MECHANISM OF RETROLENTAL FIBROPLASIA*

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TERRY (1942-48) published the first papers on a peculiar condition occurring in the eyes of premature infants, for which he coined the term "retrolental fibroplasia". Since then about one hundred papers on this condition have appeared, interest having been aroused amongst paediatricians and obstetricians as well as ophthalmologists. Terry's observations have evoked much research, but the exact nature of the condition has not yet been defined. The term "retrolental fibroplasia" persists as a label, in spite of the many attempts to find a better one (Krause, 1946; Reese, 1949; Heath, 1950a), and in spite of variations in the conditions described.

In this paper our present knowledge of retrolental fibroplasia is surveyed, with clinical and pathological descriptions of original cases, and a vasculo-developmental hypothesis of its aetiology is advanced.

Clinical Picture

The condition affects the eyes of premature infants, its incidence rising steeply in those whose birth weight is 3 lb. or less. Terry's original clinical description included:

retrolental membrane, "foetal blue" iris, posterior synechiae, microphthalmos, shallow anterior chamber, visible dentate processes of ciliary body, glaucoma, photophobia, blindness.

Terry was describing old-standing cases, but Owens and Owens (1948; 1949) after 5 years of following up all the premature infants in their hospital, described the complete course of the disease, thus establishing retrolental fibroplasia as a clear-cut clinical entity. They confirmed the occurrence of the condition in premature infants—as described by Terry—but disproved his pathological conceptions.

The course of retrolental fibroplasia as described by Owens and Owens and later by various other authors, including Kinsey and Chisholm (1951) and Unsworth (1948), may be summarized as follows:

- (a) All remnants of the tunica vasculosa lentis disappear shortly after birth.
- (b) The period of normality is from 2 to 3 weeks.
- (c) In the 3rd or 4th week the retinal vessels become tortuous and engorged. This change can affect the whole fundus or a single sector of it.
- (d) Small greyish areas of retinal oedema appear in the extreme retinal periphery. The rest of the retina may look oedematous.

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(e) The vitreous becomes cloudy, mainly in the vicinity of patches of retinal oedema. Opaque bands may proliferate into it or haemorrhages may occur.

(f) Retinal detachments, at first shallow and then gradually deepening and spreading, become visible, starting in the affected sectors.

(g) A membrane encroaches on the posterior surface of the lens, which becomes vascularized.

(h) Posterior synechiae develop.

(i) The eye stops growing when the membrane is formed.

(j) The eye enters into the final phase, as described by Terry, about 6 weeks from the beginning of the process.

The process may become stationary at any stage, or it may regress (Unsworth, 1948; Heath, 1950a, b, 1951; Owens and Owens, 1948, 1949). The regression tends to occur if the process is arrested in the earlier stages. As the descriptions of stationary cases are very few, three cases of this character are described below.

Case Reports

Case 1.—Ann S., aged 3 years, was referred in August, 1951, to the Eye Clinic, Beckett Hospital, Barnsley, on account of a squint in the right eye, which was noticed soon after birth. She was a premature baby, born in the 7th month and weighing 3 lb. at birth. Right concomitant convergent strabismus of 25° was found; both eyes were small and the right pupil gave a dull grey reflex. She was given ung. atropine 1 per cent. to use for 5 days; the left pupil dilated well but the right did not.

On September 15 the eyes were examined under general anaesthesia:

Right eye: grey retrolental membrane occluding view of fundus. Irregular vascularization. Lens clear. Blue, pale iris. Ciliary processes visible. Numerous small posterior synechiae all round, better seen between 6 and 9 o'clock.

Left eye: clear lens and media. Lower retinal vessels normal. Upper temporal vessels tortuous and fuller than the rest. One branch coursing towards 12 o'clock is elevated from a point about two disk diameters from its entry and forms the peak of a tent-like detachment of the retina. The extreme periphery from 11 to 12 o'clock is affected by shallow whitish detachment. No haemorrhages. No vitreous haze. No remnants of hyaloid system of vessels.

The child was put on mydriatics and her eyes examined under general anaesthesia on two subsequent occasions (the last on December 15, 1951). There has been no change in her condition. She can see with the left eye, plays with toys, and greets the sight of an ophthalmoscope with fearful screams.

Case 2.—Anthony L., aged 6 years and 5 months, was referred to the Eye Clinic, Beckett Hospital, Barnsley, from the Children's Welfare Clinic in May, 1950, because the mother noticed that he did not follow objects with his eyes. He was 7 weeks premature, and born at a time when the mother was entering the menopause. Ophthalmoscopic examination under general anaesthesia was conducted on May 10, 1950, and the picture in both eyes was identical:

Anterior chamber shallow, pupil well dilated with atropine, media clear. There was a retinal detachment like an elevated sleeve extending from the optic disk towards the temporal periphery. This band had a rugged appearance peripherally and was considerably elevated (about 8 dioptries). There were a few minute exudative spots in the central retina. The calibre of the vessels was normal. No remnants of hyaloid system were seen.

When the eyes were examined again on August 12, 1950, the right fundus was unchanged, and the left showed a large mass extending far forward on the nasal side of the globe. Enucleation of the left eye was advised, and was performed the next day; the histopathologist reported retrolental fibroplasia.

The right eye has been examined on several occasions since (last examination

November 10, 1951) and is still unchanged. The mother states that the child sees much better, but there is no fixation.

Case 3.—**Frederick W.**, aged 17 years, attended the Eye Clinic, Beckett Hospital, Barnsley, on May 10, 1950, because of poor sight and left squint. His squint was first noticed when 1 year old. He was born prematurely—the mother was unable to state in which month—and his weight at birth was 3 lb. “with clothes on”. He looks infantile, is mentally retarded and illiterate, cannot tell the time, and does not know numbers, but in spite of that is happily working in the building trade.

Vision is 6/18 in each eye and he has alternating concomitant strabismus of 10°. The pupils dilated well with atropine and the fundi showed a symmetrical picture:

Disks pale. Vessel entry abnormal, in one perpendicular axis. Folds of detached retina streaming down and out from the disks towards the periphery covered the temporo-inferior parts of the disks, and involved nearly the whole of the temporo-inferior quadrants. No remnants of the hyaloid system of vessels were seen.

The fundi were examined again on November 10, 1951, when the picture in each eye was as follows:

Areas of retinal detachment much smaller, now look like sleeves and stream down from the disks only to mid-periphery. Distally to them are pigmented and atrophic patches like those normally seen in a spontaneously re-attached retina. Small vitreous floater in the left eye. Vision unchanged.

These three cases are of interest because they seem to be undoubtedly genuine, in spite of being diagnosed at an age later than usual. In Case 1 the other eye shows a typical late picture of retrolental fibroplasia. In Case 2 the pathological findings confirmed the real nature of the condition. Case 3 gives an appearance identical with Case 5 of the original series of Owens and Owens in spite of the difference in the ages of the patients.

Histopathology

PREVIOUS STUDIES

Klien (1941, 1949) observed angioblastic overgrowth of the primary vitreous in response to some factor “as yet unknown”, and accepted as most significant the association of the retrolental fibroplasia with cutaneous haemangiomas (as did Reese and Payne, 1946). She considered the condition to be related pathologically to Hippel-Lindau angiomatosis.

Dixon and Paul (1950) reviewed eleven cases; no remnants of the hyaloid system of vessels were seen, nor were there signs of an inflammatory process. Detachment involved primarily the pars ciliaris retinae, which caused dilatation of the retinal vessels supplying and draining the area. Ciliary epithelium accompanied by vessels proliferated thence and formed the retrolental membrane, which thus arose from retinal elements. To explain the glaucoma frequently affecting these eyes, Dixon and Paul suggested that the zonular fibres originating from the pars ciliaris become lax when this is detached and allow the lens to be displaced forward, thus blocking the angle of the anterior chamber.

Heath (1950a, b; 1951) called the condition “retinopathy of prematures”. He recognized three pathological phases:

- (1) primary retinal disease,
- (2) secondary retinal involvement and vitreous organization,
- (3) ocular atrophy and repair.

In the first phase, the capillaries at the ora serrata are primarily involved, there is retinal oedema and endothelial proliferation. The retina heaps up, forming a loop at the ora serrata, but is not completely differentiated there, being normal for the age of the foetus elsewhere. There is no cellular inflammatory reaction. Heath considers that at this stage the condition is probably reversible.

In the second phase, leakage at the ora serrata causes the capillaries to proliferate. They then grow over the retina and detach it. They also proliferate retrolentally to form the membrane. Once the retina is detached the vessels return to their normal size.

The third phase is atypical. Heath realized that only in the early stages of the condition will the slide give a typical picture, all separations of the retina looking alike later. He did not attach importance to the very anterior detachment, as the retinae are inserted much more forward even in normal premature infants.

Wolff (1950a, b) stressed that the retrolental membrane is cyclitic—that is, inflammatory. It consists of clear strands, vessels, and proliferating cells of the unpigmented layer of ciliary epithelium. Some “noxious stimulus” acts in early pregnancy and the retina does not become apposited. Subretinal fluid, by its irritant action, causes the growth of the cyclitic retrolental membrane. The “noxious stimulus” would thus have to affect the eyes before the third month of gestation, when the clear and pigmented layers of the pars ciliaris retinae firmly join. Wolff emphasized that the detachment involves the oral and even the ciliary part of the retinal epithelium, whereas a detachment caused by—say—pseudoglioma always stops at the ora serrata. He therefore suggested that the detachment in retrolental fibroplasia starts anteriorly.

Bembridge and Jackson (1951) described nine cases studied pathologically. Their findings conform with those of Wolff. They concluded that the picture is one of inflammation of aetiology as yet unknown.

PRESENT INVESTIGATIONS

Our pathological material consists of three eyes enucleated ? glioma, of which Case 2 (above) supplied one, and the other two were obtained as follows:

Case 4.—Elsie R., aged 6 months, attended the Eye Clinic, Beckett Hospital, Barnsley. She was 7 weeks premature, and presented a typical bilateral picture, as described by Terry. Membrane full, no fundus seen, pupils fixed, anterior chambers shallow, no glaucoma.

The right eye was enucleated. This infant has since died from a superior sagittal sinus thrombosis.

Case 5.—Christine W., aged 4 months, was brought to the Eye Out-patient Dept., Beckett Hospital, Barnsley, in June, 1949. She was 8 weeks premature. Both eyes presented a typical late picture of retrolental fibroplasia, with grey vascularized membranes behind the lenses. The left eye was enucleated ? glioma. The pathological report was

one of retrolental fibroplasia. The right eye when examined recently (January 8, 1952) showed no change.

All the slides show a fairly uniform picture not different from that previously described by various authors. The retinae are completely detached and bunched behind the lenses. The detachment goes as far forwards as the pars ciliaris retinae. The retinae are in the foetal state and show attempts at rosette formation. The retrolental membrane grows from the region of the ciliary body, inserting itself between the lens and the retina. Posterior synechiae are present in all sections. The choroid is somewhat atrophic. There are no remnants of the hyaloid system of vessels. There is no evidence of angiomatosis, but some capillary overgrowth is seen anteriorly. There are no signs of focal inflammatory reaction. Scattered round cells are present in the uveal tract.

Aetiology

There are three distinct ways in which various authors approach the problem of the aetiology of retrolental fibroplasia.

The first is that of the obstetrician. The factors influencing the premature birth itself, which were carefully considered by many authors including Gilger (1949) and King (1950), are the following:

(a) intra-uterine bleeding,	(g) Rh factor,
(b) age of mother,	(h) chronic illness of the mother,
(c) multiparity,	(i) virus infection during pregnancy
(d) multiple foetus,	(e.g., rubella),
(e) sex,	(j) toxoplasmosis,
(f) race,	(k) vitamin A deficiency of the mother.

The factors of intra-uterine bleeding and virus infection received the closest attention. However—as Ingalls (1948a, b) pointed out—prematurity is connected with late uterine haemorrhages (6 to 7 months) but not with early ones (2 to 3 months). Since the fusion of the clear and pigmented epithelia of the pars ciliaris retinae (if we accept the idea that retrolental fibroplasia is a developmental anomaly) occurs at about the third month of intra-uterine life, it is clear that any factor disturbing this fusion would be expected to act before that time. The problem of virus infection of the pregnant woman as a cause of developmental anomalies of the foetus was brought to attention by Gregg (1941) in connection with rubella and is now a well-established fact. Toxoplasmic infection as a cause of intra-ocular inflammation is also well established. Though cases of retrolental fibroplasia have no statistical relation to any infection of the mother, Ingalls thinks that late uterine haemorrhage increasing foetal anoxia may be the cause of the ocular disturbance.

The second approach to the problem is that of the paediatrician. The condition does not come to notice before two weeks or more after the birth of a premature child, and it may be connected with the problem of rearing

such a baby. Terry enumerates the following factors as likely to act adversely after birth:

(a) precocious exposure to light,	(f) inability to assimilate vitamins,
(b) precocious closure of the ductus arteriosus,	(g) birth trauma,
(c) exposure to lower than intra-uterine temperature,	(h) physiological anaemia of prematurity,
(d) lack of maternal endocrine environment,	(i) precocious establishment of blood groups,
(e) precocious rise of blood pressure,	(j) intra-ocular inflammation.

Of these Terry regarded precocious exposure to light as the most important. Unsworth (1948) stressed the importance of anaemia or some unknown deficient blood factor. Strich (1945) blamed the "germicidal lamps" used for sterilization of air in many American maternity wards.

Owens and Owens (1949) and Appelbaum (1950) stress vitamin E deficiency, their reasoning being as follows:

Premature babies have defective fat metabolism and are usually put on a low fat diet, which would mean a smaller intake of fat soluble vitamins (A, D, K, and E). The requirements of vitamin E are increased when vitamin A or unsaturated fatty acids are administered in excess. Iron, as used in combating the anaemia of premature infants, further decreases vitamin E in the organism, and as the immature organism is generally more susceptible to vitamin E deficiency, this deficiency may be the causative factor. Extensive trials were conducted by Owens and Owens in Baltimore and some successes are claimed.

The third approach to the problem is that of the ophthalmologist. This consists in clinical observation correlated with pathological findings. However, neither the fundus oculi nor the slide gives a picture which could be classed in any of the main pathological groups (inflammation, degeneration, anomaly, etc.).

Clinical observation gives the impression of an active inflammatory process, but the slide seems to point to some developmental abnormality. In fact, all the authors quoted oscillate between these two possibilities. Their clinical and pathological observations differ very little; but so far as aetiology is concerned they either accept some more or less general developmental anomaly, *e.g.*, encephalo-retinal dysplasia (Krause, 1946) or generalized haemangiomas (Reese, 1949), or presume the operation of an "unknown factor" causing inflammation. None of these theories seems to me satisfactory, because none explains both the clinical and the pathological findings.

Hypothesis of Ischaemic Mechanism of Retrolental Fibroplasia

A. EMBRYOLOGICAL CONSIDERATIONS

(1) *Intra-Ocular Vessels*.—The interior of the human eye is supplied in the course of its development by three systems of vessels: the hyaloid system, which is transient, and the uveal and retinal systems, which persist into adult life.

(a) The hyaloid artery buds out from the internal carotid and is the precursor of the ophthalmic artery. Its ramifications, the vasa hyaloidea propria and the tunica vasculosa lentis, are the sole blood supply of the interior of the optic vesicle up to the 100-mm. stage, when a bulbous enlargement appears at the place of entry of the hyaloid artery into the eye (at the optic disk). The branches of the retinal artery bud out from this bulb and commence the vascularization of a slowly increasing territory of the retina round the optic disk. Before this time (at the 40-mm. stage) the vasa hyaloidea propria reach the peak of their development, sprouting into the secondary vitreous from the central vessel and reaching the inner wall of the optic vesicle, except for a narrow clear interval at the surface of the developing retina. After the 60-mm. stage they rapidly atrophy, but the hyaloid artery persists, and lying within Cloquet's canal it acquires a thick glial sheath. At its distal end the artery breaks into the meshwork of the tunica vasculosa lentis. At the time of the appearance of the tertiary vitreous and the zonula lentis (63-mm. stage), the capsulopupillary (lateral) part of the tunica vasculosa lentis is well on the way to complete atrophy. It is gradually severed from its anastomosis with the ciliary system of vessels by the outgrowth from the rim of the optic vesicle which will form the framework of the future iris. The posterior part of the tunica vasculosa, however, persists much longer. Its persistence depends on the blood flow from the hyaloid artery and this only begins to atrophy as late as the 7th month of gestation. The tunica vasculosa then starts slowly disintegrating; this process is normally finished at birth, but is never finished in the 7th month, as witness the observed hyaloid system at birth in premature babies. One cannot help wondering what is the significance of this persisting system of vessels, for it is separated from the avascular secondary vitreous by a glial sleeve and from the avascular lens by the lens capsule. I will return to this question later.

(b) In the adult eye the retinal system of vessels supplies all the retinal surface, as deep as its outer molecular layer. It does not—as a rule—anastomose; its terminal branches form loops at the ora serrata whence start the retinal veins. The process of developing an independent retinal circulation begins at the 100-mm. stage when the retinal arteries sprout from a swelling of the trunk of the hyaloid artery at the optic papilla. The diameter vascularized by them increases slowly and concentrically round the papilla. These retinal vessels do not reach the ora serrata before the 8th month of gestation. This time coincides closely with that of the disappearance of the tunica vasculosa lentis and the final involution of the hyaloid trunk.

(c) The uveal system of vessels concerns us here in only a few respects. The long ciliary arteries end in the circulus arteriosus major which is completed in the 6th month. From it run three sets of branches: large superficial vessels to the pupillary membrane, smaller vessels to the iris stroma, and recurrent vessels to the ciliary region. These last are the smallest and latest to develop, and do not reach the ciliary process—one branch for each processus—before the 8th month of gestation.

(2) *Ora Serrata and Ciliary Region.*—The rudiment of the ciliary muscle can be seen as a condensation of the associated mesoderm on the outside of the rim of the optic vesicle in the 3rd month of gestation. It develops *in situ* and thus remains much posterior to the angle of the anterior chamber until the 5th month. On the other hand, as the pars plana and pars ciliaris retinae

develop as an epithelial outgrowth from the rim of the optic vesicle, the so-called "insertion" of the ora serrata is situated much more forward in the foetus than in the adult. It is in fact inserted at the anterior half of the developing ciliary body in the 7th month, and is still at its posterior third in the 9th month. At birth (full term) it is just behind it (Mann, 1928, 1935). This means that if the retina be stripped of its pigmented epithelium in the eye of a 7 months' foetus, it will leave about half of the ciliary body bare.

B. MECHANISM OF RETROLENTAL FIBROPLASIA

The late atrophy of the trunk of the hyaloid artery and its anterior meshwork of branches—the tunica vasculosa lentis—seems to be connected with the nutritional requirements of the anterior portion of the neuro-epithelium of the eye. The blood supply of the pars ciliaris and pars plana is at the precarious stage in the 7th month of gestation. Starting at its proximal end, the hyaloid system begins to atrophy, and less and less blood reaches the tunica vasculosa. At the same time the terminals of the retinal artery have not yet reached the ora serrata and the ciliary processes underlying this epithelium are not yet vascularized from the *circulus arteriorus major*.

In normal circumstances the "taking over" of the blood supply to this region by the definitive system from the foetal system is well synchronized. A premature birth, however, with a consequent precocious failure of hyaloid circulation will cause ischaemia of this region followed by oedema. This process can occur either all round the circumference of the ora serrata or in certain sectors, depending on the regional variation of the vasculature, that is on the irregularities of the advancing line of budding retinal capillaries. In response to local ischaemia there is an attempt at reaching the ora serrata from the retinal system. Local anoxia and the accumulating metabolites act as vasodilators and as a stimulus for exuberant budding of the terminal capillaries. Angioblastic growth of this nature has been observed pathologically.

Where the capillaries succeed in vascularizing the area (probably mainly depending on the ratio of hyaloid artery atrophy to retinal artery development) the condition may regress. Where they do not succeed the oedema progresses into a frank detachment. The subsequent proliferation of the cyclitic membrane, mild inflammatory reaction in the uvea, and posterior synechiae formation, result from the detachment existing in a developing eye.

There are three reasons why the premature birth may put this process into motion:

(i) The hyaloid system of vessels closes precociously. This may be caused by the establishment of lung circulation and better oxygenation of blood. Similarly, another embryological channel—the ductus arteriosus—closes after birth for the same reason.

(ii) The physiological anaemia of a premature baby and the lower oxygen-carrying power of the blood will aggravate the local anoxia of the precariously ischaemic region under discussion.

(iii) Exposure to light and establishment of pupillary (? accommodative) reactions will put additional metabolic stress on the ciliary region, apart from its mechanical implications.

Conclusions

A. CLINICAL.—By this hypothesis the clinical picture of retrolental fibroplasia is explained stage by stage:

(1) Premature birth of the subject: precocious closure of the hyaloid artery, anaemia, and precocious exposure to light are super-imposed on the vascular arrangements prevailing in the 7th to 8th months of pregnancy.

(2) Period of normality and disappearance of the hyaloid system before the condition is observed: the fibroplasia does not develop as long as the hyaloid system of vessels can carry on its function.

(3) Dilatation and tortuosity of vessels as the first clinical sign of the disease: an attempt to establish the circulation of the anterior part of the retina is caused by peripheral ischaemia and metabolic breakdown.

(4) Peripheral patches of retinal oedema and vitreous haze: the accumulating metabolites cause the local oedema to involve increasing areas of the retina which thus become visible ophthalmoscopically; the vitreous in front of these areas is affected secondarily.

(5) Retinal detachment: the natural consequence of progressing retinal oedema.

(6) Cyclitic membrane formation: a secondary inflammatory reaction provoked by the existence of a detached retina, accumulation of subretinal fluid, and metabolic failure. The anterior synechiae and mild inflammatory reaction in the uveal tract are of the same kind.

(7) Return of retinal vessels to normal when the detachment is established: when the retina degenerates, its metabolism and nutritional requirements drop; thus the stimulus for vascularization ceases to exist.

(8) Microphthalmos: the eye stops growing when the cyclitic membrane is formed.

(9) Regression: this may occur with restoration to normal or as an arrest of the process. In the early stages of oedema or shallow detachment, it occurs as a result of the successful establishment of circulation by retinal terminals. In the later stages, the detached retina can become spontaneously re-attached—a phenomenon known to occur in other kinds of detachment. The established cyclitic membrane, however, cannot regress.

B. PATHOLOGICAL.—The main pathological features in eyes affected by retrolental fibroplasia are:

very anterior detachment, abnormal structure of the retina, angioblastic activity, and cyclitic membrane.

(1) Every anterior detachment of the retina in a foetus 7 to 8 months old or less will involve it at least as far as the anterior half of the ciliary body. As we know, that is the normal position of the ora serrata at this stage.

(2) The structure of the retina does not differ from the normal structure for the age of the foetus. The anterior parts degenerate because of ischaemia. The

attempt at rosette formation probably occurs when this foetal retina, with its still-not-quite differentiated and multipotent cells, becomes detached and degenerates.

(3) Angioblastic overgrowth and the formation of cyclitic, inflammatory membrane, as previously accounted for.

Summary

The clinical picture of retrolental fibroplasia is described, the pathological features are discussed, and the present aetiological conceptions summarized.

Three new clinical cases of an arrested course of the condition are described, and the pathology of three sections is studied.

An hypothesis of an ischaemic mechanism of retrolental fibroplasia is advanced and correlated with the clinical and pathological findings.

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