34 Ophthalmology of Perissodactyla: Zebras, Tapirs, Rhinoceroses, and Relatives

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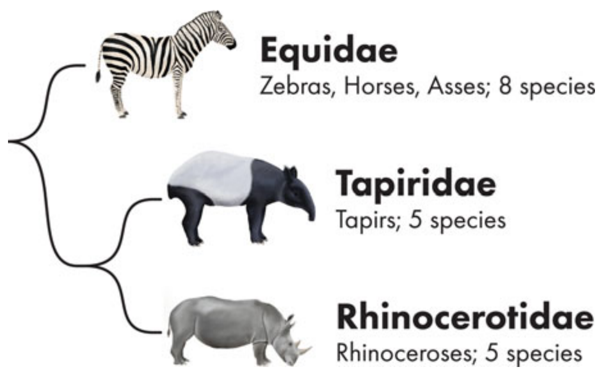

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Introduction

In phylogenetic systematics, Perissodactyla represents an order of the class Mammalia and comprises the odd-toed ungulates. The order is conventionally divided into two Sub-Orders; Hippomorpha and Ceratomorpha (Table 34.1). Hippomorpha comprises the family Equidae with eight extant species of horses, asses, and zebras in the single genus *Equus*. Ceratomorpha comprises the monogeneric family Tapiridae, with five extant species, and the Rhinocerotidae, with five currently surviving species of rhinoceros in four genera (Table 34.1).

In terms of conservation status, with the exception of the domestic horse and the kiang, the members of the order represent some of the planet's more threatened species, with some being classed currently as critically endangered (IUCN Red List of Threatened Species: https://www.iucnredlist.org).

The early ancestors of modern Perissodactyls divided into Hippomorphs and Ceratomorphs during the early Eocene period (58-52 million years ago; mya), at which time they appear to have been an abundant and highly successful group of mammals with extensive speciation widely distributed across North America, Europe, and Asia. The subsequent division of the Ceratomorphs into Tapiridae and Rhinocerotidae occurred during the late Eocene and Oligocene periods (50-25 mya) and in the case of the tapir species, evolution continued into the Miocene and late Pliocene (11-2 mya). As radiation and speciation progressed within the order, the fossil record shows concurrent extinctions and geographic migration of vulnerable species, influenced by climate change, habitat loss, competition for nutrients and, possibly, human predation, resulting in the distribution and population types now extant. In the case of the Hippomorphs, both fossil records and karyotyping studies (Trifonov et al. 2008) have shown extensive evolutionary radiation during the Miocene, but the modern horse (*Equus* spp.), the only

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Table 34.1 Species diversity of currently extant members of Order Perissodactyla (After Steiner and Ryder 2011)

Sub-order	Family	Species	Common name
Hippomorpha	Equidae	*Equus caballus* *E. przewalskii* *E. asinus* *E. kiang* *E. hemionus* *E. zebra* *E. quagga*[a] *E. grevyi*	Domestic horse Przewalski's wild horse African wild ass Kiang Asiatic wild ass (Onager) Mountain zebra Plains zebra[a] Grevy's zebra
Ceratomorpha	Tapiridae	*Tapirus indicus* *T. terrestris* *T. pinchaque* *T. bairdii*	Malayan/Asian tapir Lowland/Brazilian tapir Mountain tapir Baird's tapir
	Rhinocerotidae	*T. kabomani* *Diceros bicornis* *Ceratotherium simum* *Rhinoceros unicornis* *Dicerorhinus sumatrensis* *Rhinoceros sondaicus*	Little black tapir Black rhinoceros White rhinoceros Indian rhinoceros Sumatran rhinoceros Javanese rhinoceros

[a]Formerly known as *E. burchellii.* Burchell's zebra is now classed a subspecies of *E. quagga*

Table 34.2 Defining anatomical and physiological characteristics of members of the order Perissodactyla

	Molar dentition	Alimentary tract	Forelimb phalanges (no)	Hindlimb phalanges (no)
Equidae	Hypsodont	Simple stomach and fermentative hindgut	1	1
Tapiridae	Brachydont	Simple stomach and fermentative hindgut	4	3
Rhinocerotidae	Hypsodont	Simple stomach and fermentative hindgut	3	3

extant genus, appeared relatively late, during the Pliocene (2-4 mya) (Steiner and Ryder 2011).

All Perissodactyls are characteristically mesaxonic, where the sagittal plane of symmetry of the distal limb passes through the third phalanx. Their geographic range in the wild is restricted to mainly subtropical or tropical lowland habitats, ranging from grassland savannahs to rainforests. Outliers are the Mountain tapir, found in the central Andean cloud forest, the Mountain zebra, whose preferred habitat is the more mountainous areas of southern Africa, and the Kiang found on the Tibetan Plateau. All members of the order are herbivores, either predominantly grazers (Equidae), predominantly browsers (Tapiridae) or both grazers and browsers (Rhinocerotidae), this representing anatomical and physiological adaptation to their preferred habitats (Coimbra and Manger 2017). The defining anatomical and physiological characteristics of the Perissodactyls are shown in Table 34.2.

Ocular Anatomy and Function

In terms of foraging behavior, Perissodactyla are either cathemeral (i.e., irregularly active at any time) or diurnal (Equidae, Rhinocerotidae, *T. terrestris* and *T. pinchaque*), or are nocturnal crepuscular (i.e., twilight active) feeders (other Tapiridae) (García et al. 2012; Banks et al. 2015). These patterns of feeding activity reflect the nature of the habitat and the need to avoid potential predatory threats and will determine to a significant extent visual requirement and ocular structure and function (Peichl 2005; Veilleux and Lewis 2011; Veilleux and Kirk 2014; Banks et al. 2015).

In general, terrestrial mammal visual systems reflect specialization for habitat variation in ambient light intensity (Veilleux and Lewis 2011). Decreasing corneal diameter relative to the axial length of the eye reduces visual sensitivity but enlarges the retinal image and ameliorates peripheral distortion of the image, and is recognized as potentially conferring some survival advantage in open habitat prey ungulates. However, studies on Perissodactylae have failed to identify differences in corneal diameter: ocular axial length ratios, irrespective of their occupying primarily either open or afforested habitats (Veilleux and Lewis 2011; Veilleux and Kirk 2014).

Like the domestic horse, non-domestic *Equidae* have relatively large, laterally placed eyes with horizontal pupils and well-developed *granula iridica* (Johnson 1901; Banks et al. 2015). The horizontal, oblate pupil increases the horizontal depth of field and minimizes blurring of peripheral vision resulting from astigmatism of oblique incidence (Banks et al. 2015) (Fig. 34.1), resulting in increased image quality both of

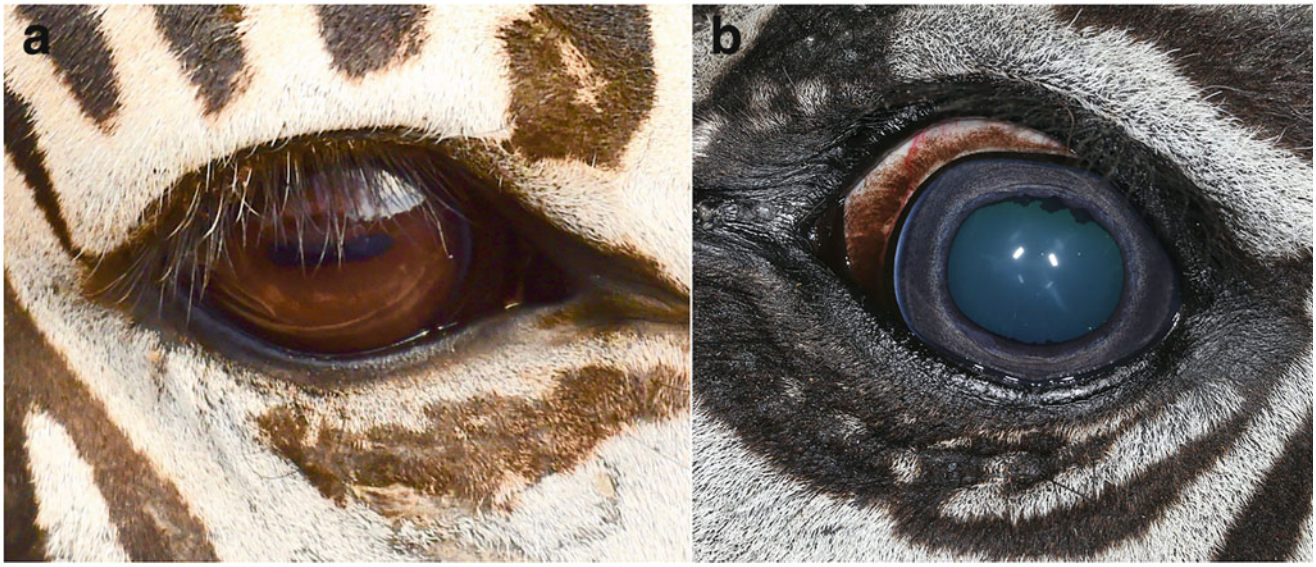

Fig. 34.1 Zebra eye. (**a**) Note the horizontal, oblate pupil similar to that observed in a domestic horse. (**b**) Dilated zebra eye, with the pupil maintaining only a slightly ovoid shape upon full mydriasis. (**a**) Courtesy of Dr. Ronald K. Cott. (**b**) Courtesy of Dr. Bret A. Moore

the ground immediately in front and of the area behind. In addition, using head pitch, the animal appears able to align the long axis of the pupil with the horizon (Banks et al. 2015). These evolutionary adaptations will confer a significant survival advantage to a cathemeral prey species occupying open grasslands.

The anatomic ocular dimensions, including anterior chamber depth, lens thickness, axial length and corneal curvature, have been measured in 12 eyes of eight Grevy's zebra, aged 4–14 years, using ultrasound biometry (Evans et al. 2009). The mean (± SD) axial length (40.7 ± 1.1 mm), anterior chamber depth (6.9 ± 0.30 mm), and lens thickness (13.83 ± 4.24 mm) were essentially similar to those recorded in the domestic horse (Grinninger et al. 2010). Mean intraocular pressure (IOP) using applanation tonometry was 21.77 mmHg (Evans et al. 2009) (Appendix C). In another study using applanation tonometry, IOP recorded in six eyes of Plains zebras (*Equus burchellii*) was 29.5 ± 3.4 mmHg (Ofri et al. 1998) (Appendix C).

The *Equidae* fundus is paurangiotic and with an extensive fibrous tapetum. The tapetal reflex in non-domestic *Equidae* varies from blue-yellow to green-yellow (Johnson 1901) (Fig. 34.2). The neurosensory retina is rod dominated, with increasing cone and ganglion cell numbers in the photoreceptor dense macular areas. These comprise the near contiguous *area centralis* and the visual streak, which are located dorsotemporally to the optic disc and in outline approximate to the shape of the horizontal pupil (Sandmann et al. 1996; Ehrenhofer et al. 2002; Peichl 2005). The macular areas are thought to be used for binocular vision and will permit high acuity dichromic blue/yellow, color vision.

The *Rhinocerotidae* eye is small relative to the domestic horse, with an ultrasonographically measured mean axial length of 2.61 ± 0.11 cm (Bapodra and Wolfe 2014) compared with 4.05 ± 0.27 cm in the horse (Grinninger et al. 2010). The rounded pupil of *Rhinocerotidae* spp. is typically associated with cathemeral foraging and the absence of significant predation risk (Banks et al. 2015). Anecdotal commentary, presumably made by smug survivors of a close encounter, has it that rhinoceroses are notoriously short sighted. However, rhinoceroses are mildly hyperopic (Howland et al. 1993), and ganglion cell topographic studies on both the black and the white rhinoceros have shown the presence of a visual streak with an *area centralis* both temporally and nasally. In the white rhinoceros, the visual streak lies dorsal to the optic disc, and in the black the optic disc lies within the visual streak (Pettigrew and Manger 2008; Coimbra and Manger 2017) (Fig. 34.3). It is thought that the appearance of a nasally located *area centralis* may compensate for limited lateral head movement in these species (Coimbra and Manger 2017). Calculations based on peak ganglion cell density and axial length of the eyes indicate that *Rhinocerotidae* has a visual resolution of 6–7 cycles/degree. This compares to 60 cycles/degree in humans, 25 cycles/degree in horses and 6 cycles/degree in rabbits, and allows for the prediction that rhinoceroses, in optimal conditions of contrast and luminance, can discern an adult human at between 100–200 m (Pettigrew and Manger 2008; Coimbra and Manger 2017). The greater visual resolution in the horse is likely to be a consequence of larger eye size rather than increased ganglion cell density (Coimbra and Manger 2017). *Rhinocerotidae* have heavily pigmented

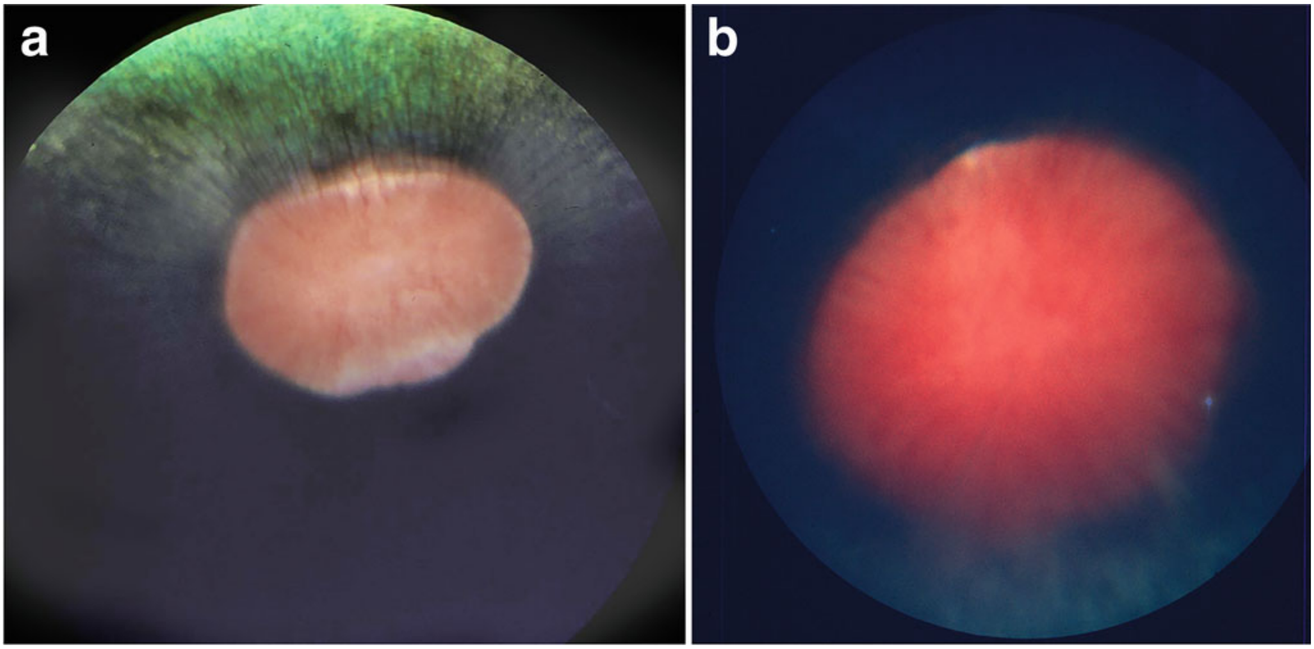

Fig. 34.2 Normal fundus images of an (**a**) adult and (**b**) foal zebra. Note the paurangiotic vasculature pattern. The blood vessels are fine and present only in the direct area of the optic disc and cross its margin to extend a short distance into the retina. The optic disc is horizontally oval, and the tapetal reflex is green to green-yellow. In the foal, the optic nerve is hyperemic

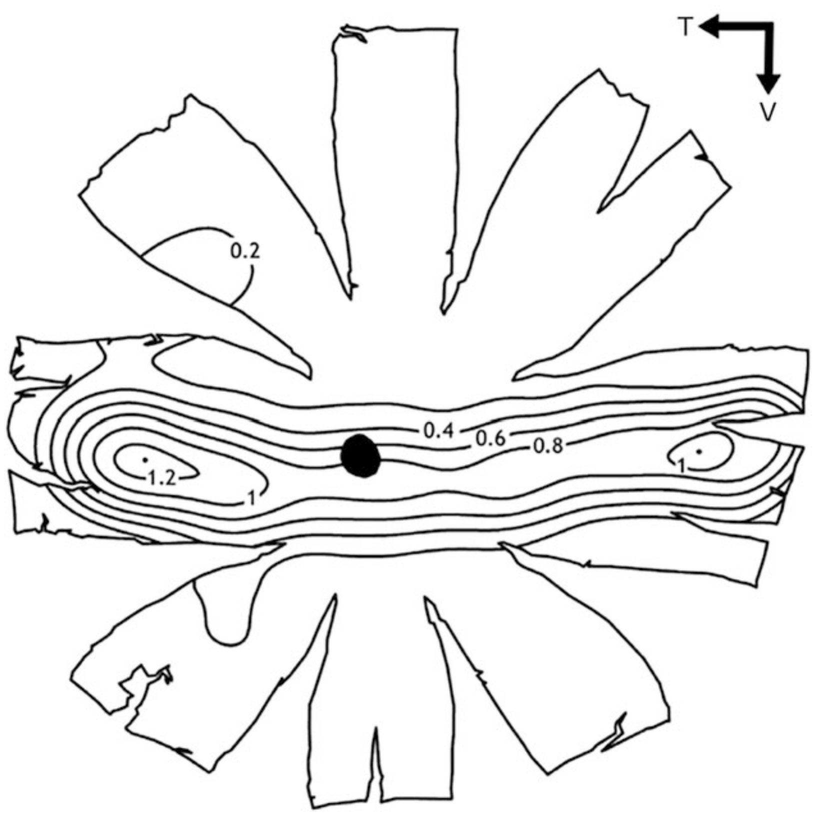

Fig. 34.3 Topographic flat-mount retinal map demonstrating retinal ganglion cell densities in the White Rhinoceros (*C. simum*). There is a well-defined horizontal streak of increased retinal density from 200 cells/mm^2 to a peak density temporally (approximately 2000 cells/mm^2 and nasally (approximately 1800 cells/mm^2). The black circle near the center of the figure represents the optic disc. T temporal, V ventral. Modified, with permission, from Coimbra and Manger (2017) Journal of Comparative Neurology 525: 2484–2498

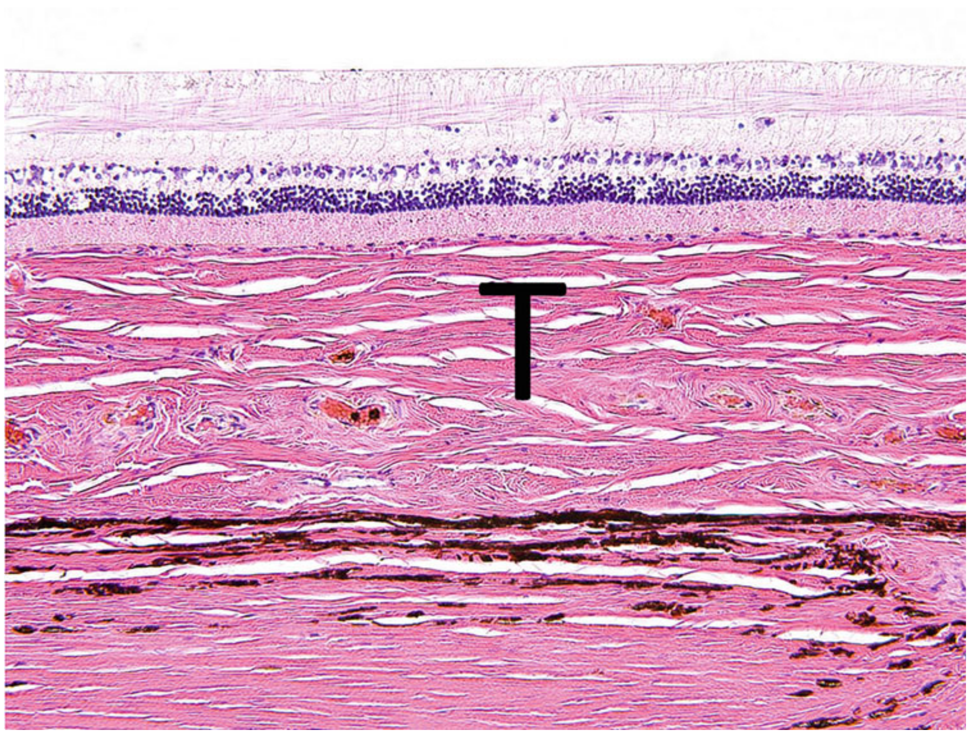

Fig. 34.4 Histologic micrograph of Tapir retina. Note the massive fibrous tapetum lucidum (T). (Courtesy of the Comparative Ocular Pathology Laboratory of Wisconsin)

atapetal and paurangiotic fundi (Johnson 1901; Coimbra and Manger 2017). The mean IOP measured by means of applanation tonometry in five adult rhinoceroses sedated with an alpha-2 agonist and opiate combination was 31.2 ± 6.62 mmHg, and the mean Schirmer tear test was 18.2 ± 3.49 mm/min (Bapodra and Wolfe 2014) (Appendix C).

Very little is known specifically about the eyes of *Tapiridae* other than that they have a rounded pupil (Banks et al. 2015) and a paurangiotic fundus with a fibrous tapetum (Fig. 34.4) (Johnson 1901; Francois and Neetens 1962).

Both the *Rhinocerotidae* and the *Tapiridae*, like the equids, will have a dichromatic vision in the blue green spectrum. This represents a neuroecological adaptation to habitat and activity patterns (Gerkema et al. 2013).

Ocular Disease

Although the ocular disease in the domestic horse is relatively common, with the exception of traumatic or other injury, ocular disease amongst captive Perissodacytl populations appears to be relatively uncommon (Greenwood A, personal communication). Immunoinflammatory, including autoimmune, diseases of the cornea and the uveal tract in the domestic horse are frequent and challenging causes of blindness or serious visual compromise (Gilger and Hollingsworth 2017; Brooks et al. 2017), and given the highly conserved nature of innate immunity and the individual diversity of adaptive immune responses in mammalian species (Holmes and Ellis 1999; Muraille 2014; Kumar et al. 2017), it is likely that the potential exists for these diseases to occur in non-domestic Perissodactyla. However, the frequency of permissive immunogenotypes, conferring susceptibility to disease is likely to have been reduced in non-domesticated populations by selective predation of affected individuals. Furthermore, wide-ranging foraging activity in these populations is likely to restrict exposure to microbial pathogens or other natural agents capable of initiating disease, e.g., *Leptospira* spp. in Equine Recurrent Uveitis. As anthropogenic pressures on wild populations prevail, loss of genetic diversity and increased exposure to potential pathogens in conjunction with increasing environmental and social stressors will inevitably skew population immunological dynamics and may result in an increased incidence of immunoinflammatory and autoimmune disease (Martin et al. 2010; Archie 2013; Ujvari et al. 2018).

Beyond the domestic horse, there is very little published data on ophthalmic physiology and disease amongst members of this order. Given the common early phylogenetic origin of the members of the order and the conserved nature of mammalian immunopathological responses, the clinical approach to managing ocular disease should be based upon the protocols current in dealing with domestic horses. This approach, however, will be constrained by compliance issue which may be overcome to some degree using local depot medications or, in the case of corneal ulceration or keratomalacia, by early recourse to conjunctival grafting procedures. Captive tapirs appear susceptible to UV exposure associated with keratomalacia, similar to that seen in captive marine pinnipeds. This may also be the case with rhinoceros.

Non-Domestic Equidae (Wild Horse, Wild Ass, and Zebra)

Very little information exists in the literature regarding the ocular disease in Grevy's zebra (*E. grevyi*), mountain zebra (*E. zebra*), or the Plains zebra (*E. quagga*). There is a single report of intracapsular lens extraction performed in an 11.5-year-old Przewalski's wild horse mare that had presented with unilateral blepharitis, corneal edema, and anterior lens luxation (Kenny et al. 2003).

Rhinocerotidae

There are a few isolated reports of ocular disease in Rhinocerotidae, most of which describe the consequences of ocular surface trauma. A 40-year-old white rhinoceros (*C. simum*) sustained repeated injuries to the right lower eyelid from a female pasture mate at a zoological park. The affected rhinoceros subsequently developed intractable uveitis and infectious keratitis resulting in enucleation (Fig. 34.5). Other than dehiscence of the skin incision, the rhinoceros recovered without incident (Gilger B, personal communication). In another zoological facility, a 34-year-old male with greater one-horned rhinoceros (*R. unicornis*), developed blepharospasm, corneal opacity, and a deep corneal ulcer with a central descemetocele. The corneal lesion was repaired surgically using a free island tarsoconjunctival graft following the initial failure of a conjunctival pedicle graft, resulting in a central corneal scar and a comfortable eye (Esson et al. 2006). A 19-month-old male with greater one-horned rhinoceros (*R. unicornis*) with severe keratomalacia in the left eye involving more than 80% of the corneal surface was managed using surgical debridement followed by a 360 conjunctival graft. The graft was removed 6 weeks later, resulting in a comfortable eye with a central corneal scar (Gandolf et al. 2000). A 3-year-old male rhinoceros in a zoological facility suffered from chronic keratitis with intermittent ulceration (Fig. 34.6). It was suspected that the ocular surface disease was immune-mediated and triggered by UV light, similar to the condition seen in tapirs (see below). The condition was partially controlled by increasing the shaded area in the enclosure and by a long-term application of topical cyclosporine and tacrolimus once to twice daily, although compliance was challenging (Ben-Shlomo G, personal communication).

A female white rhinoceros (*C. simum*) presented with intermittent, bilateral conjunctivitis, and severe conjunctival proliferation, ultimately extending across both corneas and causing loss of vision. The eyes were normal otherwise except for signs of bilateral chronic keratitis (corneal fibrosis, pigmentation, and superficial vascularization). Conjunctival habronemiasis was diagnosed based on histopathology of excised tissue, and the disease was controlled using oral ivermectin and topical antibiotics, although subsequently recurrence was recorded (Horowitz et al. 2016) (Fig. 34.7).

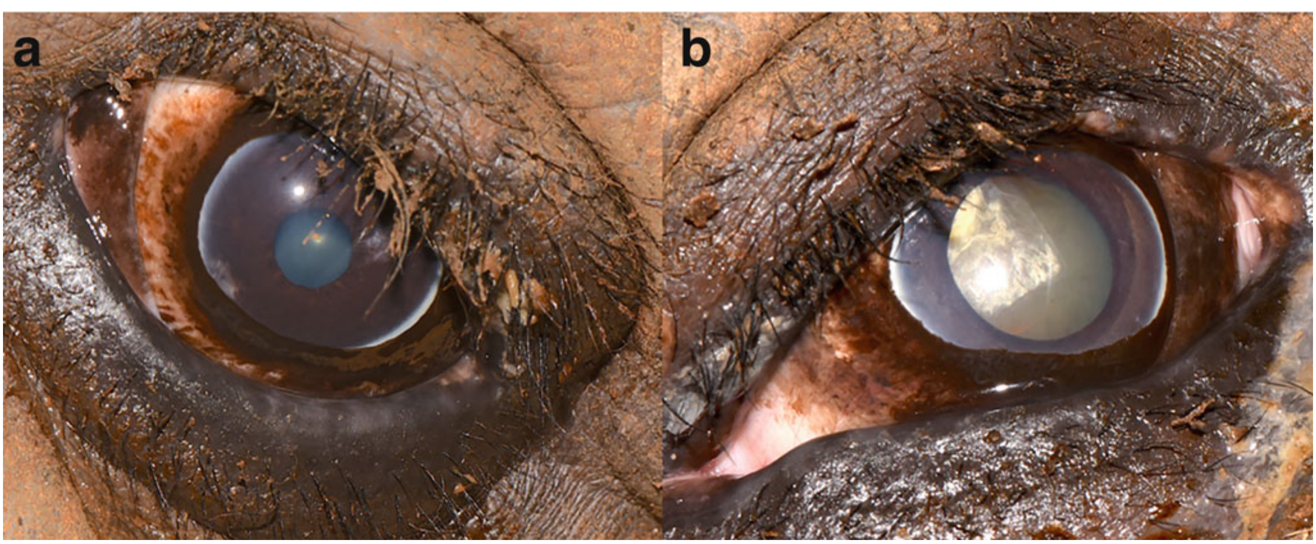

Fig. 34.5 Image of eyes of a 40-year-old white rhinoceros (*C. simum*). (**a**) The right eye appeared normal except for small white corneal scars. (**b**) The left eye had epiphora, diffuse corneal edema, and a cortical cataract. In addition, this eye had signs of active uveitis, including mild aqueous flare and low intraocular pressure (this eye has been pharmacologically dilated using topical 1% tropicamide HCL). Treatment with topical dexamethasone helped control the uveitis, but the eye was eventually enucleated following the development of a deep corneal ulcer

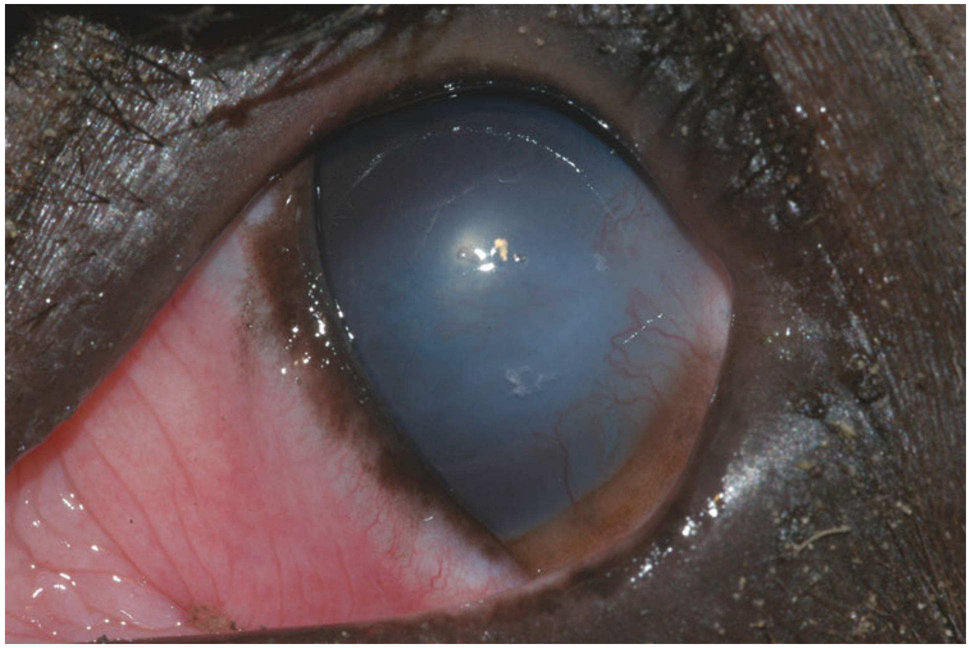

Fig. 34.6 Rhinoceros with a chronic, intermittently ulcerative, keratitis, which was suspected to be immune-mediated and triggered by UV light exposure. (Photograph courtesy of Dr. Gil Ben-Shlomo)

Fig. 34.7 White rhinoceros with a presumptive diagnosis of eyelid Habronemiasis resulting in granulomatous blepharitis and conjunctivitis. (Photograph courtesy of Dr. José Ricardo Pachaly)

Tapiridae

Ocular surface inflammation, especially ulcerative keratitis and conjunctivitis, is reported to be common in captive tapir most likely caused by trauma and exposure to UV light, which free-ranging tapirs have little exposure to since their natural habitat is primarily dense jungles (Montiani-Ferreira 2001; Da Silva et al. 2013).

Two female South American Tapirs (*T. terrestris*) at a zoological park were observed to have unilateral blepharospasm and epiphora as a result of deep central corneal ulcers. Successful treatment consisted of topical tobramycin and serum. Medication of ocular surface within the deep-set

Fig. 34.8 Chronic ulcerative keratitis in a Malayan tapir (*T. indicus*). Chronic ulcerative stromal disease developed bilaterally (**a**). Two months following placement of an episcleral cyclosporine implant (**b**) demonstrating a central corneal scar, but the resolution of the stromal keratitis. This chronic keratitis is suspected to be caused or perpetuated by excessive UV light exposure

orbits was facilitated by use of a flexible intravenous catheter inserted into the medial canthus (Da Silva et al. 2013).

Malayan tapirs (*T. indicus*) at a zoological park in South Florida develop chronic, proliferative, and bilateral corneal changes typically by one year of age or within one year of arrival at the park. Biopsy of the raised irregular corneal lesions suggested a diagnosis of papilloma. In a 26-year-old, wild caught, male Malayan tapir, presenting with similar corneal lesions, 5-fluorouracil (25 mg in 0.5 mL) was injected subconjunctivally and repeated at 3, 7, 12, and 17 weeks. The lesions decreased in size, and an improvement in visual function was present for up to 2 years following the series of injections (Karpinski and Miller 2002).

Malayan tapirs (*T. indicus*) have also been observed (Karpinski L, personal communication) to develop chronic bilateral keratopathy, including opacification and ulceration, associated with excessive UV exposure, similar to that observed in marine pinnipeds (Miller et al. 2013). As in the case of the affected pinnipeds, the Malayan tapirs responded to topical or episcleral cyclosporine (Fig. 34.8).

Summary

Very little objective information has been published on the incidence and management of ocular diseases among members of the order Perissodactyla. In terms of general clinical guidance, given the common early phylogenetic origin of the order's species and their likely broad similarity in immunopathological responses to ocular injury or insult, any approach to the diagnosis and therapy of ocular disease should be based upon protocols used at present in the domestic horse (*E. caballus*) (Gilger 2017). In the case of captive tapirs and possibly rhinoceros, the clinician should be alert to the potential role of UV exposure in the genesis of chronic destructive keratitis, as described in captive marine pinnipeds in the USA (Miller et al. 2013). In any event, the principles guiding the clinical management of the acute ocular disease are:

- Prompt and accurate diagnosis of the generic nature of the disease process and the ocular tissues involved in that process.
- Where appropriate, identify any extraneous causal agent, *e.g.*, fungi or other microbial pathogens, foreign material. This may involve microbial sampling, biopsy, or aspiration of intraocular content (Stoppini and Gilger 2017; Dwyer 2017).
- Formulate and implement an effective therapeutic strategy targetting the affected tissue and directed towards the elimination of any causal agent or other impediments to healing, e.g., foreign body, necrotic corneal or other tissue, or towards suppression of aberrant or dysregulated immunoinflammatory responses, e.g., keratolysis and ulceration driven by innate hydrolases derived from leucocytes and macrophages sequestered on the ocular surface.
- Promote ocular repair, directed towards restoring the physical integrity and normal function of the injured ocular tissues.

In the case of most non-domestic species, the above must be accomplished within the constraints imposed by limited patient contact and compliance and the perceived risks to the patient of multiple general anesthesia events. In circumstances of good management facilities and relatively tractable patients, effective topical therapy may be possible via a transpalpebral lavage system allowing remote administration of the agent. However, in many cases, effective topical therapy typically requires short interval dosing, which may limit its suitability for use. Continuous delivery pumps can be used in conjunction with subpalpebral lavage systems and may have a benefit in enhancing the bioavailability of some topical medication such as hydrolase inhibitor preparation in corneal ulceration. However, some medications, such as ophthalmic suspensions (e.g., natamycin), or drugs that require refrigeration (e.g., voriconazole, cefazoline), are not suitable to be used in continuous delivery systems, and the clinician should consider this where such systems are considered.

With the probable exception (in some instances) of the inflamed uveal tract or ocular surface, most systemically administered therapeutic agents, including those administered orally, cannot be relied upon alone to achieve and maintain therapeutic levels within the eye or on the ocular surface (Matthews 2004, 2009). This necessitates early consideration of the use of depot formulated drug preparations, where appropriate and where available, administered by local administration techniques such as subconjunctival, intracorneal, or intracameral injection. Consideration should also be given to the use of slow-release embedded devices, e.g., suprachoroidal or episcleral Cyclosporine A implants, in managing immune-mediated uveal or corneal disease, or cisplatin beads as adjunctive therapy in managing periocular tumors.

When addressing a severe corneal wound condition (e.g., keratomalacia, deep stromal ulcer, descemetocele), early recourse to single intervention conjunctival grafting surgeries (Brooks et al. 2017) in managing corneal ulceration is likely to accelerate corneal healing and repair and may preserve the eye, albeit at the expense of end-stage corneal clarity, and should be a primary consideration in any therapeutic strategy.

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