DEGENERATIONS OF THE DOG RETINA*

V. GENERALIZED PROGRESSIVE ATROPHY OF UNCERTAIN AETIOLOGY

BY

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DURING an investigation of a hereditary retinal atrophy of Red Irish Setter dogs (Parry, 1953b), we encountered syndromes which were somewhat similar to the disease observed in Irish Setters but in which evidence of a similar hereditary origin, or of distemper-complex virus infections (Parry, 1954a), or glaucoma (Parry, 1953c) were lacking. In these cases there was a generalized degeneration of the retina and an atrophy of the pigment epithelium as in the hereditary disease.

This paper reports the findings in three cases in which we were able to carry out detailed clinical and pathological observations. The cases were of two types: first, a familial type in which two of three litter mates were affected, and secondly, an idiopathic type with no pertinent medical history.

Methods and Materials

The methods and terminology have been described in previous papers (Parry, 1953a, b, c). The cases described were natural ones. The first two were kept in isolation kennels under observation for up to 2 years and the test-matings were carried out under controlled conditions (Parry, 1953b). The electroretinograms were recorded by the team (Parry, Tansley, and Thomson, 1953).

Results

(1) FAMILIAL TYPE

The dogs affected each weighing about 17 kg., came from a litter of three male pedigree Afghan Hounds. They had been vaccinated against Laidlaw-Dunkin distemper in adolescence and had no pertinent medical history of febrile illness, etc. No defects of vision were noted until they were 1½ years old.

Case 1 (DO 61).

Clinical Data.—This dog was noticed to be night blind when 18 months old. He was examined at 2 years old, when he entered the research kennels. At this time the dog was completely day and night blind in both eyes; the average pupil size was 13/15 mm., the pupillary light reactions and eye preservation reflex were absent; the retinal blood vessels were reduced to a single small dorsal vessel; the tapetal reflection was a very bright, light green, and the fundus texture was crystalline rather than granular with very few stellulae of Winslow; the non-tapetal fundus was orange brown; the lenses were clear and there was no increased ocular tension. The retina of the left eye became detached 3 months later, but the outcome could not be observed owing to the development of a posterior capsular cataract. There was no further significant change until the dog was destroyed when 4½ years old, 2 years after the development of complete blindness, by the intravitreal injection of Kolmer's cold-blood fluid under deep pentobarbital sodium anaesthesia.

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Morbid Anatomy.—The autopsy revealed no pertinent abnormalities. The eyes were normal when opened.

Histology.—The findings were indistinguishable from a case of Stage 3b of the hereditary atrophy of Red Irish Setters (Fig. 1).

FIG. 1.—Section of retina of a dog with familial generalized progressive atrophy (Case 1); equatorial tapetal fundus. The retina is reduced to a narrow sclerosed band, and the pigment epithelium has disappeared. Note the advanced atrophy of the choroid. Intravital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin ($\times 270$).

The following system of labelling the retinal structures applies to all the figures:

Sc. Sclera	3. External limiting membrane
Ch. Choroid	4. Outer nuclear layer
Tap. Tapetum	5. Outer fibre layer
C.C. Chorio-capillaris	6. Inner nuclear layer
Ret. Retina	7. Inner fibre layer
1. Pigment epithelium	8. Ganglion cell layer
2. Rod and cone layer	9. Optic nerve fibres
	10. Internal limiting membrane

Case 2 (DO 165).

Clinical Data.—This dog was said to have had normal day and night vision until it was 4 years old. When examined at $4\frac{1}{4}$ years old, it was completely day and night blind; the average pupil size was 13/14 mm.; there were early small focal nuclear cataracts in both lenses; the pupillary light and eye preservation reflexes were absent; the fundi were similar to Case 1 with very few blood vessels visible and the papillae were apparently completely avascular. The dog was destroyed when 5 years old, at least one year after the blindness had developed, the same method being used as in Case 1.

Morbid Anatomy.—The autopsy revealed no pertinent abnormalities and the eyes were normal when opened.

Histology.—The sections showed advanced sclerosis as in Case 1, but remains of the retina were beaded due to the complete disappearance of the retina in some areas while in others some layer organization remained.

The third dog of the same litter was examined with Case 1 when 2½ years old; at that time it had normal day and night vision although the test for night vision was carried out on a clear night with a full moon; the average pupil size was 11/14 mm.; the pupillary light reactions were fairly brisk. Over the tapetal fundus the reflection, blood vessels, and stellulae of Winslow were normal, although the texture was slightly crystalline. The non-tapetal fundus was normal, apart from an oval grey fundus defect 5×8 mm. (apparent size) immediately ventral to the papilla. At 4½ years old this dog was still said to have perfect sight; there has been no opportunity for another examination.

The general health of all three dogs was excellent and there were no signs of defects of the nervous system other than the blindness.

Test-Matings with Red Irish Setters carrying the Gene for Hereditary Generalized Progressive Retinal Atrophy.—As the clinical observations suggested that the Afghan Hounds might well be suffering from the hereditary atrophy of Red Irish Setters, several matings were carried out in the hope of determining whether or not this syndrome in Afghan Hounds was determined by a similar genetic factor. As no blind or closely related female Afghan Hounds were available, the dogs were mated with Red Irish Setter bitches whose genotypic constitution relative to the retinal atrophy was known from other studies (Parry, 1953b). The results are given in the Table. The diagnosis in the first two litters was based on clinical, electrophysiological, and pathological examinations; in the third litter on clinical and electrophysiological data only. As all the offspring were normal, we conclude that the blindness in the Afghan Hounds was not determined by the gene responsible for the progressive retinal atrophy in Red Irish setters.

Comment.—This type of progressive retinal atrophy is characterized by a familial incidence, the development of complete blindness by middle life without other signs of ill-health and a symmetrical degeneration of the retina and pigment epithelium without pigment dystrophy, which is very similar histologically in its advanced stages to the hereditary disease of Red Irish Setters.

TABLE
RESULTS OF MATING TWO AFGHAN HOUNDS WITH RED IRISH SETTER BITCHES
CARRYING THE GENE FOR GENERALIZED RETINAL ATROPHY

Sire	Dam		Offspring			
	Genotype	No.	Total	♂	♀	Affected
Afghan Dog DO 61	Carrier R.I.S.	DO 19	10	5	5	0
Afghan Dog DO 61	Affected R.I.S.	DO 6	9	5	4	0
Afghan Dog DO 165	Affected R.I.S.	DO 23	7	5	2	0

(2) IDIOPATHIC TYPE

In the one case of this type there was no evidence of glaucoma or of damage to the nervous system suggesting a prior distemper-complex infection and related animals were said to have normal vision.

Case 3 (Yellow Labrador Retriever Bitch)

Clinical Data.—This animal was aged 8 years, and weighed about 27 kg.; she was said to have gone blind suddenly 3–4 weeks previously without any other illness. Both eyes were found to be affected similarly; day vision was still present, but she was completely

night blind. The average pupil size was 8/15 mm.; the ocular tension was normal; the eye preservation reflex was absent but very slight pupillary light reflexes were still present; the lens showed some refractive errors without discrete opacities. In the fundus the retinal blood vessels were markedly reduced, only the main branches remaining; the tapetal fundus was a greenish orange with a crystalline texture. The blood vessels of the papilla, which was a pale beige colour, were reduced to $\frac{1}{3}$ to $\frac{1}{4}$ of their normal size. Both eyes were affected similarly.

A year later the dog was almost completely day blind; the average pupil size was 10/15 mm.; the pupillary light reflexes were absent on the left and only just present on the right; there were early nuclear cataracts in both lenses. A year later, when at the age of 10 years the dog was destroyed, the same method being used as in Case 1, the nuclear cataracts were slightly denser and there were signs of an iridocyclitis with adhesions of the iris to the lens capsule in the right eye, which had not been observed previously.

It was not possible to trace the litter mates of this bitch but they were said to have shown no signs of defective vision during their working life as gun-dogs. A daughter, examined at 2 and 3 years old, was normal, and no signs of defective vision in her litter mates had been reported to the breeder.

Morbid Anatomy.—When the right eye was opened the lens capsule was found to be adherent to the vitreous humour, which was more opaque than usual and adherent to

FIG. 2.—Section of retina of dog with idiopathic generalized progressive atrophy (Case 3); peripapillary tapetal fundus. The pigment epithelium, rod and cone layers, and outer nuclear layers have disintegrated. The inner nuclear, inner fibre, and optic nerve fibre layers are relatively intact, but the nuclei of Muller's cells are prominent. The large ganglion cells are still present, although they are degenerating, and many "ghost" forms can be seen. Note the rounded, deeply-pigmented cells in the choroid. Intravital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin. ($\times 270$).

the retina. The left eye was similar, but the abnormalities were less marked. The optic nerves and brain showed no macroscopic lesions. There were no significant lesions in the other organs.

Histology.—The retina was similar in both eyes and showed advanced degeneration and sclerosis over both non-tapetal and tapetal portions of the fundus, the central tapetal fundus alone retaining signs of the layer organization.

Over the whole fundus the rods and cones had disappeared. The pigment epithelium and chorio-capillaris were greatly reduced or missing, so that the external limiting membrane was adjacent to the choroid over most of the fundus, although in a few places next to large trans-tapetal capillaries there were foci 20–40 μ long, in which pigment epithelial cells remained alongside enlarged capillaries of the chorio-capillaris; these cells contained round brown pigment granules mostly unstained by azo-carmin. The remaining inner retinal layers were reduced to about 60 μ thick over the non-tapetal fundus, with complete loss of the layer organization and reduction of nuclei to a few lying in a sclerosed matrix with occasional large round pigment cells of choroidal type. The sclerosis was not quite as advanced over the peripheral tapetal fundus, the retina being about 100 μ wide. However, in the central tapetal fundus, the layers were still present (Fig. 2). Here in the peripapillary zone the outer nuclear layer was reduced to a single interrupted layer of nuclei, but the inner nuclear layer, ganglion cells, and optic nerve fibres were still present, although degenerate. In the mid-tapetal fundus the inner nuclear layer was reduced to 2–3 nuclei thick, only an occasional ganglion cell remained, and the nerve fibre layer had almost disappeared.

The larger retinal blood vessels were still present but buried deeply and with very marked thickening of their walls (Fig. 3); at one point a large vessel had anastomosed with the

FIG. 3.—Same preparation as Fig. 2; mid-tapetal fundus. Note the two small blood vessels with severely fibrosed walls lying in the sclerosed remains of the retina. Azo-carmin. ($\times 870$).

chorio-capillaris. The tapetum was not markedly abnormal apart from the walls of the trans-tapetal capillaries which were thickened. The choroid was much reduced, being only about 100 μ wide, and the media of the larger arteries near the papilla showed a marked regular thickening due to swelling of the cells (Fig. 4). The normally elongated choroidal pigmented cells had become rounded and in a few places some of these cells were lying against or just within the outer margin of the retina over the non-tapetal fundus. The optic papilla was vacuolated with fragmented nerve fibres, and the adjacent orbital optic nerve showed advanced degeneration.

FIG. 4.—Section of choroid from the case illustrated in Figs 2 and 3; peripapillary tapetal fundus. Note the wall of an artery (Art.) showing great thickening due to cellular proliferation. Azo-carmin. ($\times 870$).

Comment.—In this idiopathic type of generalized progressive atrophy, which appears late in life, the degeneration affects the pigment epithelium and the outer layers of the retina before the inner, and is least advanced over the peripapillary tapetal fundus, the peripheral fundus being much more severely affected. There are severe degenerative changes in the walls of the retinal and choroidal blood vessels.

Discussion

Although the data available regarding these two types of generalized progressive retinal atrophy are insufficient to establish their aetiology and the stages of their development, these cases are important as illustrations of syndromes which may be confused with the hereditary condition and must be excluded when diagnosing the latter.

The familial type in Afghan Hounds is of particular interest in this connection, for the disease appeared to be very similar to that of Red Irish Setters, even to the late development of cataracts, the only suspicious gaps in the clinical history being the absence of evidence of night blindness in infancy and adolescence and the relatively late onset of day blindness. The matings with Red Irish Setters showed conclusively that the Afghans were not carrying the gene for the Irish Setter disease in a homozygous form and probably not at all, and that, therefore, they were not suffering from the same hereditary syndrome. We cannot rule out the possibility of another form of inherited retinal atrophy controlled by genes different from that responsible for the disease in Red Irish Setters. However, more evidence will be required before such an assumption is justified. In the meantime we may exclude certain syndromes of retinal degeneration of which these two cases might be considered to be a late stage, namely post-distemper retinopathy and central progressive atrophy (Parry, 1954b), by the absence of pigment epithelial cell dystrophy, and we may exclude the atrophy secondary to glaucoma by the absence of clinical evidence of glaucoma and the symmetrical distribution of the degeneration.

The detachment of the retina observed in one case is an uncommon event in the dog and we have not seen it in any cases of the hereditary syndrome.

In the single case of the idiopathic type the well-marked degenerative changes in the walls of the retinal and choroidal blood vessels are similar to those seen in distemper and post-glaucomatous retinopathies, but the absence of pigment epithelial dystrophy and the relative sparing of the ganglion cells make previous distemper-complex infection and glaucoma unlikely causes of the degeneration. However, the varying severity of the lesions in different parts of the fundus, with the peripapillary tapetal fundus least affected, and the greater damage to the first-order neurones and optic nerve fibres, is similar to that seen in the distemper retinopathies. This distribution and sequence of the degeneration, together with the lesions in the blood vessel walls, suggest that some vascular disturbance or blood-borne noxia may have been responsible for the retinal damage. Their nature must remain a matter for conjecture since vascular sclerosis with hypertension is uncommon in dogs; the clinical and pathological findings in this case are not, apart from the sclerosis of the choroidal and retinal blood vessels, strikingly similar to the hypertensive retinopathy produced by Keyes and Goldblatt (1937, 1938) in their experimental studies of benign and malignant hypertension in the dog.

The iridocyclitis and cataracts appeared when the retinal degeneration was advanced and are probably secondary manifestations.

Until more information is available regarding the aetiology and early development of these types of progressive atrophy, their position in any general classification of the degenerations of the dog retina must remain tentative.

Summary

(1) Three cases are described of generalized progressive atrophy of uncertain aetiology of the dog retina.

(2) Two types of the syndrome are recognized, familial and idiopathic.

(3) The familial syndrome is very similar to the hereditary atrophy but its onset occurred later in life and the disease was not reproduced by test-matings with Red Irish Setters affected with the hereditary disease.

(4) In the idiopathic type the atrophy is unsymmetrical, being least severe over the peripapillary tapetal fundus. The distribution and sequence of the retinal changes, together with the presence of degenerative changes in the walls of the retinal and choroidal blood vessels, suggest a vascular origin.

(5) Cataractous changes in the lens were present in the late stages of both types. No other symptom of ill-health was noted.

(6) Possible causes of these syndromes and their relation to other retinal degenerations in the dog are discussed briefly.

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