DEGENERATIONS OF THE DOG RETINA*

IV. RETINOPATHIES ASSOCIATED WITH DOG DISTEMPER-COMPLEX VIRUS INFECTIONS

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BLINDNESS in the dog after distemper has been recognized for many years (Formston, 1952), but unequivocal evidence that it was due to retinal damage has rarely been obtained. It is probable that most cases of blindness associated with such infections are due primarily to involvement of the visual system central to the retina, as in Case 2 reported in this paper, but some are due to degeneration of the retina.

Virus distemper of the dog (Carré, 1905; Dunkin and Laidlaw, 1926) is probably due to a complex of closely related viruses, with a common complement-fixing antigen (Mansi, 1951). Hyperkeratosis of the foot pads occurs commonly but inconstantly in some outbreaks, and this form has been termed "hard pad" disease by MacIntyre, Trevan, and Montgomerie (1948). The term "para-distemper" is used to denote a type of dog distemper in which a high proportion of cases show clinical signs of damage to the nervous system (Anim. Hlth Trust, 1949; Parry, 1950). It is possible that inapparent dog hepatitis virus infection may also be involved in some cases of distemper-like illness (Parry and Larin, 1951).

In dogs affected with para-distemper, we have observed chorio-retinal damage of four primary types;

(i) a peracute generalized retinopathy occurring during the initial stages of acute encephalopathy;
(ii) a chronic generalized retinopathy in animals showing delayed neurological sequelae, so-called post-infective (distemper) encephalopathy (Parry, 1951);
(iii) a dystrophy of the cells of the pigment epithelium with or without evidence of other damage to the retina;
(iv) sporadic foci of advanced degeneration of the retina, focal retinal atrophy, and sclerosis.

This paper reports one case of peracute retinopathy after a natural para-distemper infection (Case 1), two cases of chronic generalized retinopathy developing some months after natural para-distemper infection and associated with extensive brain damage (Cases 2 and 3), and observations on dystrophy of the pigment epithelium in twenty dogs affected with natural

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para-distemper infection and in one which went blind after experimental infection (Case 4).

Methods and Material

The methods and terminology employed have been described in previous papers (Parry, 1953a,b,c). Cases 1, 2, and 3 were natural cases diagnosed on clinical and pathological evidence. Case 2 and the twenty cases used for the observations on the pigment epithelial cell dystrophy were natural cases of epidemic para-distemper, which occurred at the Research Station (Anim. Hlth Trust, 1949, 1950); in this epidemic the clinical and pathological diagnoses were confirmed by inoculating organ suspensions into ferrets which died or were killed with the lesions typical of this disease from the 12th to 15th day after inoculation (Dunkin and Laidlaw, 1926). Case 4 was a survivor of experimental infection with distemper-complex viruses by Mansi (1951).

The electroretinograms were recorded by the team as described previously (Parry, Tansley, and Thomson, 1953).

Results

(1) PERACUTE RETINOPATHY IN SEVERE PARA-DISTEMPER

Case 1, a Golden Cocker Spaniel male, 2 years old, weight about 12 kg., was said to have had perfect vision until the onset of a febrile distemper-like illness, when in 3 days it went blind with dilated pupils. When it was examined on the seventh day of illness there was tremor and rigidity of some skeletal muscles, especially of limbs and head, the average pupil size was 12/14 mm., the eye preservation reflex was absent, there were no pupillary light reflexes, the optic media were clear, and there was no day vision. In the fundus the optic papilla and retinal vessels were normal, but there was swirling of the tapetal fundus. Detailed observation of the fundi was difficult owing to an irregular, vertical, oscillatory movement of the eyeball synchronous with a tremor of the upper eyelids. The animal was destroyed with intravenous pentobarbital sodium owing to the severity of the tremors and continued blindness on the 9th day, when hyperkeratosis of the foot pads was marked.

Morbid Anatomy.—The lesions in the parenchymatous organs were similar to those observed previously in para-distemper (Anim. Hlth Trust, 1949). The brain and optic nerves were normal macroscopically. The eyes were removed and placed in Kolmer's cold-blooded fluid 10 minutes after death.

Histology.—There was advanced degeneration of the retina and choroid, similar in degree and distribution in both eyes, but at a very much more advanced stage in the retina over the non-tapetal fundus than over the tapetal fundus, where the peripapillary zone (0.5-1 mm. from the papilla) was the least affected. These differences could not be attributed to poor fixation. Over the peripapillary tapetal zone the retina was the normal width of about 200 μ and with the normal layers. (Fig. 1).

The pigment epithelium was slightly thicker than normal with an occasional cell of twice the normal thickness. The bacillary layer was thinned, but the precise lesion was difficult to ascertain as the outer limb segments were degenerate and had broken, leaving the layer of stubby inner limb segments only 4-5 μ wide. The external limiting membrane was distinct but in places it had disappeared. The outer nuclear layer was about 50 μ wide and consisted of 8-10 layers of normal rod nuclei, but the larger cone nuclei were not contiguous as is usual and some were pyknotic; furthermore, between the external limiting membrane and the outermost layer of nuclei was a space 7-8 μ wide, in which the radially arranged processes of the rods and cones were plainly visible, producing an eosinophilic zone similar to that seen in the immature retina of the pup and the later stages of post-mortem change. The inner nuclear layer was only two to three nuclei thick, with an occasional pyknotic nucleus. The inner and outer fibre layers were essentially normal. The ganglion cells were present but their cytoplasm had undergone marked hyaline change with loss of Nissl substance. The optic nerve fibres were swollen and fragmented, and the internal limiting membrane was thickened.
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Fig. 1.—Section of retina of dog with peracute generalized distemper retinopathy (Case 1); peripapillary tapetal fundus. Note that layer organization is normal but that ganglion cells show severe degeneration and outer limbs of rods and cones are reduced in thickness and fragmented (Cf. Fig. 6). Remaining layers essentially normal. Immediate post-mortem fixation in Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. (×180).

The following system of labelling the retinal structures, etc., modified from Polyak (1941), applies to all the Figures:

- **Sc.** Sclera.
- **Ch.** Pigmented choroid.
- **Tap.** Tapetum.
- **C.C.** Chorio-capillaris.
- **Rei.** Retina.
- 1. Pigment epithelium.
- 2. Bacillary layer of rods and cones: (a) outer limbs, (b) inner limbs.
- 4. Outer nuclear layer: (a) cone nuclei, (b) rod nuclei.
- 5. Outer fibre layer.
- 6. Inner nuclear layer.
- 7. Inner fibre layer.
- 8. Ganglion cell layer.
- 10. Internal limiting membrane.

*Over the remainder of the tapetal fundus* the retina was much more degenerate, and the outer layers appeared to be folded. Its width was about 100 μ. The degeneration became progressively more severe towards the periphery (Fig. 2).

Fig. 2.—Same preparation as Fig. 1; peripheral tapetal fundus. Degeneration much more advanced than in Fig. 1. Ganglion cell and inner nuclear layers have disintegrated leaving thin outer nuclear layer with rods and cones reduced to stubby remnants of inner limbs. (×200).

The rods and cones had disappeared apart from small areas where the remnants of the inner limb segments 3–4 μ wide remained. The outer nuclear layer was four to six nuclei deep. The inner nuclear layer was two to three nuclei thick over the more central mid-tapetal fundus, but gradually...
became reduced until it had disappeared at the periphery of the tapetal fundus (Fig. 2). The inner fibre layer was vacuolated. The remaining ganglion cells, which were only present in the central fundus, showed hyalized cytoplasm, and the optic nerve fibre layer had lost its regular arrangement. The internal limiting membrane was ill-defined. The retinal blood vessels were less numerous but were not obviously abnormal, although buried beneath the surface (Fig. 2).

The central and peripheral non-tapetal fundus showed advanced sclerosis, the retina being 50 μ wide in the mid-ventral fundus and 20 μ in the peripheral fundus (Fig. 3). The remnants of the two nuclear layers were coalesced as a single layer, firmly adherent to the choroid in some places but not in others. No rod and cone layer remained, the ganglion cells had disappeared and the inner fibre and nerve fibre layers remained as a combined fibre layer with a few glial nuclei. Large round cells, containing dark brown round granules of pigment and distributed irregularly throughout the remnants of the retina, were numerous in some fields (Fig. 3).

The choroid over the whole fundus was reduced in width to about 100 μ wide, and its cells contained much less pigment than usual (Fig. 3); some of the larger arteries showed vacuolation and degeneration of the media, and the endothelial cells lining some of the venous sinuses were swollen.

The optic papilla was raised gradually towards the centre through swelling and fragmentation of the nerve fibres, but there was no abrupt thickening at the papillary margin. The optic nerve head showed increased numbers of glial cells and the nerve fibres had lost their regular arrangement and in places were markedly vacuolated; there was considerable perivascular exudate around the central vessels.

Comment.—There is a severe generalized chorio-retinal degeneration which has developed presumably within 9 days. In the retina the severity of the degeneration is not symmetrical, the non-tapetal fundus being more severely damaged than the tapetal. The degeneration appears to have developed from the periphery to the centre of the fundus, and, within the retina, from the optic nerve fibre layer outwards and from the rods and cones inwards at the same time, leaving the two nuclear layers to be affected last.

(2) CHRONIC DELAYED RETINOPATHY AFFECTED PARA-DISTEMPER.—Although we have seen a number of cases, which may be placed in this category on clinical grounds alone, we have two cases only which have been under adequate supervision and have come to autopsy, thereby allowing a pathological confirmation of the clinical diagnosis.

Case 2 (DO 18), a Red Irish Setter bitch, sent to the Research Station for observation when 4 months old was an unaffected offspring of a test-mating for suspected hereditary retinal degeneration (Hodgman and others, 1949). When a year old she was severely ill
during an epidemic of para-distemper (Anim. Hlth Trust Rep., 1949) with signs of acute disseminated encephalopathy, which persisted for 7–10 days, after which she made a complete recovery without immediate residual neurological defects. Day and night vision and the fundus were normal until she was about 2 years old, when her vision was noticed to be defective by day and night. However, the average pupil size was not greatly increased, although the pupillary light reactions were sluggish. The fundus was normal although the texture was not as beaded as usual. When 26 months old the electroretinogram was recorded using contact electrodes, a small potential was recorded from the left eye but none from the right eye.

About this time she became very timid and refused to play with her companions, wandering about aimlessly. During the following 6 months her mental condition and sight gradually deteriorated until, when 2½ years old, she was almost totally day and night blind. The average pupil size of both eyes was still 6/14 mm., the pupillary light reactions were still present, the lenses and media were clear, but the fundi were abnormal. There was loss of retinal blood vessels: the smaller vessels were not seen, while the outlines of the larger vessels were indistinct as if they had become partly buried. The tapetal fundus was slightly crystalline but the stellulae of Winslow were unusually prominent. The optic papillae were white, but both the primary and secondary blood vessels were still present. The clinical diagnosis was that the fundus changes did not account for the severity of the visual defect, and that damage to the central nervous system was also present, to which the mental deterioration could also be attributed.

The dog was destroyed by intra-vital injection of Kolmer’s cold-blooded fluid under pentobarbital sodium anaesthesia.

Morbid Anatomy.—Damage to the brain was confirmed at autopsy when widespread cavity formation in the cerebral cortex, especially of the occipital poles, was found, together with advanced demyelination of the optic nerves and chiasma. The eyes were normal when opened.

Histology.—There was a generalized chorio-retinal degeneration in both eyes, which was remarkably regular in severity apart from small foci of more advanced damage to the retina. The principal retinal lesions were in the first-order neurones and the nerve fibre layer with hypertrophic dystrophy of the tapetal pigment epithelium.

Over the whole fundus except the extreme periphery the retina was only about 120 μ wide. The outer nuclear layer was reduced to 12–15 μ wide and three to five nuclei thick, through loss of rod nuclei, some of which could be seen fragmenting along the inner margin. The majority of the cone nuclei were normal.

The rod and cone layer was also reduced to about one-third of normal, being 10 μ wide, the outer and inner limb segments being about 5 μ each, although in places the inner limbs were shorter than the outer. The individual outer limbs were of uneven thickness and in many places were fragmented. The cone inner limbs were foreshortened and stubby, while the number of rod inner limbs was reduced to about half. There were also foci 150–200 μ wide where the outer limbs had almost disappeared. The outer fibre layer was much reduced in width, being about 7–8 μ wide. The inner nuclear layer was essentially normal, being 15–18 μ wide and four to five nuclei thick, but the nuclei of Müller’s fibres were more conspicuous than normal and stained more deeply with most stains.

The ganglion cells were still present, although their number was reduced, particularly in some areas, but the cytoplasm of the surviving cells was disintegrating with loss of Nissl substance, and in many the nuclear membrane had disappeared. The nerve fibre layer was much widened, being 30–35 μ thick even over the mid-tapetal zone; the thickening persisted as far as the periphery. Müller’s fibres were greatly thickened (glosis) and the bundles of the intervening nerve fibres were swollen and disintegrating. The smaller retinal blood vessels were buried in the thickened nerve fibre layer, and their walls were thickened and ill-defined. The internal limiting membrane was very conspicuous, being about 2.5 μ thick.

The tapetal pigment epithelial cells were about twice their normal size, with deep brown granular cytoplasm which stained blue with the azan method; about 500 μ apart in a section were one or two giant pigment epithelial cells 10–15 μ in diameter, adjacent to which the rods and cones were greatly reduced. The normal lanceolate pigment granules of the non-tapetal fundus were present. Occasionally there were multi-cellular “nest” of pigment cells, adjacent to which the
rods and cones were lost; the pigment cells were free of pigment and the centre and base of the "nest" showed hyaline changes (Fig. 4). The tapetum was normal in the left eye but in the right eye the cells were swollen and oval, and reduced in number, and the trans-tapetal capillaries were 2–3 times their normal width.

Fig. 4.—Section of retina of dog with chronic delayed generalized post-distemper retinopathy (Case 2); dorsi-ventral non-tapetal fundus. Note multicellular "nest" in pigment epithelium composed of enlarged pigment epithelial cells free of pigment. Outer central portion comprises an eosinophilic hyaline mass. Note complete atrophy of adjacent rods and cones. Intra-vital fixation with Kolmer's cold-blooded fluid. Mallory's phosphotungstic acid haematoxylin. (×250).

In addition to the generalized degeneration described above, there were foci of more advanced change. In the left eye, there was a focus 150 μ long over the mid-tapetal fundus where the retina was only 100 μ wide, the rods and cones had disappeared, and the outer nuclear layer consisted of a single layer of cone nuclei (Fig. 5).

Fig. 5.—Same preparation as Fig. 4; mid-tapetal fundus. Small focus adjacent to a large retinal artery and vein of more advanced atrophy in which rods and cones have disappeared and cone nuclei only remain in outer nuclear layer. Few inner limbs of cones present on right. (×250).
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The extreme ventral periphery inwards for about 200 μ from the ora serrata showed advanced sclerosis with infiltration of round pigment cells similar to those seen in Case 1 (Fig. 3). The choroid all over the fundus was thinned slightly to 100 μ and its blood sinuses were greatly reduced. The optic papilla was contracted outwards and the optic nerve showed severe degeneration of nerve fibres with advanced demyelination.

**Comment.**—The generalized chorio-retinal degeneration was less advanced in this case than in Case 1. The outer nuclear and rod and cone layers were affected most severely, but the optic nerve fibre layer was also gliosed and degenerate, probably due to centrifugal degeneration from the optic nerves in which demyelination was severe and to which the early degeneration of the ganglion cells may possibly be due. There was a simple hypertrophy of the tapetal pigment epithelium with abnormal pigmentation and occasional multicellular "nests" occurred in which pigment changes were absent.

Case 3 (DH O1), Cocker Spaniel male, a house pet, weighing about 12 kg., had a history of a mild febrile illness coinciding with an epidemic of distemper in the district about 6 months before defective day and night vision was noted at 18 months old. When examined at 2 years old both eyes were similar. The dog was partly day blind, and almost completely night blind: the average pupil size was 8-9/14 mm., and the pupillary light and corneal reflexes were normal, but the eye preservation reflex was absent. The lens and media were clear. The retinal blood vessels were inconspicuous and the papillae were white, especially the left where only the horizontal branches remained. In the ventral portion of the non-tapetal fundus of the left eye were two small white plaques, 1-2 mm. in diameter and with discrete but irregular margins, thought to be due to defects, probably exudate, in the choroid. Examination of the nervous system revealed no other defects apart from a slight ataxia associated with asthenia of the limbs without disturbances of reflexes.

The choroid defects disappeared over the ensuing 3 months, but vision became worse. At 2½ years the dog was apparently completely day and night blind (average pupil size 12/14 mm., pupillary light reflexes absent) and the tapetum showed an enhanced green reflection and a crystalline texture. The ataxia was now more marked, and there was some loss of reflexes. Over the next year some mental and emotional deterioration occurred and the ataxia due to atonia and dysmetria of the hind limbs became worse. The dog was kept under observation until it was 3½ years old, *i.e.* 2 years after the visual defect was first noted, when it was destroyed by intravenous pentobarbital sodium without intra-vital fixation.

**Morbid Anatomy.**—At autopsy slight general atrophy of the cerebral hemispheres was found, but the optic nerves were normal. The eyes were placed in fixative within 15 minutes of death and were normal when opened.

**Histology.**—There was advanced sclerosis of the retina over the whole fundus in both eyes similar to the peripheral portions of Case 1 (Fig. 3), but in addition the pigment epithelium was thickened regularly to about 10 μ wide over the whole fundus except the extreme periphery; the cytoplasm of the tapetal pigment epithelial cells was filled with a yellowish-brown granular pigment, while that of the non-tapetal cells was more heavily charged with lanceolate granules than normal. Occasionally a round pigment cell was seen in the sclerotic retina. The tapetum was thin and the choroid was reduced in width to less than 100 μ over much of the fundus. The optic nerves showed advanced degeneration with demyelination.

**Comment.**—Although direct biological evidence was not available to confirm the clinico-pathological diagnosis of para-distemper in this case, the similarity of the retinal lesions to those of Cases 1 and 2, the dystrophy of the pigment epithelium, and the associated brain lesions strongly suggest that they may all be attributed to a previous distemper-complex virus infection.
(3) **Hypertrophy of Pigment Epithelium after Natural Para-Distemper.**—We have examined the eyes of nineteen dogs which died or had to be destroyed owing to peracute and acute para-distemper 2 days to 2 months after the clinical illness began. Of these, seventeen were affected in the natural para-distemper epidemic at the Research Station, and two were dogs sent to us while incubating the disease.

Fifteen were Red Irish Setters, of which seven were affected with Stage 2 hereditary progressive retinal degeneration (Parry, 1953 b), three were Greyhounds, and one was a Poodle. Their ages ranged from 3 months to 3 years. In none was any specific visual defect attributable to the virus infection noted during life, although some of those dying of the peracute disease showed signs of coma and diffuse encephalopathy. The majority of eyes were obtained at autopsy after natural death and were therefore unsuitable for studying fine changes in the retina.

**Histology.**—Changes in the pigment epithelium were observed in eight of the twelve dogs with normal retinae; no changes were observed in the seven dogs affected with the hereditary degeneration, in which the pigment epithelium was very largely missing, or in two Greyhounds, one Setter, and the Poodle, all of which died within 2-4 days of the onset of the disease. The seven normal Setters and one Greyhound, in which the changes in the pigment epithelium occurred, all survived more than 4 days of clinical illness, those with the most marked lesions surviving the longest. The changes occurred symmetrically in both eyes. The earliest stage was a swelling of the pigment epithelial cells over the tapetal fundus to a width of 7-8 μ and the development of a brownish granular cytoplasm staining a deep blue with the azan method. At first only a few individual cells were affected, but in later cases the whole pigment epithelial layer over the tapetal fundus (Fig. 6).

![Fig. 6.](http://bjo.bmj.com/)

Fig. 6.—Section of retina of dog with dystrophy of pigment epithelium after para-distemper (Case 3); peri-papillary tapetal fundus. Note hypertrophy of pigment epithelial cells, causing early compression atrophy of adjacent rods and cones. Remainder of retina normal. Intra-vital fixation with Susa’s fluid. Mallory’s phosphotungstic acid haematoxylin. (x250).
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was 15–20 μ wide with cytoplasm heavily charged with the light-brown granular pigment, while that over the non-tapetal fundus was thickened to 10 μ, but without the granular pigmented cytoplasm; the usual lanceolate pigment granules were still present. In five cases which had survived 2 to 3 weeks and had been destroyed on account of other disabling neurological sequelae, the tapetal pigment epithelium was 20–25 μ wide all over the fundus, and the rod and cone outer limbs were reduced in length to 6–7 μ, but the other parts of the retina appeared to be normal.

Comment.—Dystrophy of the pigment epithelium, particularly of the tapetal fundus, can be a sequel to clinical para-distemper if the dog survives 3 to 4 days of clinical illness; the pigment epithelial cells show hypertrophy and unusual pigmentation. The hypertrophy causes secondary pressure atrophy of the outer limbs of the rods and cones.

(4) HYPERTROPHY OF PIGMENT EPITHELIUM AFTER EXPERIMENTAL INOCULATIONS WITH DOG DISTEMPER-COMPLEX VIRUS.

Case 4, a white Alsatian male, was infected intra-nasally and subcutaneously at 3 months (by Dr. Mansi) with a strain of Laidlaw-Dunkin distemper maintained for five intracerebral-ferret passages. From the 4th to the 9th day thereafter the dog had a febrile illness with diarrhoea. On the 8th day it was noticed to be blind, but vision had apparently been recovered completely by the 18th day, when its general health was normal. Between the ages of 5 to 8 months the dog was inoculated four times with the “Glasgow S. 123” strain of dog-distemper virus without any signs of ill-health except that gradual impairment of vision was noticed again towards the end of this period. It was examined when 9 months old. The general health of the animal was excellent. The average pupil size was 5/14 mm., the pupillary light reactions were brisk, the eye preservation reflex was absent, and day vision tests indicated that the dog was totally blind. The eyeballs, lens, media, and fundi were normal. Clinical observation suggested that the blindness was due to damage central to the lateral geniculate body.

The dog was destroyed by intravitral injection with Kolmer's cold-blooded fluid under pentobarbital sodium anaesthesia.

Morbid Anatomy.—The parenchymatous organs were normal, although liver adhesions were suggestive of a previous canine hepatitis virus infection (Parry and Larin, 1951). The optic nerves and spinal cord, brain stem, and cerebellum were normal, but there was widespread cavitation in the right temporal and pyriform lobes, i.e. in those parts supplied by the middle cerebral artery.

Histology.—There was a modest retinal degeneration. The retina was about 150 μ wide; its general organization and cytology were normal apart from minor changes in the pigment epithelium, optic nerve fibre layer, and some ganglion cells.

The tapetal pigment epithelium was slightly hypertrophied, being 7–8 μ wide, while some individual cells in all parts of the fundus were more enlarged, being 20 μ long and 15 μ wide. In the tapetal fundus these enlarged cells were much more frequent and in places had caused atrophy of the adjacent outer limbs of the rods and cones; they had a brownish granular cytoplasm which stained a deep blue by the azan method. The normal lanceolate pigment granules over the non-tapetal fundus were prominent and were continued centrally beyond the junctional zone, where the pigment epithelium is usually unpigmented. No multi-cellular “nests” were seen.

The nerve fibre layer for 1 to 2 mm. adjacent to the papilla was fragmented and shrunken, and over this area the ganglion cells were reduced in number, and many surviving cells were degenerating; their nucleus and cytoplasm had lost their sharp demarcation and the small Nissl's granules had coalesced into eight to ten larger granules in each cell. More peripherally the ganglion cells appeared normal, but there was slight swelling of the nerve fibre layer with vacuolation and waviness indicative of early degeneration. The optic nerve showed marked fragmentation and waviness of the nerve fibres. The choroid was about 120 μ wide and its blood vessels were normal.

Comment.—This case shows modest choroidal atrophy, dystrophy of the retinal pigment epithelium, peripapillary degeneration of the nerve fibre layer, and loss of ganglion cells near the papilla with early optic atrophy. The absence of marked retinal changes confirm the opinion based on the clinical signs that the blindness was of non-retinal origin."
hypertrophy and the pigment dystrophy of the pigment epithelial cells were very similar to those seen in natural cases of distemper-complex infection.

Discussion

The literature on the role of virus infections in degenerations of the retina is scanty (Perdrau, 1940; Sorsby, 1948). In man there is the great difficulty of obtaining pathological confirmation of clinical observations, while in animals, although the association between dog distemper and blindness has for long been recognized, few attempts to determine the locus of the responsible lesion have been published. The observations reported in this paper provide evidence that the dog distemper virus can cause serious damage to the dog retina either during the acute phases of the disease, or as a delayed sequel to the infection. These observations seem of particular interest in view of the recent clinical reports of acute retinopathy in man following non-fatal infections with the virus of Rift Valley fever (Schrire, 1951; Freed, 1951).

The distribution and sequence in which the damage occurred in these cases of distemper retinopathy suggests that the chorio-retinal damage may be of two types: related to direct damage to the tissues or their blood supply, or related to pre-existing damage to the optic nerves.

(i) The retina may be affected from both the choroic al and vitreal surfaces simultaneously, causing atrophy of the first- and third-order neurones before the second-order neurones;

(ii) Degeneration of the optic nerves cranial to the papilla is followed by retrograde degeneration of their retinal connections, which causes a degeneration, proceeding centrifugally from the papilla, of the optic nerve fibre layer and later of the ganglion cells. A somewhat similar pattern of degeneration is seen in glaucomatous retinopathy, but damage to the third-order neurones proceeds simultaneously all over the fundus in the dog, and is probably most marked at the periphery. This second type of distemper retinopathy is probably analogous to that seen after the severing of the optic nerve in man (Landolt, 1872; Litten, 1882), although no data relating directly to dogs have been found.

Peracute Retinopathy after severe para-distemper infection (Case 1) showed generalized damage to the retina, of the first type, which was least marked over the tapetal peripapillary zone and most marked over the peripheral non-tapetal fundus. The damage presumably occurred within 9 days. All layers of the retina were apparently affected together, since the loss of rods and cones was contemporaneous with the loss of bipolar nuclei and changes in the ganglion cells and their nerve fibres. The separation of the rod and cone nuclei from the external limiting membrane is unusual, and it is not clear whether this was due to loss of cone nuclei or whether retraction of the retina inwards drew the inner limbs of the rods and cones partly through the membrane. Certainly the remnants of the cones appear swollen at their outer ends, as if cone substance had been partly drawn inwards, an effect we have
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not observed in any other sections prepared in a similar manner. The more advanced stages over the non-tapetal fundus show the varying degrees of sclerosis observed in the other types of retinal degeneration in the dog.

The atrophy of the choroid and the changes in the walls of its blood vessels suggest that an important factor in peracute para-distemper retinopathy is interference with the choroidal blood supply. The damage to and burying of the retinal blood vessels and the oedema around the central vessels of the optic nerve suggest that the damage arising from the inner surface of the retina may also be related to disturbances of blood supply. It is interesting that no intracellular inclusion bodies were seen which would indicate direct parasitization of retinal cells by a virus.

Chronic Delayed Retinopathy (Cases 2 and 3), following the virus infection after a considerable latent period and with a co-existing degenerative encephalopathy, illustrates both primary and secondary types of retinopathy which can conveniently be termed "post-infective" (Parry, 1951). The precise relationship of the virus infection to these degenerations is not known, since virus cannot be detected after the acute phase of the illness in this type of case. These cases, in which both retinal degeneration and epithelial cell dystrophy occurred, are of particular interest when considered in conjunction with the cases of simple pigment epithelial cell hypertrophy and that of delayed retinopathy after experimental inoculations of virus (Case 4). It seems probable that they may represent different stages of a single disease process. In Case 2 the rods and cones were probably still partly functional, the visual defect being due mainly to damage in the optic pathways, a view supported by the recording of an electro-retinogram from one eye after day-blindness was advanced. The degeneration appears to affect the rod nuclei near the inner edge of the outer nuclear layer and takes the form of a fragmentation of the chromatin, followed by lysis, but without infiltration of inflammatory cells. At the same time, both outer and inner bacillary layers were reduced in width, and the ganglion cells and optic nerve fibres of the central retina disappeared, leaving the second-order neurones relatively intact. Coinciding with the loss of all the rod nuclei, the two nuclear layers coalesced, the ganglion cells gradually disintegrated, and the normal layer organization of the retina was lost, as in the advanced stages of other retinal degenerations. In Case 3 the degeneration was so advanced that it was not possible to determine the sequence of its development, but it is noteworthy that the dystrophy of the pigment epithelium remained similar to that seen in the earliest cases, i.e. once it has developed it persists probably indefinitely.

Focal Degenerations (Case 2) were of two types:

(i) foci of more advanced atrophy of rods and cones and their nuclei over areas 0.5–1 mm. wide;

(ii) focal sclerosis involving disorganization of all layers of the retina and similar to the advanced sclerosis of the ventral non-tapetal fundus.
We have seen similar sclerotic foci in a case of central retinal degeneration with a history of para-distemper in puppyhood, small foci of both types in an otherwise normal horse distemper, and foci of atrophy only in a tiger's retina. The foci of atrophy appear to be very similar to those seen in the rabbit by Tansley (1951), and in the rat, mouse and ferret (Tansley, 1952) in the aetiology of which there is no reason to suspect a virus infection, and to the so-called "focal" pseudo-retinitis pigmentosa observed in a boy of 18 by Cogan (1950, Fig. 36). An acute focal retinitis with inflammatory cell infiltration was observed by Overman and Dortch (1951) after the intra-ocular inoculation of rabbits with Semliki Forest virus, which they attributed to the direct action of the virus on the retina; it is possible that these acute inflammatory foci might have developed into foci of sclerosis if their rabbits had been allowed to live long enough. However, we have seen no abnormal mitoses in the outer nuclear layer such as they described, possibly because our cases were not examined early enough. In all the dog cases there has been a history of distemper-complex infections, and although the aetiology of these focal lesions is not established, their occurrence in these dogs does suggest that they may be related to some enhanced local action of the virus infection. It seems likely that the rod-free foci described by Zürn (1902) as a fovea in the dog may have been foci of degeneration.

The advanced sclerosis seen in Cases 1, 2, and 3, in which the retinæ lie adjacent to the choroid without intervening pigment epithelium, are virtually identical with that seen in the advanced stages of hereditary atrophy (Parry, 1953b). The use by Cogan (1950) of adhesion and non-adhesion of retina and choroid as a distinguishing feature between hereditary and inflammatory lesions seems hardly warranted, and bears out the contention of Tansley (1951) that it is an unreliable criterion.

The case of blindness following experimental distemper-complex infection (Case 4) is primarily one of blindness due to damage in the brain central to the lateral geniculate body, but the changes in the retina with very early centrifugal degeneration of the peripapillary ganglion cells and the dystrophic pigment epithelial cells causing slight compression of the adjacent outer limbs are very similar to the lesions seen in the cases of natural para-distemper infection. It seems not unlikely that the retinal changes in this case illustrate an early stage of a disease process of which Case 2 is an example of a later stage, possibly related to the longer interval of 18 months since the primary virus infection in Case 2 compared with 6 months in Case 4. It is interesting to speculate on the role of the repeated exposures of Case 4 to virus in the development of the degenerative process.

*Dystrophy of the Pigment Epithelium*, seen in many dogs without serious damage to the retina, consisted of a simple hypertrophy with abnormal pigment formation, and was most prominent in the usually pigment-free tapetal pigment epithelium.
The hypertrophy took two forms:

(i) modest generalized regular hypertrophy (Fig. 6);
(ii) massive irregular focal hypertrophy, affecting foci of from one to about twenty contiguous cells.

In the first type of hypertrophy the radial width of the tapetal cells was 8–10 μ (a two to three fold increase), and their retinal and choroidal surfaces were approximately parallel. In the second type, the individual cells were 20–25 μ long and 15–20 μ wide, and their retinal surface was convex and pressed severely on the adjacent outer limbs.

The pigment abnormalities were also of two types:

(i) the occurrence throughout the cell body of round refractile golden-brown pigment granules which stained a deep blue with azo-carmine,
(ii) an increased quantity of the dense dark-brown lanceolate pigment granules normally present over the non-tapetal fundus.

Pigment cell dystrophy of these types is not a feature of the normal dog retina, nor does it follow post-mortem change (Parry, 1953a); indeed, the eyes of several of the cases examined were fixed intra-vitally or within 5 minutes of death. It is difficult not to attribute them to the effect of the virus infection on the pigment epithelium, since they can occur without retinal damage. The atrophic epithelium seen in the later stages of the hereditary retinal atrophy is not affected. Whether the dystrophy is a common reaction we do not know, but it may be significant that the strains of distemper-complex virus involved all produced damage to the nervous system. It is also of interest, if we accept the evidence of Cases 2 and 3, that once the dystrophy is initiated it apparently persists without much change for at least 2 years. If this deduction is confirmed, the presence of this dystrophy might prove of value as an indication of previous distemper-complex infection.

The effects of the dystrophic pigment epithelium on the maintenance of the integrity of the retina are not well understood. In areas where the epithelium was 25μ wide, the outer limbs of the rods and cones were undergoing simple pressure atrophy, while the remainder of the retina appeared to be normal. However, the dystrophic epithelium may well interfere with the normal extravascular circulation to the rods and cones from the chorio-capillaris in areas where no such atrophy is apparent. Pigment epithelial cell dystrophy also occurs in the syndrome of central retinal degeneration (Parry, 1953d), in which in addition to the general hypertrophy, large multicellular "nests" of pigment cells occur. These "nests" can be detected on ophthalmoscopic examination of the fundus, while the hypertrophy associated with distemper-complex infections cannot; multicellular "nests" do not occur regularly in the simple para-distemper syndromes, although an occasional one without pigment but showing hyaline degeneration occurred in the case of chronic retinopathy (Case 2, Fig. 6).

These dystrophic pigmented cells, obviously derived from the pigment
epithelium, should be distinguished from the pigmented cells of less obvious origin which invade the remnants of the degenerating retina when sclerosis is far advanced as in Cases 1, 2, and 3 (Fig. 3). The latter occur in retinal sclerosis of varying aetiology, e.g. that following the hereditary atrophy; they are usually about 30 μ in diameter, round, and loaded with dark-brown, round pigment granules which like those of the choroidal cells remain unstained by the azan method. They are hence quite different in size, shape, and pigment characteristics from the pigment epithelial cells, and no intermediate types have been seen. The pigment cells in sclerosed retinas correspond closely with the rounded cells with round, dark-brown chromatophores which occur in the degenerating choroid, and it seems most likely that these modified pigmented cells from the choroid migrate into the sclerotic retina in the advanced stage of many chorio-retinal degenerations.

The fact that pigmentary aberrations with retinal degeneration may follow distemper-virus infection in the dog (which is usually associated with fever and affections of the respiratory tract, and less commonly with damage to the nervous system) makes one ponder whether some human cases of slow loss of vision with pigmentary changes of the retinitis pigmentosa type may not be related to previous virus infection, say of influenza B, in some epidemics of which cases showing nervous signs may occur (Leigh, 1946).

Summary

(1) Chorio-retinal degenerations following natural and experimental infection with viruses of the dog distemper-complex in the dog are described. Four main types of primary distemper retinopathy are recognized:

(i) The infection may cause a peracute generalized primary degeneration (retinopathy) with bilateral day and night blindness of sudden onset.

(ii) A chronic generalized primary retinopathy with gradual loss of day and night vision may develop slowly 1 to 2 years after the primary infection.

(iii) A dystrophy of the pigment epithelium characterized by hypertrophy and aberrant pigmentation without other retinal damage may occur; this is most prominent over the tapetal fundus.

(iv) Small foci of degeneration, either of atrophy or of sclerosis, are also encountered; their possible origin is discussed.

(2) A subsidiary type of retinopathy secondary to atrophy of the optic nerve is characterized by a centrifugal degeneration of the optic nerve fibre layer and of the ganglion cells.

(3) In both types of generalized primary retinopathy (1, i and ii) the peripheral fundus is affected more severely than the central fundus, and the degeneration appears to proceed into the retina from the inner and outer surfaces simultaneously. The possible relationship of this distribution and sequence to the blood supply is considered.

(4) The origin of the pigmented cells found in the sclerosed retina is discussed.
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