RETROLENTAL FIBROPLASIA

BY

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Retrolental fibroplasia appears to be a new disease. Probably the first cases were recognized in the United States about 1936 but ideas about the disease did not crystallize until Terry first wrote about retrolental fibroplasia in 1942. In his earliest publications he reported infants with bilateral retrolental fibrous masses which appeared during the first six months of life. It was on this finding that Terry proposed the name. He was of the opinion that the condition was the result of a 'fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens'. This pioneer work aroused widespread interest among paediatricians and ophthalmologists. Terry's early death four years later prevented him from joining in the modifications of his original views which are now accepted. He was describing a new hazard of prematurity which, in his experience, resulted in blindness in 20% of infants whose birth weight was below 3 lb.

Owens and Owens (1949) were the first to report on the examination of fundi of premature infants from birth onwards and they observed some of the early changes which eventually progress to the picture of retrolental fibroplasia as described by Terry. Reese and Blodi (1951), also Lelong, Renard, Rossier, Lemasson and Michelin (1951), confirmed the observations of Owens and Owens concerning the early stages of the disease. Reese and Payne (1946), Reese (1949) and Reese and Blodi (1950) in a series of publications made it clear that retrolental fibrous masses occurring in premature infants are rarely the result of either persistent hyperplastic primary vitreous or of retinal dysplasia. The former occurs in full term infants, affects one eye only, is detectable clinically at birth and is not necessarily associated with any other congenital defects. Retinal dysplasia is also found in full term infants but always affects both eyes and is associated with congenital abnormalities in the central nervous and cardiovascular systems.

Material and Methods of Investigation

This report is based upon a study of 56 premature infants suffering from retrolental fibroplasia.

The fully developed pictures of persistent hyperplastic primary vitreous, retinal dysplasia and retrolental fibroplasia are almost indistinguishable, since one retrolental fibrous mass looks much like another. Therefore it is no longer possible to regard the white pupil (leukokoria) as an important diagnostic feature, but it is necessary instead to look for earlier changes in the fundus. In this series the policy adopted in order to detect the earliest retinal changes has been that every premature baby whose general condition allows of it has a thorough ophthalmoscopic examination at the age of 7 days. The pupils are routinely dilated with 1% homatropine and 2½% phenylephrine. Satisfactory examination can be completed without any anaesthetic, but each such examination may take as long as 30 minutes. Giving the infant a teat to suck usually overcomes any resistance to the examination. Only twice has sedation been required (both infants were over 4 months old) and on these occasions rectal pentothal was excellent. Following the first examination each infant is carefully re-examined at weekly intervals until discharged from the premature baby unit. It is not possible to see these babies so frequently once they have left hospital, so as a compromise they are re-examined as outpatients at fortnightly intervals until they reach the age of 6 months. Only by such a regular follow-up can the natural history of this disease be fully unfolded. Examinations at all stages are of course made more often when there is any reason to regard the retina as abnormal. On several occasions the retinal picture has been noted to change beyond recognition in as short a time as four days. The earliest age at which changes were noted was 8 days and the oldest baby showing early lesions was one of 5½ months. It should be pointed out that retinal haemorrhages may, rarely, be present in the eyes of premature

FIG. 1.

FIG. 1.—D.C. Birth weight 2 lb. 11 oz. Age 6 weeks. Right eye. Shows full retinal veins, tortuous vessels, new vessel formation at periphery and a central retinal haemorrhage. This retina was normal 30 days before this drawing was made.

FIG. 2.—E.T. Birth weight 4 lb. 0 oz. Age 8 weeks. Right eye. Shows full veins, slight tortuosity of the vessels, flat retinal detachment in the upper temporal area. There are two folds of detached retina at the periphery and moderate new vessel formation.

FIG. 3.—B.O. Birth weight 3 lb. 8 oz. Age 5½ months. Left eye. Central retinal detachment raised into a fold obscuring the nerve head. This retina was normal two weeks previously.

FIG. 3.

infants at the end of the first week, just as they are in some full term infants. These haemorrhages are thought to have occurred during labour; they are absorbed spontaneously without apparent sequelae.

Description of the Disease

As the early stages of retrolental fibroplasia are still relatively unfamiliar in this country it is proposed to outline the development of the disease adding some previously unrecorded features. Figs. 1-6 illustrate many of these. The earliest clinical sign is an excessive fullness of the retinal veins (i.e. exceeding that degree of fullness which is normal for premature infants). Increasing tortuosity of the retinal arteries occurs next, a change which soon involves the veins. The tortuous veins may even

FIG. 2.

form loops (see Fig. 6). The distribution of these changes in the retina is variable; one segment may be involved several days before changes are seen in a neighbouring area. Soon the retina is noted to be oedematous and new blood vessels appear, mainly at the periphery of the retina. All retinal vessels show marked pulsation. Retinal haemorrhages, varying in number, size and distribution, occur in about one quarter of the cases. The vessels mentioned above proliferate rapidly

FIG. 4.—A.J. Birth weight 2 lb. 8 oz. Age 4 months. Left eye. Shows vessel changes as in preceding figures. There are also peripheral haemorrhages and peripheral retinal detachment. In the upper temporal area a vessel is partly obscured by retinal oedema. Three months later this retinal picture was unchanged apart from the absorption of the haemorrhages.

FIG. 5.—E.K. Birth weight 3 lb. 9 oz. Age 3 months. Shows a fine film of new vessels projecting into the vitreous. Note pigment deposits at its edges. Insets show capillary tufts arising from retinal vessels and projecting into the vitreous.

FIG. 5.

FIG. 6.—E.C. Birth weight 3 lb. 1½ oz. Age 2 weeks. Shows venous 'loop'.

FIG. 6.

and extend into the vitreous as little capillary tufts which are visible ophthalmoscopically. Less frequently these vessels form an extensive, lace-like film (see Fig. 5), also projecting into the vitreous. The edges of such a film may show pigment deposits. A mild and transient papilloedema can usually be observed. By contrast the retinal oedema may become very extensive and as the disease progresses it is associated with detachment of the retina. Commonly, detachments occur first at the periphery and are flat in type but may on occasion be either central or in the form of a fold. If the disease advances fibrous tissue develops at the periphery of the retina. As fibrosis increases it extends across the vitreous obscuring further changes in the retina. The vessels in this new-formed fibrous mass initially appear veiled as if half-buried in a woolly surface: later they become clearly visible along their length. Of 22 babies in whom the disease has been observed from its early stages, i.e. changes in retinal blood vessels only, 70% have not progressed to 'membrane' formation, the

disease appearing to have become arrested. Following such an arrest there may be varying degrees of improvement in the retinal picture which may thereafter remain stationary over several months. The time relationships of the various stages are very variable; moreover the phases may overlap. The shortest time in which the eyes have been noted to advance from a normal fundus to a complete leukokoria has been five weeks. To state the longest interval between the first and the final stages would not have an equivalent significance because of the interposed periods of quiescence. The average time from the appearance of early lesions to a leukokoria is about two months.

An attempt has been made to assess the changes in intraocular tension which apparently occur as the disease develops. Initially there is hypotension and enophthalmos; this is a short-lived phase associated with or even preceding the early venous engorgement. The next stage is one of increased intraocular pressure and this stage is associated with the vascular proliferation in the retina. Those cases which go on to 'membrane' formation concurrently develop a reduced intraocular pressure, enophthalmos and finally microphthalmos. The anterior chamber is shallow from the early stages of the disease.

The late complications of the disease deserve passing mention. The anterior chamber of the eye becomes progressively shallower and may become obliterated, possibly with the development of corneal opacities (though this latter is not a complication which has occurred in this series). In all advanced cases the iris degenerates. The most distressing complication is that of glaucoma; this occurred unilaterally in one infant and necessitated enucleation.

Associated abnormalities do not form part of the picture of retrolental fibroplasia. No increased incidence of cutaneous haemangiomas has been seen, and only one infant had a congenital heart lesion, apparently an interventricular septal defect.

Regarding mental development, of 36 babies now over 9 months of age, all but three are apparently mentally normal; these three are grossly retarded.

Incidence

Until 1949 no case of retrolental fibroplasia had been observed among the infants nursed in the premature baby units at St. Mary's and the Duchess of York Hospitals in Manchester. Since then many cases have been discovered and it was therefore decided to review all surviving infants who had been in these two units between January 1, 1947, and December 31, 1951, with a view to discovering the real incidence of the disease over this period. All infants discharged from the units were requested to attend for an examination at the hospital. Of those who failed to do so, some were examined at home. The remainder were not seen, but the fact that the child's vision was apparently normal was accepted when the information came from a health visitor or a reliable mother, provided that the child was over 1 year old. If none of these conditions were fulfilled the case was excluded from the survey.

Satisfactory information was obtained about 629 infants and represents 90% of those still alive when the enquiry was made. Table 1 shows the number of cases of retrolental fibroplasia which occurred in the different weight groups over this period. It will be seen that the incidence has risen sharply. Only one case was found among the older children. The increasing incidence cannot be correlated with an increasing survival rate in these units, for though the survival rate has varied a little over the five years it has developed no definite pattern of change. This finding is in agreement with statements from many centres in the United States (Kinsey and Zacharias, 1949).

In order to learn whether the disturbing incidence of retrolental fibroplasia in Manchester was confined to the premature baby units, those premature infants who were born and nursed outside these two

TABLE 1

INCIDENCE OF RETROLENTAL FIBROPLASIA IN 629 SURVIVING INFANTS SINCE 1947

Year	Under 3 lb.		3-3½ lb.		3½-4 lb.		Over 4 lb.	
	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia
1947	4	1	11	0	31	0	72	0
1948	7	0	13	0	27	0	92	0
1949	9	2	18	0	30	0	50	0
1950	16	5	21	2	38	2	75	2
1951	13	12	22	12	30	9	50	9
Total	49	20	85	14	156	11	339	11

units during 1951 were reviewed and examined ophthalmoscopically. No case of retrolental fibroplasia was discovered.

Aetiology

An analysis of the obstetrical notes of the mothers of the affected infants revealed no relevant common factor apart from the onset of spontaneous premature labour. This finding would appear to exclude the possibility that any known disease or treatment of the mother could be concerned in the development of the disease. A similar analysis of the infants' treatment and progress also failed to indicate any common factor other than that all, except one, had been nursed in oxygen tents. Further examination of this factor disclosed that changes in the incidence of retrolental fibroplasia at St. Mary's Hospital had been closely linked with changes in the method of oxygen administration. Before 1949 the premature babies were given oxygen by face mask as a routine and were only in very rare emergencies placed in an oxygen tent. (It is known that the case of retrolental fibroplasia which occurred in 1947 had been nursed in an oxygen tent.) In December, 1949, oxygen tents were introduced on the unit and were used routinely for all infants under 3 lb.; in the following months three cases of retrolental fibroplasia occurred in this weight group. In November, 1950, it was decided to nurse *every* infant on the unit naked in an oxygen tent. Following this, infants whose birth weight was over 3 lb. began to develop the disease. The next change came in March, 1951, when soft plastic covers were introduced for use on the Sorrento-type cot. These made it possible to maintain the infants' temperature without using a tent and resulted in the infants being removed earlier from high tensions of oxygen. Almost synchronous with this change there was a further increase in the number of affected infants of birth weight up to and including 4 lb.; about 75% of the infants in this weight group showed evidence of the disease during this period. It was later discovered that an atmosphere of 80-85% oxygen developed within the tents when the oxygen flow was 2 litres/min.; when the flow was reduced to 0.5 litres/min., which was the minimum rate possible with the apparatus, there was still 60% oxygen inside the tents. Therefore the infants on removal from the tents had been subjected to a sudden reduction in the percentage of the oxygen they were breathing of from 60% to 20%. In October, 1951, the use of oxygen was reduced to a minimum and its withdrawal was carefully graded. Since that time only one serious case and two relatively mild cases of retrolental

fibroplasia have occurred. Fig. 7 illustrates these various facts. It should be pointed out that these changes were not deliberately made with a view to influencing the incidence of the disease. The apparent association between variations in oxygen administration and numbers of affected babies has only been discovered in retrospect.

Fig. 8 shows the number of premature infants up to 4 lb. birth weight that survived during each month of 1950 and 1951 in one of Manchester's large maternity hospitals. This hospital contains no specialized units, the premature and full term infants being nursed together. Oxygen tents are not used in this hospital; the infants receive oxygen by face-mask only when necessary. None of these infants has been notified as being blind due to retrolental fibroplasia. In the two premature baby units almost every severe case of the disease progressed to complete blindness and those that did not actually lose all vision possessed definite retinal changes. It therefore seems fair to assume that no severe case of retrolental fibroplasia developed in the infants nursed in this hospital and this assumption is strengthened by the observation that the fundi of about one-third of these infants which have so far been examined are all normal.

Treatment

Treatment of a disease whose aetiology is uncertain has been difficult and largely empirical. In some of our earlier cases we attempted treatment with cortisone and A.C.T.H. Cortisone was given to eight infants of whom seven had a well-developed 'membrane' at the start of treatment. As might have been expected there was no improvement. The eighth case developed a 'membrane' during treatment. A.C.T.H. was given to nine infants who had earlier retinal changes. The results in this group were variable. In one infant there was minimal peripheral 'membrane' formation at the beginning of treatment and this progressed to a bilateral leukokoria during treatment. Of the other eight cases, one developed a small area of detachment during treatment and two showed serious extension of the disease after completion of the treatment. In one of these bilateral leukokoria developed and in the other the retinal detachment increased in extent. In the remaining five cases there was an apparent arrest of the disease synchronous with the treatment, and although they are still too young for a full assessment of their vision, apparently see quite well. The potential dangers of cortisone and A.C.T.H. therapy must not be overlooked and must be balanced against the uncertain benefits. In view of the reports by

Fig. 7.—Diagram illustrating the incidence of retrolental fibroplasia related to the method of oxygen administration in premature infants at St. Mary's Hospital, Manchester.

Szewczyk (1951) it was decided to treat early cases of retrolental fibroplasia by replacing them in high tensions of oxygen. Six infants have so far been treated in this way with dramatic results. The

vascular engorgement disappeared within 48 hours, capillary tufts ceased to be visible and retinal oedema subsided. The speed with which these changes took place greatly exceeded the rate at

FIG. 8.—Diagram illustrating similar data to that of Fig. 7, but relating to another series of infants treated at a large maternity hospital in Manchester.

which spontaneous regression occurs. Two cases are still in oxygen tents. The other four infants were kept in a high concentration (80%) of oxygen for four weeks and then the oxygen was withdrawn very gradually. In three cases the retina remained normal after the babies were removed from oxygen. The fourth infant's subsequent progress has not been so satisfactory, perhaps because of the more advanced changes with a definite retinal detachment which existed at the time of replacement in oxygen.

Discussion

In the United States a high incidence of retrolental fibroplasia was reported from Boston, and only from Boston, for some considerable time. For example, between 1938 and 1942 in Boston 20% of infants whose birth weight was less than 3 lb. were found to have the disease, whereas in Baltimore between 1935 and 1941 there were no reported cases.

In considering these figures it is necessary to bear in mind the thoroughness with which these infants were followed after leaving hospital; in Boston 85% of the infants were traced as opposed to only 33% in Baltimore (Kinsey and Zacharias, 1949). In addition to the completeness of a survey the criteria of diagnosis are of equal importance in assessing the incidence of the disease. However in the series reported here, if the diagnosis had rested upon a complete leukokoria, thus omitting many cases, an increase in the number of affected infants would still have been obvious (Table 2).

It is of interest that endothelial proliferation is

known to occur as a result of anoxia. It remains to be discovered whether such proliferation can be histologically identified in the early phases of this disease. The retinal picture in the early stages presents many of the features suggestive of venous obstruction. Apart from the venous engorgement, the looping of the veins and the capillary tufts are similar to features described by Ballantyne and Michaelson (1947) in obstruction of the retinal

TABLE 2
NUMBER OF CASES PROGRESSING TO LEUKOKORIA

Year	No. of Cases of Retrolental Fibroplasia developing Leukokoria
1947	1
1948	0
1949	2
1950	10
1951	18

veins in adults. The larger lace-like vascular formations projecting into the vitreous seem comparable with those described by Duke-Elder (1940) as occurring with retinal vein obstruction. In studying these cases it has been observed that the longer the venous engorgement lasts the greater is the new vessel formation, and if retrolental fibroplasia has its origin in a vascular obstruction it would seem that the length of time for which this operates determines the final outcome. Presumably only when blood vessels have proliferated into the vitreous can fibroblasts associated with them give rise to the fibrous mass. If on the other hand the obstruction subsides in a relatively short time, the prognosis is good provided that extensive retinal detachment has not already occurred. That such detachment can be disastrous is shown by the fact that one of our cases who has no retrolental membrane is totally blind because of complete retinal detachment.

From this it follows that once we are certain of the aetiology of this process the disease must receive a new name. Even in our ignorance the term 'retinopathy of prematurity', introduced recently by Heath (1951), has much to recommend it. Without a shift of emphasis to the vessel changes in the retina it is more difficult to include, in an analysis of the incidence of the disease, those cases which have become arrested at an early stage and regress leaving no permanent scar.

The facts summarized by Figs. 7 and 8 suggest that the method of oxygen administration plays an important part in the development of retrolental fibroplasia. In addition the dramatic improvement which has been observed to follow closely upon the

replacement in an oxygen tent of an infant with early retinal changes makes it impossible to ignore the relevance of oxygen tensions in the control of the disease. These two observations might superficially appear to contradict each other. However, they can be reconciled by supposing that retrolental fibroplasia may develop when the tissues of a premature infant undergo a sudden reduction in the tension of oxygen available to them. The initial changes of the disease will, however, rapidly regress when the lowered tension is restored. It would appear that an infant nursed in 60% oxygen and then suddenly transferred to normal air becomes liable to develop the disease, whereas an infant receiving oxygen by face mask only, never having been acclimatized to a high tension of oxygen, cannot subsequently be deprived of it; apparently such an infant does not develop retrolental fibroplasia. (There has been only one exception to this among 56 cases.)

If it is true that the method of administering oxygen is of great importance in the development of retrolental fibroplasia it may be possible to explain the patchy distribution of the cases and the sudden fluctuations in incidence on these grounds. However, this is difficult to do in retrospect, for the exact date of the introduction of apparently minor changes in methods of oxygen administration may be impossible to trace as the details of such changes are often worked out by the sister in charge of the unit and may actually vary with changes in nursing staff.

If the facts put forward here are confirmed by further observations then the problem will no longer involve the search for an aetiological agent and for a satisfactory treatment. Instead it will remain to be shown how it is that a change in oxygen tension, coupled with the physiological processes of the premature infant comes to play such an important rôle in this disease.

Summary

During the past five years 56 cases of retrolental fibroplasia have occurred among premature babies in two units in Manchester. A survey of 629 infants has shown that only three cases occurred before 1950.

The early stages of the disease are outlined. Phases suggestive of venous obstruction are illustrated.

Support is given to the term 'retinopathy of prematurity'.

On six occasions the early changes of the disease have been noted to regress rapidly upon replacing the infant in high tensions of oxygen.

Variations in the method of administration of oxygen appear to be closely linked with the incidence of retrolental fibroplasia.

It is suggested that retrolental fibroplasia can develop when the tension of oxygen available to the tissues of the premature infant is suddenly lowered.

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