DEGENERATIONS OF THE DOG RETINA*

III. RETINOPATHY SECONDARY TO GLAUCOMA

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ALTHOUGH the effects of glaucoma on the human retina are well known (Duke-Elder, 1940; Wolff, 1951), accounts of the retinal degeneration following glaucoma in the dog are rare. It seemed of interest therefore to record details of two cases, particularly as the degeneration differs from other types reported in this series and follows closely the changes seen in man, except that the area centralis is spared in contra-distinction to the early changes in the human macula.

The early recognition of glaucoma in animals is uncertain owing to the absence of subjective information and the difficulty of assessing changes of intra-ocular tension clinically. However, there is one syndrome following spontaneous luxation of the lens in which a diagnosis can be made before the general eye structures are seriously disorganized. This syndrome, which is described by Formston (1945), affects Smooth-coated Fox Terriers and Sealyhams and is due to an inherited weakness of the suspensory ligaments of the lens, which rupture spontaneously in early adult life, causing luxation of the lens and secondary glaucoma.

One case of this syndrome is described together with one of glaucoma secondary to idiopathic irido-cyclitis.

Methods and Material

The methods and terminology have already been described (Parry, 1953a, b). The electroretinogram was recorded by the team (Parry, Tansley, and Thomson, 1953). The two cases occurred naturally and were referred to us in consultation.

Although there is no macula or area of functionally specialized retina in the dog (Parry, 1953a), the varying distribution and severity of the lesions in different parts of the fundus in several types of non-symmetrical retinal degeneration in the dog makes it desirable to consider the anatomical regions of the fundus in more detail. These regions and their divisions are shown diagrammatically in Fig. 1 (opposite).

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I. TAPETAL FUNDUS

T 1. Peri-papillary zone within 1 to 2 mm. of the papilla over which run the short cilio-retinal vessels and in which the nerve fibre layer becomes much thickened.

FIG. 1.—Diagram to illustrate the principal zones of the fundus of the dog. Details of the lettering are given in the text. The non-tapetal fundus is shaded. ($\times 7.5$).

T 2. Area centralis over which the central retinal vessels are scanty or absent.

T 3. Main mid-tapetal area.

T 4. Junctional zone, about 1 mm. wide, between the tapetal and non-tapetal fundus, in which the tapetum is not more than two cells thick and the pigment epithelium begins to acquire lanceolate pigment granules. It comprises an equatorial zone at the periphery (T4a), and nasal (T4b) and temporal (T4c) ventral zones at the ventral margin.

II. NON-TAPETAL FUNDUS.—This consists of two regions: ventral and peripheral.

V 1. Small peri-papillary zone similar to that in the tapetal fundus (T1).

V 2. Narrow dorsal zone about 2 mm. wide, immediately adjoining the ventral margin of the tapetal fundus, and probably adjacent to the main horizontal

retinal arteries. It is divided into nasal (V2a) and temporal (V2b) portions, which are medial and lateral to the papilla.

V 3. Mid-ventral zone, comprising the main portion of the non-tapetal fundus.

V 4. Equatorial zone similar to the equatorial junctional zone of the tapetal fundus (T4a).

P 1. Dorsal peripheral zone, 1 to 1.5 mm. wide, between the ora serrata and the peripheral margin of the tapetal fundus. It may be divided into nasal (P1a) and temporal (P1b) portions.

P 2. Ventral peripheral zone at the extreme periphery of the ventral non-tapetal fundus, consisting of nasal (P2a) and temporal (P2b) portions.

Although many details of the precise anatomical arrangements of the eye of the dog are unknown, it is probable that the choroidal circulation to the peripheral non-tapetal fundus is principally from the anterior ciliary vessels, and that to the remainder of the fundus from the posterior ciliary vessels.

Case Reports

Case 1.

Clinical Data.—A pedigree Smooth-coated Fox Terrier male, 3 years old, weight about 10 kg., had shown progressive loss of day and night vision for about 2 months following spontaneous luxation of both lenses. There was no other significant medical history and no abnormalities, other than in the eyes, were noted on clinical examination.

Both eyes were affected similarly. The dog was almost completely day-blind (night vision was not tested). The average pupil size was about 8/14 mm.

The eye preservation reflex was absent, but the pupillary light reactions were present and fairly brisk. The eyeballs protruded and were somewhat enlarged, their horizontal diameter being about 18 mm. (the normal is probably 15–16 mm. in this breed). Judged by digital palpation, however, they were firmly distended. The cornea were clear, but the anterior chamber was unusually deep. The lenses were clear, but both were luxated ventrally and posteriorly. The tapetal fundi, which could be viewed dorsal to the lenses, had normal beaded texture and stellulae of Winslow; the blood vessels were inconspicuous. The ventral portions of the tapetal fundi, the optic papillae, and the ventral non-tapetal fundi could not be examined in detail owing to distortion by the misplaced lenses.

Electroretinography.—No electroretinogram could be detected from either eye 6 hours before death, which followed deep pentobarbital sodium-myanesin anaesthesia.

Morbid Anatomy.—The optic nerves and canals were normal. No macroscopic abnormality of the brain was observed. The eyes were fixed about 2 hours after death, and when opened after fixation showed a white coagulum in both anterior and posterior chambers. This was particularly dense adjacent to the retina. The optic papilla was flat.

Histology.—Both eyes showed a similar advanced chorio-retinal degeneration. In the retina the inner layers had suffered more than the outer; a central region, comprising the tapetal and the adjoining dorsal non-tapetal retina, still retained its layer organization, while the more peripheral region, comprising all the peripheral non-tapetal retina and the mid-ventral non-tapetal retina, was completely sclerosed.

Although the retina of the central region showed the normal organization into layers, it was narrower than normal, being about 120 μ wide. This was due to some reduction in the widths of all layers, but mainly to the loss of ganglion cells and bipolar cell nuclei in the inner nuclear layer (Fig. 2, opposite). The outer and inner limbs of the rods and cones were present in normal numbers, but there was considerable fragmentation with separation from the pigment epithelium, almost certainly due to *post-mortem* change. In view of the

FIG. 2.—Section through the retina of Case 1, area centralis of tapetal fundus. There are *post-mortem* changes in the rod and cone and outer nuclear layers, but note the absence of ganglion cells and the loss of bipolar cell nuclei from the inner nuclear layer, which consists of a single layer of nuclei, mostly of Müller's cells. Some cells of the pigment epithelium are slightly swollen. *Post-mortem* fixation in Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. ($\times 240$).

The following code applies to all figures:

Sc: Sclera	4. Outer nuclear layer
Ch: Choroid	5. Outer fibre layer
Ret: Retina	6. Inner nuclear (bipolar) layer
1. Pigment epithelium	7. Inner fibre layer
2. Rod and cone layer	8. Ganglion cell layer
3. External limiting membrane	9. Optic nerve fibre layer
	10. Internal limiting membrane

presence of some day-vision and of pupillary light reactions, the rods and cones over most of this zone were probably essentially normal. In a few places nuclei from the outer nuclear layer lay amongst the inner limbs. The external limiting membrane was prominent. The outer nuclear layer was about 30–50 μ wide and six to twelve nuclei thick; it was normal, except that about a quarter of the rod nuclei showed the pyknotic degeneration of early *post-mortem* change. The outer fibre layer was thinned to about 5–6 μ , while the inner nuclear layer was reduced even more to 6–8 μ thick and a single layer of nuclei, principally those of Müller's fibres. The nuclei of the ganglion cell layer had almost completely disappeared; the nuclei of a few large ganglion cells that remained were oval in outline with hyaline eosinophilic cytoplasm, and the nucleus lay at one extremity with little chromatin apart from a dense nucleolus. The inner fibre and optic nerve fibre layers appeared as a single layer 40 μ wide with numerous very thick Müller's fibres, many of which were no longer disposed radially but lay irregularly. In this layer there were an unusually large number of thick-walled capillaries. The main retinal blood vessels were still present, but their walls were much thickened by an increase of the tunica media. The internal limiting membrane was absent and the inner surface of the nerve fibre layer formed a spongy network.

Between this central region of modest degeneration and the ventro-peripheral region of advanced sclerosis, lay an intermediate area about 1 to 2 mm. wide in which the outer

nuclear layer was much reduced, the rods had disappeared, and only the stubby inner limbs of the cones remained (Fig. 3).

FIG. 3.—Section through the same retina as in Fig. 2, ventral non-tapetal fundus near the papilla. The layers of the retina are becoming disorganized. Note the stubby remains of the cones. ($\times 270$).

Outside this intermediate area and commencing centrally just ventral to the papilla, the retina of the ventro-peripheral region showed advanced sclerosis with loss of its layered structure. In the mid-ventral non-tapetal fundus, the retina was about $50\ \mu$ wide and consisted of a mass of glial fibres with a few nuclei, probably of Müller's cells. Over the extreme peripheral fundus the width of the retina was reduced to $20\ \mu$ wide, and consisted of scanty nuclei in a narrow network of fibres with an occasional large round pigment cell loaded with dark brown granules (Fig. 4); these were probably derived from the choroid.

FIG. 4.—Section through the same retina as in Fig. 2, peripheral non-tapetal fundus. Note the great reduction in width of the sclerosed remnants of the retina in which all signs of the layer organization are lost. ($\times 270$).

The pigment epithelium was intact over the whole fundus; there was no abnormal accumulation of pigment but in some small areas the cells were about twice as wide as normal and bulged inwards, while their cytoplasm was vacuolated. The tapetum was half the normal thickness, the walls of the cells being thickened and irregular while the cell cytoplasm was scanty and uneven in distribution, although the long sides of the cells still remained approximately parallel. The choroid was thinned to about $100\ \mu$ over the whole fundus, and its blood sinuses were much less conspicuous than usual. The choroidal

FIG. 5.—Section through the retina and choroid of Case 1, mid-ventral non-tapetal fundus. Note the great thickening of the walls of the large retinal and choroidal arteries and the retinal capillaries. The layer organization of the retina has disappeared and with it most of the nuclei. There is a marked gliosis, which has caused the burying of the large retinal artery. Post-mortem fixation with Kolmer's cold-blooded fluid. Azan. ($\times 270$).

arteries had very thick walls (Fig. 5), as had those of the iris and ciliary body and the capillaries running to the chorio-capillaris. The iris was swollen and oedematous and the epithelial cells of its posterior surface were vacuolated. The cornea and sclera were normal. The optic nerve showed some increase of connective tissue around the blood vessels and early fragmentation of nerve fibres.

Comment.—This case showed severe atrophy of the retina and choroid, with marked thickening of the walls of the blood vessels. In the retina the degeneration had affected the ganglion cells and optic nerve fibres most severely, the bipolar cells of the inner nuclear layer disappeared next, and the outer nuclear and rod and cone layers were relatively little affected. The degeneration was very much more advanced in the non-tapetal retina, apart from a narrow zone adjoining the ventral border of the tapetum which with the tapetal fundus was much less severely affected.

Case 2.

Clinical Data.—A Wire-haired Fox Terrier, female, 6 years old, weighing about 8 kg., had been in good health until 5 to 6 weeks previously, when the right eye had become affected, and was followed 4 weeks later by the left. The anamnesis provided no suggestion as to the cause of the eye affection.

Both eyes were enlarged and protruded; the horizontal diameter of the left eye was 19 to 20 mm., and that of the right 2 mm. greater. There was considerable increase of intra-ocular tension, which was greater in the right eye. Although probably completely day-blind, the dog showed no signs of pain. The conjunctivae were injected and there was photophobia in the left eye. Both corneae were opaque.

Over the ensuing 8 weeks both eyes gradually enlarged until the horizontal diameters of the right and left eyes were approximately 28 and 24 mm. respectively. The corneae became clear, but the pupils were now widely dilated and unresponsive to light. There were dense bilateral cataracts, preventing examination of the fundi. As the dog showed signs of discomfort it was destroyed by the intra-vital injection of Kolmer's cold-blooded fluid under deep pentobarbital sodium anaesthesia.

FIG. 6.—Right eyeball of Case 2 cut in the mid-dorsal-ventral plane. Note the cupping of the optic papilla and the remains of the white coagulum in the posterior chamber. ($\times 2.25$).

Morbid Anatomy.—No abnormalities of the cranium, brain, or optic nerves were found. The eyes showed a dense white coagulum in both the aqueal and vitreal cavities with typical glaucomatous cupping of the optic papilla (Fig. 6).

Histology.—Both eyes showed changes similar to those seen in Case 1, but the damage was more severe in the right eye. The tapetal and dorsal non-tapetal retina was rather less degenerate than in Case 1, but the remaining ventral and peripheral non-tapetal retina was completely sclerosed.

Over the central retina the ganglion cells had disappeared, apart from an odd disintegrating cell usually surrounded by a clear space (Fig. 7, opposite), and a few eosinophilic hyaline masses with irregular edges, each about $25\ \mu$ in diameter. A few bipolar nuclei remained in the inner nuclear layer, which was reduced to 1–2 nuclei thick;

the fibre layers were intact; the outer nuclear layer consisted of 5–8 nuclei and an occasional nucleus had passed through the external limiting membrane into the rod and cone layer. The rods and cones were still present and showed no signs of compression; the outer limbs gave a normal positive Feulgen reaction. The walls of the blood vessels were much thickened with new elastic tissue in the media. The internal and external limiting membranes were present; the internal one was thickened and to it was firmly attached a mass of eosinophilic detritus from the vitreous humour.

The optic nerve showed more advanced degeneration than in Case 1: the central artery and vein were surrounded by oedema, the larger arteries and veins at the periphery were very conspicuous, and the walls of the arteries and intra-septal capillaries were greatly enlarged with connective tissue. The nerve fibres showed advanced fragmentation.

The choroid and sclera were much thinned and together were only about $120\ \mu$ wide. The pigment epithelium and the chromatophores of the choroid were similar to those of Case 1, as were the iris and ciliary body; the cornea showed new blood vessels at its periphery.

Comment.—The relative sparing of the central fundus with advanced sclerosis of the

ventral and peripheral fundus, and the sequence of the degeneration in the retina from within outwards were essentially the same as in Case 1.

FIG. 7.—Section through the retina of Case 2, dorsal non-tapetal fundus adjoining the tapetal fundus. Note the loss of ganglion cells. The remains of a degenerating large ganglion cell surrounded by a clear space can be seen to the left. Some bipolar nuclei remain in the inner nuclear layer, while the outer nuclear and rod and cone layers are well preserved. Intra-vital fixation with Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. ($\times 240$).

Discussion

Although the aetiologies of the glaucoma in the two cases were different, the striking similarity in the changes in the retinæ suggest that these changes can be attributed to the increased intra-ocular tension which alone was present in the first case. The degeneration of the ganglion cells and optic nerve fibres followed by gradual loss of the bipolar cells, the sparing of the rods and cones even when blindness is well established, the gliosis from proliferation of Müller's fibres, the thinning of the choroid and thickening of the walls of blood vessels are, of course, well recognized sequelae in the human eye subjected to prolonged intra-ocular hypertension. There are, however, certain points of difference. As the dog has no macula we might well expect to find no focus of advanced degeneration in the area centralis, but the sparing of the central fundus and much more advanced stage of the degeneration over most of the non-tapetal fundus was not expected. We have found no signs of compression of the rods and cones such as were described by Berenstein (1900) and von Hippel (1901) in human cases, although in Case 2 the intra-ocular tension was sufficient to cause an increase of 50 per cent. in the horizontal diameter of one eye. No signs of cystic degeneration at the ora serrata, a feature of certain human cases, were seen.

The classical explanation of the effects of glaucoma on the retina is that the intra-ocular hypertension causes interference with the blood supply to the retina, and that the early damage is due to retinal ischaemia followed by

pressure atrophy, to which the outer layers of the retina are remarkably resistant. In a consideration of the possible effects of ischaemia on the retinal cells of the dog, certain experimental studies on quinine amblyopia provide pertinent data. The intravenous administration of toxic doses of quinine to the dog is followed by temporary or permanent blindness accompanied by marked constriction of the retinal arteries (de Schweinitz, 1896, 1907; Holden, 1898). These authors considered that the amblyopia was secondary to ischaemia due to intense vaso-constriction. These observations were confirmed by Giannini (1934) in dogs, but he made the discovery that the vaso-constriction did not occur and blindness did not develop, if acetylcholine were administered with the quinine. He considered that the acetylcholine inhibited the action of quinine on the autonomic nervous system and thereby prevented the vaso-constriction, retinal ischaemia, and consequent amblyopia. Although Wolff (1951) considers that in man quinine amblyopia is due in part to the direct action of quinine on nerve cells, it seems probable that in the dog the retinal damage is due very largely to vaso-constriction and consequent retinal ischaemia. In this connection it is interesting to note how closely the changes in the ganglion cells observed in our cases follow the illustrations given by Holden (1898) of the early changes in quinine amblyopia, and that eosinophilic masses in the optic nerve fibres described by Holden and probably representing ganglion cells in the last stages of disintegration were also occasionally observed in our cases. It seems likely therefore that the early changes in post-glaucomatous atrophy of the retina of the dog are due to obstruction of the blood flow through the central retinal and peri-papillary cilio-retinal vessels, which are more immediately exposed to the effects of intra-ocular hypertension than are the choroidal blood vessels.

The difference in the severity of the degeneration between the central, ventral, and peripheral fundi was very striking. The tapetal retina, and a narrow portion of the adjacent dorsal non-tapetal retina adjoining it dorsal to the papilla, were affected much less severely than the remainder of the ventral and peripheral non-tapetal retina; in particular the outer layers of the retina, the first-order neurones, were spared. As all parts of the fundus are exposed to the same pressure, this distribution suggests either that the anatomical arrangement of the blood supply to the tapetal and immediately adjoining dorsal non-tapetal retina is less susceptible to interference by intra-ocular hypertension, or that this portion of the retina is more resistant to ischaemia. It is possible that normally the flow of blood through the tapetal chorio-capillaris, having traversed the trans-tapetal capillaries, is less good than that through the non-tapetal chorio-capillaris which lies closer to the main choroidal blood vessels. If this is so, the outer layers of the tapetal retina might be accustomed to a lower oxygen tension and be less susceptible to ischaemic damage than the non-tapetal areas.

It is of interest that these abnormalities of the internal environment pro-

duced very little change in the pigment epithelium, which was intact (except for a small area at the extreme periphery in Case 1), and showed no abnormalities of pigmentation, although some of the cells were slightly swollen inwards towards the rods and cones.

The sequence of the cellular damage and the fundal distribution of the degeneration is quite distinct from that seen in the hereditary generalized atrophy of Red Irish Setters (Parry, 1953b), but a degeneration with a similar distribution in the fundus but a different sequence of cellular damage has been noted in chronic virus retinopathy following distemper-complex infection.

The failure to detect an electroretinogram in Case 1, which still had some day vision and pupillary light reactions and in whose central retina there were many intact rods, is noteworthy. The electroretinogram cannot be detected in the hereditary degeneration even when some night vision (and therefore considerable rod function) remains (Parry, Tansley, and Thomson, 1953). In the hereditary disease the loss of the electroretinogram can be attributed to the fact that the decreased number of functional rods proves insufficient to set up potentials detectable by the method used. It is interesting to speculate whether a similar explanation should be applied to Case 1, or whether the loss of ganglion and bipolar cells may not play some role in the loss of the electroretinogram in the glaucomatous eye.

Summary

- (1) Two natural cases of retinal degeneration secondary to glaucoma in dogs are described.
- (2) The main morbid anatomical and histological features of the degeneration are similar to those seen in human eyes with chronic glaucoma, but there are certain minor differences.
- (3) Compression of the rods and cones and cystic degeneration at the ora serrata were not found.
- (4) The peripheral and mid-ventral non-tapetal retina was more severely affected than the central (mainly tapetal) retina; possible reasons are discussed.
- (5) Some effects of ischaemia on the retina of the dog are considered.
- (6) Failure to detect an electroretinogram in the eyes of one case is noted.

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