DEGENERATIONS OF THE DOG RETINA*

VII. CENTRAL NON-PROGRESSIVE DEGENERATION DUE TO AN ANOMALY OF THE GANGLION CELLS AND THEIR AXONS

BY

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PRIMARY degeneration of the ganglion cells and their axons without concurrent involvement of other retinal structures is uncommon in the dog. A centrifugal degeneration secondary to severe damage to the optic nerves following para-distemper infection occurs occasionally in adolescent and adult life (Parry, 1954a). This paper describes a syndrome in a strain of Cocker Spaniel dogs in which an anomaly of the ganglion cells and the optic nerve fibres of the central retina gives rise to a central scotoma in infancy. The presence of congenital cataracts suggests that there has been some disturbance within the eyeball during the later part of foetal life.

Material and Methods

The methods and terminology have been described previously (Parry, 1953a, b, c). The material has consisted of natural cases referred in consultation.

Case 1, a tricolour Cocker Spaniel male pup, weighing 2.5 kg. at 8 weeks old, was one of a litter of six whelped at full-term after an uneventful first pregnancy. Parturition was normal and the pups were strong. One male pup had a cleft palate and was destroyed. The four surviving litter-mates are said to have normal vision.

Case 2, a blue-roan Cocker Spaniel, dam of Case 1, was first examined when 3½ years old and was found to show signs of a moderate central scotoma of which the animal's owner was unaware.

Cases 3 and 4, blue-roan Cocker Spaniel litter-mates, were first examined when 3 years old; they were said to have had defective vision and cataracts since puppyhood.

Results

(1) Changes in the Eye

Clinical Data.—Detailed observations of the disease in infancy were only possible in Case 1. The general growth and development of this pup were normal and the eyelids opened at the normal time. When 3–4 weeks old it was noticed to be slower than its litter-mates in moving round the kennel, and by 6 weeks old the owner considered it to be partly blind owing to its clumsiness in finding the food bowl. It moved about freely but tended to look out of the corners of its eyes as if using the peripheral part of the fundus. The pup was examined when 8 weeks old. It was well grown and no abnormalities were observed apart from those in

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the eyes. The eyeballs and adnexa were normal, although the owner considered that the eyes were rather smaller than usual; the average pupil size was $2/8$ mm.; the eye preservation and pupillary reflexes were present and brisk. The media were clear, but in both lenses a dense suture cataract of the foetal nucleus was present. The inverted Y of the posterior suture was a dense white line about 1.5 mm. high and 0.2 mm. wide, surrounded by a less dense zone 0.1 mm. wide. The cataract was about 1 mm. deep antero-posteriorly, becoming less dense anteriorly where it was joined to the anterior suture by several fine spider-web opaque strands. The anterior suture was also opaque but less dense than the posterior one, the dorsal arms of the Y not being clearly defined. The outer 1.5 mm. of the lens was normal. Examination of the fundus was unsatisfactory owing to refractive distortion in the lens. The pup retained some vision.

Three affected adult dogs (Cases 2, 3, and 4) were examined; they all had a "bold eye", *i.e.* an unusually dilated pupil, carried their heads with the poll high and looked sideways at objects close to them. Night vision was not more affected than day vision and both eyes were affected similarly. Vision was not obviously abnormal as long as the dogs were on their "home ground", but away they were timid and tended to keep close to their owner's heels. The size and tension of the eyeball, adnexa, and media were normal. The average pupil size was about 10/14 mm. when the light was projected towards the central area, but was reduced when the peripheral fundus was illuminated. The eye preservation and pupillary reflexes were present but could be elicited much more readily from the peripheral fundus. If the attention of the dog's eyes was fixed on a hand held at about the tip of the nose, there was an arc lying approximately between 30° and 60° from the rostro-caudal axis of the head in which no eye preservation reflex could be elicited. The lenses were symmetrically abnormal in all three cases; in Case 2 there was a general distortion of refraction without cataractic foci, while Cases 3 and 4 both showed the-suture cataracts similar to those in Case 1, although the anterior suture was not clearly defined but consisted of a fine spider-web network. The fundi in these cases showed swirling of the tapetal fundus and the secondary blood vessels were less conspicuous than normal; there were no pigment foci. The optic papillae of Case 2 were normal in size but they were very pale and on the dorsal margin of each was a dark grey cone with ragged edges. In Cases 3 and 4 the papillae were much enlarged, being about half as big again as normal; they were flat, pale grey, and with irregular margins. The principal blood vessels were normal, but the secondary vessels were inconspicuous.

Morbid Anatomy.—Case 1 was examined when 8 weeks old. The pup was destroyed by intra-vital fixation with Kolmer's cold-blooded fluid under deep pentobarbital sodium anaesthesia. The right eyeball was enucleated prior to fixation for immediate dissection. The position of the cataracts noted in life were confirmed; they consisted of rather firm dense, white, non-gritty material, which separated quite readily from the outer transparent portions of the lens, which were of normal consistency. The anterior chamber was about 1.5 mm. deep and the iris and ciliary body were normal; no hyaloid vessels were found and the vitreous chamber was normal. The brain and optic nerves were normal. There were no defects of the heart or hard palate, and no abnormalities of other parts of the body were noted.

Histology.—The left eye was examined. The choroid, sclera, tapetum, and outer

FIG. 1.—Section of retina of 8-weeks-old Cocker Spaniel pup affected with central retinal degeneration due to ganglion cell dystrophy; peripapillary non-tapetal fundus. Note marked cavitation of optic nerve fibre and ganglion cell layers. The outer layers of the retina, the pigment epithelium, and the choroid are normal. The separation of the rod and cone layer is due to artefact. Intra-vital fixation with Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. ($\times 120$).

The retinal structures are labelled in the right hand margin in the same way as in previous papers.

layers of the neuroepithelium were normal over the whole fundus (Fig. 1). However, in the central fundus the optic nerve fibre and ganglion cell layers were degenerate (Fig. 1). The zone of degeneration extended from the papilla to the middle of the mid-non-tapetal zone ventrally, and involved the tapetal fundus dorsally to a slightly less extent. In this central zone the optic nerve fibre layer was much thickened, and many of the fibres, especially along the outer margin, had disappeared leaving large cavities (Fig. 2*a*, overleaf). Across these cavities ran enlarged strands of Müller's fibres terminating in conspicuous fans against the internal limiting membrane. The ganglion cells were still present in approximately normal numbers, but the large ganglion cells were probably less numerous and the Nissl substance of the remaining giant cells was agglomerated into large clumps which stained deeply with basic dyes (Fig. 2*a*). The retinal blood vessels appeared to be normal in frequency and structure, but many of the larger vessels were buried rather deeply in the ganglion cell layer, possibly due to the thickening of the optic nerve fibre layer, which might account for the apparent loss of the subsidiary vessels on clinical examination of the fundus. The optic papilla was slightly convex and its surface layers contained many small cavities, which have been seen in normal Greyhound and Red Irish Setter pups of the same age. The optic nerve beyond the lamina cribrosa was 2.5 mm. in diameter and it appeared to be essentially normal. No abnormalities of the choroid, sclera, and anterior parts of the uveal tract were noted. The lens showed a normal peripheral zone and capsule with equatorial formation of new fibres in the normal way, but the central portion was

FIG. 2.—(a) Higher magnification of same preparation as Fig. 1. (b) Section of retina from normal Red Irish Setter pup of the same age; peripapillary non-tapetal fundus about 1 mm. from the papilla. Note in affected retina that outer layers of retina are normal, but that optic nerve fibre layer is greatly thickened and vacuolated. The inner portion of the layer still contains nerve fibres, but the outer portion is composed of cavities traversed by conspicuous strands of Müller's fibres, the fan-shaped terminations of which are unusually prominent against the internal limiting membrane. In the ganglion cell layer the number of nuclei is probably not reduced, but an unusually large number of small cells are seen and the cytoplasm of the large cells shows agglomeration of their Nissl substance. Fixation and staining as in Fig. 1. ($\times 590$).

fragmented and in places consisted of a fine granular, faintly eosinophilic material only.

(2) Development of the Disease

From the limited data available it appears that the extent of the lesion is probably determined by the time the eyes are opened and that the defect of vision remains largely unchanged thereafter, although the defect may not be noticed in early life. The extent of the retinal defect and the cataracts varied a little; Cases 3 and 4 were nearly totally blind and had large papillae and suture cataracts, while Case 2 had better vision, a more normal papilla, and no suture cataracts.

(3) Associated Defects

The general health and breeding performance of affected and related animals were normal as far as could be ascertained. The dogs were kept for showing and as house pets. No other abnormality of their nervous system was detected on physical examination, although Case 3 was said to have little sense of smell.

(4) Occurrence of the Disease

The syndrome has only been observed in this family of blue-roan and tricolour Cocker Spaniels. Data were available concerning 36 dogs in ten litters born since 1944, but details of all litter-mates were only available for three litters. Eight of the 36 dogs were probably affected, three males and five females, although only four of these have been examined personally. The paternal and maternal grand-sires of Case 1, and the dam of Cases 3 and 4 were litter-mates, although none of the seven members of this litter was known to have defective vision. A litter-sister of Case 2 was affected from puppyhood. The sire of Cases 3 and 4 had three affected pups by another bitch. The syndrome obviously has a familial incidence, but the evidence is as yet inadequate to establish that it has an hereditary basis.

Discussion

This syndrome of central retinal degeneration differs from the central atrophy described previously (Parry, 1954b) in its early, probably congenital, onset, its tendency to be non-progressive after defective vision has been recognized, the absence of pigment epithelial dystrophy, the location of the primary damage in the third-order neurones near the papilla, and the occurrence of cataracts of congenital type. These features also serve to distinguish this syndrome from any others we have found in the literature.

A consideration of the possible pathogenesis of the syndrome raises some intriguing problems. The presence of suture cataracts in the foetal nucleus of the lens immediately suggests that some disturbance of intra-ocular development has occurred during intra-uterine life (Mann, 1935). The foetal nucleus of the lens is laid down in man between the 3rd and 8th months of pregnancy (Duke-Elder, 1938). Precise information on the development of the lens in the dog has not been found, but since the maturation of the retina takes place in the dog much later than in man—the differentiation of the nuclear and rod and cone layers occurring after birth (Parry, 1953a)—it may be that the foetal nucleus of the lens may be formed later in the dog than in man, and that its development may not be complete by birth. The occurrence of the suture cataracts and their increased density towards the outer part of the foetal nucleus where they stop abruptly, leaving the outer layers of the lens clear, strongly suggests that the intra-ocular disturbance occurred during the later part of intra-uterine life. Such a dating is also supported by the lesions in the retina. While we do not know precise details of the development of the ganglion cells and the outgrowth of the axons to form the optic nerve in the dog, these occur between the 3rd and 4th months of pregnancy in man (Mann, 1949), *i.e.* before the middle of gestation. As the optic nerve

and papilla are normally developed in the dog syndrome, this stage of development must have been essentially normal. Thus the lesion in the optic nerve fibre and ganglion cell layers must be due to a later degeneration, which has occurred most probably during late intra-uterine life. The clinical and histological evidence suggests that the optic nerve fibre and ganglion cell layers of the peripheral fundus are functioning normally and that the fibre connections to the optic nerve are intact. The development of this part of the retina occurs partly after birth (Parry, 1953a) when normal conditions had presumably been re-established, if one may judge from the normal structure of the infantile lens and the normal development of the nuclear and rod and cone layers of the retina in these affected eyes.

The evidence thus points to some disturbance within the developing eyeball during late intra-uterine life. We can only speculate as to the nature of the disturbance, but the fact that the more highly differentiated tissues comprising the posterior part of the lens and the inner layers of the retina are the most severely involved, suggests that some temporary insufficiency of the blood supply through the hyaloid system may have occurred; this insufficiency was presumably not enough to disturb the more primitive and as yet undifferentiated single nuclear layer of the retina, which is also probably nourished in part by the choroidal circulation.

The aetiology of this disturbance is obscure. The studies of Gregg (1941) have drawn attention to the association of ocular and other developmental anomalies in man with certain virus infections of the mother during early pregnancy, but there was no clinical evidence of a virus infection during pregnancy in these dog cases and no defects of the heart wall or of the hard palate were found in the case coming to autopsy, although one litter-mate did have a cleft palate. On the whole the familial incidence would suggest that acquired environmental factors were of less importance than hereditary ones, although the data are insufficient to establish the genetic basis of the syndrome.

There are other reports of congenital disorders of the optic pathways of the dog which indicate that this part of the dog's nervous system is especially liable to developmental abnormalities. Saunders (1952) described a syndrome of congenital hypoplasia and aplasia of the optic nerve in a litter of Collies, the offspring of a primipara, in which the inter-osseous and orbital portions of the optic nerve were much thinned or even absent, but not always symmetrically on both sides. The optic papilla was small in several eyes and there was a degeneration of the ganglion cell and optic nerve fibre layers of the retina, while the inner layers were said to be normal. Unfortunately the eyes were fixed some time after death and the sections of retina show the stigmata typical of severe *post-mortem* change (Parry, 1953a). It is difficult therefore to make any detailed comparison between the retinal lesions in Saunders' cases and that reported in this paper, particularly as his details of the visual defect and the extent of the retinal lesion are incomplete. However, since in his cases the intra-cranial optic nerves and the optic chiasma were present

although somewhat smaller than normal, the lesion in the optic nerves must have been due, at least in part, to a degeneration occurring after the optic nerve fibres had grown out and reached the brain-stem rather than to simple aplasia or hypoplasia of development as suggested by Saunders. True, the optic papillae were small in several of the eyes he examined, and in one no nerve could be found penetrating the sclera, but in these cases the central portions of the optic nerves were present and were larger than the peripheral portions. The use of smallness of the optic papilla as a diagnostic criterion whereby one can distinguish between hypoplasia and aplasia of the optic nerve on the one hand and degeneration and atrophy on the other, would seem unreliable in these congenital anomalies. The precise relationship of this syndrome in Collies to the one reported here in Cocker Spaniels must remain unsettled for the present; if they are similar in pathogenesis, the degeneration in the Collies must either have commenced earlier in intra-uterine life or have proceeded more rapidly once it began. The data are insufficient to decide whether in the Collies the optic nerve degeneration is primary or whether it is secondary to degeneration of the third-order neurones of the retina.

Cases of congenital hypoplasia and aplasia of the optic nerve in man have been reported by Jerome and Forster (1948) and Scheie and Adler (1941) respectively. These authors, who added three new cases to the five in the literature, relied on the smallness and pallor of the papilla in life as the diagnostic criterion of hypoplasia and they considered that their cases were probably due to failure of development of the optic nerve at the 17–25 mm. stage of embryonic life (Mann, 1949). However, in the light of our further consideration of the syndrome in Collie dogs, it would seem unwise to rely too heavily on these signs as a diagnostic criterion of hypoplasia and failure of development of the optic nerve without anatomical evidence that the central portions of the optic tracts are reduced in size to the same extent as the papilla. It seems not unlikely that some of these human cases may represent a degeneration of the optic nerve fibres in the retina and more peripheral portion of the optic nerve similar to that encountered in the dog.

Summary

- (1) A series of eight cases of non-progressive, probably congenital, degeneration of the central retina with anomalies of the lens in a family of Cocker Spaniel dogs is described. Four cases have been examined clinically and one pathologically.
- (2) Affected dogs have a central scotoma from infancy and three of the four cases examined had suture cataracts of the foetal nucleus of the lens. Peripheral vision by day and night is apparently normal and is retained at least until middle age.
- (3) The scotoma is due to a degeneration of the optic nerve fibre and ganglion cell layers of the central fundus. These layers of the peripheral fundus and the outer layers of the whole retina are normal.

(4) The pathogenesis of the degeneration is discussed and it is suggested that the syndrome may be due to a disturbance operating during the later part of foetal life.

(5) The possible relationship of the dog syndrome to hypoplasia of the optic nerve in man is considered.

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