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.

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

distance to allow the uninterrupted passage of light (620–640 Angstroms); and a high degree of stromal dehydration maintained by the presence of epithelial tight junctions, endothelial tight junctions, and a Na-K-dependent ATP-ase pump in the cell membrane of the corneal endothelium (Fig. 4.25A).

The cornea exists in a privileged environmental niche, bathed in the nurturing and antimicrobial saline of the tear film and protected from other irritation by the movable eyelids. Within this protected niche, the cornea does therefore not require the protective attributes of skin (keratinization, leukocytes, blood vessels) to protect itself from the harsh external environment. If there is rapid deterioration in any component of this protective environment, the cornea is most likely to respond with ulceration and subsequent wound healing. If, on the other hand, the shift is of gradual onset, then the more likely response is adaptive metaplasia in which the cornea reaches into its embryologic cutaneous heritage and becomes skin-like.

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

Corneal edema

Corneal edema occurs rapidly following injury and results from imbibition of lacrimal water through damaged corneal epithelium, absorption of anterior chamber water at a site of corneal endothelial damage, or failure of electrolyte (and thus water) extrusion by the corneal endothelium. If the epithelial or endothelial defect is focal, the resultant edema is limited to the stroma adjacent to the defect. The edematous cornea is clinically opaque, and may be up to five times its normal thickness (Fig. 4.25B). At least experimentally, edema subsequent to endothelial damage tends to be more severe than edema secondary to epithelial injury. Edematous stroma stains less intensely than normal, and collagen lamellae are separated into a fine feltwork of pale-staining fibrils by excessive hydration of the glycosaminoglycan ground substance (principally keratan sulfate and chondroitin sulfate). Percolation of stromal fluid into the epithelium results in the intercellular and intracellular edema known as *bullous keratopathy* (Fig. 4.25C).

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

Persistent corneal edema seems to predispose to stromal vascularization and fibrosis, but numerous experimental models show that

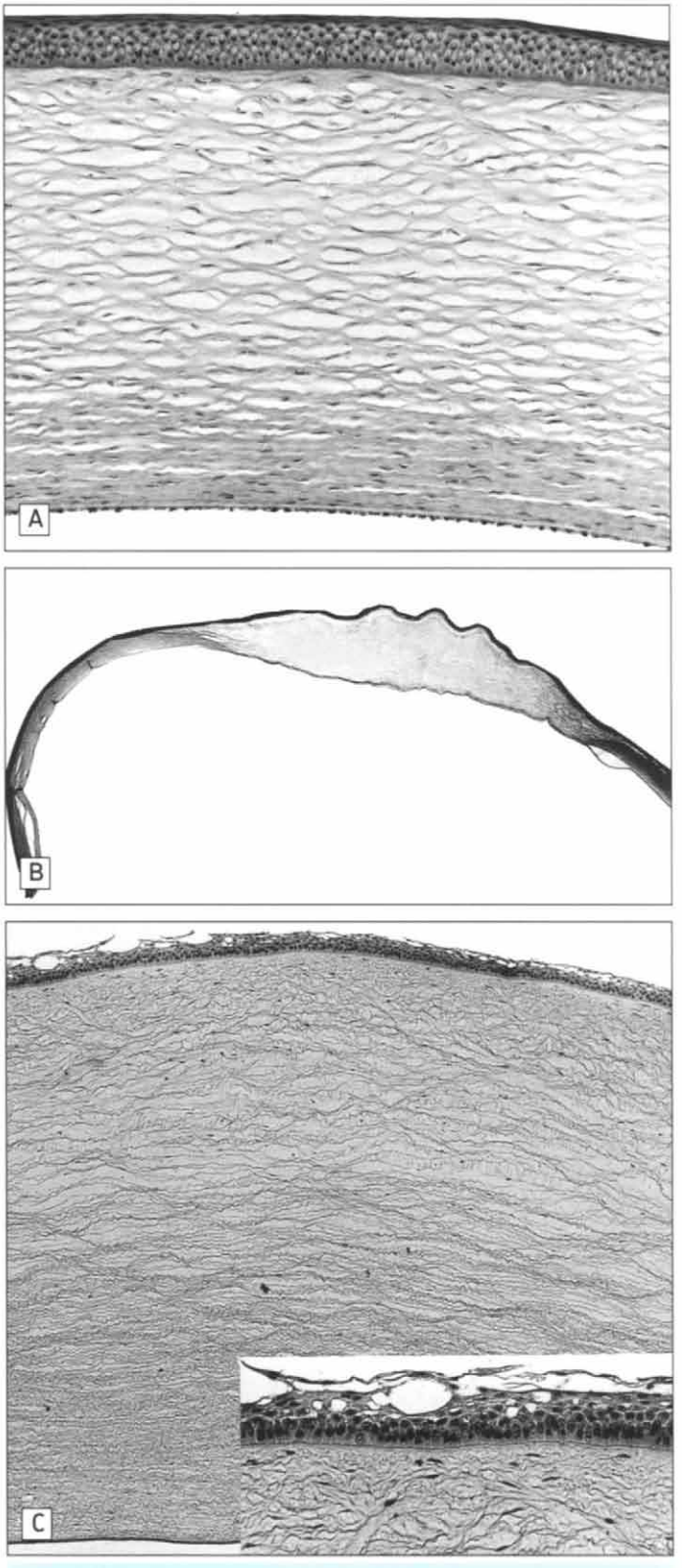

Figure 4.25 A. Normal canine cornea. Uniform, nonkeratinized epithelium without pigmentation or rete ridges. Stroma is poorly cellular. The clefts among the stromal fibers are unavoidable formalin fixation artifacts. **B. Central corneal edema** from abrasion of the corneal endothelium by lens. Foal, with congenital anterior lens luxation. **C. Severe corneal stromal edema.** Percolation of the fluid into the epithelium (insert) creates fluid vesicles known as **bullous keratopathy**.

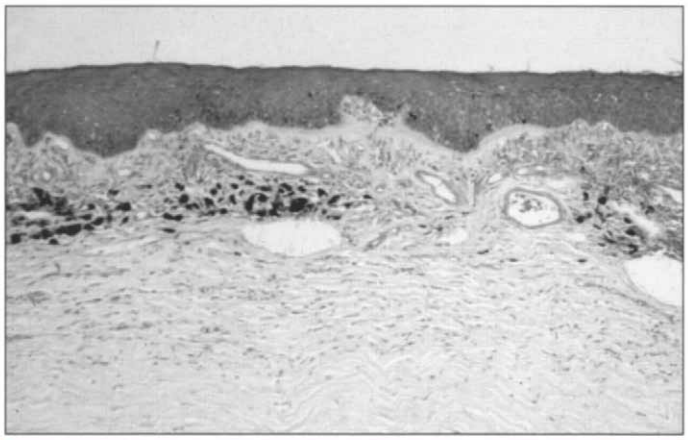

Figure 4.26 Corneal cutaneous metaplasia as a result of chronic keratoconjunctivitis sicca.

edema itself is not the stimulus. Instead, it is probably the infiltrating neutrophils that provide most of the angiogenic and fibroblastic cytokines. Damaged epithelium and stromal fibroblasts are alternative sources. A natural example of virtually permanent corneal edema, without accompanying vascularization, occurs in Boston Terrier and Chihuahua dogs with endothelial dystrophy.

Corneal cutaneous metaplasia

Injury to the corneal surface that exceeds the homeostatic ability of that epithelium resulting in corneal ulceration is described below. Less drastic change to the local environment that results in sublethal injury to the surface epithelium (qualitative or quantitative inadequacy of tears, irritation from misdirected eyelashes or from entropion) will result in adaptive cutaneous metaplasia. *The chronically irritated epithelium undergoes reactive hyperplasia with the appearance of rete ridges, melanin pigmentation, and surface keratinization.* The adjacent stroma undergoes dermis-like irregular fibroplasia and acquires vascularization via capillary migration from the limbus. These changes, while they enable the cornea to survive in a hostile environment and to combat the inflammatory stimulus, also deprive it of its transparency (Fig. 4.26).

Corneal wound healing

Corneal ulceration represents a loss of the surface epithelial barrier. It causes rapid osmotic imbibition of the tear film water, resulting in corneal edema. Neutrophils may be absorbed as well, and if present in large numbers they may initiate stromal lysis as they release their cytoplasmic enzymes. Persistent recruitment of neutrophils is usually a manifestation of sepsis, and is discussed further in the sections dealing with keratitis. In any corneal wound, however, there will be at least a few neutrophils.

The mechanisms of healing of corneal wounds vary with the severity of the injury, and involve an extremely complex interaction of epithelium, stroma, and innumerable cytokine growth factors derived from tear film, infiltrating leukocytes, and resident epithelium and stroma. Only the major elements will be described here, with an emphasis on histologically detectable events rather than on chemical mediators.

It is probably true that virtually any corneal injury results in at least some degree of both epithelial and stromal injury, but *from a purely histologic perspective one can sort corneal injuries into those involving primarily the epithelium and those involving a combination of the epithelium and underlying stroma. Those nonseptic defects involving epithelium alone, or epithelium and superficial stroma, heal by epithelial sliding followed after about 24 hours by mitosis.* One cannot claim that depth alone is the deciding factor, since even very deep wounds will sometimes heal just with epithelial sliding and eventual mitotic rebuilding, as long as the epithelium is satisfied with the quality of the underlying stroma. The sliding begins within a few hours, initially from wing cells from the immediately adjacent, viable cornea. Migration by basal cells rapidly follows. The sliding is preceded by lysis of the hemidesmosomes. Adhesion of the sliding epithelium is initially to adhesion molecules like fibronectin and laminin deposited along the exposed stromal surface. Reformation of the hemidesmosomes and their anchoring filaments may take weeks or even months, during which time epithelial adhesion remains precarious. Healing of shallow, uninfected corneal ulcers is rapid; experimentally induced 7-mm ulcers in horses heal within a mean of 11 days.

Persisting or reoccurring ulcers that cannot be healed just by sliding and replication of adjacent corneal epithelium may require the recruitment of cells from the epithelium at the corneoscleral junction, which is the site of the permanent replicative population. Such cells, when recruited for corneal wound healing, seem prone to retaining a conjunctival phenotype that includes pigmentation and a tendency to form rete ridges. One of the characteristics by which we recognize *chronic, stubborn corneal ulceration* is to observe this *conjunctival "metaplasia" of the surface epithelium.* Another is to recognize a *thickened basement membrane*, as the regenerating epithelium always seems to produce its own new basement membrane even if preexisting basement membrane still seems available. If the injurious stimulus disappears, the conjunctival character of the epithelium slowly fades, being replaced within a few weeks by a normal corneal epithelial configuration. Epithelial adhesion to the underlying stroma remains fragile for 6–8 weeks until the hemidesmosomal attachments of epithelium to basal lamina reform, and until the new epithelium secretes type VII collagen fibrils that anchor the basal lamina to the stroma. In the interim, the cells adhere to a mixture of fibrin and fibronectin derived from the inflamed conjunctival vessels via the tear film or from the injured cornea itself. In many cases, the only evidence of previous shallow ulceration is a thickened basal lamina resulting from secretion by the regenerating epithelium, and gentle undulation of the normally flat epithelial–stromal interface.

Stromal damage may be a direct result of the severity of the initial injury, but more often it is the result of neutrophil-mediated stromal lysis in those corneal injuries that were initially, or later became, septic. Shallow nonprogressive defects in the superficial stroma may be ignored, or may become filled by a thickened plaque of epithelial cells that create an epithelial facet. *Deeper defects that include more than the outer third of stroma will usually require rebuilding of the damaged stroma before epithelial sliding and regeneration can occur.* Within a few hours of the insult, neutrophils enter the wound via the tear film. They migrate into the stroma and control bacterial contamination, degrade damaged collagen, and stimulate both fibroplasia and vascularization via production of various cytokines, especially basic fibroblast growth factor derived from injured epithelium, stromal neutrophils, and injured stromal fibroblasts themselves. Viable stromal cells (keratocytes)

adjacent to the wound undergo fibroblastic metaplasia and secrete large amounts of sulfated ground substance, particularly chondroitin sulfate. Most of the new stroma is usually produced by fibroblasts recruited from the limbus. Their ingrowth is always accompanied by a similar ingrowth of new blood vessels. This ingrowth begins about 4 days after substantial corneal injury, and migrates from the limbus centrally at a maximal rate of about 1 mm per day. This 4-day lag time is, presumably, a period of grace in which small or shallow defects can heal with epithelial regeneration alone, without the visual impairment that inevitably follows stromal fibroplasia. Once the epithelium seals the defect, there is immediate cessation of neutrophilic influx and, presumably, a similarly abrupt drop in the production of fibroblastic/angioplastic stimulatory cytokines. *The scarring and vascularization that are the manifestations of stromal rebuilding are permanent*, even though the fibrous tissue gradually becomes less cellular, the collagen fibrils reorient to resemble more closely the parallel arrays of normal stroma, and the ground substance gradually reverts from an embryonic configuration dominated by chondroitin sulfate to the normal predominance of keratan sulfate. Complete restitution of normal stroma, however, never occurs, although the residual scar may be subtle and better detected by clinical examination than by histology. Undesirable though such scarring may be, it is certainly better than the alternative of ineffective corneal healing and inevitable corneal rupture.

Healing of a corneal perforation involves the same events as does healing of a deep corneal ulcer, but there are some added challenges and complications. The cut edges of Descemet's elastic membrane retract from the wound and the transcorneal gap is initially plugged with fibrin and, sometimes, by prolapsed iris. If the gap is not closed by suturing or by a provisional matrix supplied by fibrin and/or iris stroma, there is the risk that the surface epithelium will grow downward along the cut surface of the stroma and into the anterior chamber (Fig. 4.27A). Its migration will be inhibited only by contact with viable corneal endothelium. If it does not encounter that endothelium, there is nothing to stop the epithelium from growing as a layer of stratified squamous epithelium all over the inside of the globe (Fig. 4.27B, C). Obstruction of the filtration angle inevitably causes glaucoma.

As with the surface epithelium, the corneal endothelium at the deep edge of the perforation attempts to bridge the defect by sliding over the fibrin scaffold to restore endothelial continuity. Replacement by mitosis begins within about 24 hours in some experimental models, but *the regenerative capability of the corneal endothelium in adult animals of most domestic species is very limited, and repair occurs by endothelial sliding and hypertrophy.* So potent is this capability that normal stromal dehydration can be maintained even in the face of a 50% reduction in endothelial cell density. The cut ends of Descemet's membrane make no apparent effort at regrowth, but rather the endothelium gradually secretes a new membrane that may eventually fuse with the old or remain separated from it by a layer of fibrous tissue.

The sequence of epithelial sliding and regeneration, remodeling stromal fibrosis and endothelial repair is not uniformly successful. Large gaping wounds fill with proliferating epithelium and stromal fibrous tissue that may protrude into the anterior chamber. The fibroblasts, most of which are probably derived from keratocytes but which may also evolve via endothelial metaplasia, tend to grow along the posterior surface of Descemet's membrane. Regenerating or sliding endothelium is then separated from the coiled remnants of the

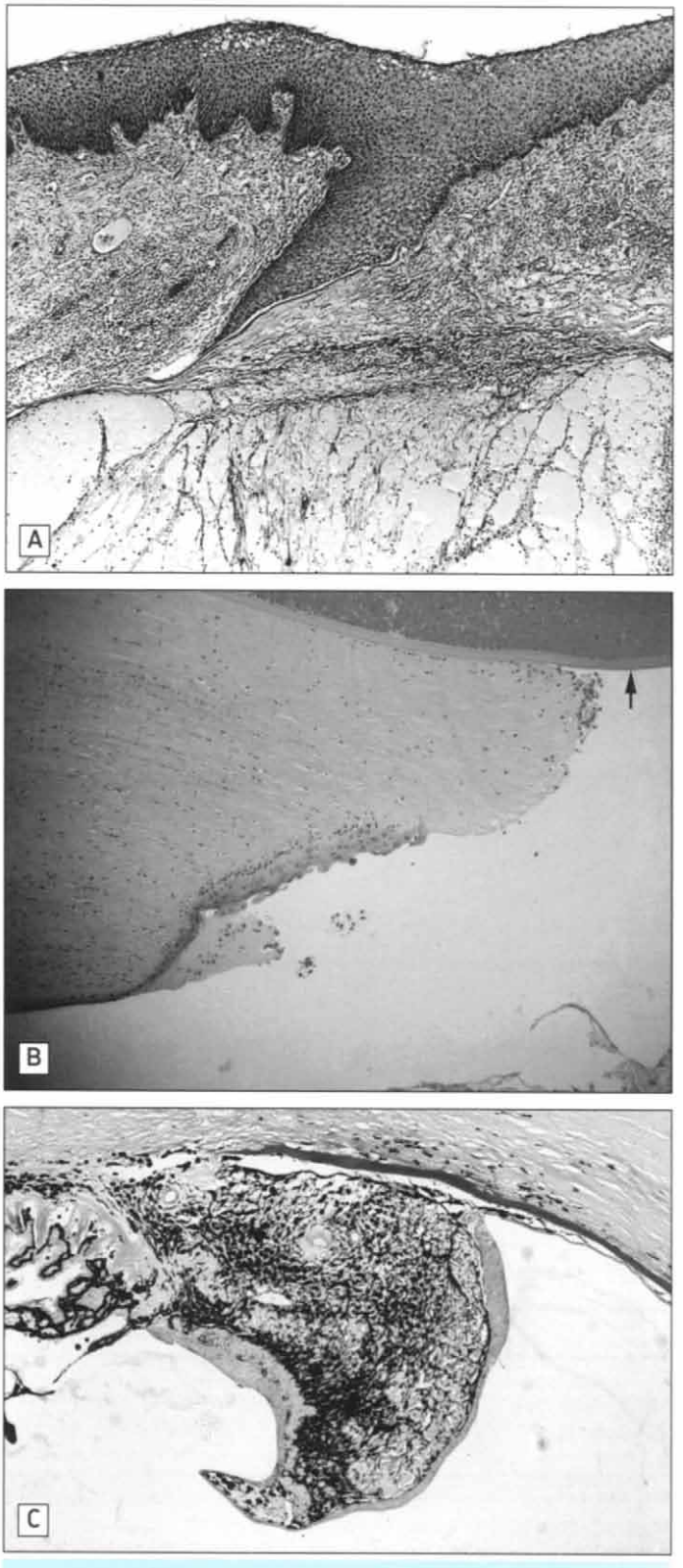

Figure 4.27 A. Corneal perforation in a steer. Defect filled by downgrowth of hyperplastic corneal epithelium. Adjacent stroma is vascularized and chronically inflamed. Edematous iris adheres to the innermost aspect of the lesion, creating focal anterior synechia. **B. Corneal epithelial downgrowth** along the gaping edge of an unsutured corneal laceration. Arrow points to Descemet's membrane that remains intact. **C. Corneal epithelial downgrowth** into the anterior chamber extends over the anterior and posterior surfaces of the iris.

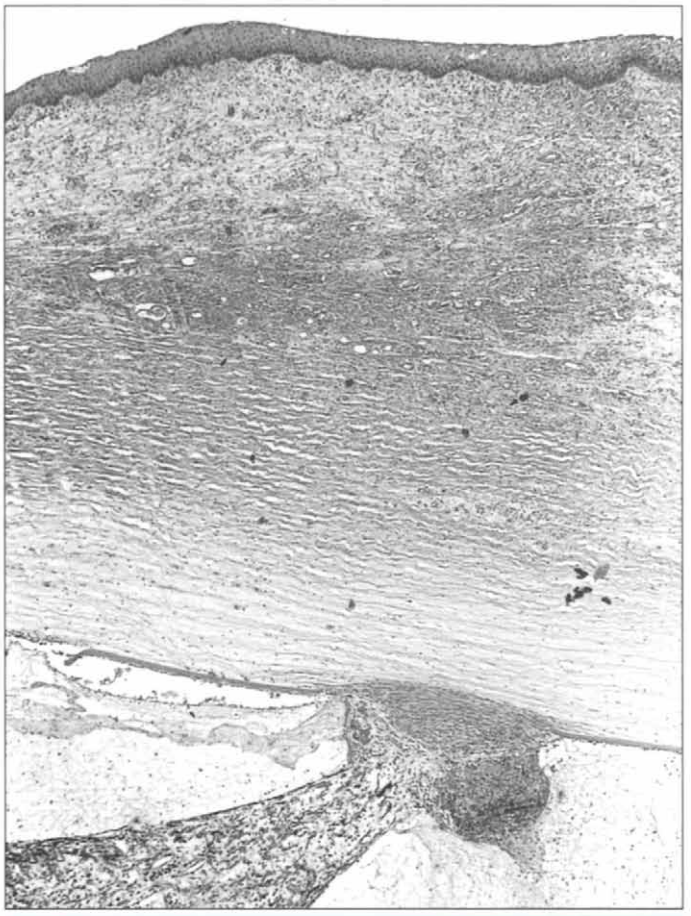

Figure 4.28 Corneal cutaneous metaplasia and chronic superficial stromal inflammation with vascularization. **Anterior synechia** adherent by fibrous plaque that is partly formed by metaplastic corneal endothelium.

original Descemet's membrane by a dense fibrous layer, called a *retrocorneal fibrous membrane*. Eventually, the corneal endothelium may regain continuity on the posterior surface of this membrane, secrete a new Descemet's membrane, and result in a cornea with two separate Descemet's membranes. Those perforations leading to iris prolapse will usually heal with permanent incorporation of the iris into the huge corneal scar, creating a permanent anterior synechia (Fig. 4.28).

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Corneal dystrophy

Corneal dystrophies are bilateral, inherited (but not necessarily congenital) defects in structure or function of one or more corneal components. They are subclassified as epithelial, stromal, or endothelial. They are all uncommon, and almost all examples have been described in dogs. The list grows daily, with more than 30 different breeds affected. The least infrequent are the stromal dystrophies characterized by the deposition of lipids and/or minerals within an otherwise normal-appearing stroma. The deposition of mineral or lipid secondary to inflammatory disease or systemic metabolic abnormality should not be interpreted as corneal dystrophy.

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

Posterior polymorphous dystrophy is characterized by multifocal random degeneration of corneal endothelial cells, accompanied by compensatory endothelial hypertrophy. Cellular loss causes exposure of Descemet's membrane, and adjacent deep stromal patchy edema.

A rare, juvenile-onset, genetically transmitted *endothelial dystrophy in Manx and domestic shorthair cats* is manifest as bilateral, progressive central epithelial and stromal edema. Fluid accumulates within superficial stroma and within the epithelium. Primary morphologic abnormalities are not described in the Manx, but in shorthairs there is irregularity and vacuolation of corneal endothelium.

Corneal stromal dystrophies include a wide range of breed-specific lipid and/or mineral deposits within the corneal stroma, with the exact age of onset, location, and clinical appearance being relatively specific in each breed. Specimens are rarely available for histologic assessment since the disease does not cause blindness and is not associated with any systemic abnormality. In most, the chemical nature of the deposit and character of the metabolic abnormality have not been determined.

Other corneal deposits

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

Corneal hypermelanosis often accompanies *chronic corneal irritation in dogs* and less frequently in other species, particularly horses. The pigment is found in the basal layer of the corneal epithelium and in the superficial stroma. *It is the result of progressive ingrowth of new germinal cells that have retained pigment from the bulbar conjunctiva.* The clinical name, "*pigmentary keratitis*," is purely descriptive. The corneal epithelium is invariably hyperplastic and often has the other features of corneal cutaneous metaplasia, such as rete ridge formation, keratinization, and abnormally thick basement membrane. There is usually evidence of chronic stromal inflammation, including vascularization. Corneal stromal pigmentation without evidence of epithelial cutaneous metaplasia occurs infrequently, associated with previous iris prolapse that has contributed uveal melanin to the corneal stromal scar.

Other types of corneal pigmentation are rare. *Hemosiderin* will be found within corneal endothelial cells subsequent to anterior chamber hemorrhage or within stromal macrophages if there has been hemorrhage into the corneal stroma itself. Similar pigment may occur following implantation of corneal foreign bodies containing iron or other metals.

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

Regardless of pathogenesis, the histologic lesion is similar. Cholesterol crystals and lipid vacuoles are found principally in anterior stroma, and are sometimes surrounded by lipid-laden macrophages and variable numbers of other leukocytes (Fig. 4.29). Vascularization is often present, but its pathogenesis is unknown. It appears that corneal vascularization can predispose to stromal lipidosis in animals with hyperlipemia, but it is also true that some animals with primary corneal lipidosis will develop secondary inflammation and vascularization.

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

An unidentified corneal deposition is often seen in canine eyes suffering from multiple anomalies, particularly those involving uvea.

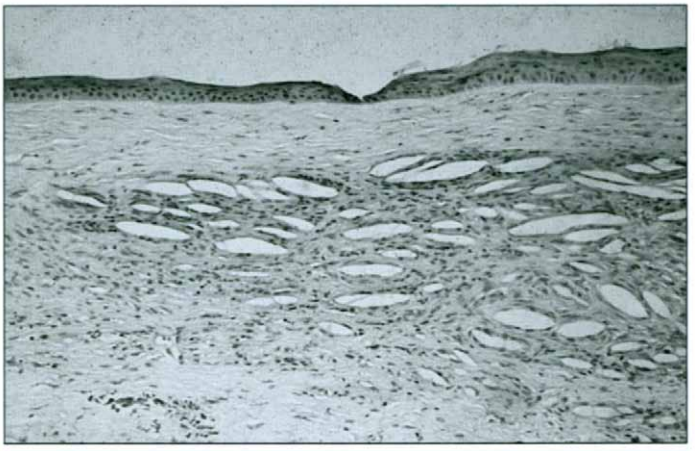

Figure 4.29 Lipid keratopathy. Clefts of cholesterol within the corneal stroma trigger mild nonseptic granulomatous inflammation.

Similar deposits are seen, with less regularity, in the horizontal midportion of the cornea of many normal puppies. Fine basophilic periodic acid-Schiff positive linear deposits are associated with the epithelial basement membrane or superficial stroma. There is some disarray of superficial stromal fibers but no inflammation. The nature and pathogenesis of the deposit are unknown, but most disappear after a few months.

Corneal degeneration

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

The only degenerative, noninflammatory, acquired corneal lesions presented here are corneal sequestrum in cats and horses, and canine persistent erosion syndrome. It is quite possible that all three diseases have a similar pathogenesis, but for the moment they will be listed as three different diseases because of differences in clinical presentation.

Feline corneal sequestrum *is recognized clinically as a discrete orange-brown discoloration of the central cornea, affecting one or both eyes* (Fig. 4.30). Persian and Himalayan cats are more frequently affected than other breeds. Histologically, *the lesion is noninflammatory necrosis of stromal keratocytes, accompanied by pallor, hyalinization, and slight orange discoloration of the affected stroma.* The discoloration may be absent in very early cases. The overlying epithelium may be ulcerated or intact, but in those cases with an intact epithelium there is virtually always histologic evidence of previous ulceration. In older lesions, the periphery of the sequestrum may be marked by a zone of reactive mononuclear leukocytes and, perhaps, a few giant cells. The pigment is derived from porphyrins within the tear film, absorbed into the cornea as part of corneal edema that follows ulceration. *The sequestrum will eventually slough, and the defect heals by granulation* (although most lesions are treated by excision before that stage is reached).

The pathogenesis remains controversial. In flat-faced Persian and Himalayan cats, the pathogenesis probably involves corneal ulceration secondary to desiccation because of abnormal facial configuration. In

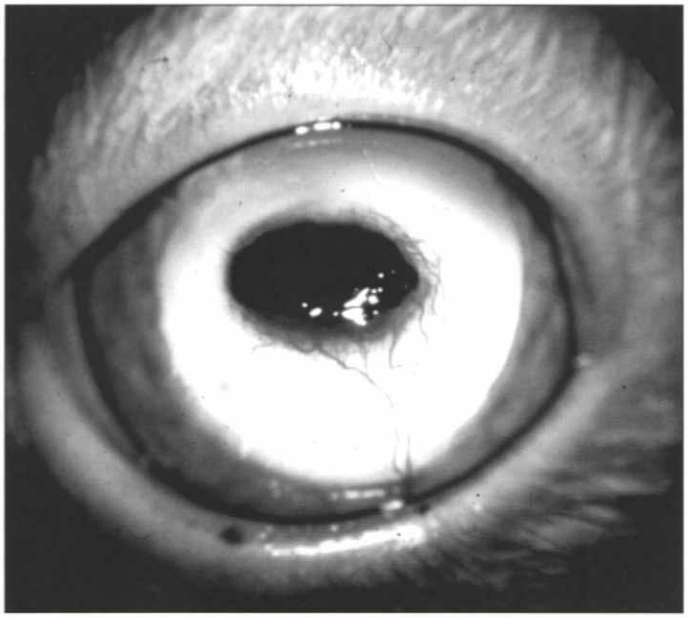

Figure 4.30 Feline corneal sequestrum.

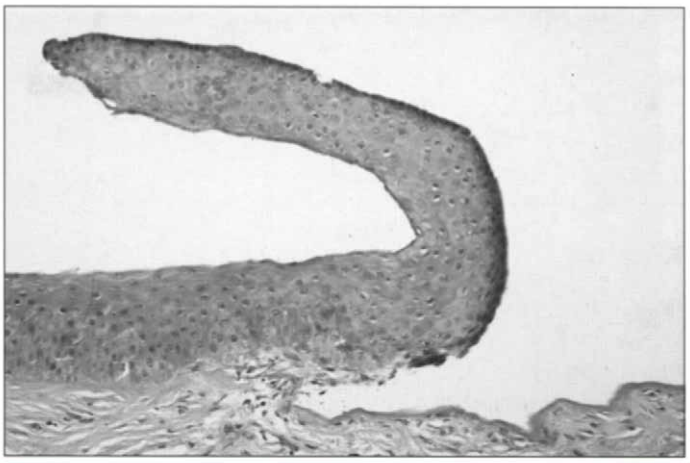

Figure 4.31 Canine persistent ulcer. Dysplastic, strongly regenerative epithelium is unable to adhere to the underlying superficial stroma.

non-Persian cats, there is a loose statistical association with herpesviral infection, and *it is reasonable to propose that corneal sequestrum is an uncommon sequel to any corneal ulceration in cats*. As will become clearer below, the brown discoloration is unique to cats and, for a long time, caused us to overlook the histologic similarity between the feline disease and similar histologic entities in horses and dogs. Not all feline cases acquire the characteristic brown pigmentation, and indeed some examples are virtually indistinguishable from canine and equine persistent ulcers described below.

Canine persistent (recurrent) ulcer syndrome was first described in Boxer dogs (hence the name "*Boxer ulcer*"). Although Boxers and related breeds may be predisposed, similar recurrent erosions are encountered in a wide variety of breeds. *The clinical syndrome is distinctive, characterized by a shallow central corneal erosion with scant edema and (at least initially) no vascularization*. The lesion refuses to heal, or repeatedly re-ulcerates, because of poor adhesion of the epithelium to the underlying stroma. The defect appears not to be in epithelial healing per se, since sliding and mitotic activity are normal in affected dogs. Keratectomy specimens reveal poorly adherent hyperplastic epithelium at the ulcer margins, usually with multiple clefts separating epithelium from stroma even in areas distant from the obvious ulcer (Fig. 4.31). The basal lamina is usually not visible with light microscopy, and the epithelium appears to be attempting to adhere to a thin zone of hypocellular, pale-staining stroma that could correctly be interpreted as a very shallow sequestrum qualitatively similar to what was described above in cats. *The observation of pyknotic and lytic keratocyte nuclei within this superficial zone suggests that the basic defect is degeneration of the superficial stroma*, so that epithelial hemidesmosomes and anchoring collagen fibrils attempting to reform after ulceration have no substrate in which to anchor. Very chronic cases usually acquire superficial stromal granulation tissue appropriate to any chronic ulceration, but its onset is much delayed in comparison to infectious or traumatic ulcers.

The lesion in **horses** is less frequent and less well characterized than in dogs or cats. It is histologically identical to what occurs in dogs, although it seems to be more often complicated and thus disguised by superimposed fungal infection (see Fig. 4.35B).

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Keratitis

Corneal inflammation is called **keratitis** *and has traditionally been divided into epithelial, stromal (interstitial), and ulcerative keratitis.* It is probably time to abandon this arbitrary classification, at least when dealing with ocular histopathology. In realistic terms, almost all corneal inflammatory lesions reaching a pathologist are chronic and severe, and it is difficult to determine how they started. By the time we see them, almost all are ulcerated or show extensive stromal scarring below a healed ulcer. Regardless of cause, corneal inflammation initially follows the stereotyped sequence of edema and leukocyte immigration from tears and distant limbic venules. With severe lesions, corneal stromal vascularization, fibrosis and epithelial metaplasia with pigmentation may occur.

Keratitis usually results from physical, chemical, or microbial injury to the cornea, but the cornea may also be affected by extension of disease from elsewhere in the eye, adnexa, or conjunctiva. The stroma and endothelium may become involved in diseases of the uvea by extension via the aqueous or by direct extension from iris root or ciliary apparatus across the limbus.

Purely **epithelial keratitis** is rarely encountered in histologic preparations, either because the clinical lesion is transient and so mild that eyes are unavailable for histologic examination, or because the lesion progresses to ulceration (as in acute keratoconjunctivitis sicca).

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

The usual role of bacteria and fungi in the pathogenesis of corneal ulceration is opportunistic. However, these opportunists contribute significantly to the perpetuation and worsening of the lesion. Proteases and collagenases of microbial, leukocytic, or corneal origin progressively liquefy corneal stroma, a process termed **keratomalacia** (Fig. 4.32). Ulcers contaminated by *Pseudomonas* and *Streptococcus* spp. are particularly prone to rapid liquefaction because of the potent collagenases and proteases produced by these organisms. *Pseudomonas* ulcers have been extensively investigated because of the devastating liquefaction

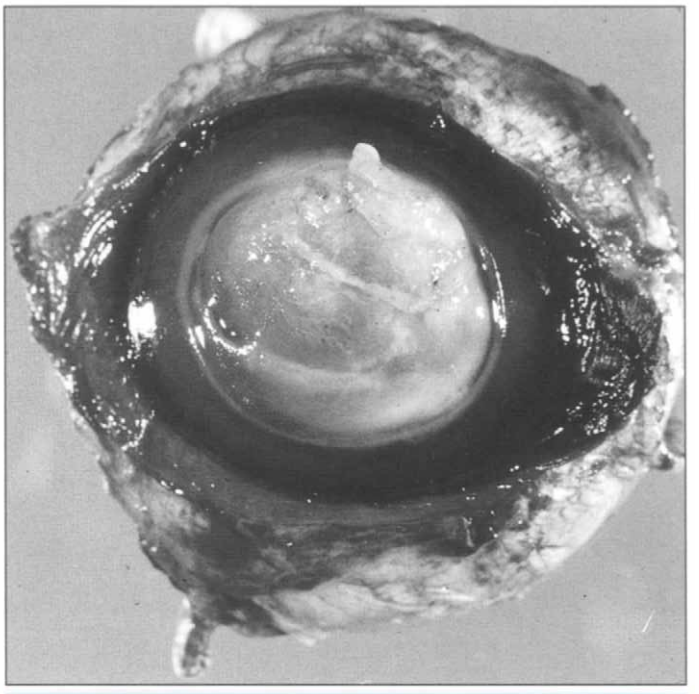

Figure 4.32 Keratomalacia in a horse with *Pseudomonas* keratitis.

of cornea that commonly accompanies this infection. The bacteria themselves produce numerous proteases and other toxins that may be important in the establishment of the early infection, but most of the characteristic stromal malacia results from the action of proteases originating from leukocytes, reactive corneal epithelium, or injured stroma. The stroma contains a variety of proenzymes (for collagenases, elastases, gelatinases, and other stromal lysins) that are cleaved by the *Pseudomonas* toxins to produce the active enzymes. Which toxins are produced, and in what quantities, is very strain dependent. The stepwise degradation of stroma is seen histologically as a featureless eosinophilic coagulum, which occurs with progressive septic ulcers regardless of the species of bacterium. Neutrophils may encircle the liquefying focus as a thick wall of live and fragmented cells. The resulting localized suppurative keratomalacia is called a ring *abscess* (Fig. 4.33), although that terminology is rarely used today. It is seen more commonly in cattle than any other species, perhaps because of the prevalence of untreated, contaminated corneal ulcers in that species and the prevalence of septic corneal perforation.

The sequelae of ulcerative keratitis involve cornea, conjunctiva, and uvea. *The ulcer itself may heal with vascularization and scarring proportional to the severity of the initial lesion. It may persist as a stubborn but nonprogressive lesion, or it may progress to involve more of the stroma and epithelium.* Stromal liquefaction that reaches Descemet's membrane results in its forward bulging as a descemetocele. This membrane, while resistant to penetration of the microbial agents themselves, is apparently permeable to inflammatory mediators and microbial toxins that diffuse into the anterior chamber. These chemicals, combined with a vasoactive sensory neural reflex from irritated cornea, are responsible for the vasodilation and exudation in anterior uvea that are seen histologically in virtually all globes with deep ulcerative keratitis. Even in nonperforating keratitis, the anterior uveal inflammation may result in sufficient fibrin exudation so as to predispose to focal adhesions of iris to lens or (rarely) to cornea.

Figure 4.33 Severe suppurative keratomalacia accompanied by massive stromal edema, in a calf. The iris bows forward and almost obliterates the anterior chamber, a manifestation either of iris bombé or of nearby iris prolapse.

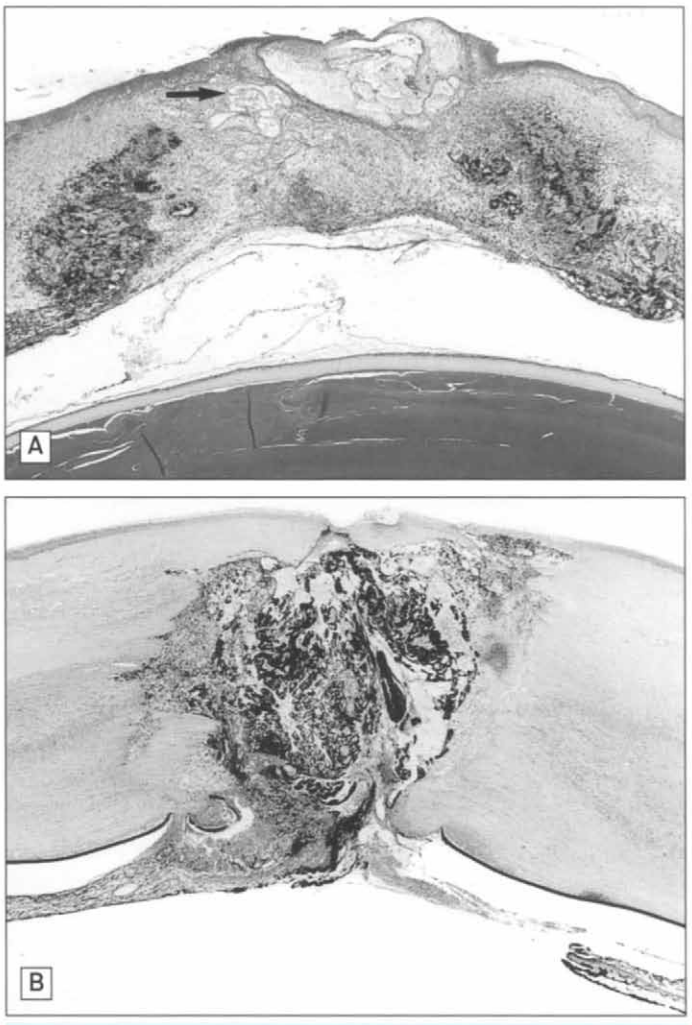

Figure 4.34 A. Healing corneal perforation. Corneal epithelium is attempting to heal across a fibrin mass plugging the defect. Iris is incorporated into the lesion and will form **anterior staphyloma**. Note coiled remnant of Descemet's membrane (arrow). **B.** Iris entrapped within the cornea following perforation of ulcer (**iris prolapse**).

In the case of corneal perforation, the iris flows forward to plug the defect (*iris prolapse*) and may subsequently become incorporated into the corneal scarring. This outcome is usually called **anterior staphyloma**, meaning a focal defect in the ocular fibrous tunic (i.e., cornea) that becomes lined by uvea (Fig. 4.34A, B). The distinction from anterior synechia is of little significance.

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

There are some instances in which the lesions are found primarily within the stroma. Examples of bacterial or fungal keratitis in which the organisms were implanted into the stroma may cause chronic suppurative keratomalacia with negligible involvement of superficial stroma or epithelium. Alternatively, deep ulcerative septic keratitis may heal superficially, yet persist deep within the stroma. In either of these two situations, the deep lesion is referred to as *stromal abscess*.

Midstromal corneal vascular ingrowth from the limbus is a very common lesion in response to vascular endothelial growth factors elaborated in the course of chronic uveitis of virtually any cause. It appears to be a purely accidental lesion with no obvious purpose, but it does serve as a valuable and permanent histologic marker for previous or ongoing intraocular inflammatory disease. Its liability as a marker for subacute or chronic intraocular inflammation is probably not absolute, because similar midstromal vascularization can probably occur in response to growth factors liberated from detached retina or intraocular neoplasms (see Significance of uveitis).

Pannus keratitis

The only credible candidate for a *genuine stromal keratitis*, in which the primary target for the inflammatory disease is the stroma itself, is **pannus keratitis**. *This is an idiopathic disease seen most frequently in German Shepherds and phenotypically similar breeds.* Its prevalence and severity are directly correlated with altitude, suggesting that *sunlight exposure* is part of the pathogenesis. The clinical disease is distinctive. The early lesion is seen in dogs of either sex, usually in early middle age, as a vascularized opacity growing into the corneal stroma from the limbus. The ingrowth is bilateral although not always of simultaneous onset, and most frequently originates from the ventrolateral limbus. There is no ulceration, but pigmentation is often marked. The untreated lesion eventually infiltrates the entire cornea, converting the superficial stroma to an opaque membrane resembling granulation tissue. At one time, superficial keratectomy was the recommended therapy and so histologic specimens were quite often available. Today, most cases are treated with potent immunosuppressive therapy, and the need to perform a keratectomy to restore vision is rare indeed.

The histologic appearance varies with the duration of the lesion. *The initial lesion is superficial stromal infiltration of mononuclear cells, especially plasma cells.* Subsequently, there is progressive vascularization and

fibroplasia in the superficial third of the stroma, accompanied by epithelial hyperplasia and pigmentation that may include the stroma. The deep stroma is never affected.

The pathogenesis of the condition is unknown, but an immune reaction to altered corneal epithelial antigens is hypothesized. Its response to continuous corticosteroid administration supports this hypothesis, as does it striking histologic similarity to discoid lupus and other lupoid dermatoses. Despite the similarity, immunofluorescence tests for intraepithelial or basement membrane immunoglobulin are negative. Infectious agents are not consistently isolated. A histologically similar lesion of the bulbar conjuctiva of third eyelid occurs in the same breed (so-called "*plasmoma*") and may reflect the same mysterious pathogenesis.

Keratoconjunctivitis sicca and desiccation keratitis

The response of the cornea to desiccation depends on the rapidity of onset and the severity of the desiccation. *It is seen as a consequence of inadequacy in the quantity or quality of the tear film* (usually called **keratoconjunctivitis sicca**). It also occurs as a consequence of exophthalmos, improper eyelid closure because of eyelid developmental anomaly, acquired eyelid disease, nerve injury to prevent blinking, profound CNS depression in which the blink reflex is lost, or conditions such as glaucoma or orbital mass that prevent proper eyelid closure because of abnormal ocular size or position. Under such circumstances, the corneal lesion is usually referred to as **desiccation keratitis**, although the effect upon the cornea is exactly the same as in acute keratoconjunctivitis sicca. In those cases in which the desiccation occurs only in a horizontal band not adequately covered by the eyelids for whatever reason, the lesion is sometimes referred to as *band keratopathy*.

If the desiccation is profound and occurs rapidly, the cornea has no time to adapt and the outcome is *acute ulceration*. It can be distinguished from other types of corneal ulceration histologically because *it is the only example of corneal ulceration that occurs in the absence of edema or neutrophilic infiltration* (because there is no tear film to provide either the water or the leukocytes). If the desiccation is only mild, or occurs over a long interval that allows corneal adaptation, the resulting lesion is *corneal cutaneous metaplasia*.

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

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

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

Herpetic keratitis of cats

Feline herpetic keratitis, caused by *Felid herpesvirus 1*, is seen either as the sole ocular lesion or in concert with conjunctivitis. Clinical signs associated with herpesviral infections in cats include conjunctivitis, keratitis, rhinotracheitis and, in neonates, systemic disease with encephalitis and necrosis in visceral organs. Acquired immunity alters the manifestations of the disease and results in different lesions predominating in different age groups. *Keratitis is commonest in adult cats* and seems to result from activation of latent infection during concurrent immunosuppressive disease or corticosteroid therapy. Concurrent mild respiratory disease may be present, but *in adults the disease is often purely corneal and may even be unilateral*. In contrast, *the infection in adolescent cats causes nonspecific bilateral erosive conjunctivitis without keratitis*. Intranuclear inclusions are numerous within cells prior to sloughing, and leukocytes are sparse until ulceration permits opportunistic contamination. Upper respiratory disease is almost always present.

The corneal lesions fall into two very different categories: *shallow transient erosions and ulcers* that represent the direct cytopathic effect of acute viral infection, and *more severe stromal keratitis* that is probably an immune response to viral antigen in persistent or recurring infections. The typical acute superficial corneal lesions are multifocal minute corneal erosions and ulcers that have a tendency to coalesce into branching dendritic ulcers. Early in the disease, typical herpesviral inclusions may be seen with histology, and herpesviral antigen can be demonstrated with immunofluorescence or other techniques. Severe or recurrent lesions in immunosuppressed cats may result in underlying stromal keratitis with lymphocytic infiltration, persistent edema, and vascularization.

There is much more written about the clinical features and clinical diagnosis of herpesviral keratitis than there it is about its pathology, simply because most cases are never subjected to histologic evaluation. By the time a sample of conjunctiva or cornea is taken for histologic assessment in cases that have been therapeutically resistant, histologic detection of inclusion bodies is futile and immunofluorescence is usually negative. Virus can usually be detected with PCR, but interpretation of that result is almost impossible because of the

high prevalence of carriage in asymptomatic, healthy cats. For the same reason, attempts to link persistent herpesviral infection with feline corneal sequestrum or feline eosinophilic keratitis have been less than convincing.

Feline eosinophilic keratitis

Another uniquely feline ocular lesion is seen clinically as unilateral or bilateral proliferative, "fluffy" white stromal keratitis. There is no breed, age, or sex predilection, and no proven association with other ocular or systemic disease. Since the diagnosis is made by cytologic evaluation of superficial scrapings or (occasionally) by histologic examination of surgical keratectomy specimens, this disease is more likely to be seen by pathologists than most other corneal disorders. Scrapings of the surface of the lesion reveal numerous eosinophils and fewer mast cells and other mononuclear leukocytes. Eosinophils may be less conspicuous on histologic examination of keratectomy specimens, perhaps because most seem determined to emigrate through the epithelium and into the tear film rather than remain within the tissue. Instead, the stromal lesion is a *mixture of macrophages, plasma cells, fibroblasts and, unpredictably, mast cells and at least a few eosinophils.* The latter are least frequent in older lesions, either because of time alone or because older lesions are more likely to have received a lot of corticosteroid therapy. A characteristic lesion, not present in every case, is a *dense granular eosinophilic coagulum* along the surface of the keratectomy specimen. It seems to consist of free eosinophil granules. No bacterial or fungal agents have been seen. While there are histologic similarities to cutaneous eosinophilic ulcer and linear granuloma, no statistical association has been proven and the lack of understanding even of the cutaneous eosinophilic lesions makes such attempted comparisons of very limited value. While much speculation exists about the relationship between persistent herpesviral infection and eosinophilic keratitis, there is no proven etiologic link.

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Mycotic keratitis

Mycotic keratitis *is a destructive, suppurative, ulcerative and deep stromal keratitis most commonly seen in horses,* but occasionally encountered in all domestic species. The offending fungus is usually a member of the normal conjunctival flora, and its role in the disease is always that of *opportunistic contaminant. Aspergillus* is the most frequent isolate, but cases caused by other common conjunctival fungi like *Alternaria, Penicillium*, and *Cladosporium* are not rare. *Most cases are probably iatrogenic*, occurring in animals in which a corneal ulcer, laceration, or penetrating wound had been treated with long-term antibiotics and/or *corticosteroids.* The latter is a particularly common villain in this context. Horses seem particularly prone to mycotic keratitis, perhaps related to the mold-laden, dusty environment in which many horses are housed; only rarely does the lesion occur in dogs or cats. Since virtually all stabled horses have fungi as part of their conjunctival flora, *seeing hyphae within the corneal stroma is required for the diagnosis.* Isolation from a corneal swab or shallow scraping is not adequate.

Because the disease is much more prevalent in horses than any other species, most of the description below is derived from equine cases. The histologic changes in other species, however, are very similar to what occurs in horses. There appears to be a difference in the typical lesion seen in temperate climates and what occurs in horses in very warm and humid environments. In the latter, there are cases in which the fungi are found throughout the cornea and are easily identified by even shallow scraping. That is not the case in those examples of the disease diagnosed in cooler climates, which I will consider the "typical" disease.

The typical early lesion is deep ulcerative keratitis with suppurative keratomalacia. Some chronic lesions are exclusively stromal because of successful epithelial and superficial stromal healing of the initial penetration (or perhaps because therapy eliminated the infection in the superficial stroma). For whatever reason, the typical equine eye enucleated for mycotic keratitis has an intense neutrophil-rich deep stromal keratitis with several characteristic features: neutrophils are karyorrhectic, inflammation is most intense immediately adjacent to Descemet's membrane, and frequently there is lysis of the normally resistant Descemet's membrane with spillage of the corneal inflammation into the anterior chamber. *Fungi are numerous within the malacia of the deep stroma and within Descemet's membrane itself,* but rarely if ever are seen within the anterior chamber (Fig. 4.35A). When they occur within the anterior chamber, they are always anchored to the nearby Descemet's membrane. Despite ample opportunity, there has never been a reported case of disseminated intraocular mycosis as a sequel to mycotic keratitis. Fungi are sparse or absent within the superficial half of the stroma, which explains why corneal scrapings or even keratectomy specimens may fail to reveal the agent. The reason for the apparent targeting of Descemet's membrane is not known, but the presence of the tropism even in untreated eyes suggests that it is a

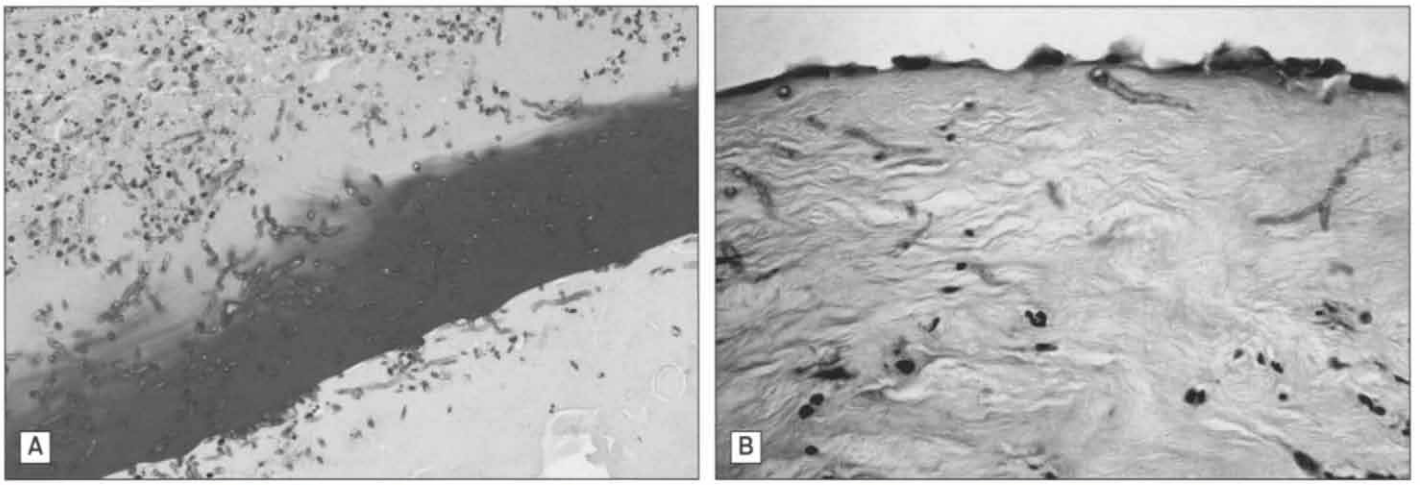

Figure 4.35 A. Equine mycotic keratitis. The fungi typically are found within and adjacent to Descemet's membrane, accompanied by karyorrhectic neutrophils and stromal malacia. **B. Opportunistic fungal contamination** of an equine superficial corneal sequestrum, but distinctly different syndrome from traditional mycotic keratitis. Note the absence of leukocytes.

genuine tropism and not just persistence of a previously generalized stromal infection in the site least likely to be reached by topical fungicides.

In horses in tropical and near-tropical climates (many reports, for example, come from Florida), the fungi are more diffusely distributed within the cornea and are thus more easily captured by routine cytology or culture swabs. While the distribution of the lesion within the cornea is also more diffuse, its fundamental lytic character remains the same.

In horses, cats, and dogs, we will occasionally see *corneal sequestra contaminated with fungal hyphae*; the fungi are easily found on scraping, leading to the mistaken impression that this is true mycotic keratitis (Fig. 4.35B). One could debate the issue, but it seems better to keep this as a separate syndrome quite different from the lesion described above.

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Infectious bovine keratoconjunctivitis

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

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

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

In addition to variation in the virulence of different strains of *M. bovis*, sunlight, dust and, perhaps, concurrent infection with infectious bovine rhinotracheitis virus (*Bovine herpesvirus 1)* increase the severity of the disease. Calves are usually affected more severely than cattle over 2 years of age, although absolute resistance to infection seems fragile. The protective effect of serum antibody against the disease is controversial. Specific IgA is found in tears of infected

calves, and there is substantial evidence that locally produced IgA is strongly protective.

Following experimental inoculation of virulent *M. bovis* onto the cornea, pilus-mediated adhesion and production of bacterial cytotoxin result in microscopic ulceration in as little as 12 hours. Initial adhesion is to older surface epithelium ("dark cells") and results in the development of microscopic pits in the cell surface. *Moraxella* is found within degenerate epithelial cells, but it is not known whether invasion is necessary for subsequent cellular destruction. *In field epizootics, the earliest lesion is bulbar conjunctival edema and hyperemia, followed in 24–48 hours by the appearance of a shallow central corneal ulcer.* The ulcer is a small (<0.5 cm) focus of epithelial necrosis that may appear as erosion, vesicle, or full-thickness epithelial loss. In untreated animals destined to develop the full clinical expression, the ulcer enlarges, deepens, and frequently attracts enough neutrophils to qualify as a *corneal abscess*. Stromal liquefaction ensues, probably as a result of neutrophil lysis, which is itself initiated by *Moraxella*-derived leukotoxins. By the end of the first week, there is extensive stromal edema and vascularization extending from the limbus. As with any severe ulcerative keratitis, the subsequent progression or regression of the lesion varies with each case as modifications by therapy, opportunistic bacterial and fungal contamination, trauma, inflammation, and immunity interact. Keratomalacia frequently leads to forward coning of the weakened cornea (*keratoconus*). In most instances, whether treated or not, the cornea heals by sloughing of necrotic tissue and filling of the defect by granulation tissue. Re-epithelialization may take up to a month, leaving a cornea that is slightly coned and variably scarred. The scarring often is scant and interferes little with vision in spite of the severity of the primary lesion.

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

Infectious keratoconjunctivitis (contagious ophthalmia, pinkeye) of sheep and goats

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

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

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LENS

The lens is a flattened sphere of epithelial cells suspended in the pupillary aperture by a large number of transparent elastin-like fibers known as *lens zonules*. These originate from the lens capsule near the equator, and fuse with the nonpigmented ciliary epithelium along the lateral surfaces of the ciliary processes or in the valleys between adjacent ciliary processes. *The range of histologic reaction of lens to injury is very limited due to the simplicity of its structure and physiology, and its lack of vascularity.*

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

Below the capsule is a layer of simple cuboidal *lens epithelium* that, in all but fetal globes, is found below the capsule of only the anterior half of the lens. The apex of these cells faces inward toward the lens nucleus. At the equator, these germinal cells extend into the lens cortex as the *nuclear bow*, an arc of cells being progressively transformed from cuboidal germinal epithelium to the elongated spindle shape of the mature *lens fibers* (Fig. 4.36). The bulk of the lens is composed of onion-like layers of elongated epithelial cells anchored to each other by interlocking surface ridges, grooves, and ball-and-socket protuberances. These elongated fibers contain no nucleus and few cytoplasmic organelles, relying almost entirely on anaerobic glycolysis for energy. Since the lens cannot shed aging fibers as does skin or intestine, these cells are compacted into *the*