Rabbit and rodent ophthalmology

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SUMMARY

The fascination of comparative ophthalmology lies in the amazing similarity between the eyes of very divergent species. Yet there are small but significant anatomical, physiological and pathobiological differences between the familiar eyes of the dog and cat and those of the rabbit, guinea pig, mouse and rat which have substantial implications for the treatment of ophthalmic conditions in these animals. Here we seek to outline the differences between rodents and lagomorphs and the more commonly seen dog and cat and discuss the effects these differences have on diagnosis and treatment of ocular disease in these small mammal species.

Introduction

Rodents and lagomorphs are kept more and more as pet species and thus eye disease may be presented to veterinarians in general practice. They are also seen in research environments and here three key issues necessitate a full understanding of ocular disease. First, wherever they occur, ocular pain and blindness may compromise animal welfare. Second, several eye diseases are important signs of systemic disease with important implications both for pets as well as for laboratory animal colonies. Third, ocular disease may complicate and compromise research efforts. Understanding the similarities and differences between these small mammal eyes and those of the dog and cat is therefore important for veterinarians wherever they may see these clinical cases.

Examination techniques

The small size of rodent eyes makes ophthalmoscopic examination more difficult than in dogs or cats. For magnification of the external eye and anterior segment, slit-lamp biomicroscopy is ideal. However fundoscopy can be difficult, especially in pigmented strains in which mydriasis is difficult. Tropicamide is still worth using but in the same way as occurs with atropine, it is bound to melanin in pigmented irises and thus is less effective than in albino eyes. Many rodent and rabbit irises also contain atropinase which will degrade the mydriatic rendering it ineffective. Indirect ophthalmoscopy is readily performed in larger species and can, with practice, be mastered in rodents. A 90 dioptre lens can be used with a slit lamp but many prefer a 28-D lens or 2.2 panretinal lens and an indirect headpiece.

An important feature of the rodent eye is the small volume of tear film on the ocular surface. Application of even one standard-size drop will flood the ocular surface, thereby leading to nasolacrimal overflow. Drugs delivered topically may also be absorbed systemically in significant amounts relative to the

Fig. 1 Shirmer tear test in a guinea pig with unilateral keratoconjunctivitis sicca.

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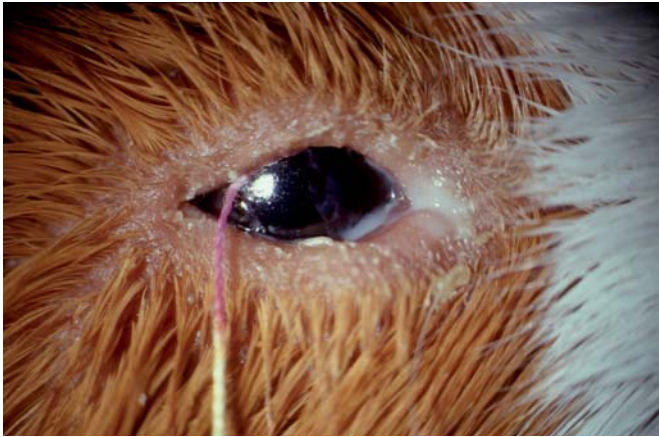
Fig. 2 The phenol red thread test used in a hamster.

size of the animal. This has important implications in both the treatment of ocular disease and potential side effects, as the drug may be acting through circulating blood levels as well as by direct ocular penetration.

Ancilliary ophthalmic tests include determination of tear production and measurement of intraocular pressure. The Schirmer tear test is applicable to rabbits and guinea pigs (Fig. 1) but the test strip is too large for rats and mice. Breed differences are significant, with Netherland dwarf rabbits having an unusually high Schirmer tear test reading of 12.0±2.5 mm/min compared with an average of 5.3±2.9 mm/min in other breeds, and a range from 0 to 15 mm/min in 142 normal eyes [1]. Evaluation of the tear film in smaller rodents is difficult, if not impossible, with the Schirmer tear test strip. Here the Phenol Red Thread Test may be useful (Fig. 2). This test has been used to measure tear volume rather than production in the mouse [2] while another study [3] compared the PRTT with the Schirmer tear test in rabbits finding mean wetting of the Schirmer test strip of 4.9±2.9mm/min and mean PRTT wetting of 20.9±3.7mm/15 s. A recent paper on tear evaluation in the guinea pig gave a mean STT of 0.6±1.83 mm wetting/min and a mean PRTT-value of 16±4.7 mm wetting/15 s) [4]. The glands contributing to the precorneal tear film differ significantly among rodent and lagomorph species [5]. We do not know what contribution to the tear film they make and why they differ so markedly between species. Yet from a pathological perspective these glands may prolapse, in the same way that the nictitans gland does in the dog. Similarly the orbital vascular plexus, present in rodents and lagomorphs, differs substantially between species and understanding its anatomy is important in orbital surgery and enucleation [6].

The small size of the globe in many species also complicates methods for measuring intraocular pressure. The Tonopen has been favorably evaluated in rabbits [7] and the small eyes of rats [8] but the footplate is too small for mice. The new rebound tonometer (TonoVet) (Fig. 3) is small enough to provide accurate measurements of intraocular pressure in even the smallest rat and mouse eyes as shown experimentally [9-10] yet its accuracy and repeatability have yet to be reported in the clinical setting for any rodent species. The paucity of reliable evidence in the two basic measures of tear production and intraocular pressure in small mammals just goes to show how much basic work there still is to undertake in this whole area.

When interpreting ocular findings in experimental species or pet animals derived from laboratory strains the prevalence of inherited disease must be seen as a background against which other ocular disease is noted. This is particularly important among inbred strains, in which recessive genes may occur in a given strain not being used to study that specific trait.

The rat and mouse

Much has been written on the ocular diseases of rats, summarized in a recent review paper [11]. A superb overview of the mouse eye has been provided by Smith et al [12]. Further information is available through those references.

Conjunctivitis is common in rodents and may often relate to mycoplasmal respiratory disease, though other agents can also be involved [13-15]. Young animals are often more severely affected [16]. Environmental changes rather than

Fig. 3 The Rebound Tonometer is invaluable for measuring intraocular pressure in the small eyes of rodents.
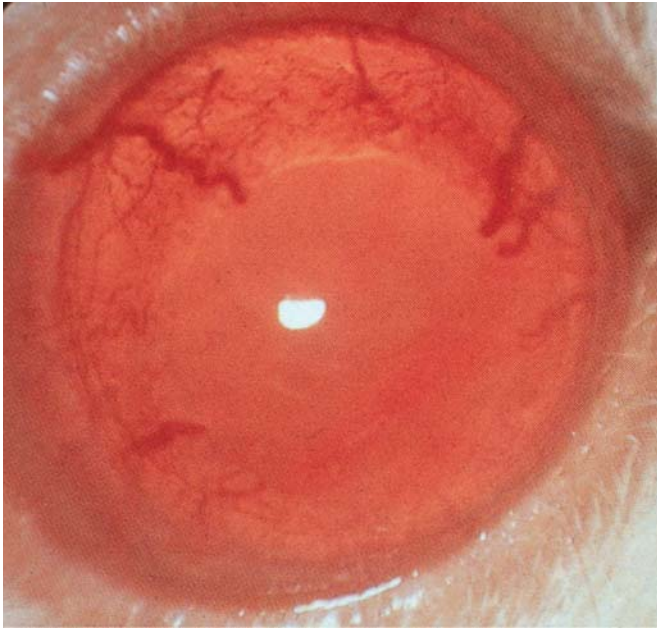

Fig. 4 Chromodacryorhoea in a rat.

Fig. 5 Murine microphthalmos with engorged episcleral and iridal vessels. Courtesy Dr. Peter Lee.
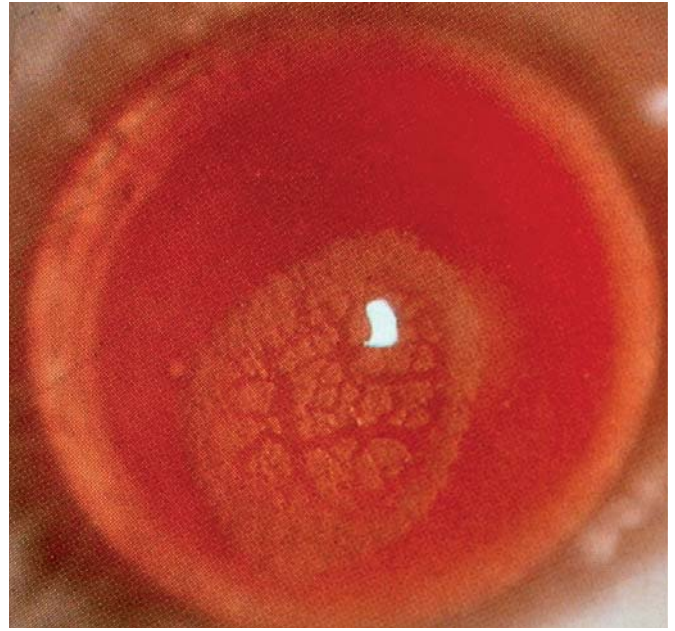

Fig. 6 Corneal dystrophy in a CD1 mouse. Courtesy Dr. Peter Lee.

primary infectious agents may be the most important factors in conjunctival inflammatory disease: ventilation currents in rodent cages may produce airborne suspensions of fine bedding matter giving rise to a severe keratoconjunctivitis [17]. Investigating a problem such as conjunctivitis in such a group of rodents thus requires a full and thorough history and clinical examination of individual animals as well as of the group as a whole.

Perhaps the most severe adnexal disease in laboratory rats is sialodacryoadenitis (SDA) virus infection [18]. This coronavirus infection causes ocular irritation with conjunctivitis and periorbital swelling, followed by sneezing and cervical swelling [19]. The condition is usually self-limiting within one to two weeks, whereas resolution of secondary signs may take longer. The immune status of the animals is a critical factor in disease severity [20]; introduction of a naive group of rats into a subclinically affected animal house may provoke clinical onset of severe disease in these animals. Serologic testing has shown the agent to be present in 45% of rat colonies within the United Kingdom, though the incidence of overt disease is significantly lower [21].

Many laboratory rodents exhibit red crusting around their eyes in cases of ocular irritation, upper respiratory tract infection, and stress (Fig. 4). Porphyrin pigmented tears are produced in normal amounts by the Harderian glands in several rodent species [22] but particularly in the rat but also some other rodent species, excess tear production with characteristic red deposits on the periorbital fur, nose, and paws after wiping the eyes, so-called chromodacryorhhoea, is seen [23]. Diseases such as mycoplasmosis and sialodacryoadentitis (SDA), nutritional deficiencies, and other physiologic stresses are factors that may cause chromodacryorrhea. Appropriate remedial action should be taken to remove the stressors involved be they infectious, environmental or managemental [24].

A common problem in laboratory rodents is microphthalmos with a valuable overview provided by Smith et al [25]. A number of transgenic rodents are inadvertently affected by this condition with clinical features [26] including microcornea, engorged episcleral vessels, and abnormal ocular vasculature (Fig. 5) and welfare implications given visual dysfunction and the propensity to develop defective tear drainage together with microbial contamination of the deep conjunctival sac [27].

Corneal opacification is relatively common in rodents. Spontaneously occurring dystrophic lesions manifest as elliptical paracentral corneal opacities, characterized by a deposition of basophilic material in the subepithelial stroma (Fig. 6). Some workers consider them heritable [29] while others suggest the

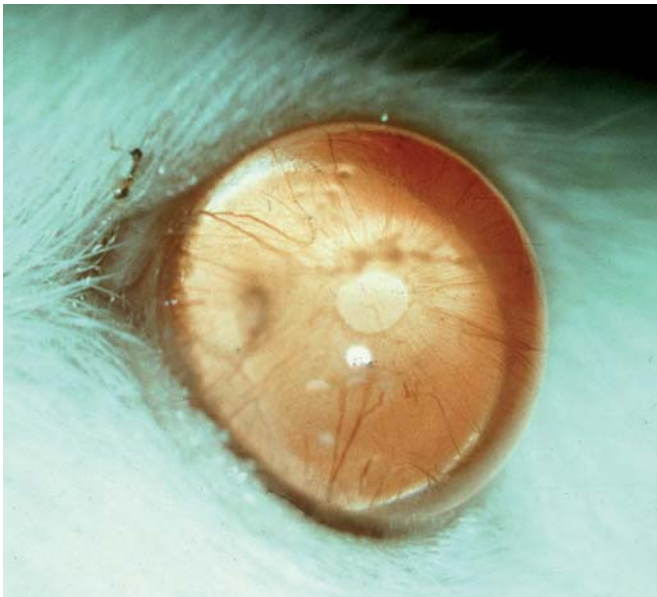*Fig 7 Post-anaesthetic exposure keratopathy in a rat.*
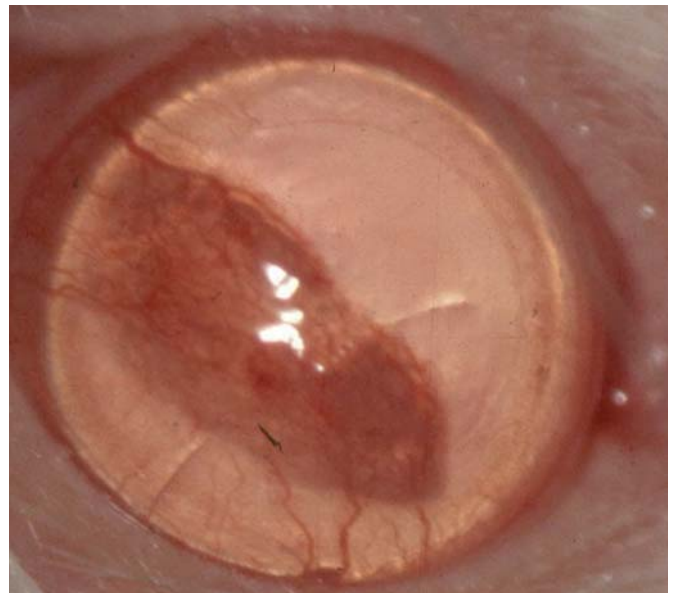
Fig. 8 Glaucoma with buphthalmos in a rat.

Fig. 9 Dyscoria in a young mouse, probably colobomatous in origin.

lesions are sequelae to excess ammonia in the cage bedding [30]. Inter-strain variation in rats suggests that there is probably an interaction between genetic factors and environmental influences, in lesion pathogenesis. Exposure keratopathy in rodents causes corneal ulceration in the interpalpebral band during prolonged anesthesia (Fig. 7) when the lids are wide open unless they are prophylactically taped shut during surgery or protected with a lubricant. The problem is more associated with xylazine and ketamine than with other anaesthetics [32].

Glaucoma has also been noted in rodents (Fig. 8) [33]. The failure of aqueous drainage here, however, is often not caused by iridocorneal angle abnormality, as in many inherited glaucomas in the dog, but rather results from persistent pupillary membranes causing pupil-block glaucoma or from peripheral anterior synechiae in uveitis preventing drainage. Lesions of the anterior uvea in rodents are mostly either congenital or associated with inflammatory disease. The former include adhesions between the cornea and lens and the persistence of the pupillary vasculature. Synechiae from iritis may cause opacities in either the cornea or lens [34], Blood in the anterior segment is, however, more likely to be associated with persistent embryonic lens vasculature while blood in the vitreous often relates to persistent hyaloids vessels. Dyscoria and other abnormalities in pupil shape among young rodents and especially mice (Fig. 9) are considered by some to be colobomatous lesions, but others suggest that eccentric pupils are associated with iritis [35].

In the rat and mouse, cataracts may occur spontaneously, congenitally (Fig. 10) [36] and in aging animals [37]. In rats with retinal degeneration cataracts may occur secondarily, because of the release of various metabolic byproducts [38]. In mice, cataracts may arise from infection with a helical spirochete termed the *suckling mouse cataract agent* [39] but more commonly in pet and laboratory strains cataracts will be inherited [40].
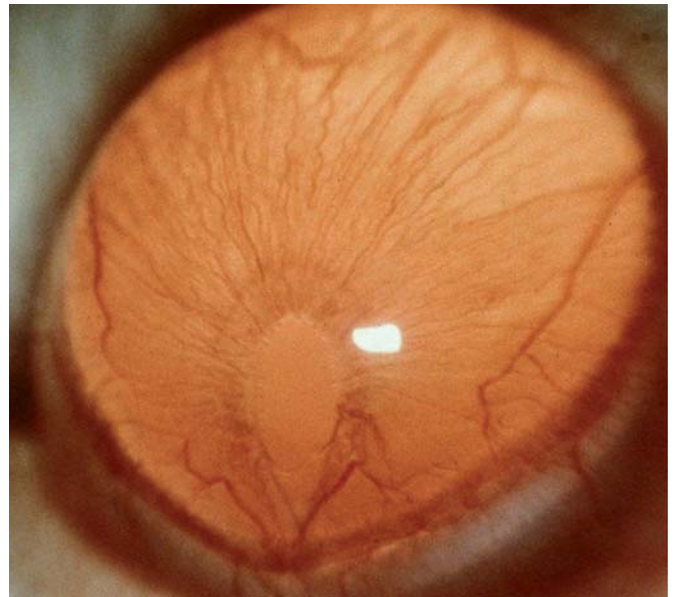
Abnormalities of the fundus may be congenital lesions, inherited retinal dystrophies, inflammatory lesions, degenerations and detachments [41]. Most congenital lesions of the rodent fundus are either abnormalities of the retinal and hyaloid vasculature as noted above, or colobomatous defects of the retina or optic disc. In young rats persistence of the hyaloid vasculature is common and while these vessels regress over the next few months considerable vitreal hemorrhage may occur during this period (Fig. 11).

Inherited retinal dystrophies and degenerations occur among experimental animals bred specifically for study of these conditions. The widespread nature of these dystrophic genes throughout rat and, particularly, mouse strains, however, means that such blindness may occur in a supposedly normal group of rodents. The rd gene, for instance, is seen in C57BL/6J, CBA, C3H, and various outbred albino mouse strains with

Fig. 10 Congenital nuclear cataract in a mouse.

retinal degeneration and blindness [42]. Laboratory rodents are also sensitive to the toxic effects of light on the retina with development of lesions causing blindness [43].

The rabbit

For many years the rabbit has been widely used in ophthalmic research, both in drug and chemical testing using the now rightly infamous Draize test [44] and in basic anatomic, physiologic and pharmacologic work. More recently the rabbit has moved from being a mere childrens' pet to becoming, at least in the UK, the third most commonly encountered pet in small animal practice with a large number of house rabbits kept by adults as valued companion animals. Associated with this increase in veterinary attention, much has been learnt about the healthy and diseased rabbit eye, as detailed here.

The rabbit eye has several anatomical peculiarities that differentiate it from that of dogs and cats. An important feature is the retrobulbar venous plexus, vital to note during enucleation. Performing this surgery transconjunctivally rather than transpalpebrally and remaining as close as possible to the globe during dissection, obviates this problem in the vast majority of cases. An unusual manifestation of disease related to the retrobulbar venous plexus is exophthalmos occurring during stress when venous drainage is compromised by a space-occupying thoracic or cervical mass [45]. Another anatomical difference concerns the nasolacrimal duct. There is a single nasolacrimal punctum in the rabbit and a duct which has a convoluted passage through the lacrimal and frontal bones, passing close to the molar and incisor tooth roots [46] and thus is likely to be affected by dental disease. Malocclusion of the molar arcades in particular results in retropulsion of the tooth into the weakened maxillary bone, with subsequent nasolacrimal occlusion. Incisor malocclusion can, perhaps more commonly, produce this same result.

Conjunctivitis and dacryocystitis are thus common and potentially problematic conditions in domestic rabbits; distinguishing between the two is important [47]. Purulent ocular discharge with conjunctival hyperemia often relates not just to conjunctivitis but also to nasolacrimal duct infections (Fig. 12). The diagnosis of infective conjunctivitis and dacryocystitis should be approached on the basis of understanding the normal bacterial flora of the conjunctival sac. *Pasteurella sp.* is considered by many to be the most common bacterial pathogen in the rabbit, but it is important not to forget *Staphylococcus aureus*. In a survey of staphylococcal disease in rabbits, more than 60% had nasal exudate with conjunctivitis [48] and in another report of conjunctival flora in rabbits with conjunctivitis and dacryocystitis, Pasteurella was not the most commonly isolated species: bacteria were isolated from 78% of swabs with Staphylococcal species found in 42% of isolates while Pasteurella species were only detected in 12% [48]. Culture of nasolacrimal flushes from affected rabbits [46] showed a wide range of organisms, including *Neisseria sp.*, *Moraxella sp.* and *Bordetella sp* among others but *Pasteurella multocida* was not detected in animals affected by epiphora rather than by dacryocystitis. The same diversity of organisms was found in nasolacrimal flushes from unaffected rabbits.
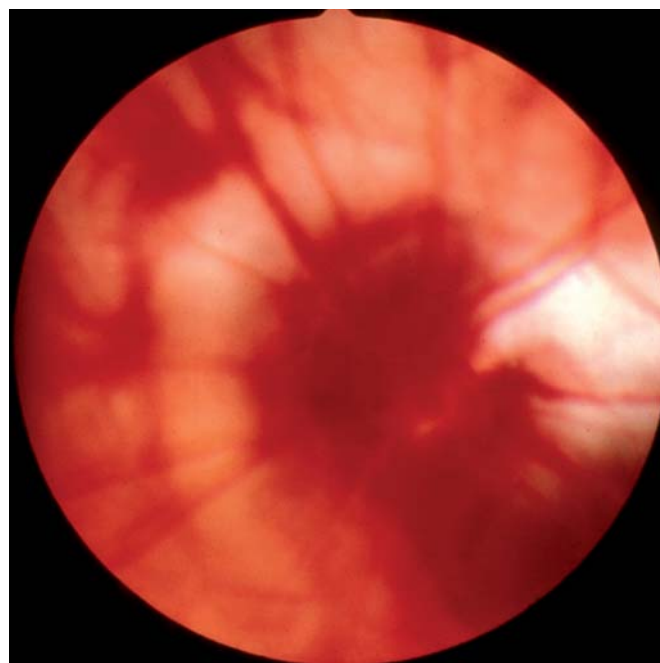

Fig. 11 Persistent hyaloids vasculature with haemorrhage in a rat.

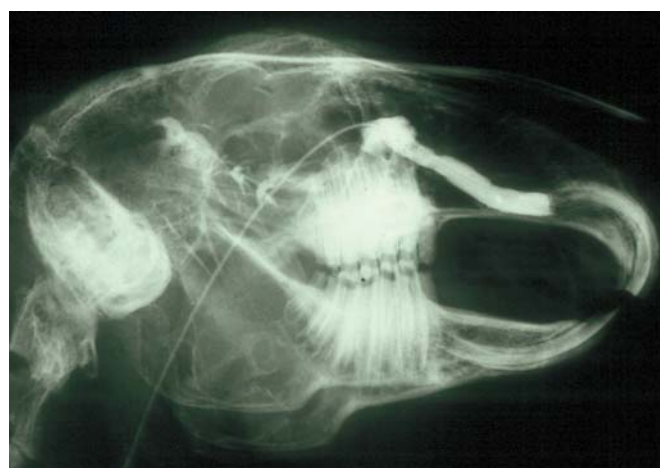*Fig. 12 Dacryocystitis in the rabbit.*

Fig. 13 Dacryocystorhinogram of rabbit with dilated cystic nasolacrimal duct. Courtesy of Francis Harcourt-Brown.

Fig. 14 Cannulation of the rabbit nasolacrimal duct.

Fig. 15 Florid conjunctivitis with dacryocystitis.

Dacryocystorhinography can show substantial lakes of discharge in dilated portions of the duct (Fig. 13), demonstrating why the discharge can be profuse and continuous. Treatment of dacryocystitis in the rabbit is by cannulation of the single nasolacrimal punctum and flushing of the duct (Fig. 14). If cannulation from the ocular punctum is difficult, cannulation of the duct opening at the nasal meatus is possible, but the small diameter of the duct at its nasal end renders this procedure difficult. The proximal end of the nasolacrimal duct can also be difficult to visualize in a rabbit in which dacryocystitis has extended to produce a florid conjunctivitis (Fig. 15). Pressing on the lower eyelid will often manifest the duct as a pair of lighter pink lips "pouting" through the darker red, inflamed conjunctiva. In most cases, cannulation and flushing of the duct with a drug such as orofloxacin or gentamicin will resolve the problem but this will require repetition potentially over several days to weeks. When this does not have the desired effect, the duct can be cannulated in a more permanent manner with fine monofilament nylon. There are problems and potential hazards with this technique, however, especially given the tortuosity of the rabbit nasolacrimal duct. Nevertheless, sometimes there is no other option in stubborn cases of dacryocystitis.

Blepharitis in the rabbit may be associated with *Treponema cuniculi*, the agent of rabbit syphilis. The diagnosis here is made on the basis of identifying the spirochaete on conjunctival-scrape cytology. Treatment is three injections of penicillin G at 40,000 IU/kg given at 7-day intervals. Conjunctival disease in the rabbit can be caused by viral as well as bacterial agents. The myxoma virus causes inflammatory and edematous lesions of the lids and conjunctiva as well as of the mouth, anus, and genitals (Fig. 16). In the acute form, death may supervene before any obvious ocular signs occur but conjunctival hyperemia may be the only sign before death. In the more common subacute or chronic form, conjunctival hyperemia progresses to chemosis, with a copious ocular exudate. The profound white ocular exudate in the disease may be caused by *Pasteurella multocida* dacryoadenitis in all cases, because the pathogenesis of this disease involves profound immunosuppression and, often, subsequent multifocal infection with *Pasteurella sp.* [49].

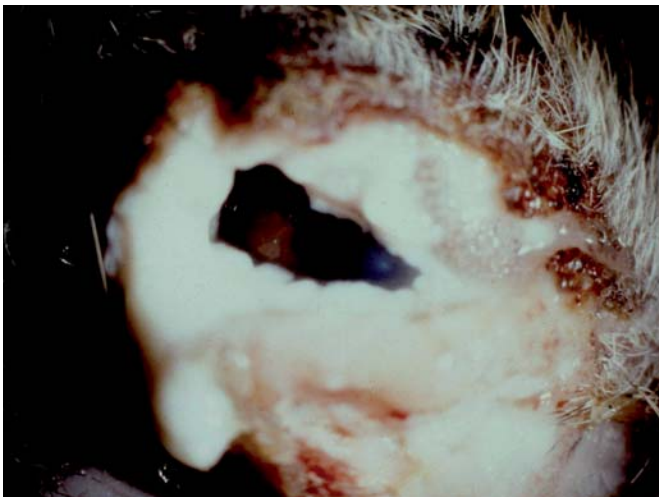*Fig. 16 Myxomatosis in a rabbit with blepharitis and discharge.*

Fig. 17 Perioxular myxomas in a vaccinated rabbit with myxomatosis.

Fig. 18a Retobulbar abscessationin a rabbit.

Fig. 18b Magnetic imaging study revealing the extent of abscessation.

Vaccinated rabbits will not succumb to this severe manifestation but may develop the myxomas from which the virus derives its name (Fig. 17). Thus, the ocular signs of myxomatosis are a complex mixture of virally induced ocular signs and secondary infections because of a reduced immune response.

Pasteurella is also often associated with retrobulbar abscessation in rabbits, often linked to a tooth root abscess (Fig. 18). Orbital exenteration is the only option in such cases, with the additional use of antibiotic-impregnated methacrylate beads being useful in some circumstances just as they are used in dentistry for infected tooth roots and orthopaedics to treatment osteomyelitis. In all too many cases eventual recurrence of the abscess occurs with breakdown of the enculeation woundsite, euthanasia being the preferred option on welfare grounds.

Entropion, which is relatively commonly seen in rabbits, is a condition rarely of sufficient interest to warrant reporting in the literature, but the few reports that have appeared confirm this lesion can be severe and is only corrected by surgery.

An unusual abnormality in rabbits is aberrant overgrowth of conjunctiva (Fig. 19). This condition is poorly documented in the literature and may be termed precorneal membranous occlusion, conjunctival centripetalisation or pseudopterygium [50]. The latter term is inaccurate as pterygium in man is an inflammatory conjunctivalisation of the cornea itself while in rabbits the conjunctiva has a free margin and is not attached to the underlying cornea except at the limbus. It appears as a thin annulus extending a few millimtres form the limbus or may cover a considerable portion of the cornea. Surgical removal results only in reformation of the aberrant tissue, whereas suturing the fold back onto the sclera or using topical cyclosporine postsurgically are more effective method of preventing recurrence. The cause of this condition is unknown.

Corneal epithelial dystrophy in the rabbit similar to that seen in epithelial basement membrane dystrophy in the boxer dog or Reis-Buckler's or mapdot fingerprint epithelial dystrophy among humans [51]. As in the dog, treatment by debridement with or without grid keratotomy but followed by protection of the

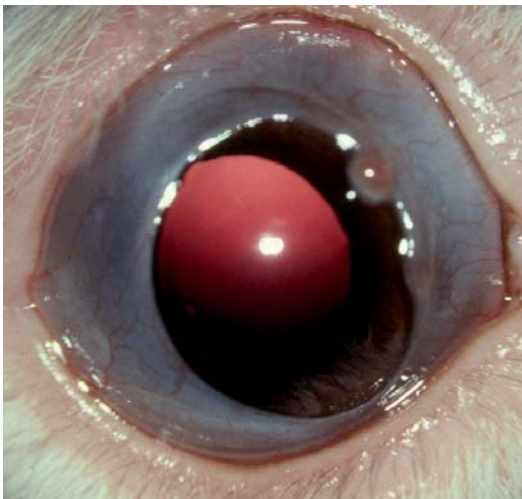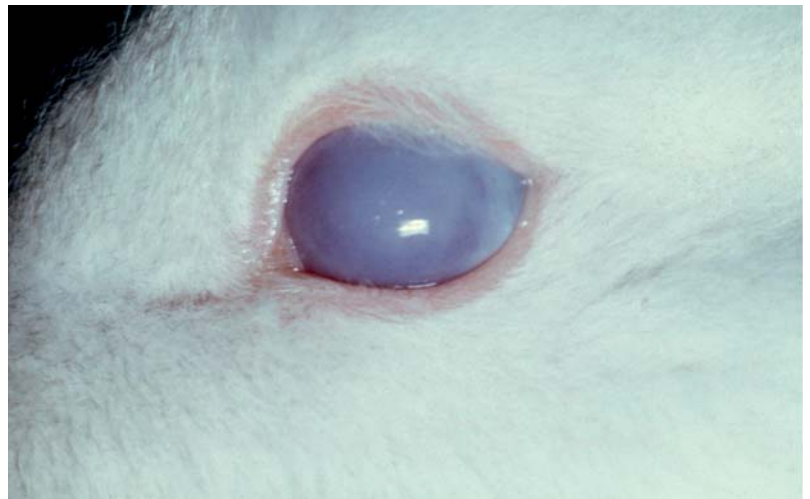*Fig. 19 Conjunctival overgrowth in a rabbit.*

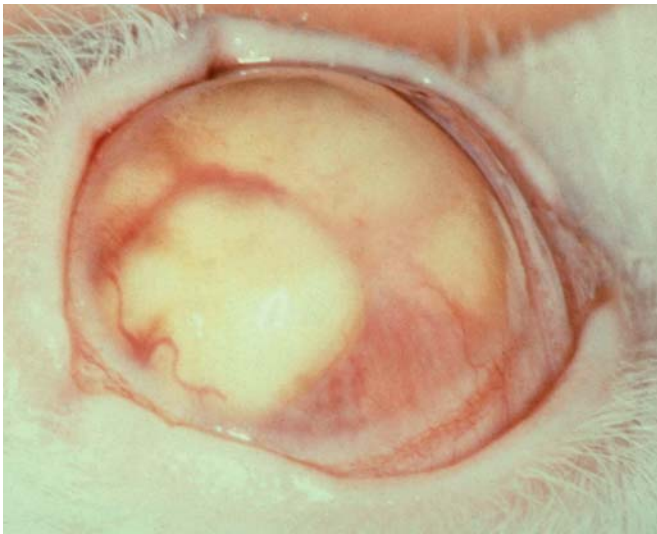*Fig. 20 Glaucoma in a bu/bu New Zealand White Rabbit.*

Fig. 21 Staphylococcal endophthalmitis in a rabbit.

Fig. 22 Encephalitozoan culiculi phacoclastic uveitis.

Fig. 23 Merangiotic fundus of the rabbit.

corneal surface with a contact lens can resolve the persistent ulceration seen in this condition.

Hereditary glaucoma in the New Zealand white rabbit has been well-researched since the early 1960s but can also be seen in other breeds of rabbit (Fig. 20) [52]. Neonatal bu/bu homozygotes have normal intraocular pressure (15–23 mm Hg), but after 1 to 3 months of age, the pressure rises to between 25 and 50 mm Hg. Histopathologic features of these glaucomatous eyes involve goniodysgenesis of the pectinate ligaments and trabecular meshwork. Eyes enlarge (become buphthalmic, hence the bu gene terminology) with cloudy corneas, but whereas vision is lost at this stage, the eyes do not appear to be painful, probably because of the gradual increase in size accompanying the raised pressure . Over a period of several months, pressure reduces, probably associated with ciliary body degeneration rendering medical treatment for this condition unnecessary. The bu gene

is a recessive trait that is also semilethal, with heterozygotes giving birth to small litters of unthrifty offspring.

Uveitic changes in the rabbit eye may be associated with infectious disease such as Pasteurella or Staphylococcal panophthalmitis (Fig. 21) but are more likely to be related to lens induced uveitis linked to capsular rupture caused by intralenticular infection by the protozoan *Encephalitozoon cuniculi* [53]. While the former is charcaterised by a yellow-white exudate filling the eye, the latter has a more defined and often vascularised white mass in the iris often associated with cataract formation (Fig. 22). Treatment is lens removal, predominantly by phacoemulsification, with concurrent topical anti-inflammatory medication or by medical treatment with the antiparasiticides fenbendazole or albendazole as well as topical anti-inflammatory medication.

The finding of cataract in a rabbit should prompt the evaluationof serum titres of antibody to E. cuniculi, since the parasite is responsible for a large, but as yet unknown, proportion of rabbit lens opacities. Congenital cataracts have been documented in rabbits with nuclear lenticular opacities with persistent pupillary membranes in some affected animals but age-related cataracts seem much less prevalent than in the guinea pig (see below).

The fundus of the rabbit is merangiotic in nature with a band of blood vessels and mylelinated nerve fibres traversing the retina in a horizontal plane from the optic disc (Fig. 23). Optic disc cupping is seen in glaucoma in the rabbit although it can be difficult to differentiate from the deep physiological cups which can be part of normal variation in this species. No spontaneous diseases of the rabbit fundus have been reported but for one retinal degeneration in a strain of laboratory rabbits.

The guinea pig

There is very little work published on ocular disease in this species although they are used widely in research and regularly kept as pets. Our as yet unpublished findings suggest that 45% of pet guinea pigs in a survey of over a thousand animals had some degree of ocular pathology, mostly involving incomplete lens opacification. Congenital defects ranging from those as severe as clinical anophthalmos to mild posterior polar subcapsular cataract are seen in a sizeable proportion of guinea pigs, particularly those of Roan x Roan matings. Ocular surface defects in young animals may be caused by trichiasis in Texel
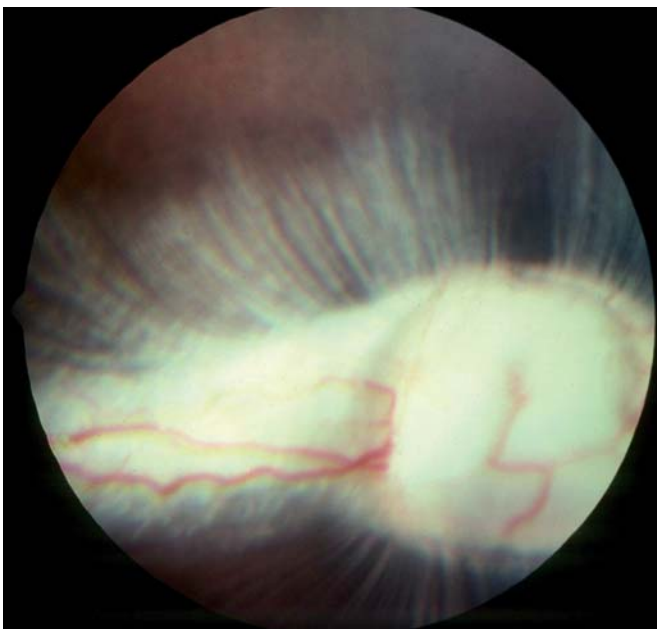
Fig. 24 Heterotopic bone formation in a guinea pig.

Fig. 25 Diabetic cataract and subconjunctival fat deposit in a guinea pig.
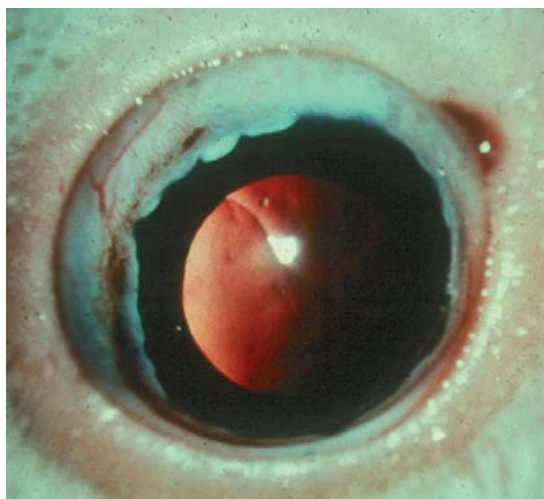
animals where the coat is composed of short bristly hairs which can easily abrade the eye in the first few days of life. Vaseline can be used to direct periocular hairs away from the ocular surface but even so corneal ulceration and edema can still occur.

Conjunctivitis among guinea pigs has been associated with chlamydial organisms for over forty years [54]. Some animals have only slight reddening of the eyelid margins, whereas others have thick, purulent exudate. Other infectious causes of conjunctivitis in guinea pigs include listeriosis and salmonellosis. Infectious agents are not the only cause of conjunctival lesions in this species; because they are incapable of forming their own vitamin C, guinea pigs are at considerable risk of scurvy, one of the early signs of which is conjunctivitis

Excess lipid deposition in the inferior conjunctiva occurs in obese animals while smaller pink masses in the medial canthus are probably analogous to prolapsed nictitating membrane in the dog. Calcium deposition is reported in the ciliary body of guinea pigs (Fig. 24) and termed heterotopic bone formation [55]. In one recent report, a link was suggested between secondary glaucoma and osseous choristoma [56] but our findings suggest that intraocular pressure is generally lower in affected animals rather than higher. Regarding the cause of this bone formation, ciliary body concentrates plasma ascorbic acid into the aqueous humor which may be important as ascorbic acid is known to promote bone formation in the presence of a rich blood supply, such as occurs in the ciliary body.

As noted above cataracts are commonly seen in guinea pigs – 18% of outbred animals in our study were affected while inherited cataracts have been reported in the N13 strain of guinea pigs [57]. Diabetic cataarcts occur commonly in the species rapidly progressing to maturity (Fig. 25).

The guinea pig has an anangiotic retina but no reports of fundus abnormalities have been reported in the literature although a recent report documents a spontaneous disorder of rod function as determined by electroretinography in a group of animals as a result of consanguineous mating [58].

Other rodents: the chinchilla, degu and hamster

The scientific literature yields little regarding diseases of the chinchilla eye. Peiffer and Johnston (236) report the examination of 14 aged chinchillas revealing a shallow orbit, a rudimentary nictitating membrane, a large cornea, a densely pigmented iris with a vertical slit pupil, and an anangiotic fundus with variable vascularization of the optic disc. Mean intraocular pressure was 18.5±5.8 mmHg while glaucoma with lens luxation has been noted. Bilateral posterior cortical cataracts and asteroid hyalosis were observed in 2 animals. Dental disease is common in pet animals and can lead to epiphora [60]. Exophthalmos, while it may be related to molar retropulsion, has also been reported with parasitic invasion of the orbit [61].

Degu's have unremarkable eyes expect for their propensity to develop diabetes with secondary cataract [62]. The high level of aldose reductase in their lens may have a role to play in the rapid development of lens opacity in these situations.

Few reports exist of ophthalmic abnormalities in hamsters, but individual cases of conjunctivitis, keratoconjunctivitis sicca, eyelid melanoma with pulmonary metastasis [63] and retinal dysplasia [64] are seen. Such single reports suggest that more assiduous evaluation of ocular disease in this species would reveal yet more pathology. Over-enthusiastic handling of hamsters by scruffing the neck will lead to globe prolapse which can be treated by tarsoraphy but with a generally poor prognosis for full eye function subsequently.

Conclusion

The similarity of the eyes of these rodents and rabbits yet also the differences in anatomy, pathology, treatment and prognosis render laboratory mammal ophthalmology a continually fascinating and challenging area. Much still remains to be discovered with new diagnoses and improved treatments to be determined and evaluated. It is hoped that this review will provide a platform for such further study.

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