectious pathogenesis). Rarely is a specific allergen identified and, like its counterparts in allergic skin diseases, the diagnosis is based upon 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. Eosinophils are much more likely to be identified in cats than in dogs, a species difference that is also true of allergic skin disease in general. More chronic lesions, which are the more usual to be biopsied, have squamous metaplasia and lymphocytic-plasmacytic subepithelial infiltrates and the formation of lymphoid nodules.

There are a few histologically distinctive examples of conjunctivitis that are assumed to represent immune-mediated disease, mostly because they respond only to aggressive immunosuppressive therapy. In some dogs with chronic conjunctivitis (perhaps particularly German Shepherd Dogs), the infiltrate sometimes becomes particularly plasmacytic, diffuse, and thick in a fashion resembling an interface dermatitis. The bulbar surface of the third eyelid is the favorite location, and many believe this lesion (sometimes referred to as "*plasmoma*") to be the conjunctival variant of pannus keratitis.

Cats and horses may develop a severe **eosinophilic conjunctivitis** that is thought, by some, to be a conjunctival counterpart of the eosinophilic keratitis syndrome. Lesions may be unilateral or bilateral, and at least in cats there is almost always a concurrent ulcerative marginal blepharitis. Histologic changes include ulceration, epithelial hyperplasia, squamous metaplasia, and a heavy lymphocytic infiltration with a large proportion of eosinophils. Lesions in cats contain no detectable infectious agent, and no herpesviral DNA can be detected (the role of herpesviral infection in the pathogenesis of histologically similar eosinophilic keratitis in cats remains controversial). The clinical syndrome is rapidly responsive to topical corticosteroid administration.

Ligneous conjunctivitis is a distinctive clinical and histologic entity, thus far described only in Doberman Pinscher dogs. The clinical disease is bilateral and characterized by marked thickening and opacity of the palpebral conjunctiva and conjunctiva of the third eyelid. Histologically, the conjunctival lamina propria is thickened by massive deposition of hyaline material and a diffuse scattering of mononuclear leukocytes. Most of the leukocytes are T-lymphocytes, and the hyaline material stains weakly for IgG and IgA.

Feline lipogranulomatous conjunctivitis is probably the feline counterpart of canine chalazion. The lesion occurs almost exclusively in the lamina propria of the palpebral conjunctiva adjacent to the margin of either the upper or lower eyelid. The histology is very repeatable, consisting of a nodular accumulation of clear lipid lakes intermingled with large foamy macrophages and a few small or mononuclear leukocytes. Although the original report contained no mention of adjacent Meibomian lobules, the similarity between this entity and some cases of canine chalazion (or granulomatous dermatitis adjacent to injured cutaneous sebaceous glands) is striking and impossible to ignore (see Fig. 4.22B).

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CORNEA

The cornea of domestic mammals is a horizontal ellipse varying from 0.6–2.0 mm in thickness among the various species. In general, the larger and older the animal, the thicker is 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 sclera both ophthalmoscopically and histologically. Embryologically, the epithelium is derived from surface ectoderm; the stroma and corneal endothelium are from neural crest mesenchyme.

The major attribute of cornea is its clarity, and it is the loss of clarity that 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 separated by a critical