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|                                                                                                                                                                                                                                                         |                                                    | Retinal Degeneration; rd mouse                                                                 |                            |
| 19. ABSTRACT (Continue on reverse if necessary and identify by block number)<br>Inherited retinal degeneration was identified in a Swiss-derived mouse strain. The histologic lesions are described and the pathogenesis of the condition is discussed. |                                                    |                                                                                                |                            |
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# Diagnostic Exercise: Retinal Lesions in a Mouse

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### History

A group of 16 - 22 g, female, ICR Swiss mice was obtained from a commercial supplier for a toxinology experiment. One mouse of this group was submitted for routine necropsy and histologic examination as part of the quality control program at the research institute. No abnormalities were noted clinically.

### Pathology

Gross lesions were not seen at necropsy. Histologic lesions were limited to the eyes. Changes were present and similar in the retina of both eyes. (Figure 1A)<sup>1</sup> The outer layers of the retina were characterized by attenuation and loss of the outer plexiform, outer nuclear, and photoreceptor layers. (Compare with Figure 1B)<sup>2</sup> The outer nuclear layer was reduced to a discontinuous single row of nuclei. The photoreceptor layer was represented by an eosinophilic, granular coagulum or was absent altogether. An outer limiting membrane could not be defined by the use of special stains. The (nonpigmented) retinal pigment epithelium was unaffected.

### Questions

What is the differential diagnosis for the eye lesions seen in this animal? What is the most likely diagnosis, given the above signalment? What is the pathogenesis of the lesion?

## Legends for Illustrations

### Figure 1

(A). Retina with marked attenuation of outer plexiform, outer nuclear, and rod and cone layers.

Retina is artifactually separated from retinal pigmented epithelium. Original magnification 400X.

Hematoxylin and eosin stain.

(B). Normal mouse retina for comparison. Original magnification 400X. Hematoxylin and eosin stain.

## Diagnosis and Discussion

Retinal degeneration occurs in a number of species and may be a result of a variety of different etiologies, including toxic, phototoxic, nutritional, metabolic, and genetic. In the rat, unilateral, focal or generalized, retinal degeneration is most likely to be a sequela of sialodacryoadenitis (of a number of possible etiologies), and results from extension of the inflammation of the orbital gland with resultant choroiditis. If, however, the retinal degeneration is generalized and bilateral, the more likely etiologies in both rats and mice include heredity, phototoxicity, and drug-induced toxicity.<sup>1</sup> Since the animal of this report had not yet been placed on a study, the differential diagnosis here included light-induced retinal degeneration (phototoxic retinal degeneration) and inherited retinal degeneration. Based on the young age of the animal, strain, and the uniformity of the lesion bilaterally, the most likely etiology is inherited retinal degeneration.

In the mouse, retinal degeneration is reported as an autosomal recessive trait, particularly prevalent in Swiss-derived strains; and the allele responsible is designated *rd* (affected mice are known as "*rd* mice"). Inherited retinal degeneration is seen in both pigmented and albino laboratory strains of mice, as well as in wild mice.<sup>3</sup> The incidence is variable, and may be as high as 25% in some colonies.

The pathogenesis of the lesion involves maldevelopment of the outer limbs of the rods followed by a degeneration of the entire photoreceptor cell.<sup>2</sup> The retinal degeneration is apparently due to a direct effect of the gene on the photoreceptor cells rather than the retinal pigment epithelium, as no difference in the pigmented epithelium of *rd* mice compared to normal mice can be demonstrated histochemically.<sup>4</sup> Mice with inherited retinal degeneration have a deficiency of cyclic GMP-phosphodiesterase activity, which results in an accumulation of cyclic GMP within affected photoreceptor cells. The defect is present before photoreceptor cells begin to degenerate.<sup>5</sup> Elevation of cyclic GMP levels has been shown *in vitro* to cause photoreceptor cell degeneration.<sup>6</sup>

In addition to the changes present in the photoreceptor layer, there is a reduction in the vascularity of the retina which is temporally associated with the photoreceptor degeneration.<sup>7</sup> It is unclear whether the reduced vascularity is a cause or an effect of the retinal degeneration.

Mice are born with immature retinas, which develop to morphologic maturity at about 28 days after birth. In normal mice, retinal rods demonstrate some electroretinogram activity in the second week of life, and continue to develop, reaching full electrical activity around 4 weeks of age.<sup>2</sup> Electroretinograms of *rd* mice show some rod activity in the second week of life, but the activity progressively deteriorates after this time. The degenerated retina remains light-sensitive, however, the sensitivity being reduced.<sup>8</sup>

The retina of *rd* mice ceases development after the 11th day, and extensive degenerative changes are present by day 14.<sup>3</sup> Microscopic changes can be detected as early as 8-9 days post partum.<sup>9</sup> As seen in this case, degeneration involves the photoreceptor processes and the outer nuclear layers. By day 20, the retina consists almost entirely of the inner layers. In time, the degeneration may progress to involve the inner retinal layers resulting in the transformation of the retina into a fibrous remnant without obvious layer organization. In my experience, however, the lesion rarely progresses beyond that present in the animal of this report.

The presence of this condition in animals used in acute or, especially, chronic toxicity studies may confound interpretation of the ocular effects of the substance under study. Only stock that is free of clinical disease should be used for breeding purposes. Affected mice can be identified by indirect ophthalmoscopy at 3 weeks of age.<sup>10</sup> This precaution alone will not guarantee unaffected offspring, however, as only homozygous individuals are identified; animals heterozygous for the allele will not be detected in this manner. Mice to be used in research in which critical evaluation of ocular tissues is necessary, especially when those animals are of Swiss derivation, should be carefully screened prior to initiation of the study.

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