Chronic Corneal Edema in Aged Ranch Mink

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Abstract. Chronic corneal edema occurred in 53% of 116 ranch mink (Mustela vison) 8 to 11 years old. Most were royal pastel females, the main group at risk. Bilateral in 46 of 66 affected mink studied, the edema evolved over a month or so until the cornea became opaque, diffusely pale blue-gray or white, and greatly thickened. The swollen cornea did not become ulcerated, pigmented, or vascularized, even after it had been severely edematous for a year or two. The edema supervened as a consequence of spontaneous deterioration of the corneal endothelium. Attenuation and loss of the endothelial monolayer were the most common light microscopic changes. Other changes included discrete excrescences (guttata) along the posterior surface of the thickened Descemet's membrane and a subendothelial fibrillar or fibrocellular layer (posterior collagenous layer) often apposed to the excrescences. Likened to the primary endothelial dystrophies of man and the dog, this endothelial disorder of mink is regarded as an abiotrophic degeneration with its own distinguishing features in this species.

Far from being the static structure it seems, the cornea depends on dynamic balances to maintain its normal thickness and transparency. Its stroma, rich in glycosaminoglycans, has a propensity to swell by absorbing water (mainly from aqueous humor) across the endothelium covering the posterior corneal surface. Such movement of water occurs passively through intercellular junctional complexes controlling the permeability of this fragile cell layer to various substances. Normally, water leaking into the stroma is compensated for by the energy-dependent endothelial pump that transfers bicarbonate ions into the aqueous humor. Thus, the remarkably constant level of stromal hydration, or state of deturgescence, that maintains the normal thickness and transparency of the cornea reflects the delicate balance between water leaking into the stroma and that pumped back into the aqueous humor. If the amount of water imbibed exceeds the capacity of the metabolic pumping mechanism, because of dysfunction or loss of endothelial cells, corneal edema ensues.

An example of such imbalance, or decompensation, resulting in chronic corneal edema is reported here in ranch mink (Mustela vison). Affecting mainly those that were 8 or 9 years old, the edema supervened as a consequence of spontaneous deterioration of the corneal endothelium.

Materials and Methods

The male and female mink whose eyes were examined represented an aging population that remained from earlier studies on slow viral diseases. They were much older than mink found in commercial herds in which few ever become more than 3½ years old before they are killed for their pelts. The population included three color phases: royal pastel, homozygous for a single mutant gene; sapphire, homozygous for two genes (platinum and gunmetal); and opaline, homozygous for three (platinum, royal pastel, and Moyle-Olsen buff). Some affected eyes were among those collected at random from these mink, as previously reported. Others were from similar mink chosen for necropsy because they had longstanding corneal edema. They were anesthetized with ether and exsanguinated by cardiac puncture. The eyes were removed promptly, freed of orbital soft tissues, fixed in Zenker's fluid, and then processed in paraffin by a described procedure. Eyes from 46 affected mink were examined by light microscopy.

Results

Clinical features

Corneal edema occurred in 66 mink—one sapphire, four opalines, and 61 royal pastels. Except for four pastel mink, all were females. (The population at risk comprised mostly pastel females.) They ranged in age from 6 to 11 years, but 51 (77%) were 8 or 9 years old at the time of necropsy. Both eyes were affected, usually to the same extent, in 46 mink. In the other 20, the right eye was affected slightly more often than the left. Although corneal edema was common in the older mink, its true prevalence was not determined. Yet, of
They remained normally active and in a good state of nourishment until succumbing to some other disease commonly affecting older mink. Their corneal edema had no adverse effect on the general health of the mink. Affected mink did not act as though it was in pain; they did not resist or change during that period. The edematous cornea did not become vascularized; its exposed surface usually remained intact and smooth. When the edema was mild, faintly-stained smudgy patches of lamellae dispersed, often irregularly, into fine fibrils and were distributed randomly in the stroma (Fig. 3). In moderately edematous corneas, these rarefied patches had fewer fibrils and were larger and more numerous (Fig. 4). Throughout the stroma, nuclei of keratocytes were enlarged. When the edema was severe, lamellae had disappeared from much of the stroma, leaving the cornea mostly occupied by large spaces or lakes that accounted for its great thickening (Figs. 5, 6). Although often largest centrally, the lakes extended peripherally to the limbus and from the epithelial basement membrane (Bowman’s layer is absent in mink) almost to Descemet’s membrane; a band of stroma overlying it was usually preserved. Some lakes contained a few neutrophils, nuclei of keratocytes, or fibrillar remnants of lamellae, but most were optically empty.

Seven corneas had foci of proliferated keratocytes (corneal fibroblasts) under the epithelial basement membrane, mainly centrally (Fig. 7). But none had incipient pannus; neither fibroblasts nor blood vessels had invaded the subepithelial stroma from the limbus, nor were deeper layers of the stroma vascularized. Although occasionally distorted by folds and undulations or pulled away from the overlying stroma, Descemet’s membrane was mostly intact. In some corneas, it was thickened diffusely or segmentally, but often not more so than it may be in some nonedematous corneas of older mink. Sometimes the membrane appeared lumpy or unevenly stained by periodic acid-Schiff reagent. In about half of the corneas, the typically smooth membrane bore discrete ex crescences irregularly spaced along its posterior surface (Figs. 8, 9). Some were broad, flat, and block-like; others were truncated and flared or were simply small nubs. These

### Table 1. Prevalence of chronic corneal edema in female mink 8 to 11 years old at necropsy.

<table>
<thead>
<tr>
<th>Color Phase</th>
<th>Age in Years</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Pastel</td>
<td>17/41*</td>
</tr>
<tr>
<td>Opaque</td>
<td>2/2</td>
</tr>
<tr>
<td>Sapphire</td>
<td>0/6</td>
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* Number with corneal edema/number at risk.
Not shown are 1/3 8-year-old and 2/2 10-year-old pastel males, the only males in this group of 116 mink.

116 8-to-11-year-old mink whose eyes were examined histologically or were looked at clinically several times before necropsy, 53% had corneal edema (Table 1).

Little was learned about the onset of the corneal edema, but it was first obvious as a general haziness of the cornea. Then, over a month or so it became opaque, diffusely pale blue-gray or white, and greatly thickened (Fig. 1). The edematous thickening made the cornea bulge well beyond the normal contour of its anterior curvature. When severe, the edema occasionally deformed the curvature even more, resulting in keratoconus or keratoglobus. Because the eyes of most mink were not looked at regularly, many affected corneas were already severely edematous when first seen. Once the edema had become fully expressed, it persisted unchanged for many months or even a year or two. None of the edematous corneas improved or returned to normal during that period.

Although the severely edematous cornea protruded through the palpebral fissure, it seldom became traumatized; its exposed surface usually remained intact and smooth. When the edema was long-standing, however, the anterior corneal surface sometimes acquired a textured or finely wrinkled appearance. But epithelial bullae or erosions rarely supervened; superficial ulcers did not. The edematous cornea did not become vascularized or pigmented. Nor was it accompanied by signs of conjunctival irritation, such as hyperemia and increased lacrimation. The eyelids remained unchanged, though often they could not close completely over the bulging cornea.

When bilateral, the diffuse corneal edema blinded the mink, but this did not affect their normal behavior as long as they were kept in surroundings familiar to them. Whether the corneal edema was painful was uncertain. Affected mink did not act as though it was; slight pressure on the edematous cornea failed to elicit a response indicating unusual discomfort. Even when the corneal edema was present for a year or more, it had no adverse effect on the general health of the mink. They remained normally active and in a good state of nourishment until succumbing to some other disease commonly affecting older mink.

### Microscopic appearance

Except for minor changes, the corneal epithelium was intact. In most severely edematous corneas, it was reduced from a normal thickness in older mink of three or four cells to often only two cells. Three corneas had one or more small epithelial bullae (Fig. 2). In another, the epithelium was eroded, but not one was ulcerated. The basal cells were focally loosened or jumbled in several corneas. In all others, the epithelium remained in orderly contact with its thin basement membrane, which was seldom disrupted, thickened, or otherwise changed. Apart from slight intercellular edema of the basal cell layer in a few severely swollen corneas, the epithelium was not edematous, regardless of the degree or duration of the stromal swelling. Nor was the epithelium pigmented with melelin granules.

In the corneal stroma, the imbibed water separated the lamellae well beyond the slits and clefts commonly occurring as a processing artifact in paraffin sections. When the edema was mild, faintly-stained smudgy patches of lamellae dispersed, often irregularly, into fine fibrils and were distributed randomly in the stroma (Fig. 3). In moderately edematous corneas, these rarefied patches had fewer fibrils and were larger and more numerous (Fig. 4). Throughout the stroma, nuclei of keratocytes were enlarged. When the edema was severe, lamellae had disappeared from much of the stroma, leaving the cornea mostly occupied by large spaces or lakes that accounted for its great thickening (Figs. 5, 6). Although often largest centrally, the lakes extended peripherally to the limbus and from the epithelial basement membrane (Bowman’s layer is absent in mink) almost to Descemet’s membrane; a band of stroma overlying it was usually preserved. Some lakes contained a few neutrophils, nuclei of keratocytes, or fibrillar remnants of lamellae, but most were optically empty.

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Fig. 1. Severe corneal edema; 10-year-old mink.
Fig. 2. Epithelial bullae protrude centrally from severely edematous cornea; 11-year-old mink. HE.
Fig. 3. Early corneal edema; 9-year-old mink. HE.
Fig. 4. Moderate corneal edema centrally; 8-year-old mink. Keratocyte nuclei enlarged. HE.
Fig. 5. Typical appearance of severely edematous cornea; 9-year-old mink. HE.
Fig. 6. Large empty lakes replace stromal lamellae in severely edematous cornea; 9-year-old mink. Intact band of stroma next to Descemet's membrane. HE.
Fig. 7. Central subepithelial proliferation of keratocytes in severely edematous cornea; 10-year-old mink. HE.
Fig. 8. Central excrescences covered with atrophic endothelium in severely edematous cornea; 9-year-old mink. Descemet’s membrane thickened. PAS.

Fig. 9. Large central excrescences on Descemet’s membrane in severely edematous cornea; 9-year-old mink. PAS.

Fig. 10. Descemet’s membrane studded with small excrescences toward periphery of severely edematous cornea; 9-year-old mink. PAS.

Fig. 11. Posterior collagenous layer apposed to excrescences on thickened Descemet’s membrane centrally in severely edematous cornea; 9-year-old mink. PAS.

Fig. 12. Dense acellular posterior collagenous layer centrally in severely edematous cornea; 9-year-old mink. PAS.
so-called warts were seldom numerous. Yet in some corneas, stretches of the membrane were studded with them (Fig. 10). They occurred centrally (cornea guttata) and peripherally (Hassall-Henle bodies). The larger ones seemed more common centrally, but at the two sites the excrescences had much the same form. Unlike the peripheral ones seen occasionally in nondematous corneas of older mink, the central ones (with one exception) were found only in edematous corneas and then mainly in those severely so. Some excrescences were covered with atrophic endothelium; others were embedded in a layer of fibrous tissue.

The layer of fibrous tissue had formed over the posterior surface of Descemet's membrane in about half the corneas, nearly all severely edematous. Varying in thickness and staining like stromal lamellae, it was often apposed to the excrescences (Fig. 11). It generally occurred in short and long stretches, which were slightly more common centrally than peripherally. In some eyes, though, this posterior collagenous layer extended over most of Descemet's membrane as a continuous sheet. Thinner stretches of it were composed of densely aligned fine fibrils (Fig. 12); thicker ones comprised loosely arranged coarser fibers and cells resembling fibroblasts (Fig. 13). Occasionally, the thicker stretches caused folds in Descemet's membrane. Having arisen under the endothelium, the posterior collagenous layer was sometimes still partly covered by it.

In contrast to the thin continuous layer of somewhat foamy endothelial cells bearing oval nuclei normally present in older mink (Fig. 14), the endothelium of edematous corneas was usually greatly attenuated and often discontinuous, especially centrally. This left long stretches of Descemet's membrane bare. When the attenuation was pronounced, cytoplasmic extensions of the much thinned endothelial cells were nothing more than a dark line (Gomori's trichrome stain) along Descemet's membrane (Fig. 15). The darkly stained elongated nuclei, disposed singly or in small groups, were widely separated so few were seen, except at the periphery where the endothelium was preserved better than elsewhere. In severely edematous corneas, the endothelium was completely absent or nearly so (Fig. 16). All that remained were a few isolated cells which sometimes were enlarged (Fig. 17). Occasionally, remnants of cells that had become detached from Descemet's membrane were dispersed in eosinophilic granular debris often present in the anterior chamber.

In addition, the affected eyes had several other pathologic changes commonly found in older mink. None had a bearing on the occurrence of corneal edema. Some degree of retinal degeneration was present in almost all eyes and cataract in many. In three of 20 mink affected with lymphocytic lymphoma, neoplastic lymphocytes had infiltrated the iris, the only notable lesion in the uveal tract. Changes solely attributable to increased intraocular pressure were not seen.

**Discussion**

In the absence of other changes that might give rise to chronic corneal edema in the mink, spontaneous deterioration of the corneal endothelium was the most likely cause of it. The process took place slowly, ostensibly as a phenomenon of aging. Yet the microscopic findings indicated the process was not simply an expression of advancing age; it included more than impaired function of the endothelium incident to the gradual decrease in number of cells per unit area (cell density) that occurs with aging in other animals and man. Although not entirely separable from such age-related events, the microscopic findings were more consistent with those of a primary disease of the endothelium similar to that reported in several small breeds of dogs, notably the Boston terrier and Chihuahua. Affecting mainly older females, the disease in dogs has been likened to Fuchs' endothelial dystrophy in man.

Fuchs' endothelial dystrophy, probably inherited as an autosomal dominant trait, occurs most often in postmenopausal women. With a clinical course usually spanning 10 to 20 years, it leads to blinding corneal edema complicated by painful epithelial bullae and stromal scarring. Its most striking histopathologic features occur in the endothelium and Descemet's membrane. Foremost are focal accumulations of abnormal basement membrane, the excrescences (cornea guttata), that arise centrally along the posterior surface of the thickened Descemet's membrane. Some merely disrupt the endothelium and protrude into the

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**Fig. 13.** Coarse fibrocellular posterior collagenous layer peripherally in moderately edematous cornea; 8-year-old mink. PAS.

**Fig. 14.** Normal corneal endothelium centrally in 8-year-old mink without stromal edema. Gomori's trichrome.

**Fig. 15.** Greatly attenuated endothelium centrally in severely edematous cornea; 9-year-old mink. Gomori's trichrome.

**Fig. 16.** Descemet's membrane denuded of endothelium centrally in severely edematous cornea; 10-year-old mink. Gomori's trichrome.

**Fig. 17.** Residual endothelial cells, some enlarged, centrally in severely edematous cornea; 9-year-old mink. Gomori's trichrome.
anterior chamber. Others are embedded in a layer of fibrillar or fibrocellular tissue, the posterior collagenous layer. A dense acellular layer of fine fibrils may form unassisted to the excrescences. All these structures, appearing clinically as a much thickened Descemet's membrane, are products of a stressed or diseased endothelium that undergoes metaplasia and behaves like fibroblasts. Although the endothelium consists of normal and degenerating cells, it is generally thinned, especially over the excrescences. It may be so thin that it is not visible by light microscopy, though usually is demonstrable by electron microscopy.

Clinically important changes in the corneal stroma and epithelium that contribute to the fully-developed disease are secondary to the endothelial dystrophy. The underlying endothelial abnormality is unknown.

As in Fuchs' dystrophy, the histopathologic changes in the mink disease included excrescences on a thickened Descemet's membrane and a posterior collagenous layer. Yet their presence and relative prominence varied among the mink. For instance, however striking the excrescences were when multiple, they were an inconstant expression of the endothelial disease, at least before the stromal edema became severe. They are sometimes absent in Fuchs' dystrophy also.\(^{10,18}\) Attenuation or atrophy and loss of the endothelium were far more common and conspicuous. As might be expected, the microscopic features of the dystrophy in dogs also differed from those of classic Fuchs' dystrophy.\(^{8,14}\) And even in the dog, they have varied from one breed to another.\(^{14}\)

These differences aside, the microscopic findings in the mink still pointed to a primary endothelial disease with its own distinguishing features in this species. Several clinically important attributes of the super-vening corneal edema also set the disease apart from the endothelial dystrophies in man and the dog: essentially no epithelial edema at any time; no epithelial pigmentation; little tendency to form epithelial bullae and erosions; no ulceration; and no vascular invasion or scarring of the stroma, even after the cornea had been severely edematous for more than a year. All these attributes exemplify peculiarities in the way tissues of the mink's eye respond to long-standing corneal edema. They give distinction to corneal edema as a clinical entity in mink.

Other comparisons can be made with the primary endothelial dystrophies. By their very nature, they affect both eyes, though often asymmetrically.\(^{8,24}\) That the corneal edema affected only one eye in about a third of the mink would seem to argue against its likeness to the dystrophies. But this disparity may have merely reflected wide variation in the onset of the edema—an extreme asymmetry in the overt clinical expression of bilateral endothelial disease.\(^{22}\) The dystrophies of man and the dog affect females more often than males. Although nearly all mink with corneal edema were females, not enough males were in the population at risk to conclude that this is also true of the mink disease. Nevertheless, given the high prevalence of corneal edema in the large group of pastel females, it might be so.

As a stable group of cells, the corneal endothelium ordinarily has little potential for renewal.\(^{3,16,22}\) The decrease in cell density with aging attests to this. As cells are lost, a functional endothelium is maintained by undamaged cells that enlarge and spread or migrate over gaps in the monolayer.\(^{1,15}\) Sometimes repair comes about also by cell proliferation.\(^{1,16,32}\) Such regeneration by mitotic division is especially notable in the young domestic rabbit.\(^{16,21}\) In other animals and man, though, endothelial cells do not divide as readily, if they do at all.\(^{1,3,20,21}\) Regeneration then plays a minor role in repair, especially in adults. Nothing is known about the regenerative capacity of the mink's corneal endothelium. Whatever reparative processes (cell migration or cell division, or both) may have taken place in the mink with corneal edema, none restored the integrity of the endothelium. Its dysfunction was permanent, and the stromal edema persisted indefinitely. Neither stromal scarring nor the pronounced loss of stromal lamellae during prolonged edema reduced the thickness of the swollen cornea.\(^{6}\)

The common occurrence of corneal edema in older mink indicates the underlying endothelial disorder, like retinal degeneration in mink,\(^9\) is an inherent constitutional weakness or abiotrophy in this species. Its full expression no doubt is controlled genetically, as endothelial dystrophy is in man\(^{10,24}\) and probably is in the dog.\(^{8,14}\) Whatever that genetic control may be in mink, it is not clearly related to the autosomal recessive genes affecting primarily coat color;\(^{11,17}\) corneal edema occurred in two color phases (sapphire and opaline) other than royal pastel, the main one affected. Even so, too few sapphire and opaline mink were in the population at risk to decide whether coat color genotype influences the prevalence of corneal edema.

Given the proneness of the mink's corneal endothelium to spontaneous deterioration during advanced age, a systematic study of it (including Descemet's membrane), especially by electron microscopy, might disclose abnormalities that long antedate the late onset of corneal edema, as is so in Fuchs' dystrophy.\(^2\) Besides characterizing the abiotrophic disorder in mink more thoroughly than reported here, such a study might also further the general understanding of naturally occurring primary disease of the corneal endothelium. Good animal models of it are scarce.\(^5,7\)
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References


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