Advances in treating ocular issues

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Categories : Vets

Date : November 24, 2014

CHRISTINE HEINRICH DVOphthal, DipECVO, MRCVS considers the latest advances in treating a variety of eye issues, including bandage contact lenses and their effectiveness during the healing process

THINKING back over the past 20 years spent devoting my working life to the discipline of veterinary ophthalmology, I considered the significant milestones, regarding the development of drugs and treatment modalities for eye conditions, the profession has experienced.

For me, the most groundbreaking development in ophthalmology to touch the work of the small animal practitioner must have been the introduction of a topical ciclosporin formulation (Optimmune: MSD Animal Health) to treat keratoconjunctivitis sicca (KCS) – also known as dry eye.

Dry eye is a common condition in certain dog breeds, and while a pattern of inheritance has not been reported, most ophthalmologists would agree the condition appears breed-related for many, such as the West Highland white terrier, the bulldog or the pug (Helper, 1996). An immune-mediated destruction of the gland is proposed for these patients, while trauma, infection or nerve damage are less likely causes and often are unilateral.

Canine dry eye is a painful and blinding disease, which, unfortunately, is not usually successfully managed with only the use of tear replacements – even if the client has the time and inclination to comply with complex treatment schedules. In the past, it must have been disheartening – even with frequent applications of tear replacements – for colleagues to watch patients with severe dry eye continuing to suffer from excessive amounts of tenacious ocular discharge, progressive corneal pigmentation, vision loss and, at times, devastating corneal ulceration ([Figures 1] to [4]).

Historically, transposition of the parotid duct into the conjunctival fornix was often the only way to maintain vision and comfort in severely affected patients, but while the procedure has a high overall success rate, it is a suboptimal solution, with the end result being an excessively wet eye and face. The option to restore the patient’s own tear production is, therefore, always preferable and the best way to maintain a healthy ocular surface.

The discovery of the immunomodulating and tear-stimulating properties of topical ciclosporin on canine KCS – first reported in 1989 – were, therefore, ground-breaking (Kaswan et al, 1989). The T-helper cell plays a pivotal role in the proposed immune-mediated mechanism of canine KCS and it is ciclosporin’s suppressive effect on the activation of this cell line that is pivotal in preventing progressive destruction of the tear gland.

Having started my career in ophthalmology as an intern in 1995, I‘ve never had to manage dry eye patients without the benefit of this drug. The ability of Optimmune to restore tear production and resolve chronic keratitis and pigmentation can be astonishing and, in many patients, normal ocular surface health can be restored with ongoing use of the drug ([Figure 5a] to [5c]).

Initially, most vets would have formulated their own ciclosporin eye drops in oil, until Optimmune was launched in the mid-1990s as the licensed drug to treat immune-mediated canine dry eye. It is often criticised as a relatively expensive drug that is required life-long to maintain tear production in dry eye patients. The use of alternative, less costly tear replacements might, therefore, be tempting to the vet and owner; however, even in initially mild cases of dry eye, this is, in my view, a false economy, as without the use of immune-modulators, the destruction of the tear glands will progress, eventually resulting in a blind eye at risk of corneal ulceration.

Finally, eyes with advanced KCS and Schirmer tear tests (STT) of 0mm to 2mm of wetting have a much-reduced chance to respond positively to the use of Optimmune than those diagnosed and treated earlier in the course of the disease, when STT readings still exceed 2mm of wetting.

Careful client education is, therefore, crucial in ensuring compliance with the ongoing use of the drug and efficient dry eye control. To date, it remains the mainstay in the management of immunemediated canine KCS and only few refractory patients require the use of more concentrated formulations of ciclosporin or of more potent topical immunomodulators, such as tacrolimus. However, veterinary licensed preparations of the latter are not yet available and their use has to follow the cascade system.

Spontaneous chronic corneal epithelial defect

An area that has also received much attention during the past two decades is the management of the so-called indolent ulcer. Many alternative terms have been used to describe the condition, ranging from boxer ulcer to recurrent epithelial erosion, but it was Bentley (2005) and Bentley et al (2001) who carried out extensive research around the problem and coined the widely accepted name spontaneous chronic corneal epithelial defect (SCCED).

SCCEDs are characterised by being chronic epithelial (that is superficial) corneal erosions that fail to resolve through the normal wound healing process and can persist for several months if left without treatment. On examination, a superficial (epithelial) defect is visible and the loose epithelial edges are under-run by fluorescein stain (Figure 6a). The condition is extremely painful, probably because the anterior corneal stroma is richly innervated with sensory nerve endings of the trigeminal nerve. Affected patients are middle-aged to older and do not have adnexal anomalies or tear film deficiencies that would account as the cause of the ulceration.

The research by Bentley et al (2001) revealed a number of changes on a histological level that were shared by the affected patients – namely the absence of basement membrane and of adhesion complexes in the affected area and the presence of excessive amounts of fibronectin, which is covering an abnormal hyalinised and acellular zone of anterior stroma. Research concludes the abnormal anterior stromal zone plays a pivotal role in this corneal defect, which explains why treatment approaches that involve the breaching or removal of this zone following removal of the loose epithelium (Figure 6b) are so successful in managing SCCEDs. Specifically, the creation of small grooves or punctures into the anterior stroma (grid or punctate keratotomy; Figure 6c) and the excision of the anterior stroma (superficial keratectomy) following epithelial debridement have been advocated and widely used as treatment options for SCCEDs.

A study by Stanley et al (1998) comparing three different treatment regimes in 92 cases of dogs with SCCEDs reported 100 per cent of patients were found to have healed ulcers following a superficial keratectomy (median healing time of seven days) or debridement and grid keratotomy (median healing time of 11 days), but that debridement only resulted in delayed healing times (median 21 days), with healing achieved in 83 per cent of the cases only. Twenty-one days does not seem a terribly long time, but anyone who has ever experienced the excruciating pain of a corneal ulcer would agree that a few more days to heal, matters significantly, which surely also applies to our canine patients.

A superficial keratectomy, though, is really a referral procedure that incurs significant cost as it should be carried out under general anaesthesia with adequate magnification and instrumentation by a surgeon who has the materials and training to cope with a complication such as a corneal perforation. Keratotomies, however, can be carried out in practice on the conscious or sedated patient – and have thus become popular treatment methods to manage SCCEDs. Many ophthalmologists prefer a punctate keratotomy over a grid keratotomy as the former is likely to result in less permanent scarring. For those vets who cannot stomach the thought of taking a sharp needle tip to the 0.5mm thick cornea of a patient (remember, a credit card is approximately 0.75mm thick), there is further good news with the arrival of reports showing the use of a single diamond burr debridement can result in healing SCCED in 92.5 per cent of canine patients (Gosling et al, 2013).

Even in horses, which can suffer from the equine equivalent of SCCED, the use of the diamond burr has been described and appears extremely successful (Lassaline-Utter et al, 2014). The battery operated, hand-held diamond burr instrument (Algerbrush II, Eickemeyer, London) is incredibly easy to use and well-tolerated by the patient – even under local anaesthesia (Figure 7). Following removal of all obviously loose epithelium with a damp cotton bud, the burr is repeatedly run over the entire ulcerated area and into the surrounding 1mm to 2mm of healthy epithelium with gentle pressure over a period of 30 to 45 seconds. Unlike the needles used for grid keratotomies, the burr presents minimal risk of causing inadvertent corneal perforation and appears a much safer tool for the practising vet (da Silva et al, 2011). However, whichever tool is used to treat the SCCED adequately, it remains of utmost importance the diagnosis is made correctly, as stromal ulcers, and those caused by dry and adnexal anomalies, should not be treated in this manner, but require other treatment considerations and modalities.

Another medical aid that has firmly secured its place in veterinary ophthalmology over the past two decades is the corneal contact lens (often described as a bandage contact lens). In fact, the first report of contact lens use to manage corneal conditions in dogs and cats was published in 1977. The idea of using contact lenses most probably came from human ophthalmology, where contact lenses have long been a mainstay in managing patients with recurrent erosion syndrome (RES) – a painful condition very similar to SCCED in dogs.

In human patients, bandage contact lenses are thought to improve comfort, provide mechanical protection and promote corneal healing. Veterinary contact lenses have been developed (Acripat: Acrivet, Berlin; i-protex: Veterinary Speciality Products) in a variety of sizes to cater to the variable globe sizes and corneal contours vets encounter, ranging from feline and canine to equine lenses (Figure 8a). Careful measuring of the cornea with specific rulers is recommended by contact lens manufacturers (Figure 8b); however, some ophthalmologists are also comfortable using a "one size fits all" extended wear human contact lens for the management of corneal conditions in dogs and cats (PureVision Plano: Bausch and Lomb).

The main argument for using a bandage contact lens, as it is in human patients, is to provide pain relief in patients with corneal wounds by protecting the exposed anterior stromal nerve endings from the constant abrasive effects of the eyelids during the blink motion. However, evidence for the analgesic effect of a bandage contact lens remains anecdotal and a study (Wooff and Norman, 2014) failed to show a significant positive effect on subjective comfort scores of canine patients. More extensive evidence-based research is required (Figure 9).

As an eye specialist who uses bandage contact lenses every day and who has a strong clinical impression they do add pain relief, it is clear this is one of the areas where personal observation and evidence-based medicine do not meet. While bandage contact lenses do not provide tectonic support (they are not a stabilising method for deep corneal ulcers), they may potentially be able to act as a scaffold for migrating epithelial cells and Wooff and Norman (2014) have shown where the use of a bandage lens speeded the healing of SCCEDs treated with a grid keratotomy by up to three days.

The greatest factor deterring vets from using contact lenses has been their variable retention rate.

From personal experience, there are fewer embarrassing things than to open the consulting room door to a client from the previous appointment who is clinging on to a shrivelled, dirty contact lens scraped off the practice car park. However, by using contact lenses appropriately, including the use of measuring devices provided with specifically manufactured veterinary lenses, retention rates of 71 per cent to 95 per cent of have been reported.

Apart from the advantages I've described, the bandage contact lens has helped to precipitate another change in veterinary ophthalmology – the "going out of fashion" of the third eyelid flap. Traditionally used to manage a variety of corneal ulcers, the profession had come to the conclusion the benefits of the third eyelid flap were extremely limited, as it can neither provide tectonic protection to fragile eyes with deep corneal ulcers nor speed up the healing of superficial ulcers. Furthermore, there is, of course, always the risk an ulcer might progress to deteriorate – unbeknown to owner and vet – underneath a third eyelid flap, which has resulted in many a nasty surprise when the sutures holding the flap in place are finally removed and one is greeted by an iris that has prolapsed through a ruptured ulcer.

The third eyelid flap's main remaining benefit – reducing pain caused by the abrasive action of the eyelids on exposed corneal nerves – can now be easily mimicked with the use of a contact lens, which, of course, does not require an anaesthetic for application and that also allows observation of the healing progress by owner and vet. To my mind, the third eyelid is best left alone to perform its important functions, which include providing tears and distributing the tear film.

A significant development has also occurred over the past two decades in management options for feline ocular disease associated with herpesvirus (FHV-1) infection. Every vet who has had to deal with the often devastating, painful and protracted ways in which this virus can manifest itself on the feline eye must have felt depressed and helpless at some point when treatment options for these patients were very limited. In kittens, FHV-1 infection can readily result in globe perforation, secondary glaucoma, extensive symblepharon ([Figures 10a] and [10b]) and corneal scarring, while in adults, painful recrudescence of FHV-1 leads to prolonged episodes of painful corneal ulceration, and, potentially, stromal keratitis ([Figures 11a] and [11b]). Conditions such as eosinophilic keratitis, dry eye and corneal sequestrum formation have all been linked to the virus – even if the aetiopathogenesis remains unclear ([Figure 12]). Any of us who have suffered cold sores or shingles will have at least a small amount of understanding for the discomfort feline patients with FHV-1 keratitis may suffer. But as with herpes-simplex virus (HSV-1) infection, treatment directed at destroying the virus has usually some damaging effect on the host organism itself, and eradication of the virus, which remains dormant in the trigeminal ganglion, conjunctiva and cornea in a large proportion of individuals, is not possible.

Until recently, only a limited number of topical antivirals were available for use in cats and previously tested antivirals for systemic use (such as acyclovir) had proven to be extremely toxic to feline patients. Therefore, a newer antiviral for systemic use famciclovir (Famvir: Novartis) was welcomed. Famciclovir is not only tolerated well when given systemically to cats (Thomasy et al, 2007), but is also effective at reducing the duration of disease and clinical signs in experimentally infected cats (Thomasy et al, 2011). The only snag appears to be research suggests the use of three times daily application of 40mg/kg famciclovir, to achieve tear and serum levels, is expected to be required to have a clinical effect (Thomasy et al, 2012).

Compliance with such a dosing regime is, of course, a concern, even with devoted cat owners, but the relatively high cost of the drug is a factor that may be prohibiting its use at the recommended doses in some patients. Interestingly, before the experimental data above was available, many ophthalmologists would anecdotally report a marked clinical improvement in patients that had failed to respond to multiple previous treatments – even being given doses as low as 62.5mg famciclovir once daily (Malik et al, 2009). Further work to find the minimally effective dose will hopefully be carried out.

Other advances

The aforementioned points are only the foremost significant changes in the past 20 years affecting everyday work in companion animal ophthalmology. Advances in microsurgery, and especially in cataract surgery, have also been enormous and referral for small incision cataract surgery with the placement of foldable, acrylic lens implants now results in successful restoration of vision in more than 85 per cent of canine patients. Intraocular lens implants are not only available for dogs, but also for cats and horses – and the success of surgery can be measured by our patient’s visual behaviour, and by determination of their refractive errors with retinoscopy. However, many forefronts remain open in veterinary ophthalmology – for example, the treatment of canine glaucoma, where our understanding of the condition remains limited and where the medical and surgical tools we have are not adequate.

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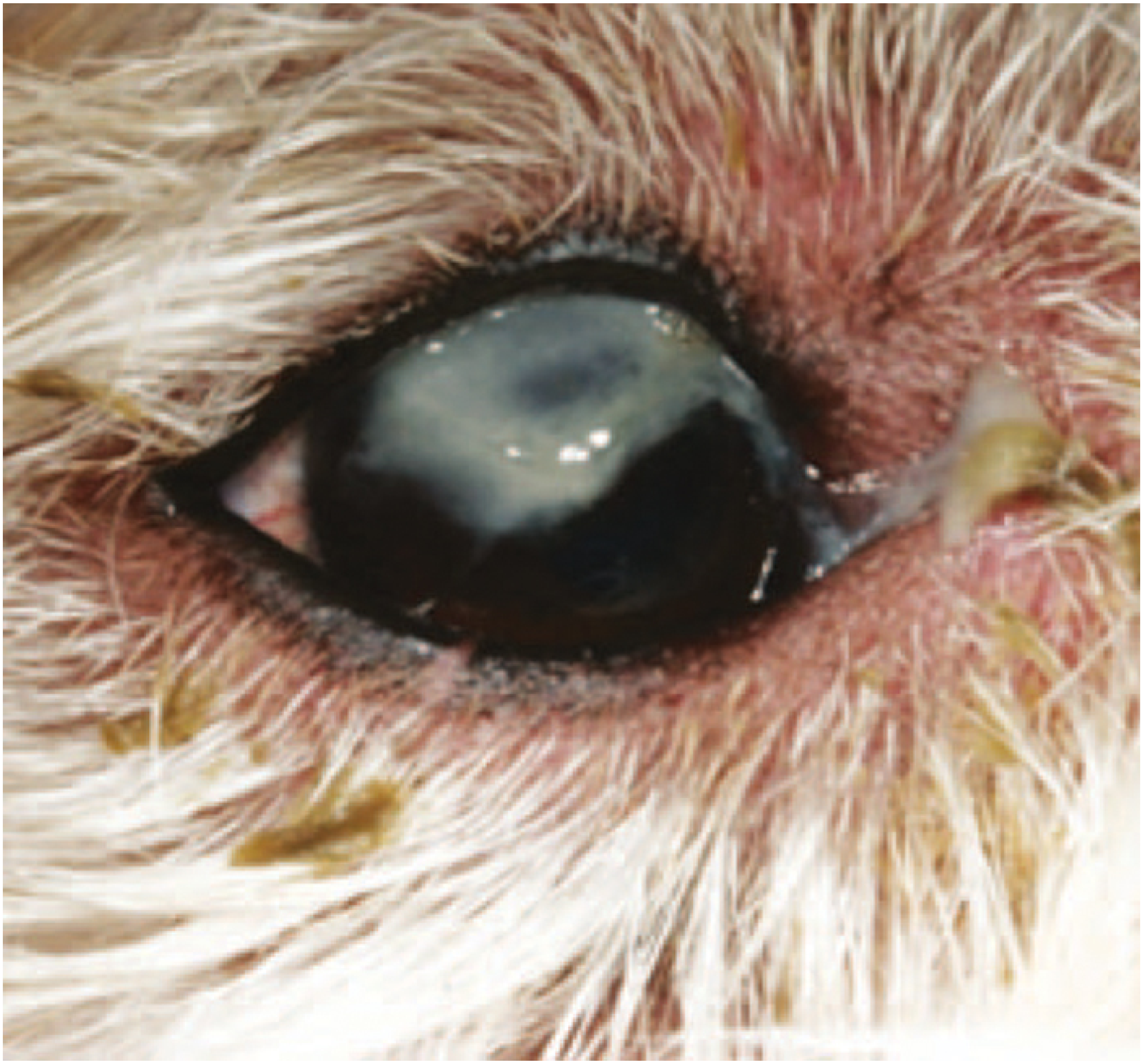

Figure 1a. West Highland white terrier with severe KCS. Note the tenacious mucopurulent discharge “stuck” on the corneal surface and also dried on the periocular skin and hair.

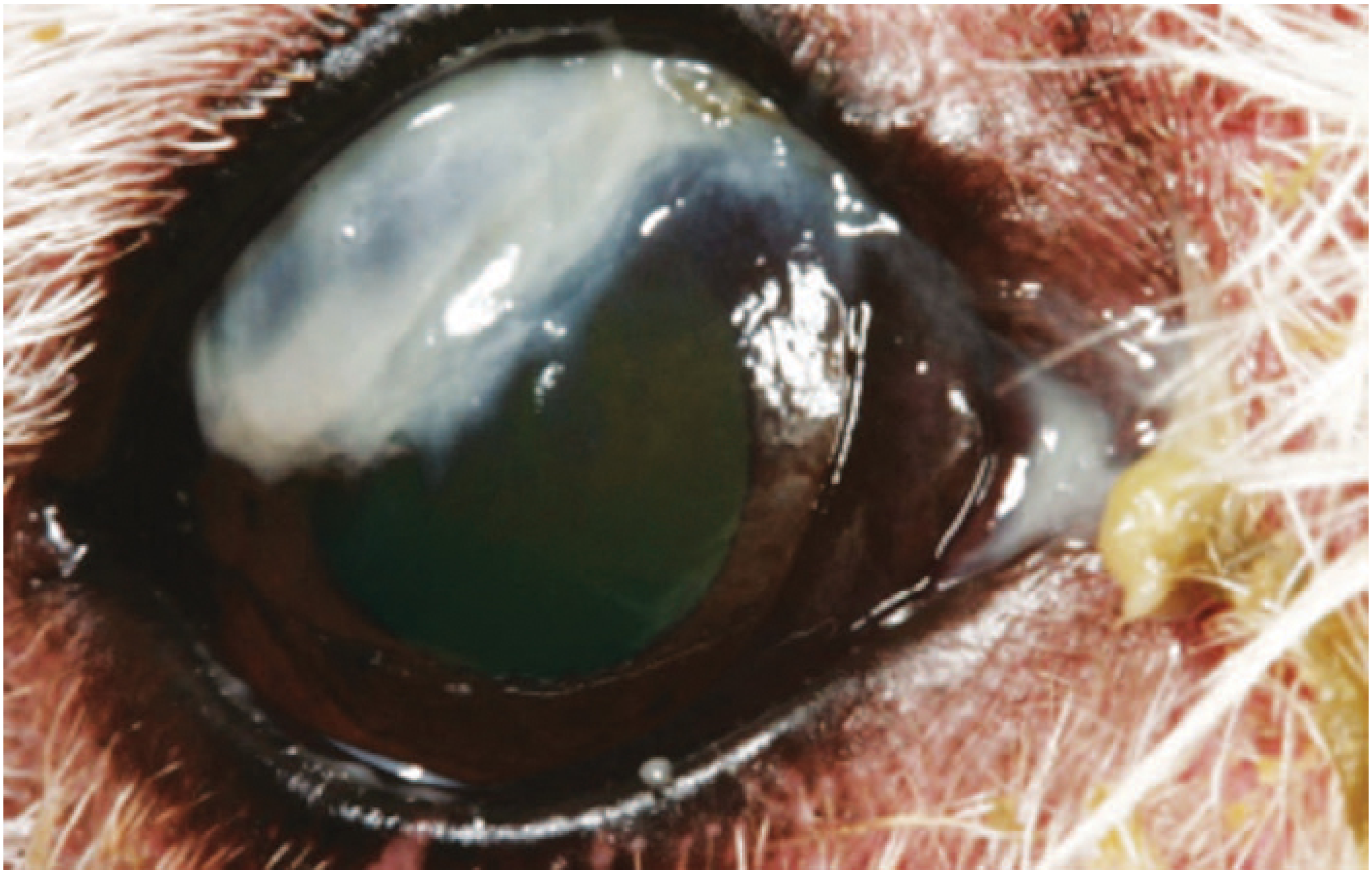

Figure 1b. Close up of the same eye. Remarkably, the corneal surface in this patient is not yet vascularised or pigmented.

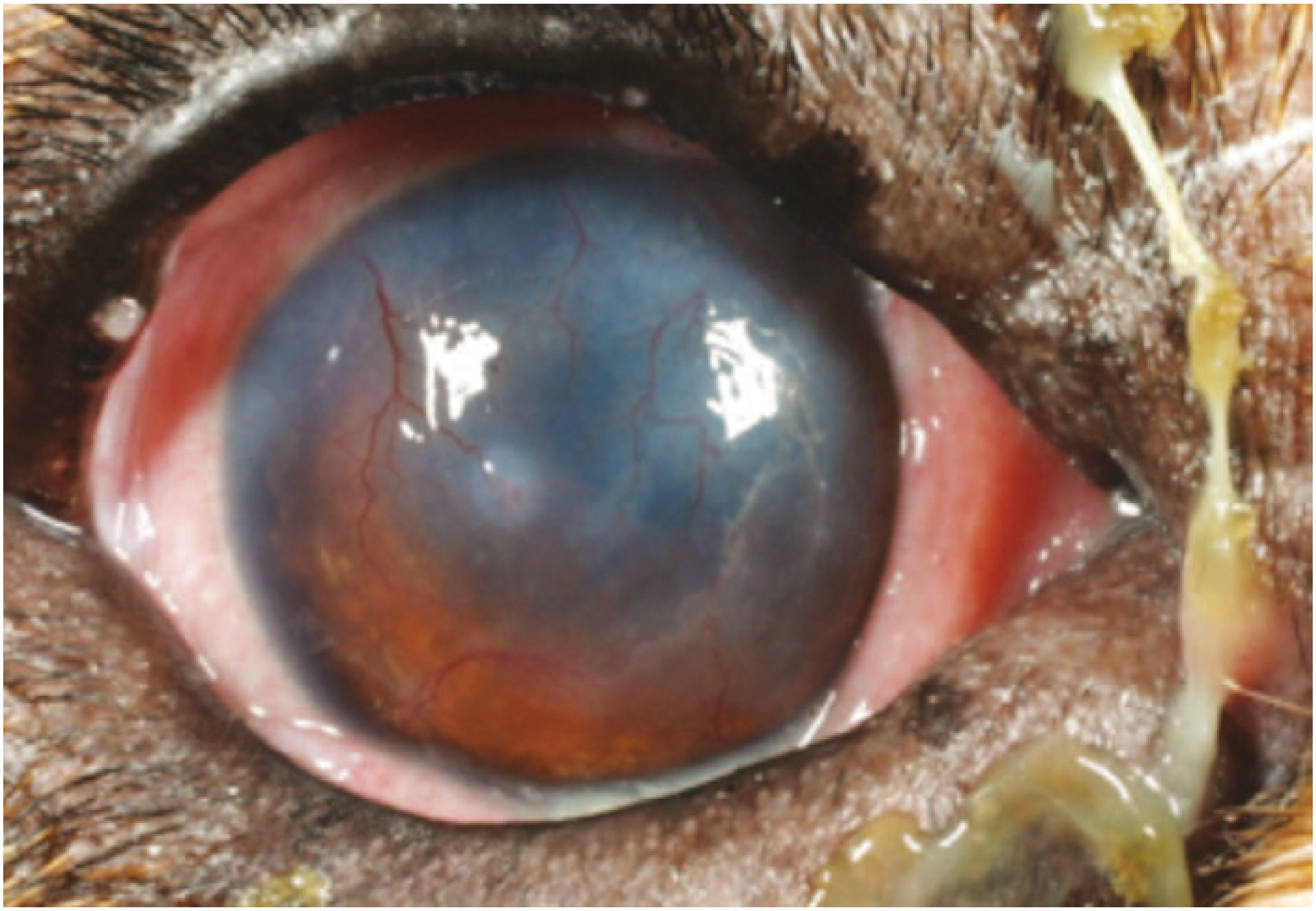

Figure 2. More chronic case of KCS in a bulldog. Note the extensive vascularisation and opacification of the chronically dry cornea.

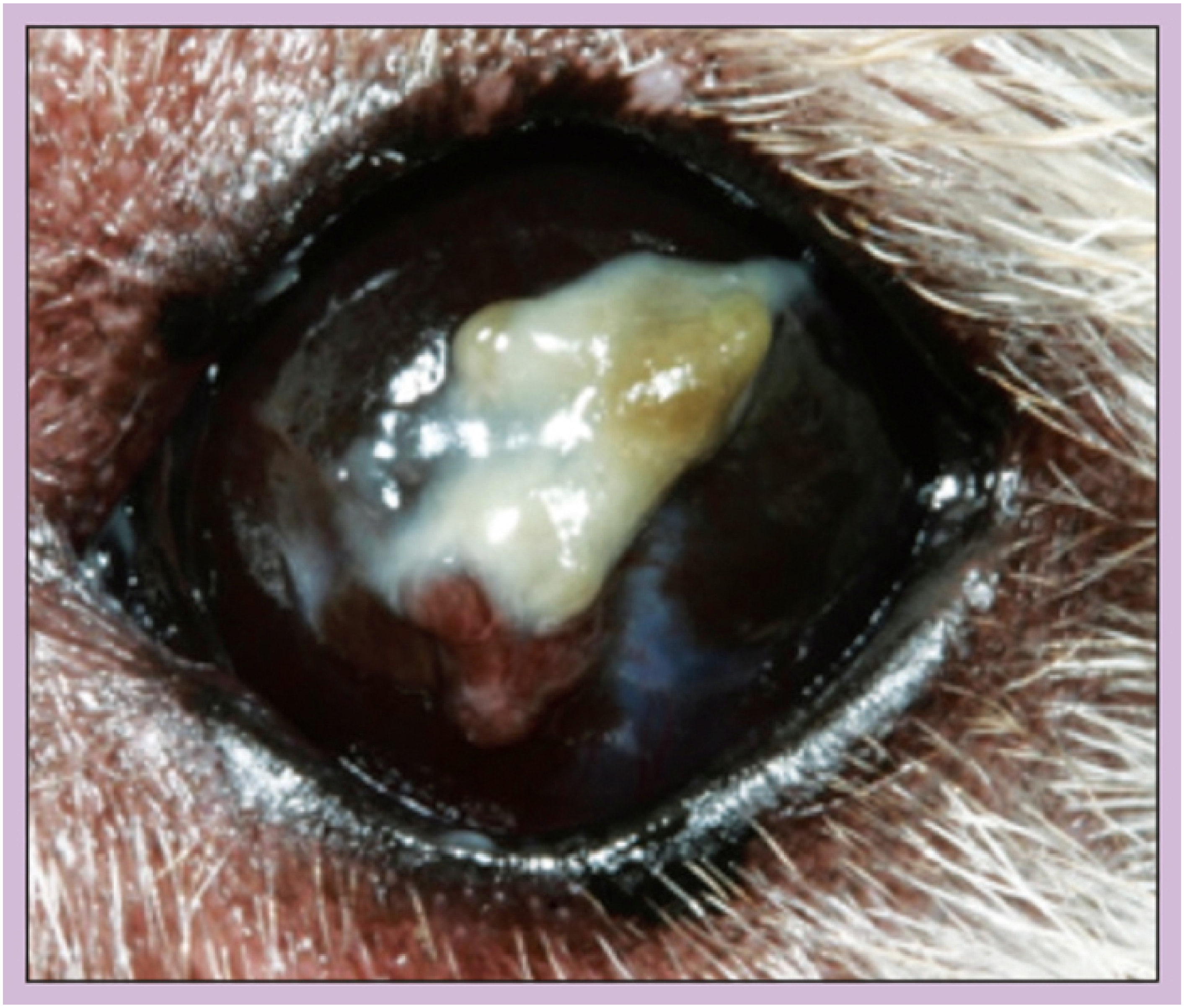

Figure 3. With chronicity, dry corneas will often pigment and develop focal areas of granulation tissue formation, resulting in visual impairment and eventual vision loss.

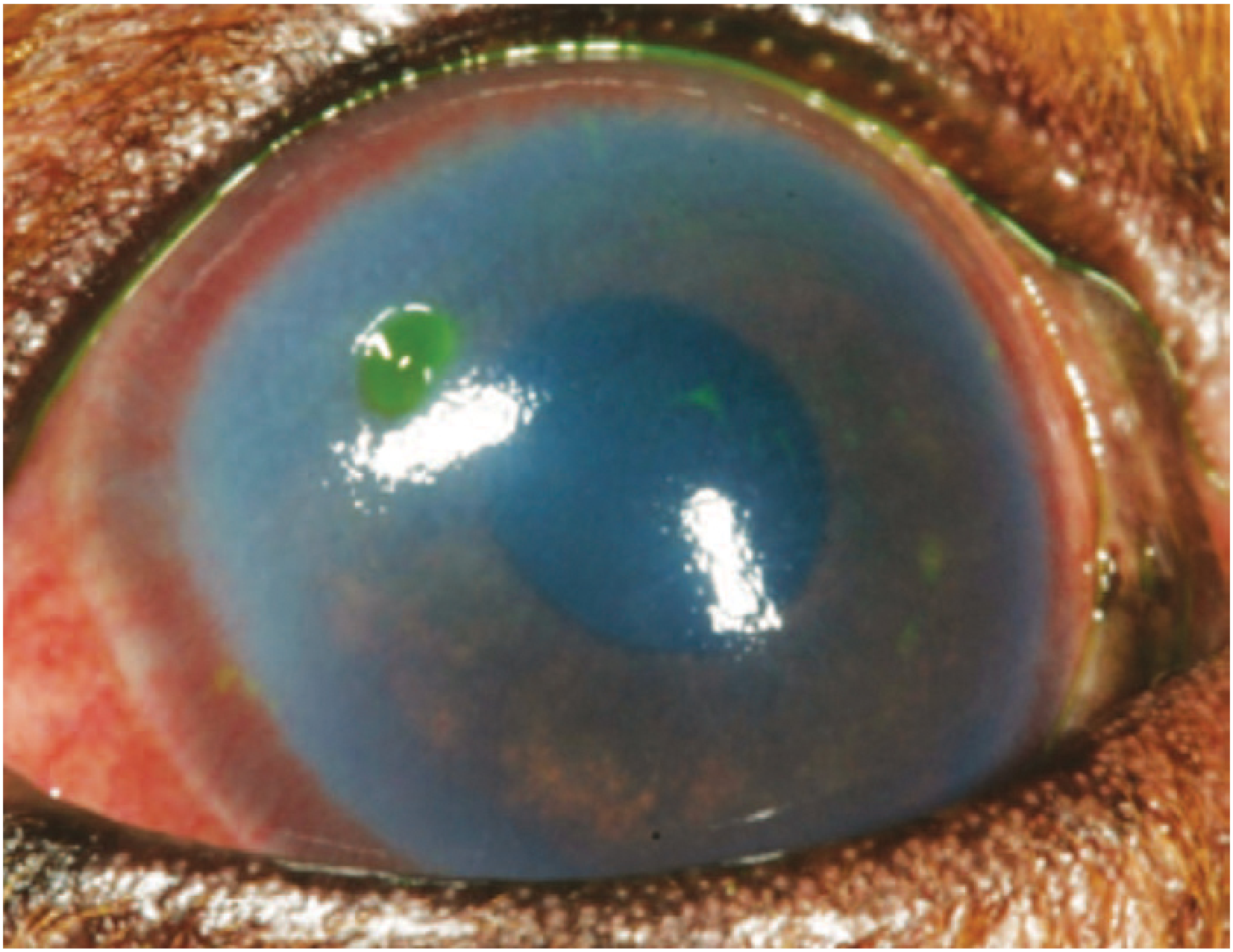

Figure 4. Dry eyes are at risk of developing rapidly progressive corneal ulceration. As in this cavalier King Charles spaniel (STT 0), dry-eye associated ulcers are often stromal, well demarcated and situated paracentrally.

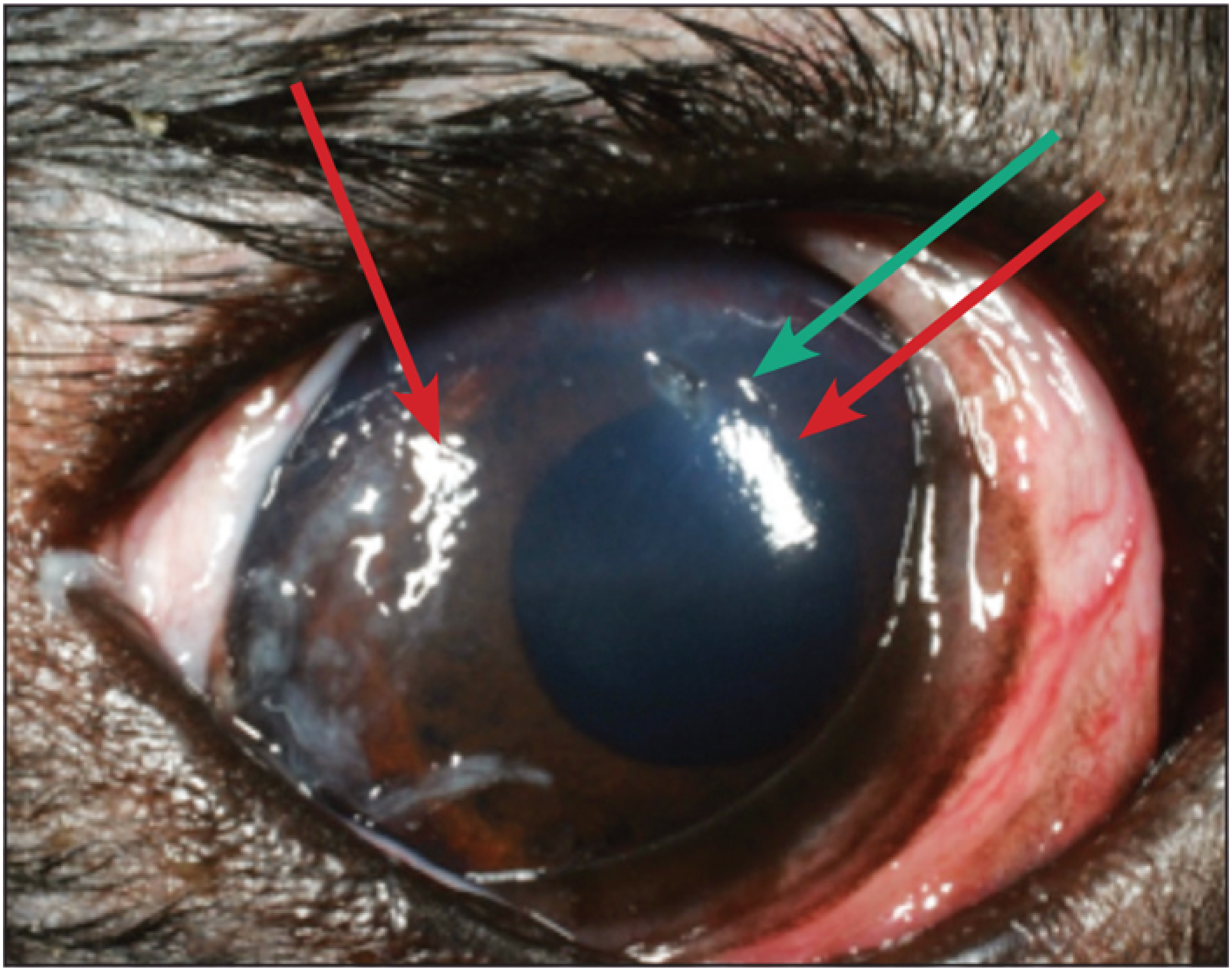

Figure 5a. Severe KCS in a four-year-old cavalier King Charles spaniel. Note the tenacious mucopurulent discharge, the poor specular reflection of the flash artifacts (red arrows) and shallow depression of an anterior stromal ulcer in the paracentral dorsal cornea (green arrow).

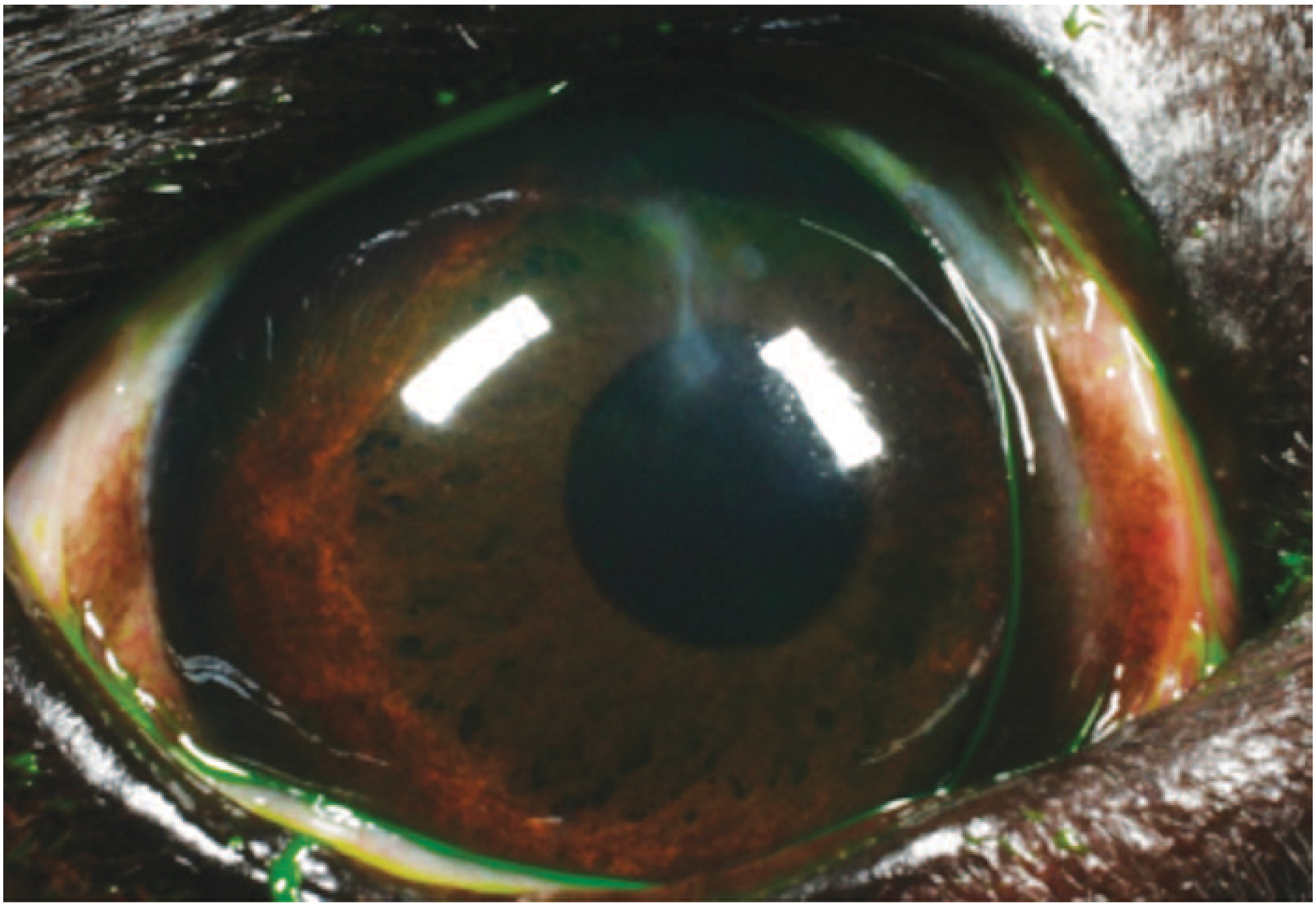

Figure 5b. Same patient as in **5a** after four weeks of treatment with Optimmune. The topical antibiotics and tear replacements, which had initially also been used, have been discontinued at this point and tear production has returned to normal levels with 15mm of wetting on the STT.

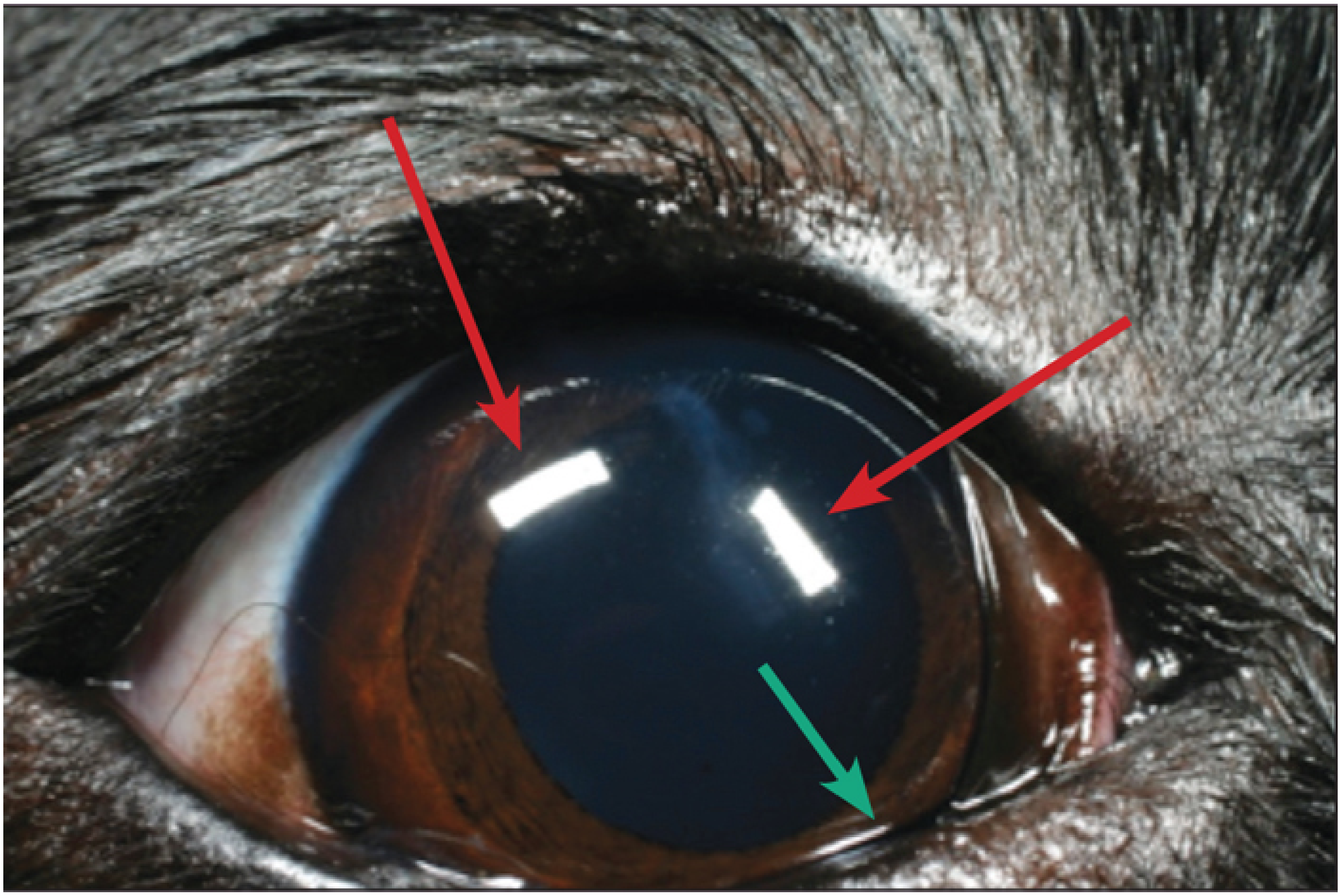

Figure 5c. Same patient after six months' treatment with Optimmune twice daily. Apart from faint scarring at the site of the previous ulceration, the ocular surface health is excellent as evidenced by the normal specular reflections (red arrows) and tear film meniscus in front of the lower lid (green arrow).

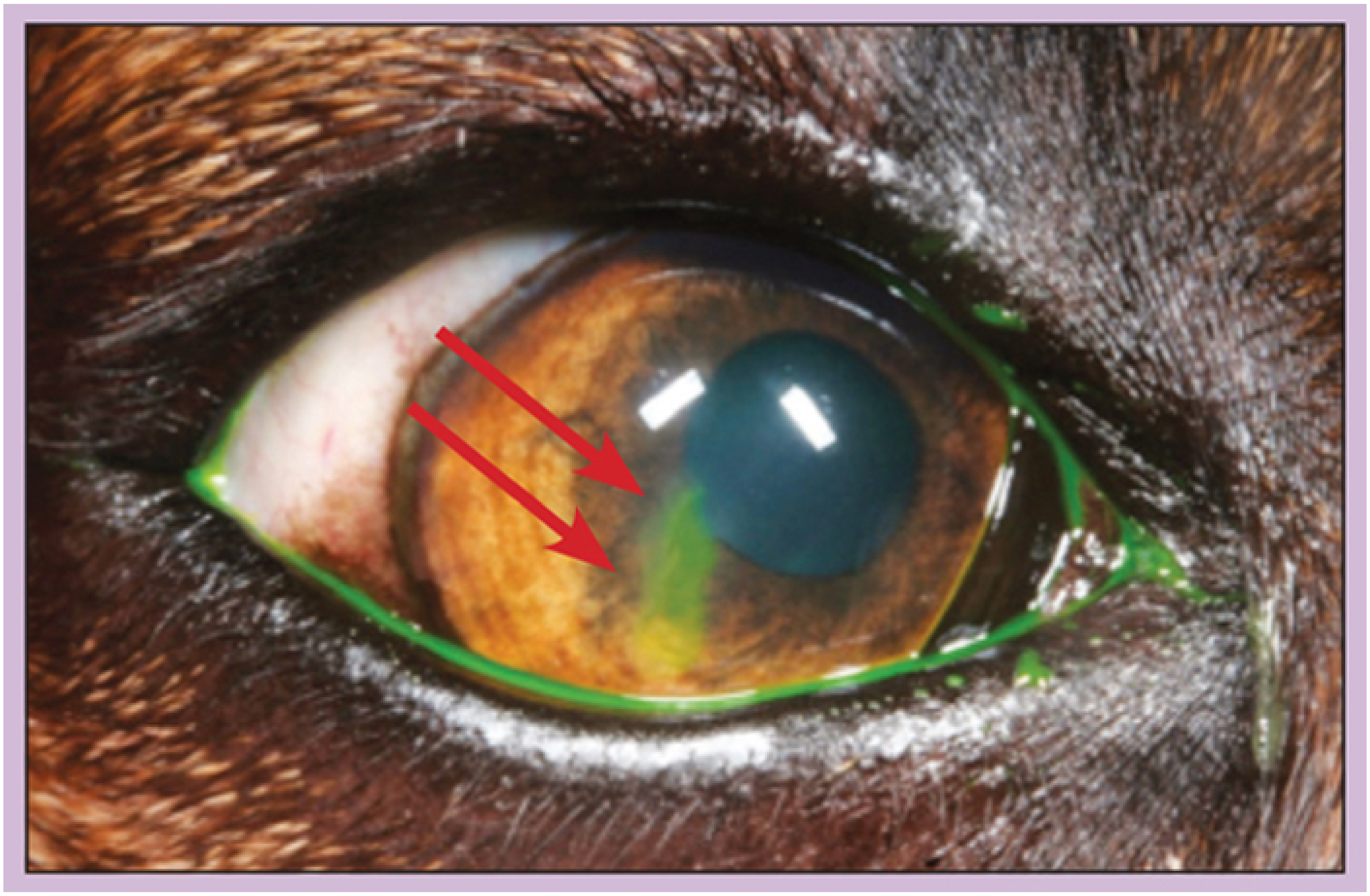

Figure 6a. SCCED characterised by a superficial corneal ulcer surrounded by loose surrounding epithelium (red arrows) – which is under-run by fluorescein.

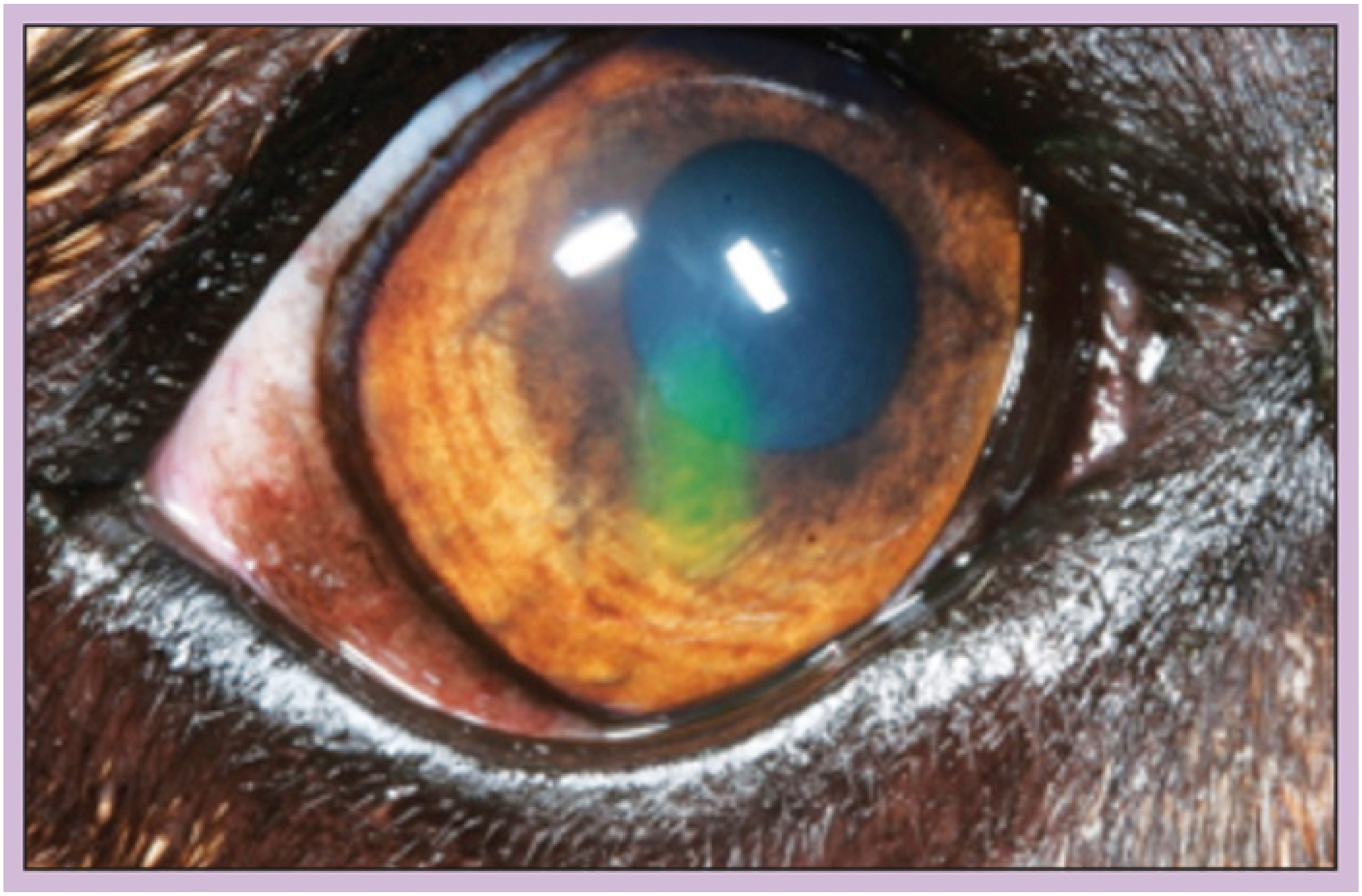

Figure 6b. Same eye as **6a** – SCCED following debridement with a cotton bud. Note the clearly demarcated epithelial edges.

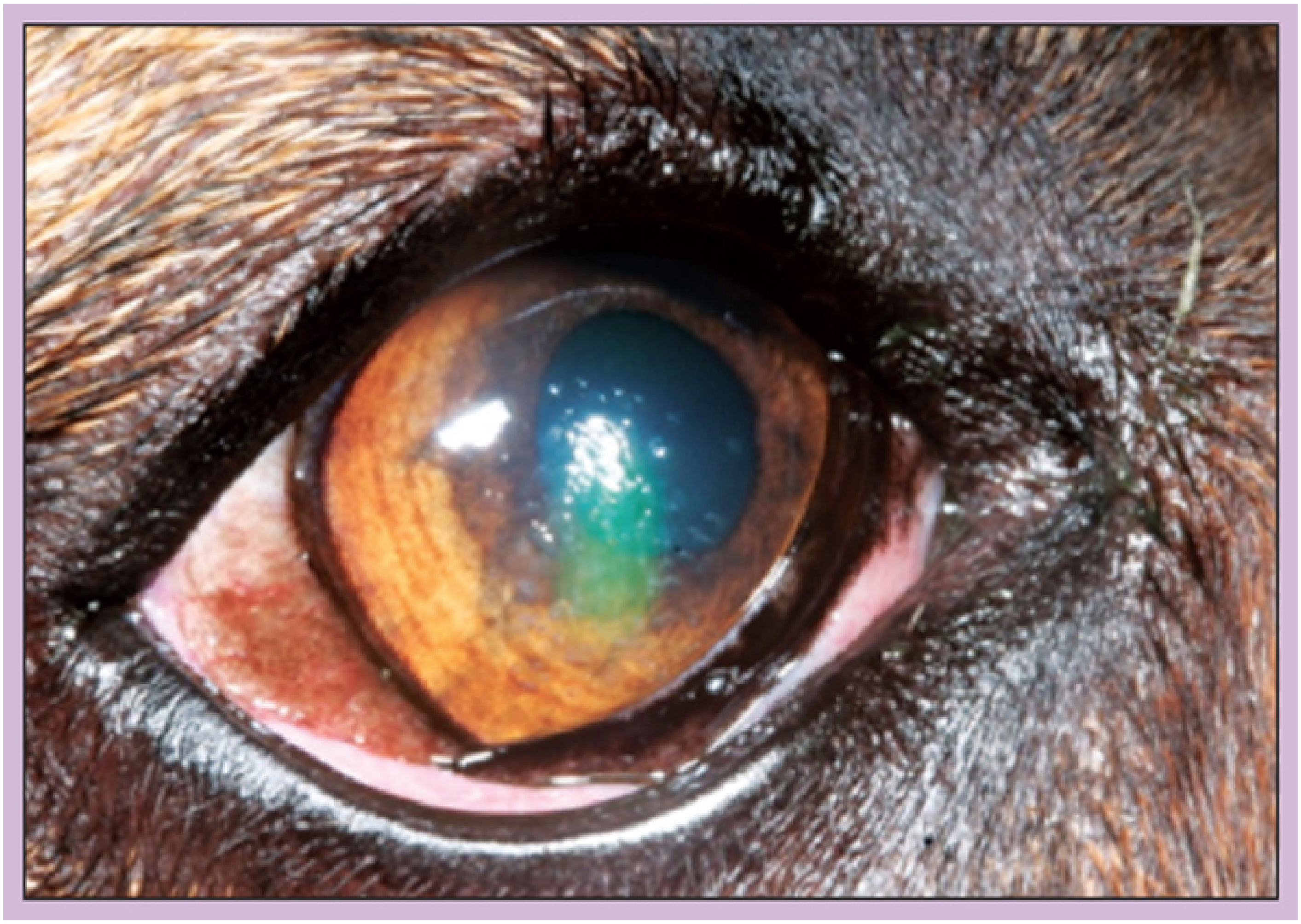

Figure 6c. Same eye as **6b** – a punctate keratotomy has been performed. Note the anterior stromal punctures extend about 2mm beyond the epithelial edges of the defect.

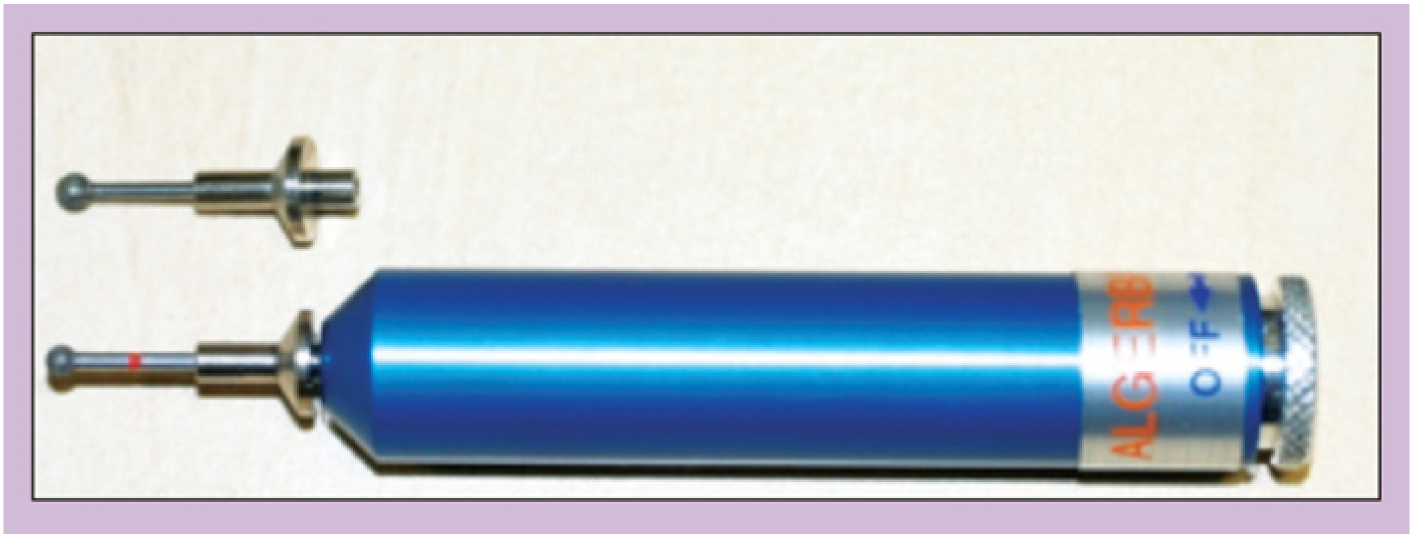

Figure 7. Diamond burr (Algerbrush). The device is battery operated, hand held and the tip can be removed for cleaning and sterilisation. Note two different round tip diamond burr-tip sizes with 2.5mm and 3.5mm diameter.

Figures 8a and **8b**. Specific veterinary bandage contact lenses in different sizes and measuring aid (right) to allow optimal fitting of the lens, which should enhance retention rates.

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Figure 9. Application of a bandage contact lens with the help of a cotton bud.

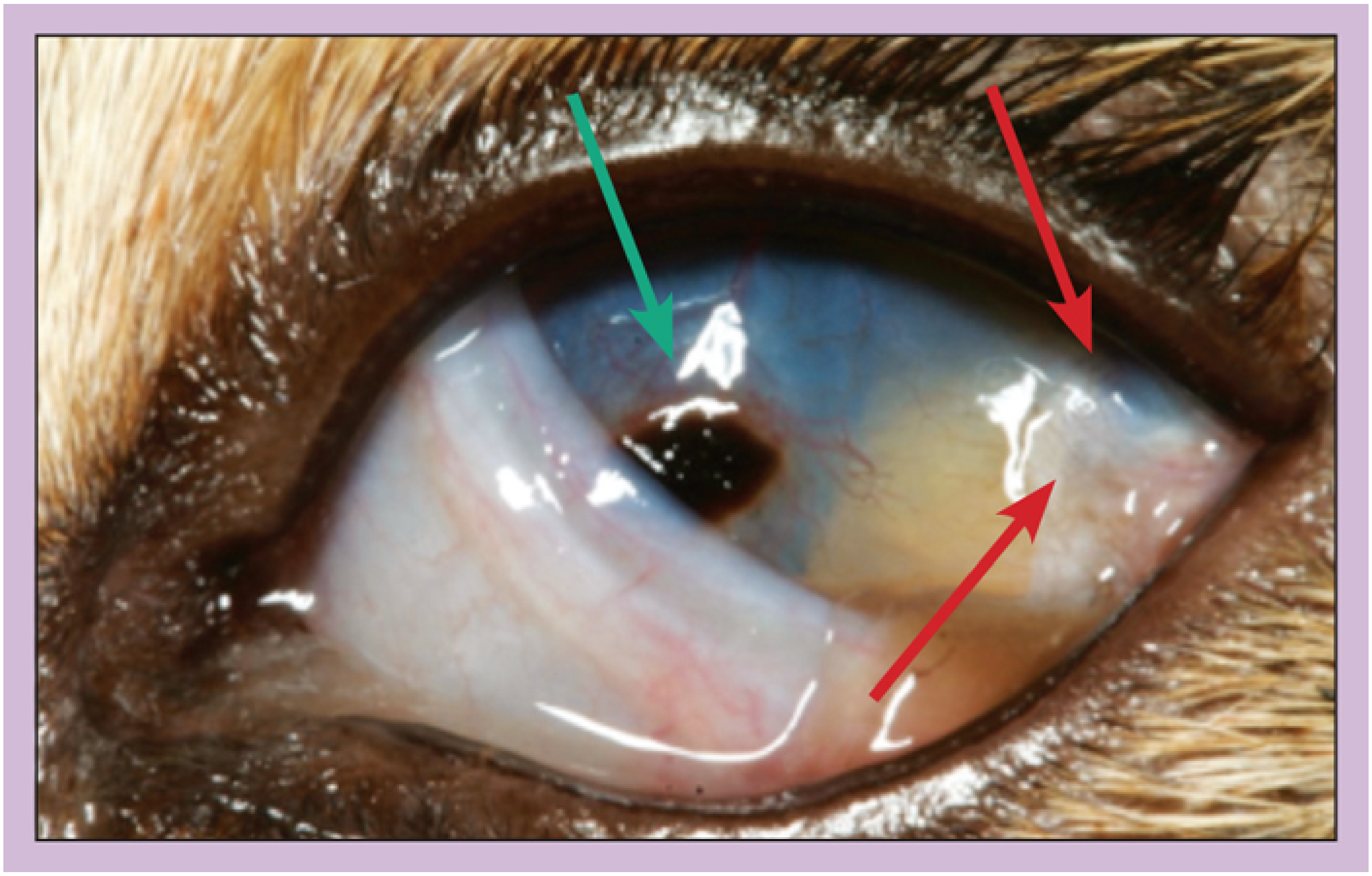

Figure 10a (above left). Multiple ocular complications as result of feline herpesvirus infection. Symblepharon is present affecting the lateral cornea (red arrows) and the third eyelid is also adhesed and protruded. In addition, a corneal sequestrum has formed in the central cornea and has evoked a vascular response.

Figure 10b (above right). Fellow eye to **10a** with severe symblepharon – resulting in total obstruction of the palpebral fissure due to fusion and deformation of upper and lower lid.

Figure 11a. Chronic stromal keratitis in a domestic shorthair cat after recrudescence of FHV-1 infection.

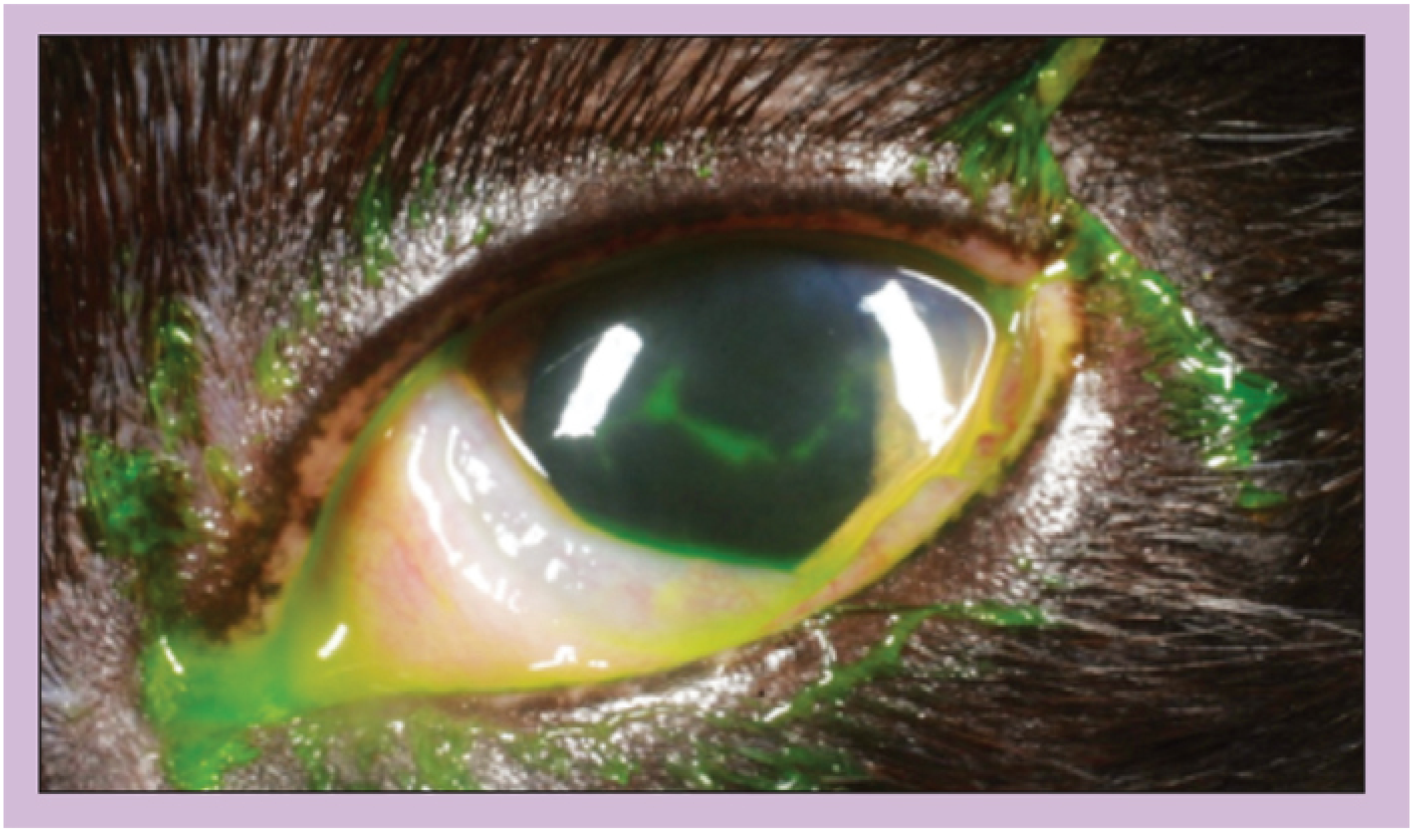

Figure 11b. Fellow eye to dendritic ulceration is pathognomonic for recrudescence of FHV-1 as the virus travels along the route of trigeminal neurons into the cornea.

Figure 12. Feline eosinophilic keratitis has been suggested to be due to an over-active response of the host-immune system to FHV-1 infection.