

# Tutorial Article

## Nonulcerative keratopathies in the horse

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### Introduction

The cornea is quite literally a window on the eye, and corneal disease is often overt and dramatic in its presentation. This is a matter of immense convenience to the examining clinician, but it can also incite the curiosity, and can trigger the anxiety, of the horse owner. Although gross corneal abnormalities are often the result of primary disease, e.g. bacterial ulceration, the clinical status of the cornea can reflect the overall health of the eye and may be an important clue to the presence of intraocular disease, e.g. glaucoma. It is essential that the cornea is not examined in isolation from the rest of the eye. Not infrequently, horse owners are prompted to seek veterinary advice because of a corneal abnormality which, on investigation, turns out to arise secondarily to intraocular disease or, less commonly, from disease of the adnexa.

In addition to ulceration, the cornea responds to insult by a number of nonmutually exclusive mechanisms, including:

- Oedema
- Vascularisation
- Pigmentation
- Fibrosis
- Facet formation
- Mineralisation

**Oedema (Fig 13)** results from hydration of the corneal GAG ground substance, causing derangement of the regular lamellar collagen array and subsequent scatter of transmitted light. The characteristic turgidity and opacity of the oedematous cornea are easily recognisable clinically. Water may enter the corneal stroma from the aqueous tear film following physical disruption of the anterior epithelial barrier, or from the anterior chamber aqueous following functional disabling of the posterior endothelial cells.

**Vascularisation (Figs 17 and 18)** of the injured cornea is a complex and poorly understood process, involving cytokine-mediated interaction between extravasated leucocytes and the corneolimbic vascular endothelium. The location of leucocyte extravasation corresponds to the site and level of vessel ingrowth into the cornea (Becker *et al.* 1999).

**Pigmentation (Fig 11)** involves the migration of melanophore-bearing cells from the limbus into the cornea. Pigmentation is typically superficial and follows blood vessel ingress into the cornea. The equine cornea appears less susceptible to pigmentation than that of other domestic species.

**Fibrosis (Fig 1)** results from delayed or disordered stromal repair, causing laying down of *Type III* collagen and creating a permanent and dense opacity.

**Facet formation (Fig 2)** arises where the repair of a superficial stromal defect is incomplete and normal epithelium overlies a shallow depression on the corneal surface.

**Mineralisation (Figs 9 and 10)** may be subepithelial or intrastromal, and is a nonspecific response to chronic or recurrent anterior segment inflammatory insult.

The descriptive term '**nonulcerative keratopathies**' identifies a group of principally degenerative or inflammatory corneal disorders, characterised clinically by the presence of some or all of the above pathologies.

### Classification of nonulcerative keratopathies

The nonulcerative keratopathies may be classified as follows:

- Dystrophic?
- Degenerative
- Of unknown aetiology
- Inflammatory - keratitis  
- keratouveitis
- Neoplastic
- Congenital

Neoplastic and congenital keratopathies are dealt with separately in this series of papers on equine ocular disease to be published in forthcoming issues of EVE.

### Corneal dystrophy

In strict ophthalmological terms, corneal dystrophies are defined as primary inherited biochemical abnormalities which are typically associated with bilateral, central and progressive opacities. There is no neovascularisation. Keratopathies meeting all of these criteria have not been described in the horse. However, progressive unilateral dystrophic-like stromal lesions are occasionally encountered in the horse (**Fig 3**). There is no treatment.

### Corneal degenerations

Corneal degenerations are a group of secondary disorders associated with previous or concurrent primary corneal

injury, or with intraocular or extraocular disease. The group includes:

- Secondary corneal oedema
- Exposure keratopathy
- Keratoconjunctivitis sicca
- Corneal mineralisation
- Corneal staphyloma
- Retrocorneal opacities (retrocorneal membranes)

### *Secondary corneal oedema*

This is a common sequela of many ocular diseases. Anterior stromal oedema follows corneal epithelial disruption, e.g. laceration or abrasion, and usually remains localised to the area of injury and resolves rapidly as the epithelium heals. However, caution should be exercised where local superficial oedema persists. In such instances, the corneal lesions should carefully be checked for embedded foreign bodies and the adnexa examined for abnormalities such as fornix-based foreign bodies or ectopic cilia.

More generalised stromal oedema results from biochemical or physical injury to endothelial cells. This may have a number of causes, including:

- Anterior uveitis (**Fig 4**)
- Blunt ocular trauma (**Fig 5**)
- Glaucoma (**Fig 6**)
- Iridial neoplasia (melanoma) (**Fig 7**)
- Endotheliitis (**Fig 19**)

In all cases, correction of the primary problem determines resolution of the oedema. The capacity for endothelial repair is limited in the adult, and the persistence of oedema despite resolution of the primary cause may herald permanent opacification.

### *Exposure keratopathy*

This appears as a superficial vascularised keratitis, complicated by intermittent epithelial sloughing and occasionally by shallow ulceration. It results from abnormal distribution and break-up of the precorneal tear film and is a sequela of a number of adnexal disorders, including:

- Ptosis e.g. facial paralysis
- Exophthalmos e.g. retrobulbar neoplasia or hydatid cyst
- Eyelid neoplasia and trauma
- Chronic conjunctivitis, meibomianitis and chelazion

Treatment involves regular application of ocular lubricants or artificial tears. Temporary tarsorrhaphy or bandage contact lenses may be useful in a selected few cases. In all cases the primary cause must be identified and, where possible, be corrected.

### *Keratoconjunctivitis sicca (KCS)*

This is rare in the horse and is usually unilateral. There is a deficiency in the aqueous component of the precorneal tear film, resulting in surface drying of the cornea. Affected corneas appear lacklustre, with epithelial sloughing and superficial vascularisation (**Fig 8**). In some cases, aqueous tear production may be only marginally reduced, resulting in recurrent or persistent conjunctivitis with little obvious corneal involvement. In these cases, the corneal surface may have a vaguely 'oil slick' appearance. Diagnosis involves Schirmer testing of tear production. Comparison of tear production in both eyes is helpful. Schirmer testing should be carried out in all cases of superficial keratitis or chronic conjunctivitis.

KCS most frequently results from disruption of the parasympathetic supply to the lacrimal gland within the superficial petrosal nerve caused by fracture of the stylohyoid bone or proximal part of the vertical ramus of the mandible. In these cases, because of the anatomical proximity of cranial nerve VII, facial palsy may also be present. KCS may also be evident in some cases of vestibular disease and in temporohyoid osteoarthropathy (middle ear disease) (Blythe and Watrous 1997).

In the USA, KCS has been associated with locoweed poisoning, and eosinophilic granulomatous dacryoadenitis, putatively caused by *Thelazia lachrymalis* larval migration, has been recorded (Collins *et al.* 1994). Congenital KCS does occur, but the cause is unknown.

KCS is generally managed using topical ocular lubricants. However, where possible a primary cause should be identified and treated. Cyclosporine A is known to be lacrimomimetic in horses (Collins *et al.* 1994), but its successful use in managing KCS has not been reported and is likely to be ruled out on economic grounds in most cases. Surgical transpositioning of the parotid duct to the medial canthus is possible in the horse (Wolf and Meredith 1981) and has been used to manage a few cases.

### *Corneal mineralisation*

Localised subepithelial calcium deposition is occasionally observed in cases of equine recurrent uveitis (Rebhun 1992) and in chronic keratitis (**Fig 9**). These usually resolve spontaneously once the primary disease is under control, but removal by superficial keratectomy may be necessary in some instances.

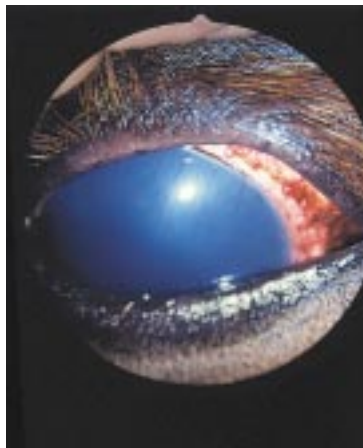
Central stromal mineralisation (**Fig 10**) may follow recurrent deep keratitis or endotheliitis. In these cases, spontaneous resolution may occur. Surgical intervention is not recommended.

### *Corneal staphyloma*

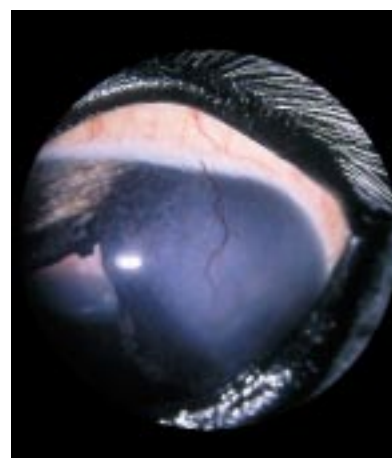
In the horse, perforating injuries of the cornea frequently seal with prolapsed iris. If left untreated and infection does not supervene, a bridge of organised fibrovascular tissue will close the defect. This staphyloma will tend to



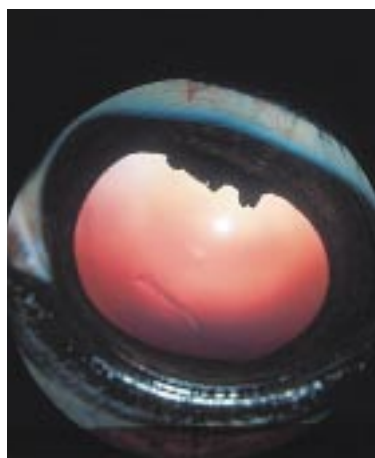
**Fig 1:** Dense leukoma associated with stromal fibrosis caused by delayed correction of entropion.



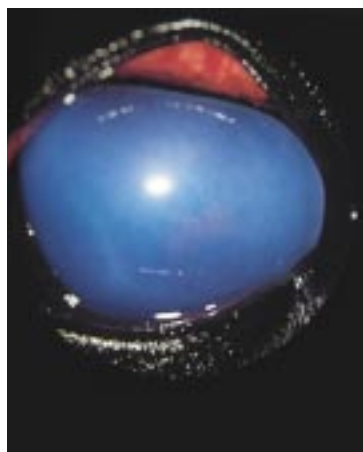
**Fig 4:** Secondary corneal oedema associated with equine recurrent uveitis (ERU).



**Fig 7:** Secondary corneal oedema caused by an iridial melanoma impinging on the endothelium.



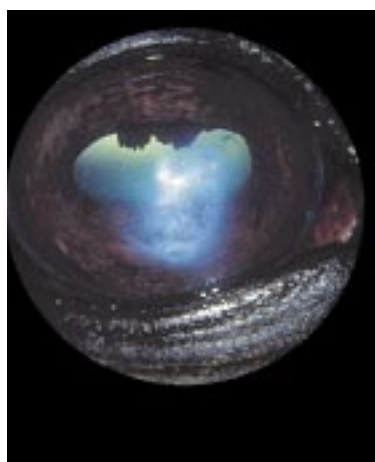
**Fig 2:** Corneal facet. Normal epithelium covers a shallow stromal defect.



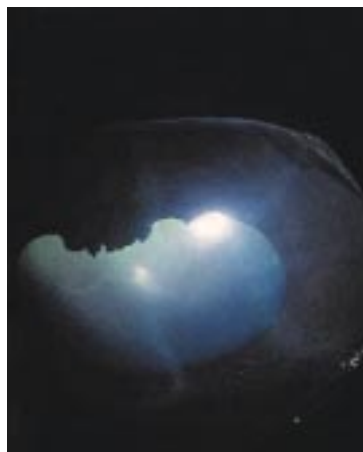
**Fig 5:** Secondary corneal oedema resulting from blunt ocular trauma. There is associated hyphaema.



**Fig 8:** Keratoconjunctivitis sicca in a horse. Note the lacklustre appearance of the ocular surface and the areas of abraded epithelium (photograph courtesy of Dr Keith Barnett).



**Fig 3:** Unilateral and progressive dystrophy-like lesion in an adult horse.



**Fig 6:** Secondary corneal oedema associated with glaucoma. Note the deep linear opacities (Haab's striae) caused by fractures in Descemet's membrane resulting from ocular hypertension (see Fig 14).



**Fig 9:** Subepithelial mineralisation in a case of ERU.

prolapse anteriorly under the influence of aqueous pressure, creating a keratoconus. Affected corneas usually become heavily pigmented and owners may regard this as a cosmetically acceptable alternative to enucleation (**Fig 11**). However, these eyes carry a theoretical risk of recurring injury and infection, and most clinicians will advise enucleation.

### *Retrocorneal opacities*

These present as long-standing, nonprogressive, nonoedematous opacities. They are usually caused by direct blunt trauma tearing Descemet's membrane, which effectively seals with disorganised stromal collagen. These opacities may have a fusiform configuration due to elastic distraction of the edges of the tear (**Fig 12**).

### *Keratopathies of unknown aetiology*

This is a heterogeneous group of disorders of unknown aetiology, but each of which may involve dystrophic, degenerative or inflammatory processes.

### *Bullous keratopathy (idiopathic primary oedema) (Fig 13)*

This is an uncommon condition apparently arising from primary endothelial dysfunction. The disease is usually unilateral. The entire cornea is grossly oedematous and turgid and is generally nonpainful. However, subepithelial bullae commonly form and these may rupture or be abraded by lid action, causing moderate ocular discomfort. The cornea does not usually become vascularised, and intraocular pressure (IOP) is normal. No other abnormalities are present.

Treatment is difficult and prognosis is always guarded. Topical hyperosmotic preparations, e.g. 5% sodium chloride, may provide temporary clearing, but are irritant. Topical corticosteroids are usually tried but results are disappointing and they should be avoided where epithelial erosions are present. Recently, the successful use of Cyclosporine A in clearing these corneas has been reported (K. Knarfstrom, personal communication).

### *Linear keratopathy (Walde 1983) (Fig 14)*

These are posterior, striate, refractile opacities, with well-defined, parallel margins. They are present in otherwise normal eyes. They may be unilateral or bilateral and most commonly traverse the horizontal meridian of the cornea. They are nonoedematous and nonprogressive, and have been shown to result from local thinning of Descemet's membrane.

The cause is unknown, although a transient periparturient rise in IOP may be responsible. Similar striate opacities can result from blunt trauma to the globe and in cases of glaucoma. In these instances, the opacities are usually associated with other ocular signs. Glaucoma is clearly an important differential diagnosis of eyes with

linear keratopathy, and a careful and thorough examination is necessary in all cases. Some clinicians have expressed the concern that linear opacities occurring in otherwise normal eyes may have resulted from a transient postnatal elevation in IOP and may be indicative of incipient glaucoma. However, in the absence of more generalised ocular disease, it is reasonable at present to regard these opacities as a benign and incidental finding. There is no treatment.

### *Multifocal punctate opacities (Rebhun 1992) (Fig 15)*

This is a sporadic, usually unilateral disease. It is characterised by persistent multiple focal anterior stromal opacities, generally located in the central or medial cornea. Affected eyes are nonpainful and there is no adverse effect on vision. The lesions are generally nonprogressive, although in some instances there may be a precipitate increase in the extent and density of the opacities, with some becoming confluent. The cause is unknown. There is no treatment; however, topical corticosteroids are indicated in cases where the opacities progress.

### *Nonulcerative inflammatory keratopathies*

These are broadly divided into:

- Keratitis - pathology restricted to cornea
- Keratouveitis - cornea and anterior uvea involved

### *Nonulcerative keratides*

This is a broad group of disorders of presumptively different aetiologies. They are characterised by nonulcerative opacification occurring at varying levels in the cornea, the absence of overt anterior uveitis and the response to topical anti-inflammatory or immunosuppressive medication. Most are associated with vascularisation and typically there is only minor ocular discomfort, even in the presence of extensive corneal pathology. Some, or all, of these disorders are probably immunogenic in origin. They appear to have no direct equivalent in other species and are unique to the horse. Within the general group of nonulcerative keratitides, 4 diseases can currently be recognised as specific entities. These are identified using descriptive terminology:

- Epithelial keratopathy
- Chronic superficial keratitis
- Chronic recurrent deep keratitis
- Endotheliitis

### *Epithelial keratopathy (Fig 16)*

This is a sporadic unilateral disease affecting horses of any age. There is a diffuse, central epithelial opacity associated with slight blepharospasm and ocular discomfort. There is no vascularisation or conjunctival hyperaemia. The opacity is caused by irregular coalescing

islands of thickened and elevated epithelium. There is no stromal involvement and the unaffected cornea within the area of the lesion appears normal. Fluorescein stain is transiently retained in the interstices between the islands of abnormal epithelium.

Topical dexamethasone q.i.d. results in clearing of the cornea within 3–4 days and the lesions have not recurred in any treated cases.

### *Chronic superficial keratitis (Fig 17)*

This disease is characterised by an insidious onset and lack of response to topical corticosteroids. The disease is initially unilateral, but may become bilateral after 7–12 months. Affected eyes show slight to moderate discomfort. There is prominent superficial vascularisation with perivascular oedema, which may cause the affected cornea to have a stippled ‘orange peel’ appearance. The lesions are usually restricted to the area under the upper eyelid, although the cornea under the lower lid and third eyelid are occasionally involved.

Affected eyes should be treated with topical Cyclosporine A t.i.d. for 7–10 days. Early on, affected eyes were successfully treated with human saliva and this remains an economical alternative to using Cyclosporine A. Once resolved, the disease does not recur. However, long-standing cases appear to be refractory to medical treatment.

### *Chronic recurrent deep keratitis (Fig 18)*

This is an episodic deep keratitis, recurring at intervals of up to several years. There is commonly a history of ocular trauma which precedes the onset of the keratitis. During the active stages of the disease there is extensive and deep fibrovascular reactivity in the cornea, with blood vessels encroaching on the affected areas at varying levels. Despite the often dramatic appearance of the cornea, there is no ocular discomfort. However, subepithelial bullae may form and subsequently rupture causing transient discomfort. Some affected corneas may develop intrastromal lacunae containing green tinged fluid, and subepithelial mineralisation may occur.

During the quiescent stages, the corneas show a variable and modest diffuse stromal fibrosis with some isolated vascularisation.

Active episodes will subside without treatment, usually over a protracted period. The therapeutic benefit of topical corticosteroids is very limited in most cases. However, topical Cyclosporine A t.i.d. will usually suppress the corneal response after 7–10 days, but treatment may need to be maintained at a reduced frequency until the cornea remains quiescent.

### *Endotheliitis (Fig 19)*

This is a sporadic unilateral disease characterised by stromal oedema and deep vascularisation. The disease is of sudden onset and affected eyes are nonpainful. There is a deep fibrocellular opacity associated with prominent

oedema of the central cornea, often resulting in corneal hydrops. Isolated arborising blood vessels encroach on the central cornea at the level of Descemet’s membrane. The anterior chamber is normal.

Topical corticosteroids will result in clearing of the cornea in 3–7 days, and with appropriate treatment most cases do not recur.

### *Nonulcerative keratouveitides*

Three diseases are included in this group. These are:

- Nonulcerative keratouveitis (NUK)
- Corneal abscesses
- Onchocerciasis

### *Nonulcerative keratouveitis (Brooks et al. 1990; Gratzek et al. 1995) (Fig 20)*

This is a generic term describing a sporadic disease first described in the USA. The disease has not been recorded in the UK, but there is anecdotal evidence of its occurrence. It is characterised by a fleshy, nonulcerated stromal infiltrate with a prominent anterior uveitis and moderate to severe ocular pain. The stromal infiltrate extends to and involves the limbus.

The disease is difficult to differentiate from corneal stromal abscessation. However, repeated negative cultures from corneal scrapings or biopsies are strongly suggestive of NUK.

The disease is presumed to be immune-mediated and treatment involves the use of topical Cyclosporine A in combination with topical corticosteroids. Mydriatics and parenteral or topical NSAIDs (e.g. flurbiprofen) are used to control the anterior uveitis. Protracted treatment may be necessary in some cases to control the disease and, in a significant number of cases, the eye progresses to phthisis despite treatment and enucleation is necessary.

### *Corneal abscess (Brooks 1999) (Fig 21)*

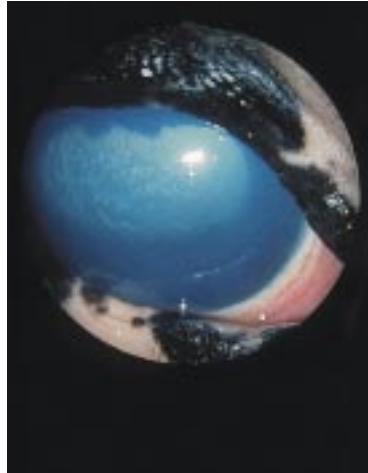
Epithelial closure over purulent debris and abscess formation may follow corneal penetrating injuries or ulceration and is increasingly being recognised as a problem in horses. Gram-positive cocci and *E. coli* are commonly implicated pathogens, but mycotic abscesses do occur and some abscesses may be sterile.

There is usually increasingly severe ocular pain, with a dense white-pink or yellow stromal infiltrate, with marked peripheral oedema and vascularisation from the limbus. A small epithelial defect may overlie the lesion, but otherwise affected corneas do not take up fluorescein. Anterior uveitis and hypopyon are usually present and endophthalmitis is a possibility in deeper abscesses. Corneal scrapings taken from the lesion reveal PMNs and mononuclear phagocytes.

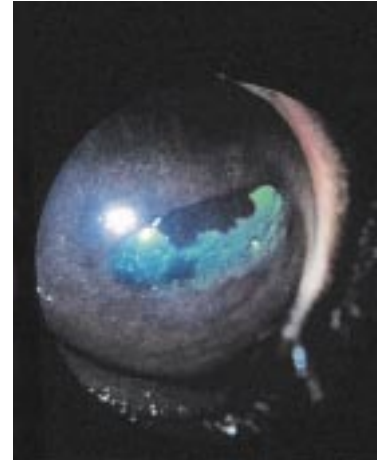
Small focal abscesses, provoking minimal anterior uveitis, are occasionally encountered in horses (Fig 22).



**Fig 10: Stromal mineralisation in a case of endotheliitis.**



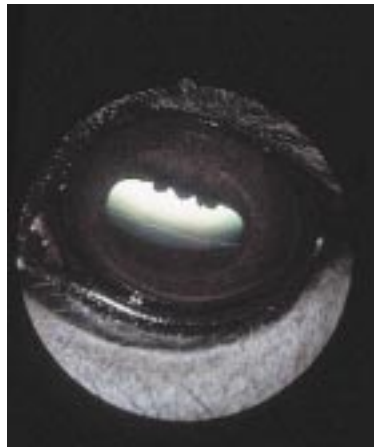
**Fig 13: Bullous keratopathy (idiopathic primary oedema).**



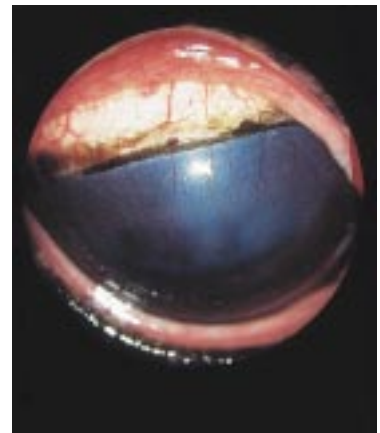
**Fig 16: Epithelial keratopathy, showing the islands of thickened and elevated epithelium.**



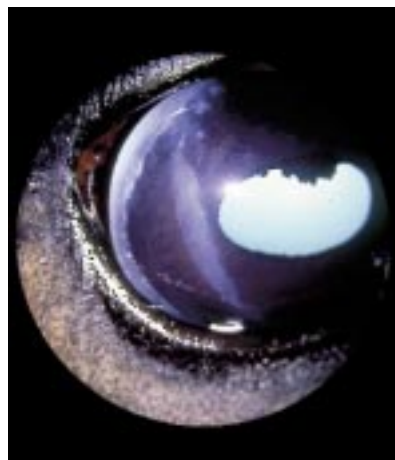
**Fig 11: Central corneal staphyloma with typically marked surface pigmentation.**



**Fig 14: Linear keratopathy. Nonoedematous refractile opacity traversing the horizontal meridian of an otherwise clinically normal eye.**



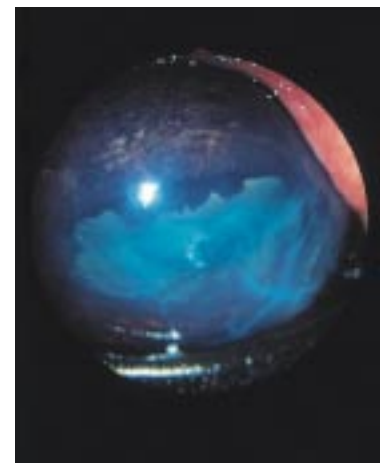
**Fig 17: Chronic superficial keratitis. Note the pronounced superficial vascularisation and perivascular epithelial oedema. The lesions are confined to area under the upper eyelid.**



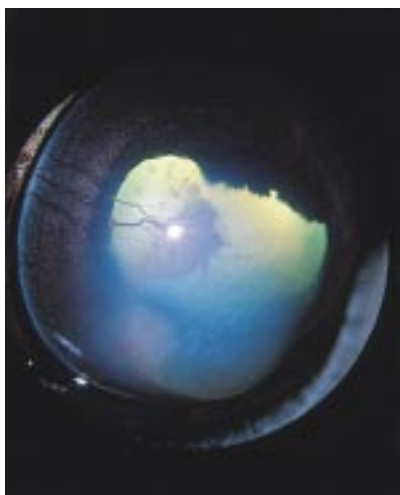
**Fig 12: Retrocorneal opacity following direct blunt trauma. Note the fusiform configuration of the opacity.**



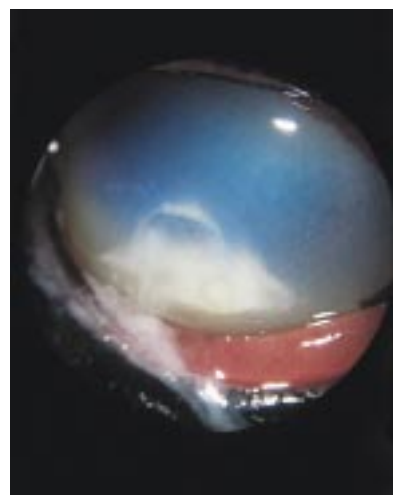
**Fig 15: Multifocal punctate opacities, showing focal stromal opacities in the ventromedial cornea.**



**Fig 18: Chronic recurrent deep keratitis. There is a pronounced stromal fibrovascular response.**



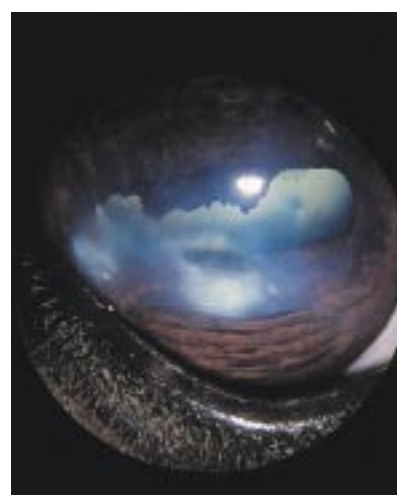
**Fig 19: Endotheliitis.** Note the central stromal oedema with deep vascularisation and cellular infiltrate.



**Fig 21: Corneal abscess.**



**Fig 20: Nonulcerative keratouveitis (NUK)** (photograph courtesy of Dr Dennis Brooks).



**Fig 22: Corneal abscess.** Small quiescent abscess in a cornea which had been injured some months previously.

Aggressive empirical use of topical chloramphenicol or ciprofloxacin will resolve many smaller bacterial abscesses over a period of 7–10 days. Otherwise, antibiotic selection should be based upon culture and sensitivity testing of scrapings taken from the lesion. Systemic antibiotics may be a useful adjunct to topical therapy in some cases. Surgical debridement of the abscess as part of the sampling procedure will facilitate antibiotic penetration of the lesion and may need to be repeated. In severe and extensive abscessation, surgical keratectomy and conjunctival grafting may be necessary to produce healing. Mycotic abscesses present a particular problem and are discussed in a separate paper in this series.

Treatment of concurrent anterior uveitis or endophthalmitis may be necessary. However, it has been suggested that topical or parental NSAIDs may delay healing of the abscess by suppressing corneal vascularisation (Brooks 1999), and should initially be used

with restraint.

All except the smallest abscesses will leave a permanent leukoma in the healed cornea.

#### *Onchocerciasis (Munger 1983)*

Aberrant migration of the microfilaria of *O. cervicalis* into the bulbar conjunctiva and perilimbal cornea may be associated with keratitis, keratoconjunctivitis and keratouveitis. It is believed that an immunogenic response is initiated by the death of the microfilaria. The disease is rare in the UK, but should be considered where the ocular signs coincide with ivermectin treatment, or in imported horses. Clinical signs range from focal floccular subepithelial opacities associated with significant ocular pain to deep fibrovascular stromal infiltrates with minimal ocular pain. Typically, the lesions occur in the

temporal perilimbal cornea, but can be more generalised.

Diagnosis is supported by demonstration of microfilaria in perilimbal conjunctival or corneal biopsies, but false negatives may occur.

Treatment is based upon suppression of the inflammatory response using topical and parenteral corticosteroids or NSAIDs.

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