RETINITIS PIGMENTOSA* PATHOLOGICAL FINDINGS IN TWO CASES

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ALTHOUGH retinitis pigmentosa is a fairly common affection and an important cause of blindness, relatively few cases have been examined histologically. Cogan (1950) found some twenty cases in the literature and himself described three more. The condition most commonly shows a recessive mode of inheritance (Sorsby, 1951), and all the cases so far described for which family histories are recorded appear to be of this type.

The present paper records two further cases, one of which shows a clearcut dominant mode of inheritance.

Case Records

Case 1, a male aged 63, dying of carcinoma of the tonsil with terminal bronchopneumonia, was totally blind and gave a history of nightblindness from the age of 28 and subsequent progressive deterioration of vision. Ophthalmoscopy showed very extensive pigment formation, pale waxy discs, attenuated vessels, and bilateral posterior polar cataract. A sister was similarly affected; two of her three children were seen and found normal and the third was reputed normal.

Case 2, a female aged 60, dying of carcinoma of the breast, gave a history of long-standing nightblindness and poor vision; her maternal grandfather went blind, and her two brothers and her mother were almost blind. Both eyes showed typical retinitis pigmentosa, the right disc was waxy, and the left showed early atrophy; there was no cataract; visual acuity was 6/24 in the right eye and 6/36 in the left eye; there was peripheral field contraction and annular ring scotoma.

Pathological Examination

Case 1.—Both eyes had been fixed intact in Zenker's fluid shortly after death. The left eye had been divided horizontally through the optic nerve and fovea and the right vertically through the equator, and the lenses removed. Paraffin sections were stained with haematoxylin and eosin, Mallory's trichrome stain, phosphotungstic acid haematoxylin, and azan.

Right Eye

Retina.—In the immediate vicinity of the macula a few short, thick cones with a single row of nuclei are preserved. Beneath the cone nuclei is a thick layer of glial tissue. The inner nuclear layer and layer of ganglion cells are preserved although the number of cells is considerably diminished (Fig. 1, opposite). More peripherally no visual cells are preserved and the inner layers are considerably disorganized by patches of gliosis. There is extensive deposition of pigment in the retina, most pronounced just central to the

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FIG. 1.—Case 1, right eye, retina in immediate vicinity of fovea. A somewhat ragged row of cone remnants is seen with a layer of glial tissue. The inner layer shows a good degree of preservation. H and E. $\times 300$.

equator but not confined to this region. The pigment is in the form of large globular masses clustered about rounded hyaline bodies some of which can clearly be identified as hyalinized blood vessels (Fig. 2). The pigment epithelium is intact at the posterior pole and periphery, but in places in the equatorial region it merges into the retinal remains and

FIG. 2.—Case 1, right eye, retina in equatorial region showing masses of pigment surrounding what appears to be a hyalinized blood vessel. H and E. $\times 300$.

cannot be identified as a separate structure. In this area there are patchy adhesions between the retina and Bruch's membrane (Fig. 3). Bruch's membrane is intact throughout the sections. The inner limiting membrane is markedly thickened.

FIG. 3.—Case 1, right eye, retina in equatorial region showing area where pigment epithelium is disrupted and adhesions have developed. PTAH $\times 150$.

Choroid.—The choroid is enormously thickened at the posterior pole for roughly 2 mm. each side of the macula. The large arteries show mural thickening and periadventitial deposition of fibrous tissue. Pigment is scanty in the thickened area, but normal elsewhere. The choriocapillaris is within normal limits, except in the foveal region where the capillary walls are thickened (Fig. 4). Fig. 5 (opposite) shows the appearance of the choroid in Case 2 for comparison.

Optic Nerve.—The optic nerve shows no obvious atrophy.

Left Eye.—Equatorial sections only are available of this eye so that a full description cannot be given. The changes in the equatorial region are like those in the right eye.

FIG. 4.—Choroid in foveal region of right eye, Case 1, scleral edge only just visible at lower edge of picture. Note enormous increase in thickness and sclerosis of large vessels and choriocapillaris. Fixation in AZ. H and E. $\times 150$.

Case 2.—The right eye was fixed in Zenker's fluid and the left in 10 per cent. formalin. Both were divided horizontally through the posterior pole. Paraffin sections were cut and stained with haematoxylin and eosin. Cellular detail was poorly preserved in both specimens.

Right Eye

Retina.—A row of short thick cones is preserved in the foveal region and small groups of cone remnants persist on the temporal side right to the periphery. The inner retinal layers are also best preserved in the foveal region, although readily recognizable everywhere. The number of cells in the inner nuclear and ganglion cell layers is somewhat reduced and there is some disorganization of these layers and gliosis on the nasal side. Pigment deposition is most pronounced just central to the equator; on the nasal side it takes the form of large globular masses forming cuffs to hyalinized retinal arteries; on the temporal side it is mostly in relatively small discrete masses or granules with no vascular localization, and hyalinized retinal arteries without pigment cuffs are seen. The pigment epithelium is everywhere intact and loaded with pigment. Bruch's membrane and the inner limiting membrane are intact.

Choroid.—The choroid is of normal thickness and shows no obvious abnormality (Fig. 5).

FIG. 5.—Choroid in foveal region of right eye, Case 2. Fixed in AZ. H and E. $\times 150$.

Optic Nerve.—The optic nerve is not obviously atrophied.

Left Eye.—After fixation in formalin, macroscopic examination of the left eye showed a well-defined zone of branching filamentous pigment deposits between the posterior pole and the equator (Fig. 6, overleaf). The retina was thin and transparent except for an area about 3 mm. in diameter round the macula where it had a filmy grey opaque appearance.

Retina.—No visual cells are present in the sections which did not, however, pass through the centre of the fovea. Disorganization of the retina is more severe than in the right eye, pigment deposition is almost exclusively in the form of large pigment clumps surrounding hyalinized vessels. The pigment epithelium is broken up and merges into the retina in localized areas in the equatorial region. Bruch's membrane and the inner limiting membrane are intact and normal in appearance.

Choroid.—The choroid is not obviously abnormal.

Optic Nerve.—The optic nerve shows no apparent atrophy.

FIG. 6.—Case 2, left eye, macrophotograph of fundus between equator and posterior pole showing characteristic branched pigment deposits.

Discussion

So far as the retina is concerned, the histological changes in retinitis pigmentosa recorded in the literature are relatively consistent. The essential features are loss of the visual cell layer, preservation to a greater extent of the inner nuclear layer and ganglion cells, varying degrees of gliosis, and pigment invasion along the retinal blood vessels. Retinal structure is best preserved in the immediate vicinity of the fovea, and pigment invasion is most pronounced in the equatorial region.

Some authors have found the choroid normal, others have reported abnormalities. The most consistently recorded changes are sclerosis of the larger arteries, which, considering the age of most of the cases examined, is not altogether surprising, and partial or complete disappearance of the choriocapillaris. The loss of the choriocapillaris has been found to correspond to the most severely damaged areas of the retina. A much more serious degree of sclerosis of the choroid affecting its stroma was reported by Wagenmann (1891) and Ascher (1932). The question arises whether the variations in the choroid can be ascribed to physiological variation, senile changes, incidental complications, or just to poor preservation in *post-mortem* material, or whether, as suggested by Ascher (1932), there may be two varieties of retinitis pigmentosa corresponding to the different modes of inheritance, the primary seat of the lesion in one being the retina and in the other the choroid.

Optic atrophy has been recorded by some authors, others specifically stated the nerve to be normal, and some were doubtful, or recorded no opinion.

Posterior polar cataracts are often present, especially in longstanding cases.

As already pointed out by Cogan (1950), many of the cases in the literature are either not adequately established as genuine cases or have serious

secondary complications which may be difficult to differentiate from the primary lesion. In order to try to establish how far the various discrepancies can be accounted for in the ways mentioned and how far they are likely to represent real differences in the primary lesion, all the cases in the literature have been scrutinized. Table I contains those cases in which the clinical and pathological detail is adequate to establish the diagnosis beyond reasonable doubt and to exclude the presence of serious secondary ocular disease. Table II (overleaf) contains cases excluded from Table I for the reasons stated.

The retinal lesion has frequently been attributed to deficiencies in the choriocapillaris (Gonin, 1903; Nettleship, 1907; Hepburn, 1938; and most authors reporting a deficiency). Six of the eleven cases in Table I are reported to show complete or partial absence of the choriocapillaris. Leber (1916), however, considered that, taking into consideration the age of the patient and nature of specimen, the variations reported in the choriocapillaris could well be within normal limits. It is of interest to note that in the three cases in which the eye was enucleated during life (Stock, 1908; Sukanuma, 1912; Verhoeff, 1931) the choriocapillaris was found to be within normal limits. The evidence presented does not establish a lesion of the choriocapillaris as essential to the pathology, far less as a causal factor.

The increase in choroidal stroma and loss of vascularity described by Wagenmann (1891) and Ascher (1932) seem to make their cases exceptional.

Six of the ten cases in Table I are recorded as showing optic atrophy, so

TABLE I
ACCEPTABLE UNCOMPLICATED CASES

Author	Date	Age of Patient (yrs)	Age at Onset (yrs)	History of Night-blindness	Surgical or Necropsy	Fixative	Optic Atrophy	Choroid
Landolt	1872	59	14	Yes	Necropsy	—	Yes	Choriocapillaris diminished
Wagenmann	1891	—	—	—	Necropsy	Muller	Yes	Gross thickening (choriocapillaris partially absent) vessels reduced
Aubineau	1903	52	—	Yes	Necropsy	1 sublimate 1 formalin	No	Atrophy of choriocapillaris; sclerosis of large vessels
Lister	1903	60	—	Yes	Necropsy	Spirit	"discs pale"	Choriocapillaris atrophied
Stock	1908	57	23	Yes	Surgical	Zenker	Yes	Normal
Sukanuma	1912	67	19	Yes	Surgical	Formalin	Yes	Slight atrophy; choriocapillaris normal
Verhoeff	1931	64	"Early life"	Yes	Surgical	Zenker	No	Normal (some endarteritis)
Koyanagi	1931	67	28	Yes	Necropsy	Formalin	Yes	Choriocapillaris absent in stretches and thickened; choroidal arteries reduced in number
Ascher	1932	47	"Many years ago"	—	Necropsy	—	Yes	Choriocapillaris lacking in stretches; gross thickening centrally
Cogan 5th	1950	46	—	—	Necropsy	—	No	Choriocapillaris normal

TABLE II
CASES WHICH ARE UNACCEPTABLE IN PRESENT SURVEY

Author		Date	Reason for Non-Inclusion in Table I
Leber		1869	History of blindness from birth
Poncet		1875	Case of stationary nightblindness
Deutschmann		1891	Unilateral
Bürstenbinder		1895	Age at onset late; complicated by acute inflammatory changes
Gonin		1902	Unilateral
Henderson	1st	1903	Complicated by glaucoma, no history
	2nd	1903	Complicated by total glaucoma
Stein	2nd and 3rd	1903	No family or clinical details
	4th	1903	Retinal changes atypical; probably syphilitic
Ginsberg		1908	Complicated by tuberculous choroiditis and optic neuritis
Greeves		1912	Complicated by tuberculous choroiditis
McKee		1913	No family or clinical history—description very short
Friedenwald		1930	Wassermann reaction positive
Blum and Babel		1948	Details lacking and description rather short
Cogan 3rd and 4th		1950	Complicated by glaucoma

that this cannot be regarded as an incidental feature resulting from the presence of other ocular disease, nor is there any correlation with the age of the patient and duration of the disease.

Present Cases.—In both the cases recorded here the clinical findings were entirely characteristic of retinitis pigmentosa and no other ocular complications were present. The family histories are available and some of the relatives were seen so that the mode of inheritance can be established with some certainty. Case 1 shows a recessive mode of inheritance. In Case 2 the occurrence of the disease in three generations establishes clearly a dominant mode of inheritance, which is of particular interest since the cases in the literature for which a family history is available are not of this type.

The histological changes in the retina in both cases conform to the general description already given. In Case 1 they are a good deal more advanced, and in Case 2 the changes in the left eye are more advanced than in the right. Thus in Case 1 and in the left eye of Case 2, there is some breaking up of the pigment epithelium in the equatorial regions with glial adhesions developing between the retina and Bruch's membrane.

Cogan (1950) considered that breaking up of the pigment epithelium and the formation of glial adhesions to the choroid, as seen in both these cases, were more consistent with pseudo-retinitis pigmentosa. The latter is a confusing term used by Blum and Babel (1948) to cover acquired retinopathies, but, since the latter are frequently inflammatory in origin, each term wrongly describes the lesion to which it is applied. Coats (1913) attempted to distinguish between inflammatory and degenerative lesions in a series of

animal retinopathies by applying a similar criterion. Various other authors, including Stock (1908), Sukanuma (1912), Koyanagi (1931) and Verhoeff (1931), have also reported breaking up of the pigment epithelium in localized areas and, provided Bruch's membrane is intact, there is no reason to consider this feature as throwing doubt upon the diagnosis.

Cogan (1950) has pointed out that the hyaline masses with cuffs of pigment are generally assumed to be occluded vessels, but are, in fact, more numerous than can be accounted for in this way. Some are undoubted vessels but, unless a lumen containing red cells or a vena comites can be demonstrated, it is impossible to be sure. In the cases recorded here this was seldom the case, although in several instances apparent lumina were seen (Fig. 2).

The choroid in Case 1 is of particular interest since the appearances closely correspond with Ascher's (1932) description. No photographs of Wagenmann's case are available, but his description is also similar. These three cases are therefore exceptional in showing a degree of choroidal sclerosis which cannot be accounted for by age or apparent incidental complications and it remains to be decided whether these choroidal changes justify separating retinitis pigmentosa into two types, or have any causal significance. If the three cases are to be regarded as a distinct entity, there is no correlation with the mode of inheritance as suggested by Ascher (1932), since Wagenmann's case and Case 1 are, like most of the reported cases, recessive. As to causal significance, no vascular lesion can readily account for the selective destruction of the rods which occurs early in the disease, as is shown by the early onset of nightblindness.

The choriocapillaris in Case 1 shows fairly well marked thickening of the walls in the foveal region (Fig. 4) and this is where the retina is best preserved.

The choroid in Case 2 shows no obvious abnormality (Fig. 5).

In neither case was the optic nerve noticeably atrophied, and the present cases, like those of Cogan (1950), offer no histological explanation for the characteristic "waxiness" of the discs.

Integrating the present cases with those listed in Table I, the final position with regard to the two controversial aspects of choroid and optic nerve is that nine of the total of twelve cases have shown no positively established lesion of the choroid; six have shown marked optic atrophy, five have not, and one is uncertain. Since Case 2 is the only known dominant case, there is no correlation between either of these variables and the mode of inheritance and, if the choroidal variety is to be regarded as a separate entity, the behaviour of the optic nerve is still inconsistent in both types since both Wagenmann's and Ascher's cases showed atrophy whereas Case 1 does not. On the evidence at present available it must therefore remain an open question whether retinitis pigmentosa can be regarded as a single entity showing different modes of inheritance.

It is perhaps of interest finally to note the occurrence of similar diseases in the animal kingdom. Verhoeff (1931) suggested that retinitis pigmentosa

might be comparable with the recessive character "rodlessness" in the mouse described by Keeler (1924, 1926); and Bourne, Campbell, and Tansley (1938) considered it directly comparable with a recessively inherited retinal degeneration occurring in the rat. The latter considered* that their findings lent experimental support to the suggestion of Collins (1919) that retinitis pigmentosa was an abiotrophy of the neuro-epithelium. More recent work on the inherited retinopathies in the experimental animal has shown, however, that the degeneration commences during the later stages of retinal differentiation (Karli, 1952; Sorsby, Koller, Davey, Attfield, and Lucas, 1954; Tansley, 1954; Lucas, Attfield, and Davey, 1955).

Summary

The histological findings in two cases of retinitis pigmentosa have been described. One is of interest because it shows an abnormality of the choroid noted in only two previous cases and the other because it is the first case with a dominant mode of inheritance to be examined pathologically.

The cases of retinitis pigmentosa previously recorded in the literature have been reviewed with particular reference to inconsistent findings in the choroid and the variable occurrence of optic atrophy. The possibility of more than one type of the disease is considered. The discrepant findings could not, however, be correlated with the mode of inheritance.

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