

DEGENERATIONS OF THE DOG RETINA*

II. GENERALIZED PROGRESSIVE ATROPHY OF HEREDITARY ORIGIN

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A SPONTANEOUS degeneration of the retina of the dog, due to a generalized progressive atrophy of the neuroepithelium and called "night blindness" or retinitis pigmentosa of dogs has been known for nearly half a century, since Magnusson's recognition of the syndrome in Gordon Setters in Sweden about 1905 (Magnusson, 1909, 1911, 1917); he considered the condition to be similar to retinitis pigmentosa in man. More recently a somewhat similar syndrome has been reported in Red Irish Setters in England (Hodgman and others, 1949; Parry, 1951). These workers described in detail the clinical stages of the syndrome and presented evidence indicating that the disease was inherited as if determined principally by a recessive autosomal Mendelian factor.

The present paper presents data obtained in a series of matings under controlled conditions designed to establish whether or not the syndrome is hereditary, to provide material for detailed histological and electrophysiological studies, and to establish the relationship of the canine syndrome to human retinitis pigmentosa.

Materials and Methods

The retina of the normal dog, the details of the management of the dogs, and the methods and terminology used, were described in the first paper of this series (Parry, 1953a).

The dogs were pedigree Red Irish Setters. About 120 dogs were used, including 93 in sixteen litters born and reared in isolated premises at the Research Station, of which 58 were affected with the degeneration and 35 unaffected.

The condition of the eyes was established by clinical ophthalmoscopy, vision tests, and pathological examinations of animals at varying stages of the disease. The objective test for the disease described by Parry, Tansley, and Thomson (1951; 1953), namely inability to detect the electroretinogram, was used on thirty dogs.

All the matings were carried out in our isolation kennels by an experienced kennelman to reduce to a minimum the chance of promiscuity.

All the animals were known to be "affected" (with defects of vision and carrying the recessive gene in a homozygous state), "carriers" (with normal vision but carrying the recessive gene in a heterozygous form), or "clear" (with normal vision and not carrying the recessive gene), according to the criteria previously given (Parry, 1951). By mating "carrier" and "affected" parents, mixed litters of affected and unaffected pups were produced, the unaffected pups serving as controls for management and other factors which might give rise to acquired forms of retinal degeneration.

Special care was taken to exclude other forms of blindness known to occur in dogs, so far as present knowledge permits. Apart from the retinal defect and the absence of an electroretinogram, the criteria of normality were similar to those described previously

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(Parry, 1953a). In addition, disease of the optic pathways and visual cortex was excluded by clinical and pathological examinations, and particular care was taken to ensure that the other types of retinal degeneration (to be described in later papers of this series, Parry, 1953b etc.), some of which have been found in Red Irish Setters, were not present. All the dogs mated in a "test-mating" (Hodgman and others, 1949) produced affected and unaffected offspring in the numbers one would expect if they were suffering from the simple hereditary disease only.

Results

(1) CHANGES IN THE EYE

The disease can be considered conveniently in the three stages (Hodgman and others, 1949) in which vision progressively disappeared. During Stage 1 night vision was gradually lost but day vision remained normal. During Stage 2 the dog was completely blind at night and gradually lost its powers of day vision. In Stage 3 the dog was completely day and night blind and cataract often developed. All dogs showed a similar stage of the disease in both eyes and all parts of the fundus were affected to a similar extent. The progress of the disease is summarized in Table I.

TABLE I
SIGNS AND LESIONS OF THE THREE STAGES OF THE HEREDITARY

Stage	Age	Vision Defects		Ophthalmoscopy	Pupil		
		Night	Day		Average Size (mm.)	Light Reflexes	
1	<i>a</i>	3-6 wks	?	0/5	Media not yet clear	4/10	++
	<i>b</i>	2-6 mths	2-4/5	0/5	Swirling of supra-tapetal retina, tapetum shows increased reflectivity and crystalline texture	5-7/12	++
2	<i>a</i>	3-18 mths	5/5	1-2/5	As Stage 1 <i>b</i> with loss of secondary retinal blood vessels Optic papillae still normal Non-tapetal fundus pavement grey	6-8/14	++
	<i>b</i>	5-24 mths	5/5	3-4/5	Changes more marked and optic papilla pale owing to loss of secondary arterioles	8-12/14	+
3	<i>a</i>	6 mths to 3 yrs	5/5	5/5	Only three main blood vessel groups and chief collaterals remain Tapetal reflectivity greatly increased	12/14	0
	<i>b</i>	1-4 yrs	5/5	5/5	Little change Pigment of non-tapetal fundus may become patchy	12/14	0

Stage 1.—This stage falls into two parts:

- (a) before the development of normal powers of vision at about 6 weeks of age (105 days post-conception) when the retinal degeneration can only be detected by electroretinography or histology,
- (b) after the age of 6 weeks when clinical methods can also be employed.

Stage 1a.—The post-natal differentiation of the retina proceeded as in normal eyes. Eyes of known affected pups could not be recognized as abnormal earlier than about the 78–80th day post-conception (15th to 20th day after birth), when a small number of pyknotic nuclei, with rounded densely-staining chromatin, appeared in the outer nuclear layer, five to ten in each field of about 5,000 nuclei (incidence of 0.1–0.2 per cent.). These pyknotic nuclei showed up well in Feulgen and azan stained preparations. By the 80–85th day post-conception the outer limbs failed to develop their regular palisade arrangement, and the number of pyknotic nuclei rose to 20–25 per field (0.4–0.5 per cent.). These pyknotic nuclei disintegrated completely and were resorbed without the appearance of inflammatory or phagocytic cells. At the same time the contiguous nuclei moved together and took up the space previously occupied by the lysed nucleus, thereby causing a gradual reduction in the width of the outer nuclear layer and the number of nuclei in each radial palisade. By about the 90th day post-conception (4 weeks after birth), the outer

GENERALIZED PROGRESSIVE RETINAL ATROPHY IN RED IRISH SETTERS

Electro- retinogram	Histology	Figure	Approx. Widths of Retina in μ , area centralis 5 mm. from Optic Papilla		
			Total	ONL	RCL
Absent after 30 days old	A few pyknotic rod nuclei in the outer nuclear layer with some loss of substance in the outer limbs	—	200– 220	50	12–15
Absent	Reduction of outer nuclear layer to 2–3 nuclei, loss of all outer limbs and of rod inner limbs, those of the cones being shortened	—	120– 130	17– 19	12–15
Absent	No rods or rod nuclei remain; outer nuclear layer reduced to cone nuclei 1–2 thick; inner nuclear layer and ganglion cells unaffected; cone inner limbs gradually lost	1	100– 120	12– 15	5–6
Absent	A few cone inner limb segments remain but these disappear and the external limiting membrane becomes adjacent to the pigment epithelium	2	120– 130	10– 12	3–4
Absent	Layer organization of retina retained in parts, where loss of inner limbs retarded; inner limbs absent in foci, but cone nuclei remain as distinct layer; inner nuclear layer little affected, apart from some increase of cytoplasmic bodies of Müller's cells; ganglion cells still normal	3, 4	80– 120	7–8	—
Absent	Loss of layer organization; marked reduction in width of retina; retina sclerosed with gliosis and remnants of nuclear layers; very occasional pigment cells; loss of pigment epithelium	5	30– 80	—	—

nuclear layer was reduced to seven to eight nuclei, the outer limbs were more fragile than usual, and the electroretinogram was not detected. Thus by the 6th week of life, when ophthalmoscopic and visual tests could be applied, the atrophy of the rods and their nuclei was already advanced.

Stage 1b.—Progressive loss of night vision occurred. At 6 weeks of age, on a night with a moon or much star-shine, affected dogs could still find their way about, but when 3 to 4 months old they lost all powers of night vision even at dusk. Day vision, the eye preservation, and pupillary light reflexes were normal, but the average pupil size increased slightly from 5 to 7/12 mm. as night vision deteriorated.

In the fundus there was some loss of the granular "beading" of the tapetum, the reflection from which was increased, usually with an augmented green component in the colour of the reflection. The supra-tapetal tissues showed a disturbance of refraction called "swirling", *i.e.* on examining the fundus by direct retinoscopy, the supra-tapetal tissues were fully transparent but there was a ripple-like distortion of the tapetum not unlike that produced on the surface of a quiet pond by the dropping of a small pebble.

In histological preparations the retina was markedly reduced in width, chiefly because of the progressive loss of rod nuclei. At the end of this stage the outer nuclear layer consisted of a layer of cone nuclei two to three deep, with an occasional rod nucleus. Coinciding with the reduction of the outer nuclear layer, the rods and cones were progressively reduced in width, the loss of the outer limbs being followed by that of the inner limbs of the rods, until only the inner limbs of the cones foreshortened to 1/3 of their normal size remained.

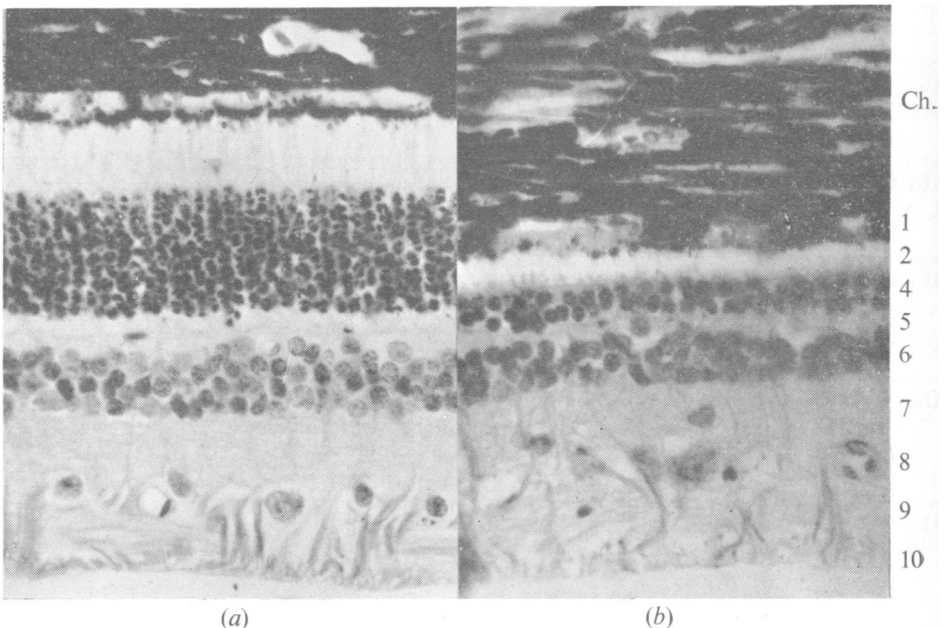


FIG. 1.—Sections through retinae of two 3½-months-old dogs, litter-mates: (a) normal, (b) showing Stage 2a of the atrophy; non-tapetal fundus. Note the great reduction of the outer nuclear and bacillary layers in the affected pup without changes in the inner layers of the retina. There is almost complete loss of rod nuclei, leaving only cone nuclei in the outer nuclear layer. The bacillary layer is reduced to the ragged remnants of a few cone inner limbs. Intra-vital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin (x 270).

Stage 2.—The dogs were completely night blind, but they retained some powers of day vision for periods of from 3 to 18 months, during which time the average pupil size increased gradually from 6 to 10/14 mm., but the pupillary light reactions though sluggish were not lost until day vision was also lost. There was a progressive loss of the stellulae of Winslow, the swirling of the supra-tapetal tissues became more marked, and the texture of the fundus lost its granular beading and became crystalline, *i.e.* it appeared to be composed of large rectangular crystals.

There was some general loss of secondary blood vessels of the fundus. At the same time the non-tapetal fundus became greyer and its blood vessels lost their "silver-wiring" reflection. The pupilla also became much paler and the secondary blood vessels disappeared. During the early part (Stage 2*a*) the changes of fundal texture occurred with only slight loss of blood vessels or deterioration of the pupil's response to light, but during the later part (Stage 2*b*) the loss of blood vessels was marked and the response of the pupil to light deteriorated rapidly.

Histologically, Stage 2 was characterized by the final disintegration of the cones, although the cone nuclei and the general organization of the retina remained. During Stage 2*a*, the stubby remnants of the cones (Fig. 1) gradually disappeared until in Stage 2*b* the external limiting membrane came to lie against the pigment

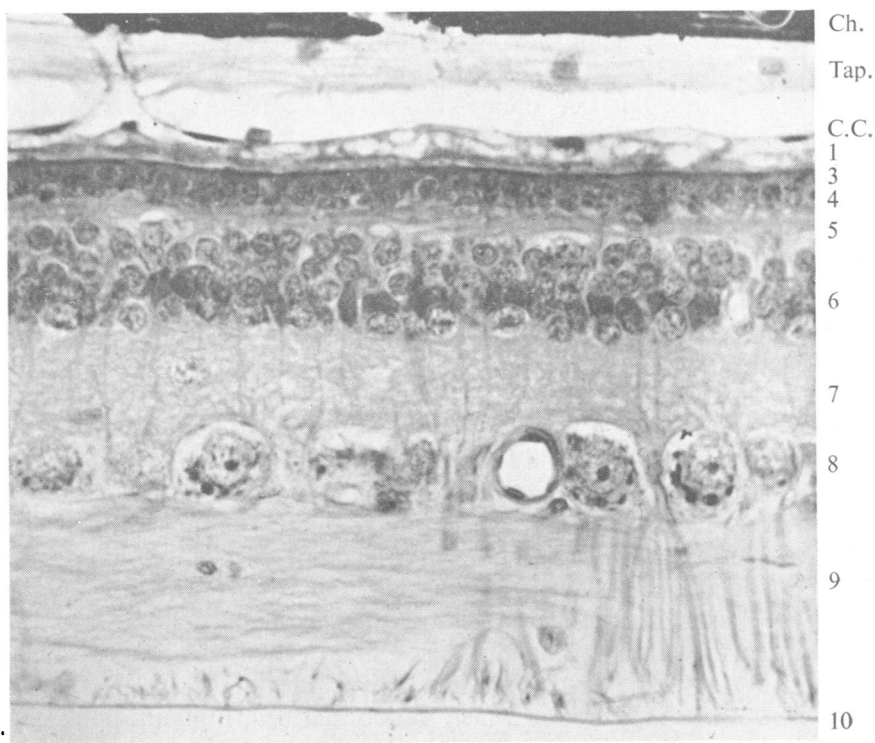


FIG. 2.—Section through retina of 6-months-old dog affected with Stage 2*b* of the atrophy; periphery of tapetal fundus. Note the complete loss of rod nuclei. The remnants of the cones form a thin layer between the atrophic pigment epithelium and the thickened external limiting membrane. The inner layers of the retina still remain normal, but the nuclei of Müller's cells stain more deeply. Note the trans-tapetal capillary, chorio-capillaris, and retinal blood vessels, which remain normal. (This dog still had pupillary light reactions and some day vision, defect about 3/5.) Intra-vital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin (x 450).

epithelium, the cells of which were flattened and losing their pigment (Fig. 2). The outer nuclear layer consisted of cone nuclei only and the outer fibre layer was much thinner. Müller's cells were more conspicuous and their nuclei stained more deeply, but the inner nuclear layer and the layers within were otherwise apparently normal. It appeared that the loss of the rods from the bacillary layer caused a gradual disintegration of the cones without loss of their nuclei. The density of the cones and of their nuclei varied slightly in different dogs but was remarkably regular in any one retina.

Stage 3.—This stage began with the complete loss of day vision and the pupillary light and eye preservation reflexes. Dogs usually showed considerable apprehension when this occurred but most of them adjusted themselves to the loss of visual perception within a week or so. An occasional dog remained very apprehensive and timid indefinitely, but most dogs moved about freely in their usual surroundings and were not molested by their normal kennel companions.

For the first few months (Stage 3*a*) the fundus remained little changed except that only the main blood vessels and their larger collaterals were visible. However, the previous location of the branches could be seen as white "ghosts", particularly in the non-tapetal fundus. The papilla was almost white, its blood vessels reduced to the three main arteries and veins, and its margin ragged and indistinct; its surface flat, level with the surrounding fundus and without any cupping. The reflectivity of the tapetum was very marked and associated with a very striking crystalline texture, but the fundus showed a distortion of the ophthalmoscope light at the periphery of the beam where the normally transparent vitreous chamber was now a cloudy white, presumably because of scattering of the light rays by the vitreous and/or at the surface of the retina. The non-tapetal fundus showed a deeper grey appearance, but in portions of the more ventral quadrants this was missing and areas of darker brown pigmentation were visible, although these appeared to be no more than the normal choroidal pigment free of the grey "overwash".

During the later stages (3*b*), the examination of the fundus was usually hampered by the development of cataracts, but in three animals affected with this stage for 2 years or more spontaneous luxation of one or both lenses occurred and thus permitted examination of the fundus. In these animals the blood vessels had almost disappeared, only short portions of the main groups being visible. The disc was very ragged and of a grey-white colour. The tapetum was less highly reflective, but remained a continuous sheet without signs of unusual pigmentation. The non-tapetal fundus showed greater unevenness of pigmentation and the darker areas were more numerous. In one dog choroidal pigmentation was so markedly reduced that the choroidal blood vessels could be seen lying in the middle of five or six light beige-coloured streaks about 8 mm. wide (after magnification) radiating fanwise from the papilla from which the normal brown pigment was completely missing. These streaks had not been visible in this dog 3 years previously before the cataracts developed.

For the first few months after complete loss of day vision (Stage 3*a*) the layers of the retina could still be distinguished in sections, although the outer nuclear layer was reduced to an interrupted layer of cone nuclei, one to two thick; these were round but their chromatin was lobulated more like that of the rod nuclei; they still retained a positive Feulgen reaction and stained bright red with the azan

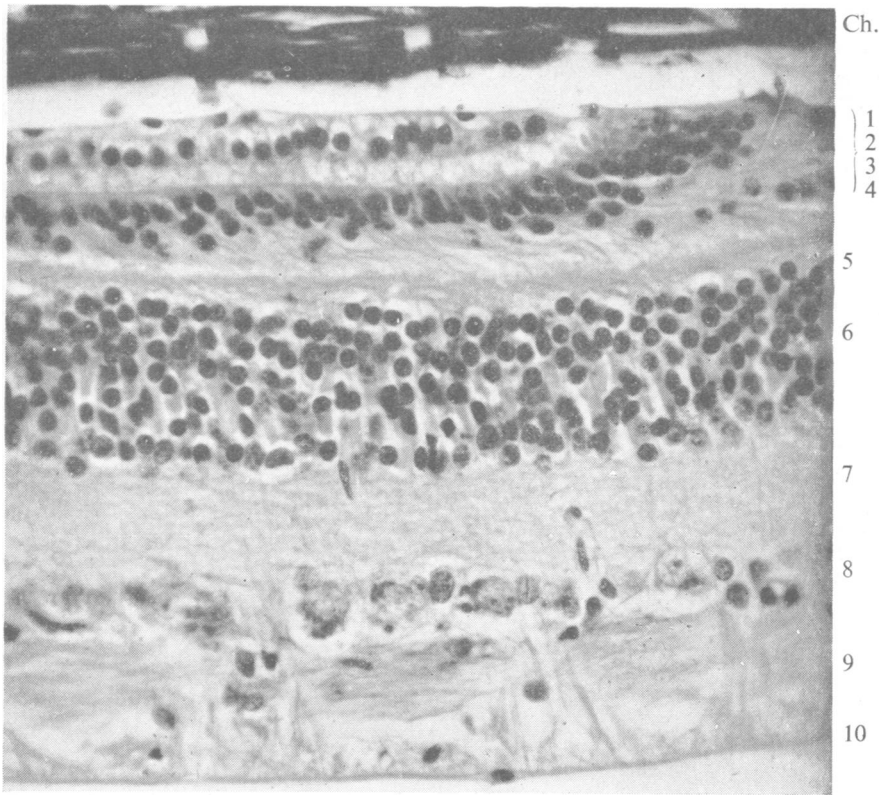


FIG. 3.—Section through retina of 4-year-old dog, which had gone completely day-blind 4 months previously, showing Stage 3a of the atrophy; non-tapetal fundus. The normal layers are still present on the left, but the pigment epithelium, bacillary, and outer nuclear layers have disappeared on the right. The nuclei of the inner nuclear layer show pyknotic change and their cytoplasmic processes are more conspicuous. The ganglion cells are losing their Nissl's substance. The fibre layers are but little affected. Intra-vital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin (x 350).

method, and this served to distinguish them from nuclei of the inner nuclear layer which still appeared normal (Fig. 3). The rods and cones had disappeared, although occasionally there remained small pockets up to 50μ long of the inner limb segments of the cones. The inner nuclear layer was almost normal, except that the fibres of Müller's cells were more prominent and their nuclei stained very darkly with basic dyes. The ganglion cells were remarkably little affected, although their Nissl's granules appeared to be disintegrating slightly. The pigment epithelium cells were little changed in shape, although they were entirely devoid of pigment, even over the non-tapetal fundus; no pigment accumulations were noted in the retina itself. The chorio-capillaris was very much reduced, many of the tapetal cells had lost their nuclei and their cell outline, and the trans-tapetal capillaries were reduced in number. Many retinal blood vessels were still present but more deeply buried in the substance of the retina; occasionally capillaries passed through the outer nuclear layer from the retinal circulation to join the choroidal (Fig. 4, overleaf). In Stage 3b these changes proceeded to definite sclerosis; the remaining cone nuclei were interspersed with the remnants of the outer nuclear layer to form an irregular single nuclear layer about three to four

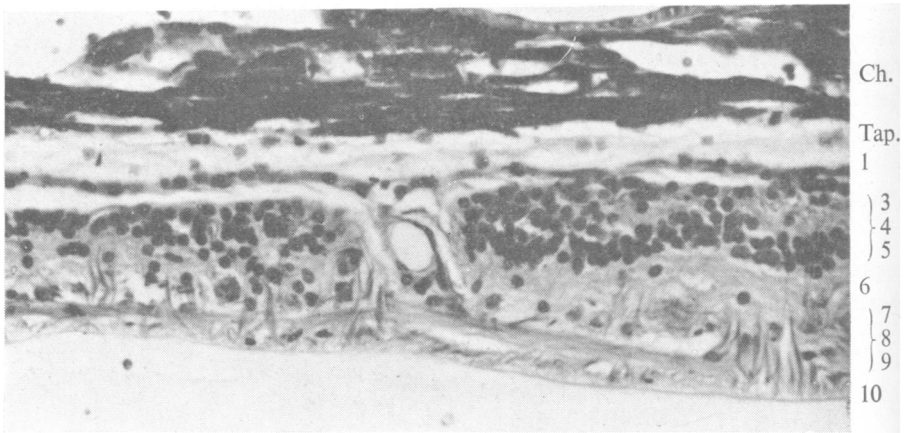


FIG. 4.—Another part of same section as that seen in Fig. 3, showing a focus of more advanced degeneration with loss of layer organization; tapetal fundus. The nuclear layers are disintegrated, but remnants of the pigment epithelium and optic nerve fibres remain. Note the blood vessel joining the retinal and choroidal circulations (x 240).

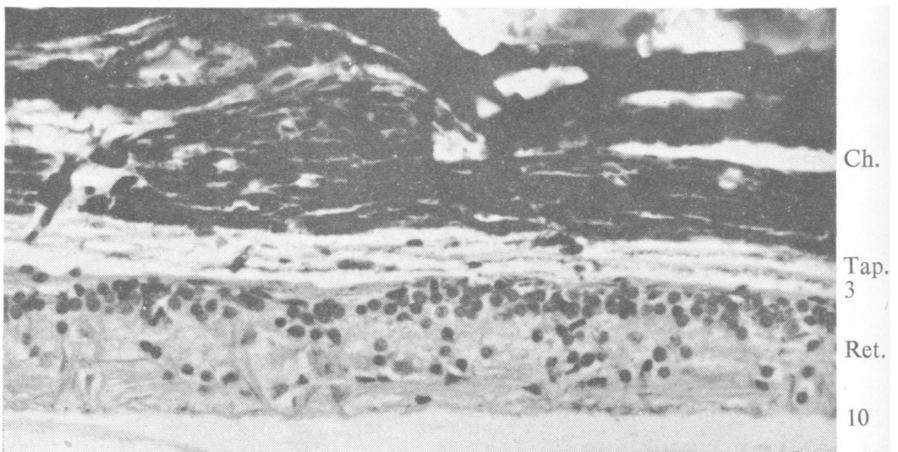


FIG. 5.—Section through retina of 6-year-old dog which had been completely blind for 4 years, showing Stage 3*b* of the hereditary atrophy; non-tapetal fundus. The layer organization is completely lost, most of the nuclei have disappeared, and the pigment epithelium is missing, so that the remains of the retina are in direct contact with the tapetum. Note the absence of pigment cells in the sclerosed retina. Intra-vital fixation with Kolmer's cold-blooded fluid. Heidenhain's iron haematoxylin (x 240).

nuclei thick in a matrix of glial fibres, the whole retina being reduced to 15–20 μ thick (Fig. 5). The cone nuclei stained brown with azan like those of the inner nuclear layer, except that their nucleoli still stained bright red. The walls of the retinal arterioles were much thickened, but the larger vessels were still present in their usual frequency, although buried in the substance of the retina. This would account for the apparent loss of the secondary retinal vessels on ophthalmoscopic examination. In places, the nuclear layers were interrupted by glial fibres running from the inner to the outer surface of the retina. Very occasionally an odd round pigmented cell was found, but these were usually single

and not disposed near any blood vessels. As the pigment epithelial layer had atrophied completely, these pigmented cells had probably arisen from choroidal pigment cells which had lost their elongated form and become round. The pigment in the choroid became aggregated into larger masses and the cells became more rounded. In cases totally blind for 2 to 3 years there was definite thinning of the choroid to half its normal thickness or less with reduction of its blood vessels, but the sclera remained little affected.

(2) RATE OF DEVELOPMENT OF THE DISEASE

The earliest signs were always detectable by ophthalmoscopic examination and by night vision tests when the dog was 6–8 weeks old. Thereafter the rate at which the fundus changes and the visual defects progressed varied somewhat. In one family strain, all affected dogs lost all powers of night vision by 3 months of age and were completely day blind by 6–8 months. In another family, night vision was not lost until 6–9 months of age and some day vision remained until they were over 3 years old. When an animal of the first strain was mated to one from the second, the syndrome tended to develop rapidly in their offspring. We have not seen any case of spontaneous arrest or remission of the disease.

(3) ASSOCIATED DEFECTS

The outstanding defect associated with the retinal disorder was cataract. During the late stages of the disease the majority of affected dogs over about 2 years of age developed complete bilateral nuclear cataracts. Small subcapsular cataritic foci 1–2 mm. in diameter were first detected in some dogs at 8–9 months old; these foci enlarged and gradually became denser until the lens was completely opaque. Of eight animals which lived more than 2 years, seven developed bilateral cataracts. In the older animals these tended to become luxated, particularly in active dogs which were not afraid to move about and were hence more liable to damage their eyes.

One dog only showed bilateral myopia, a +8 D. lens in the ophthalmoscope being necessary to bring the fundus into focus.

The oestrous cycle and breeding performance of affected bitches showed no disturbances which could in any way be attributed to the retinal degeneration. Five bitches totally blind for 2 to 4 years continued to come into season and breed regularly. Male dogs also maintained their breeding performance, one during 4 years of complete blindness; however, one which became extremely apprehensive with the onset of blindness and did not adjust itself to the complete loss of vision, became of little use as a stud dog owing to this nervousness, although a litter brother was used at stud for 2 years after complete loss of vision.

The growth and general behaviour of the affected animals were normal; some would have been potential show winners. No other neurological defects were noted, but some dogs were probably of subnormal general intelligence; some strains of Red Irish Setters known to carry the gene appeared to be less intelligent than strains not carrying the gene, and these strains were less readily trained as gun-dogs.

Should any other defects of the nervous system be closely associated with the gene, they would have been likely to appear in these dogs as 4 of the 16 litters were the result of litter brother-litter sister matings.

(4) INHERITANCE OF THE SYNDROME

Four affected dogs, four affected bitches, three "carrier" bitches, and three "carrier" dogs, known to be homozygous and heterozygous respectively with regard to the gene, and one "clear" dog were used for the matings reported in this paper.

Sixteen litters were born and 58 pups affected with the syndrome were reared to an age when a certain diagnosis could be made on the basis of clinical, microscopic and/or electroretinographic data; in nearly every case the clinical and electroretinographic diagnosis was supplemented by histological study.

The results of these controlled matings are shown in Table II. It will be seen that the mating of two affected parents always produced all affected offspring with approximately equal numbers of males and females. The mating of a "carrier" with an affected animal produced mixed litters of affected and unaffected animals in approximately equal numbers and equally divided between the sexes. The mating of an animal not carrying the gene with an affected animal produced no affected offspring.

TABLE II
INCIDENCE OF AFFECTED AND UNAFFECTED PUPS BORN OF
DOGS CARRYING THE GENE FOR HEREDITARY RETINAL ATROPHY

Type of Mating		Litters	Offspring						Ratio of Affected to Unaffected
			Affected			Unaffected			
Male	Female		Total	Male	Female	Total	Male	Female	
Affected	Affected	6	36	16	20	0	0	0	} 36 : 0 22 : 29 0 : 6
Affected	Carrier	5	10	9	1	23	13	10	
Carrier	Affected	4	12	3	9	6	2	4	
Clear	Affected	1	0	0	0	6	1	5	
Totals	16	58	28	30	35	16	19	

These data confirm the view based on field observations and expressed previously (Hodgman and others, 1949) that the syndrome is a hereditary one and that it is inherited principally as an autosomal recessive Mendelian factor. The data provide no grounds for assuming any coupling or repulsion of the factor to either sex chromosome, nor of modifying genes of any practical importance.

In the fifty dogs which came to autopsy, the optic nerves and brain were examined carefully for signs of macroscopic abnormalities. None was found. Detailed studies of the centripetal degeneration which might be expected to follow loss of the retinal ganglion cells in Stage 3 of the disease were not attempted.

Discussion

The retinal degeneration observed in these Red Irish Setters is very similar to that described by Bourne, Campbell, and Tansley (1938) in the rat, and by Tansley (1951) in the mouse, the chief difference being the more rapid progress of the disease in those species. Study of the degeneration in the dog has, however, enabled us to extend our fundamental knowledge of the disorder by correlating the results of retinoscopic examinations and vision tests with histological data, and by applying an objective measure of function in the form of the electroretinogram, techniques which are difficult to apply in the young rat and mouse.

The use of these techniques and the rather slower rate of development of the degeneration in the dog has allowed us to establish that the retina does become functionally mature, as judged by the electrophysiological evidence of an immature electroretinogram (Parry, Tansley, and Thomson, 1951), and by the histological evidence of morphology and adult staining reactions *before* the degeneration commences. The rods and cones (morphologically immature though they still appear to be) are capable of functioning as receptors by about the 80th day post-conception as judged by the presence of an electroretinogram; however, usually within 2 or 3 days, a spontaneous degeneration sets in coinciding with inability to detect the electroretinogram and the presence of degenerative changes in histological preparations.

The degeneration begins as an atrophy of the rods and their nuclei, which is seen at first mostly clearly in the outer bacillary layer. The rod nuclei undergo pyknotic condensation and liquefaction *in situ*, for no signs of phagocytic or inflammatory cells were observed. During the first stage, when the rod cells are being lost, night vision is present, but deteriorates progressively; it is of interest that during this period, when some powers of night vision remained, the electroretinogram was not detectable.

The complete loss of the rods only, while leaving the other retinal structures intact, produces a pure cone retina with which the dog although completely night-blind is able to see quite well by day. This cone retina produces no detectable electroretinogram under our conditions. The cones survive functionally for some 3 to 18 months, although they now consist of stubby foreshortened inner limbs only; they then disintegrate with the apposition of the external limiting membrane to the pigment epithelium. The cone nuclei, the inner nuclear layer, and the ganglion cells survive for several years after the retina has ceased to function as a visual organ, and small pockets of morphologically intact cones may persist, but a gradual loss of nuclei and disintegration of retinal layers occurs with some increase of glial nuclei until a state of generalized sclerosis supervenes. During its early stages the sclerosis is often uneven, there being foci of advanced sclerosis with thinning of the retina and gliosis surrounded by retina still showing organization in layers, but in Stage 3*b* these foci of advanced sclerosis enlarge until they cover the whole retina. At the same time the pigment epithelium, having lost its

pigment in the earlier stages, undergoes complete dissolution, until the sclerosed remains of the retina are contiguous with the choroid. Thus the degeneration leads finally to the atrophy of all structures derived from the ectoderm of both surfaces of the primitive optic vesicle.

The choroid only shows changes in the late third stage, when it becomes less wide, its blood sinuses become fewer and smaller, and its pigment granules become larger, more rounded, and often much fewer. The tapetum never loses its continuous identity, although its cells become swollen and lose their parallel arrangement, to which the change in colour and in the intensity of its reflection noted clinically may be in part attributed, although the loss of visual purple may also play a part. The gradual reduction of the trans-tapetal capillaries noted in sections corresponds with the loss of the stellulae of Winslow observed clinically. The reduction in the retinal blood vessels always follows and never precedes the signs of degeneration of the neuroepithelium. The clinical observation that these vessels appear to become buried as if in cotton-wool, and that, when no longer visible, the previous course of the larger branches can still be determined by lighter "ghosts", is explained by the gliosis, for in sections the larger vessels are found buried well below the surface of the retina by the glial overgrowth, and it is only in Stage 3 that an obvious reduction in the vascularity of the retina is apparent microscopically. The iris and sclera show very little change.

The occurrence of cataract in the late stages of the disease is almost certainly a late secondary effect following the primary retinal disorder, and there seems no reason to assume that the metabolism of the lens is affected directly.

These macroscopic and microscopic changes in affected eyes are remarkably specific during the first two stages of the disease. We have not seen precisely similar changes in any other syndrome. The microscopic changes always coincided very closely with the clinical signs and their temporal development; they could be readily distinguished from *post-mortem* and other artefacts, such as local nuclear pyknosis thought to be due to faulty fixation, and from those seen in other retinal degenerations of the dog (Parry, 1953b). However, during Stage 3 it becomes increasingly difficult to distinguish the signs and lesions of the hereditary disease from those seen in other degenerations, and it is probable that the final stage of most degenerations is similar, namely, one of generalized sclerosis. Thus, unless data is available regarding the early stages of a retinal degeneration in the dog, it is very difficult to establish an aetiological diagnosis by histological examination of the advanced stage alone.

The data from these matings under controlled conditions establish conclusively that the aetiology of the disease is hereditary. The experimental conditions have eliminated, as far as present knowledge allows, acquired forms of blindness due to nutritional or infectious agents (Parry, 1953a). Indeed, the rearing of pups of mixed litters of affected and unaffected animals

under identical standard conditions for all the pups makes it difficult to see how any environmental factor could be involved. The elimination of acquired forms of blindness is most important, because we have seen cases which, on the clinical evidence available, might be confused with the hereditary disease but which by controlled matings were shown not to be suffering from the hereditary atrophy here described (Parry, 1953b). The data confirm that the syndrome is inherited as a simple recessive Mendelian factor, affecting both sexes in equal numbers, and we know of no adequately documented exception to this conclusion. Whether subsidiary factors may be involved in the rather more rapid loss of vision in certain families is at present uncertain. The data are not sufficiently extensive to arrive at a valid opinion, for the results of the clinical evaluation of visual defects in animals are determined so much by their intelligence and mental adaptability.

The syndromes described by Magnusson (1909, 1911, 1917) in six related Gordon Setters in Sweden, by Seiferle (1949) in one Spaniel in Switzerland, and by Yataka (1935) in Japan have been assumed to be the same disease as that in Red Irish Setters described above. However, the recognition of other degenerative diseases affecting the dog's retina (Parry, 1953b), which can now be distinguished from the hereditary disease of Red Irish Setters, makes a critical review of this assumption necessary. Thus, Magnusson's data showed a familial incidence and suggested a hereditary basis, but the microscopic findings, in two cases he examined,* are not consistent with our findings in the uncomplicated hereditary atrophy of Irish Setters. Indeed they suggest very strongly a post-infective (distemper) retinopathy (Parry, 1953b) and it is possible that he was dealing with more than one form of degeneration.

Seiferle described one case in which histologically the degeneration was at a very advanced stage, when the various syndromes are very difficult to distinguish; he also quoted unconfirmed reports that four other Spaniels related to his case were said to be night blind. In the light of recent evidence about the acquired forms of retinal degeneration, more data would be necessary before we could assume that his case was affected with the hereditary generalized atrophy and that Spaniels in Switzerland carry the gene. Indeed the evidence that the gene occurs in any breed of dog other than the Red Irish Setter is far from satisfactory.

This type of spontaneous hereditary degeneration presumably falls into the category of an hereditary abiotrophy (Treacher Collins, 1919), a classification which does not throw much light on the mode of development of the retinal defect. Two possibilities may be considered: first, failure of the blood supply to the retina and, second, an inherent metabolic defect in the first order neurones of the retina. The idea of a vascular component in retinal degenerations has received much support since the report by Wagenmann (1890) of the experimental production of such degeneration

* Thickening of the pigment epithelium, and accumulations of pigment with thinning of the choroid and unevenness of the atrophy in different parts of the fundus, the periphery being more affected than the central area.

in rabbits by occlusion of the ciliary arteries. Although Nicholls (1938) reproduced these results; he found that some two-thirds of the posterior ciliary arteries had to be tied off before degeneration occurred, and that this degeneration affected rods and cones similarly as regards rate and extent. He concluded that the necessary interference with the blood supply was so extensive that a similar interference was unlikely to be the cause of spontaneous retinal degeneration in man. Moreover, there is little evidence for a vascular origin of this generalized atrophy in the dog. Although the ciliary arteries were not dissected out, the main vessels of both the choroidal and retinal circulations showed no reduction in size and distribution until a late stage of the disease, and no stasis was detected by retinoscopy. Furthermore, the histological evidence is that atrophy of the rods precedes that of the cones and is already advanced before any reduction of the capillary network of the outer fibre layer, the chorio-capillaris, or the trans-tapetal capillaries can be detected, and no signs of occlusion of these vessels (which have always been washed free of blood cells during adequate intravital fixation) or of disease of their walls was seen. We conclude, therefore, that the retinal degeneration is not due to primary failure of the blood supply to the retina but to some metabolic defect.

We might assume that this defect involves the rod cells only, and that the loss of cones and the later disintegration of the retina merely follow on the primary loss of the rod cells. What this postulated metabolic defect may be we do not know; we can only say that it is genetically determined, does not preclude the normal development of the retina to functional maturity, begins to express itself within a very short time (probably usually 2 to 3 days or less) of the attainment of that functional maturity, and continues without remission thereafter. Although our knowledge of the metabolic architecture of the rods is scanty, vitamin A (Tansley, 1936), nicotinic acid (Wald, 1950), and possibly vitamin E (Youmans, 1950) are known to be involved. Yet in our dogs there was no sign of nutritional insufficiency of any of these substances; indeed growth, general health, and reproduction were perfectly normal. Thus, if these substances are concerned in the metabolic defect, we must assume that the retina is either unable to utilize them from the general circulation or that its cells require them in quantities or in concentrations greatly in excess of the normal.

An interesting possibility is opened up by the recent work of Noell (1952), who has produced by the intravenous administration of iodoacetate in rabbits, cats, and monkeys a type of degeneration affecting the rods first and very similar to the hereditary degeneration of rats, mice, and dogs. He considers the degeneration to be most likely due to interference with the carbohydrate metabolism of the visual receptor cells by the iodoacetate. If a similar defect were responsible for the hereditary disease, one would have to postulate that these neurones were particularly sensitive to interference with their carbohydrate metabolism, for we have no evidence that other first-order

neurones of the nervous system are abnormal in dogs affected with the retinal atrophy.

From time to time much has been made of the similarity of this syndrome in the dog to retinitis pigmentosa in man, and Magnusson (1911) called his dog disease retinitis pigmentosa; but the similarity between the two is perhaps more superficial than real. In the dog disease the pigment epithelium loses its pigment and finally atrophies and no proliferation or migration of pigment from this source has been observed, although it does occur in other syndromes of retinal degeneration in the dog (Parry, 1953b). The areas of darker pigment seen in the non-tapetal fundus during the third stage of the disease are not very similar to the star-shaped accumulations in the human disease, and are probably due to differences in the density of the overlying sclerotic retina, since in sections there are no accumulations of pigmented cells along blood vessels such as occur in the human disease. Indeed, the occasional pigmented cells found in the sclerosed dog retina are usually single and not close to the blood vessels, and probably arise from the choroid, which is now contiguous with the remains of the retina. A point of resemblance is the early loss of the electroretinogram in both diseases, for Karpe (1952) has found it absent in a one-year-old child of a family affected with retinitis pigmentosa. However, in the dog disease the degeneration is symmetrical all over the fundus and does not begin at the equator as in man. On these grounds, therefore, it seems wise not to press the analogy between human retinitis pigmentosa and canine generalized progressive retinal atrophy, and we feel it is better not to apply the term retinitis pigmentosa to the dog disease, especially as retinitis pigmentosa in man probably represents a group of degenerations of varying aetiology but with a common final expression (Leinfelder and others, 1950), just as in the dog the various degenerations give rise in their late stages to a similar form of sclerosed retina.

One final point of interest is that, compared with the ferret and some other animals (Hammond, 1951), visual impulses from the retina must play a relatively small part in determining the pattern of reproductive behaviour in the dog, since both males and females continued to breed normally for periods of 2 to 4 years after the onset of total blindness.

Summary

1. A progressive generalized atrophy of the dog's retina due to hereditary causes is described. It is bilaterally symmetrical, affects all parts of the retina to a similar extent, and progresses evenly until the retina is destroyed.
2. The degeneration begins by the spontaneous gradual disintegration of the rods and their nuclei, at or soon after attainment by the retina of functional maturity (about the 80th day post-conception, or 18–21 days after birth).

3. The clinical signs are night blindness in adolescence followed by gradual loss of day vision in early adult life.

4. The syndrome shows three stages. The first stage, coinciding with the loss of the rods and their nuclei, is one of progressive night blindness without any detectable defect of day vision; it lasts for 2–9 months. In the second stage, which lasts from 3 to 24 months, day vision is gradually completely lost, coinciding with the loss of the cones and many cone nuclei, the other layers of the retina remaining essentially normal. In the third stage the dog is completely day and night blind. The layers of the retina become disorganized and glial proliferation occurs until terminal sclerosis develops.

5. The pigment epithelial layer atrophies and only an occasional pigmented cell is seen in the sclerosed retina. No accumulation of pigment cells such as is seen in human retinitis pigmentosa was found.

6. The electroretinogram was not detected in affected dogs older than about one month (95th day post-conception).

7. Evidence is presented to show that the syndrome is inherited in a simple Mendelian recessive manner and that both sexes are affected in equal numbers. The atrophy appeared to develop rather more quickly in certain families.

8. Most animals in the late stage of the disease developed bilateral nuclear cataracts, but other defects were not observed.

9. The pathogenesis of the disease and its relation to human retinitis pigmentosa are discussed.

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