COMMUNICATIONS

PATHOLOGICAL BASIS OF RETROLENTAL
FIBROPLASIA

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Since the pathological picture of the final stage of retrolental fibroplasia is not of a specific character, no important advance in our understanding of the disease was to be expected until the distinctive histological features of its earliest phases became known. Following a report on the clinical appearances of the developing disease (Owens and Owens, 1949), there soon appeared a number of careful microscopical studies which provided a clear concept of its pathogenesis; from the histological evidence accumulated in the works of Heath (1950a, b; 1951), Tyner and Frayer (1951), Reese and Blodi (1951), and Reese and others (1952), it became abundantly clear that the primary pathological change is angioblastic in nature and presents as an overgrowth of the developing retinal vessels. Some of the conclusions reached in these studies, however, differ in detail from our own and, while it is no longer necessary to present a detailed study of the histology of this condition, it would appear desirable to report upon the pathology of a few representative cases from our own material and to discuss it in relation to the observations already in the literature.

The features of the late stages of the disease are generally agreed upon and have already been fully described (Reese and Payne, 1946; Krause, 1946; Klien, 1949; Wolff, 1950); this report, therefore, is mainly concerned with the earlier stages of the disease and summarizes the pathological basis of our experimental work reported elsewhere in this issue (Ashton and others, 1954; Ashton and Cook, 1954).

Material and Findings

Case 1 (R.L.F. 31), female infant (case of Dr. E. Hinden).—The mother was admitted to hospital at 24 weeks with pre-eclamptic toxaemia and chronic nephritis. This was her seventh pregnancy (the other children being healthy). Caesarian section was performed; the baby appeared normal at birth which was 12 weeks premature. The birth weight was 2 lb 8 oz (1,134 g.). The infant was placed in an oxygen tent from birth until about the fifth week, and was breast-fed throughout. A blood transfusion was given at the seventh week (150 ml.). The infant died when 7 weeks old.

Ophthalmological Appearancees (Dr. M. Klein).—In the fourth week there were no abnormal findings, but a few days before she died there was an extensive greyish reflex from the temporal periphery of each fundus without definite detachment, and retrolental fibroplasia was suspected.

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Autopsy Findings (Dr. M. S. Ross).—Cardiac failure, broncho-pneumonia, and anaemia. Both eyes were removed for examination.

Pathological Examination.

Right Eye.—The globe was opened horizontally to reveal a clear vitreous and very striking retinal changes (Fig. 1). Arising from the retina in the equatorial zone and most markedly on the temporal side, there was an extensive and dense outgrowth of new vessels advancing towards the ora serrata. They formed a wide well-demarcated band around the temporal side of the equator; each vessel growing out from the retinal tissue terminated in arborizing tufts which were buried in yellow gelatinous material. The underlying retina was oedematous and showed an early localized folded detachment. Scattered throughout the retina elsewhere, but mainly equatorially, there were isolated tufts of vessels growing out of the retina and these also were surrounded with gelatinous material. Photographs and drawings were made of the specimen and of flat preparations of the retina (Figs 2, 3, and 4); carbowax and serial celloidin sections were cut and stained by haematoxylin and eosin, Masson's trichrome stain, periodic acid-Schiff stain, and Holmes' silver stain; the carbowax sections were also stained with Scharlach R. and iron-haematoxylin.

Sections.—The globe was normal in size, and the cornea, corneo-iridic angle, iris, and lens were normal. There was a mild diffuse chronic inflammatory infiltration throughout the ciliary body and choroid, and scattered focal aggregations of lymphocytes in the posterior choroid. The vessels throughout the uveal tract were engorged. The predominant pathological changes, however, were to be seen in the retina, which at the equator on the temporal side was folded, shallowly detached, thickened, and oedematous. In this area there was a profuse outgrowth of large, dilated, new vessels, which apparently emerged from the inner layers of the retina and extended into the vitreous; their growth was preceded by a solid cellular mass of vaso-formative tissue in which the new vessels were developing (Fig. 5). This cellular tissue corresponded to the yellow gelatinous material seen macroscopically. Between the retinal surface and the advancing layer of vaso-formative cells there was an irregular space, traversed by the newly-formed vessels and containing a fine, fibrillar transudate in which several large endothelial cells could be seen, many of them containing refractile globules. Adjacent to this area and at other scattered points
throughout the retina, earlier stages of this process could be seen; they consisted of foci of vaso-formative tissue within the nerve fibre and ganglion cell layers. Elsewhere, and particularly anteriorly, there was a diffuse proliferation of spindle cells associated with numerous PAS-positive granules, an association absent from the fully formed endothelial cells. It was interesting to note that within the retina the vaso-formative tissue was confined to the ganglion cell and nerve fibre layers and did not invade the retina beyond the inner molecular layer. On both sides of the globe there was an oral, folded detachment of the retina, which was more marked on the nasal side where the detached retina was thrown into several convolutions. In some sections a very early separation of the pars ciliaris retinae could be seen, but in no section was this extensive.

FIG. 2.—Case 1, flat preparation of untreated retina, showing vessels growing from the surface into the vitreous. ×22.

FIG. 3.—Case 1, flat preparation of untreated retina, showing a tuft of new vessels growing into the vitreous from an intra-retinal vessel. ×22. (Cf. Figs 11 and 15, Ashton, Ward, and Serpell, 1954).

FIG. 4.—Case 1, flat preparation of untreated retina, showing a characteristic glomerular vessel growing into the vitreous. ×206. (Cf. Fig. 11, Ashton, Ward, and Serpell, 1954).

FIG. 5.—Case 1, section of equatorial retina showing a profuse outgrowth of large dilated vessels which emerge from the inner layers of the retina and extend into the vitreous; their growth is preceded by a solid cellular mass of vaso-formative tissue. Haematoxylin and eosin ×36. (Cf. Fig. 17, Ashton, Ward, and Serpell, 1954).
Throughout the retina there was a patchy absence of the internal limiting membrane, and areas of degeneration could be seen in the stratum opticum. Fibrinous strands containing endothelial cells extended from the retina into the vitreous, particularly from those areas in which new vessel formation had occurred. The rods and cones showed post-mortem degeneration and were partially replaced by eosinophilic fluid. The remainder of the retina, optic nerve, and sclera appeared normal. Carbowax sections showed no evidence of fat in the retina or choroid.

**Left Eye.**—The globe was opened horizontally. Situated in the temporal half in the region of the equator there was an irregular band of new vessel formation growing forwards into the vitreous; each vessel had broken up into a number of terminal twigs which arborized with each other and were buried in a mass of yellow, gelatinous material. The retina was thrown into a number of folds in this area and showed a greyish-white appearance as far forward as the ora serrata. The nasal half of the retina appeared normal. The vitreous contained a few fibrinous bands. The specimen was retained for museum purposes and no sections were cut.

**Diagnosis.**—Retro lentil fibroplasia. Pathological Stage 1 (bilateral).

**Case 2** (R.L.F. 31), female infant (case of Dr. Mary Crosse).—This infant was 12 weeks premature, with a birth weight of 2 lb (907 g.); she was the second of triplets (one having died before admission, and the other being alive and well with no blindness). She was given oxygen for 43 days, the concentration starting at 45 per cent., with reduction after the first 10 days first to 40 per cent. and then to 30 per cent. She was in the oxygen tent for 37 days and was then replaced on 76th day for 6 days (pneumonia). Eight small blood transfusions were given. Breast feeding was followed by artificial feeding. The eyes were examined on the 51st day and appeared normal. The baby died when 82 days old.

**Autopsy Findings.** (Dr. H. S. Baar).—Broncho-pneumonia, severe active rickets, no congenital abnormalities. Both eyes were removed for examination.

**Pathological Examination**

**Left Eye.**—The globe was opened horizontally. Arising from the equatorial region superiorly and on the temporal side a number of fine strands extended from the retina into the vitreous and terminated in a solid white band of tissue.

**Sections.**—The cornea, corneo-iridic angle, and lens were normal. The iris, ciliary body, and choroid showed a mild infiltration with chronic inflammatory cells. In its anterior half, the retina showed a marked proliferation of spindle cells and endothelial cells in the stratum opticum. The spindle cell proliferation was diffuse and particularly well marked in the retinal periphery, whereas the endothelial cell proliferation was focal and more closely related to blood vessels. At the equator on the temporal side new vessels could be seen extending from the retina into the vitreous where they merged with a mass of vaso-formative tissue (Fig. 6). The vitreous was albuminous and contained fibrinous strands.

**Fig. 6.**—Case 2, section of retina showing marked proliferation of mesenchymal cells in the inner retinal layers and a mass of vaso-formative tissue consisting of endothelial cells and new blood vessels extending into the vitreous. Haematoxylin and eosin. × 90.
bends and occasional haemorrhages. The remainder of the retina showed a moderate degree of oedema but there was no evidence of ante-mortem detachment at any point. PAS staining showed abundant red granules confined to the region of spindle cell proliferation within the anterior optic nerve fibre layer on the temporal side (Fig. 7).

Right Eye.—Macroscopically and microscopically the eye was remarkably similar.

Diagnosis.—Retrolental fibroplasia. Pathological Stage I (bilateral).

Case 3 (R.L.F. 32), male infant (case of Professor R. W. B. Ellis). The birth was 8 weeks premature, the birth weight 3 lb 9 oz (1,616 g.), and oxygen was given (details not available). There were no blood transfusions. The infant was admitted to hospital with retrolental fibroplasia at the 10th week. He was treated with cortisone for 6 weeks, but died suddenly and unexpectedly at the 16th week.

Autopsy Findings (Dr. A. R. MacGregor).—No abnormality was found and it was thought that death was in some manner related to the administration of cortisone.

Pathological Examination

Left Eye.—The globe was opened horizontally. Postero-inferiorly there was a large retinal detachment, upon the surface of which new-formed vessels could be seen. Many vascular and fibrous strands extended from the detached area to the posterior surface of the lens. The newly formed vessels appeared to be empty. A few haemorrhages were present in the retina.

Sections.—The cornea, corneo-iridic angle, iris, and lens appeared normal. On one side there was a focus of inflammatory cells in the ciliary body. In this area extensive haemorrhage had occurred on the retinal surface, and numerous newly formed vessels and organizing fibrous strands could be seen to extend into the vitreous in company with irregular masses of vaso-formative tissue from which fibroblasts arose. Here the retina was detached and a subretinal exudate containing fibrils and macrophages was present. Elsewhere the retina showed focal aggregations of proliferating endothelial cells and diffuse hyper-
plasia of spindle cells in the stratum opticum. In general the intensity of the reaction diminished as the ora serrata was approached. The retina was not detached anteriorly and there was no separation of the pars ciliaris. PAS staining showed dense aggregations of positive-staining granules in those areas where spindle cells were proliferating in the inner layers of the retina, but not in the areas of endothelial proliferation or new vessel growth.

Right Eye.—The globe was opened horizontally. Situated posteriorly and to the nasal side, there was a folded retinal detachment covered with extensive haemorrhage, and small haemorrhages were present elsewhere. An extensive net of newly formed vessels with fibrous strands extended into the vitreous and was adherent to the adjacent retina and posterior surface of the lens.

Sections.—The cornea, corneo-iridic angle, and lens were normal. There was some albuminous exudate in the anterior chamber and the iris showed an increased cellularity. On one side there was commencing elongation of the ciliary epithelium. Posteriorly there was a folded detachment of the retina which extended almost to the ora serrata but did not involve the pars plana. A subretinal exudate containing distended macrophages was present, and within the folded retina there was a focal proliferation of endothelial cells and a diffuse proliferation of spindle cells. Masses of vaso-formative tissue extended through the internal limiting membrane, and from this area new vessels and strands of fibrin and fibroblasts invaded the vitreous (Fig. 8); there were a few adjacent haemorrhages. Elsewhere the retina showed spindle cell and endothelial proliferation in the inner layers, and there were small turrets of fibrin attached to the internal limiting membrane. The sclera and optic nerve were normal; many PAS positive granules could be seen in association with the spindle cells.

Diagnosis.—Retrolental fibroplasia. Pathological Stage II (bilateral).

Case 4 (R.L.F. 35), Male Infant, First Child (case of Mr. A. L. M. McCurry).—The birth was 11 weeks premature, and the birth weight 2 lb 6 oz (1,077 g.). He was nursed in an oxygen tent for 26 days from the time of admission to hospital; oxygen concentrations were not recorded but the flow was about 4 l/min. Artificial feeding was given throughout and no blood transfusions were given. The eye condition developed when he was approximately 1 month old, and he was given ACTH 5 mg. 6-hrly for about 6 days, but, as the eyes became worse, this was increased to 6.25 mg., and continued for 6½ days. At the end of this time the eyes were beginning to improve, but the baby had become grossly oedematous and treatment was discontinued. He died 24 hrs later.
Autopsy Findings (Dr. J. N. Dearnaley).—Apart from gross oedema no abnormality was found. Both eyes were removed for examination.

Pathological Examination

Right Eye.—The globe was opened horizontally; the vitreous was cloudy and contained numerous white strands which appeared to extend from the scarred retinal surface.

Sections.—Pupillary membrane remnants were present, the choroid was congested, and white blood cells were visible in the vessels, but no cellular infiltration was present. The retina was folded posteriorly, but there was no oral fold and no retinal detachment. In

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**Fig. 9.—Case 4, section showing diffuse proliferation of mesenchymal cells in inner layers of anterior retina.** More posteriorly there are discrete masses of endothelial cells which at one point have broken through the internal limiting membrane. Haematoxylin and eosin. ×50.

**Fig. 10.—Case 4, section showing mass of endothelial cells erupting through internal limiting membrane.** Haematoxylin and eosin. ×115. (Cf. Fig. 13, Ashton, Ward, and Serpell, 1954).

**Fig. 11.—Case 4, section showing mass of endothelial cells growing along the retinal surface beneath the hyaloid membrane of the vitreous.** Haematoxylin and eosin. ×115.

the anterior half of the retina, where there was no invasion of the vitreous, a diffuse proliferation of spindle cells could be seen in relation to the capillary bed, while further posteriorly the endothelial cells tended to form discrete masses (Fig. 9). In the posterior half of the retina and especially near the optic disc a number of endothelial masses had broken through the internal limiting membrane (Fig. 10) and others were growing along the surface of the retina beneath the hyaloid membrane of the vitreous (Fig. 11). PAS-positive granules were present in relation to the proliferating spindle cells, but only a few such granules were present in the endothelial masses. Despite the ACTH therapy the disease process appeared active.
Left Eye.—Macroscopically and microscopically the left eye showed essentially the same changes, but invasion of the vitreous was more marked.

Diagnosis.—Retrolental fibroplasia. Pathological Stage I (bilateral).

Discussion

The earliest histological change which can be distinguished as a disease process in retrolental fibroplasia is an excessive proliferation in the inner layers of the retina of vaso-formative tissue, which breaks through the internal limiting membrane, creeps along the surface of the retina beneath the hyaloid membrane, and then invades the vitreous proper. Through the freely permeable angioblastic tissue, protein transudates seep into the retina and also into the vitreous. The oedematous retina becomes folded, distorted, and shallowly detached; meanwhile fibroblasts proliferate in the plasma matrix within the vitreous and form fibrous strands, which on contracture complete the retinal detachment; the fibrovascular tissue thus comes to lie behind the lens, where it further organizes into a dense retrolental fibrous membrane. The cases described in this paper illustrate the above sequence of events and our findings are in agreement with those of Friedenwald and others (1951) and Reese and others (1952).

As in the series described by the last-named workers, the oral region was not maximally involved in any of our cases; exuberant vaso-formative tissue may extend into the ora in the later stages of the disease, but in our experience it has never been the primary site affected. Nor is this surprising, since vaso-formative tissue has not reached the extreme periphery in the more susceptible group of infants of younger gestational age. Indeed, the oral region is the area most frequently found to be normal in the initial stages of the disease, a fact which again emphasizes the angiomatous nature of the process and the absence of glial reaction. Our findings in this respect are, therefore, the reverse of those of Heath (1951), who concluded that the primary retinal disease occurred in the incompletely differentiated retina at its oral attachment and that the denser tissues elsewhere in the eye escaped the oral changes.

In retrolental fibroplasia it has frequently been observed that the retinal detachment may extend beyond the ora serrata to involve the pars ciliaris retinae, a point particularly emphasized by some workers (Dixon and Paul, 1951) and even thought to be of aetiological importance (Wolff, 1950; Bembridge, 1951). While this feature has also been noted in some of our cases (e.g. Case 1), its importance is now thought to have been over-stressed, for an examination of premature eyes has shown that the pars ciliaris retinae is not firmly coapted (Ward, 1954), and consequently readily separates with detachments of the pars optica retinae. No specific significance can, therefore, be given to such anterior detachments in the developing eye.

Within the inner layers of the retina in the early stages of the disease there is, in addition to the hyperplastic foci of endothelial cells, a diffuse pro-
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Liberation of spindle cells which had been noted by Friedenwald and others (1951), and by Reese and others (1952), who described them as "glial cells". However, when these cells are studied as regards distribution, occurrence, and staining properties, it becomes apparent that they are not of glial origin. They are not present in the normal retina before vascularization commences, they enter with the vascular ingrowth immediately ahead of the advancing vascular buds, and they are similarly confined to the inner layers of the retina; as the endothelial cells multiply and canalize into vessels, so the spindle cells disappear and are again absent in the mature retina. They are always intimately associated with PAS-positive granules, which have been identified as glycogen (Serpell, 1954), whereas fully-developed endothelial cells are never so associated. These features are not the characteristics of retinal glial cells, and the only explanation of their nature which appears to be consistent with all the facts is that they are mesenchymal precursors of the retinal vascular system. Indeed, such mesenchymal tissue would be entirely necessary for the formation of the other vascular components, such as connective and muscle tissue, which presumably could not derive from a simple endothelial ingrowth. They probably originate from the mesodermal coats of the hyaloid artery and grow into the retina as solid cords which canalize and differentiate into endothelium and eventually form the complete vascular network, a process exactly comparable with the formation of the closed vascular system elsewhere in the body. In future, therefore, we shall refer to them as mesenchymal cells; they are discussed in greater detail by Serpell (1954).

In the sections of our cases-no new vessels were found on the iris; this is somewhat surprising, for their clinical appearance in the active stages of retrolental fibroplasia has been described by a number of writers; Von Winning (1952) for instance described and illustrated convoluted tufts of engorged vessels at the pupillary margin. Such proliferations have also been produced in the iris experimentally (Ashton and others, 1954), but they were found to occur inconstantly and to disappear rapidly, and they are not readily demonstrable in sections unless one is fortunate enough to obtain an eye at the right stage and to cut through the particular area involved. That vascularization of the iris may be demonstrated in sections of eyes with retrolental fibroplasia has been shown by Reese and Blodi (1951).

It has been claimed that the early stages of retrolental fibroplasia may occur pre-natally, since proliferative changes have been noted in the retina in still-born infants, and in premature infants dying soon after birth. It is to be remembered, however, that the developing retina of the normal foetus must show some degree of endothelial and mesenchymal proliferation as part of the process of retinal vascularization. Thus the matrix of retrolental fibroplasia is present in the normal developing retina, and the histological diagnosis of the early stages of the disease will depend upon the degree of proliferation regarded as excessive. Here we are at the boundaries of normal and abnormal activity, and, although proliferations are occasionally seen which are more
exuberant than is commonly found, it cannot be said with certainty that they are beyond the limits of normal variation. No departure from normal can confidently be assumed until the vaso-formative tissue appears in an abnormal situation, either extending into the vitreous or proliferating to a marked degree in posterior regions, where, in the last months of intra-uterine life, the formation of the vascular network should be nearing completion.

In order to avoid doubtful diagnoses, we have taken the former criterion as an indication of a definite disease process, and we regard the first pathological stage of retrolental fibroplasia as the early extension into the vitreous of vaso-formative tissue which has erupted through the internal limiting membrane (Fig. 10). When this strict criterion is adopted many of the proliferative retinal changes described in the literature become of doubtful or no significance, and it is of interest that in none of our cases of stillborn and short-lived premature infants, has a Stage I pathological change been observed. It is true that Reese and others (1952) described a stillborn infant showing typical vascular proliferations into the vitreous, but this appears to be the only well-authenticated case in the literature, and it cannot be said that it has yet been established that retrolental fibroplasia, as generally understood, may occur pre-natally. Neither have we encountered, in our whole collection of about 280 cases of retrolental fibroplasia investigated clinically or histologically (or both), a single example of the disease where oxygen had not been administered therapeutically. Nor have we seen the disease in a fully mature infant. This is not to deny, however, that the disease may occur pre-natally or may develop apart from prematurity or oxygen therapy; since the basis of the disorder is merely an aberrant overgrowth of developing retinal vessels, it is not improbable that there may be a variety of precipitating causes, as in the case of retinitis proliferans, which is an approximately comparable process in the adult retina; some of these factors may operate pre-natally, as in congenital encephalo-ophthalmic dysplasia, or post-natally when the retina develops ischaemic anoxaemia by some means other than through oxygen vaso-obliteration. Nevertheless, cases of retrolental fibroplasia of the type which has emerged as a clinical entity during the last 10 years, occur in premature infants who develop the disease post-natally in circumstances related to oxygen administration. Hence, while related conditions may be exactly similar histologically, they are not identical aetiologically, and there would appear to be good grounds for applying a special name to the oxygen-induced disease. This is not expressed satisfactorily in the terms "retrolental fibroplasia", "retinopathy of prematurity", or "hypoxic retinopathy"; it is probable, however, that a revision of the nomenclature, although clearly desirable, should await further clarification of the problems of pathogenesis. It is for this reason that we have retained the familiar name of "retrolental fibroplasia" throughout our papers, realizing that it describes only the final non-specific phases of the disease, that it may embrace a number of different entities, and that it may eventually give place
to a more accurate classification.

Our conclusions are, therefore, in agreement with those of most workers, in that the pathological evidence is in favour of regarding retrolental fibroplasia as a primary retinal disease of non-inflammatory origin resulting from a derangement of retinal vascularization. The intravitreal growth is an extension of the abnormal angioblastic activity in the retina and does not indicate a primary disease of the vitreous as suggested by Reese (1952). Indeed, we believe that the stimulating factor which attracts the vessels into the vitreous is elaborated in the retina. The development and course of the disease may be simply stated in the following pathological stages:

**Stage I.**—Proliferation of vasoformative tissue, consisting of endothelial and mesenchymal cells, in the inner layers of the retina, with early eruption of the tissue through the internal limiting membrane into the vitreous (Fig. 12).

**Stage II.**—Commencing retinal detachment, extension of fibrovascular tissue into the vitreous, and formation of fibrous strands (Fig. 13). At any time throughout Stages I and II new vessels may appear on the iris.

**Stage III.**—Total retinal detachment, and formation of dense retrolental fibrous membrane followed by late atrophic changes (Fig. 14).

**Summary**

(1) The pathological features of four representative cases of
the early stages of retrolental fibroplasia are described in detail, and the findings are discussed in relation to cognate work.

(2) The conclusions are in accord with the widely accepted view that retrolental fibroplasia is a primary retinal disease of non-inflammatory origin, which results from disordered retinal vascularization. Its development and course may be simply stated in three pathological stages.

(3) Since the basis of the disorder is merely an aberrant overgrowth of the developing retinal vessels it is not improbable that there may be a variety of precipitating causes, but the vast majority of cases consists of premature babies who develop the disease post-natally in relation to oxygen therapy. There would thus be good grounds for applying a special name to the oxygen-induced disease, but it is suggested that a revision of nomenclature should await further clarification of the problems of pathogenesis.

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