RETROLENTAL FIBROPLASIA

BY

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Recent investigations in America have shown that blindness must be added to the recognized hazards of premature birth. Terry was the first to describe, in 1942, a disease of the eyes which occurs in premature-born infants. He called this disease "retrolental fibroplasia." He noticed that in a number of prematurely born infants an opaque vascularized membrane forms behind the lens after birth, both eyes being affected. He studied this condition for several years, and in 1945 came to the conclusion that 10% of the infants born prematurely in the Boston Lying-in Hospital and weighing 3 lb. (1.4 kg.) or less at birth can be expected to be blind from retrolental fibroplasia. Since that date a number of ophthalmologists and paediatricians in the U.S.A. have reported on this disease.

W. C. Owens and E. U. Owens followed from birth 214 infants born prematurely in Johns Hopkins Hospital. Their investigations were limited to the children whose birth weight was $4\frac{1}{2}$ lb. (2 kg.) or less. The infants were examined from birth at monthly intervals until the age of 6 months, and at bimonthly intervals from 6 months to 1 year. None of these infants had retrolental fibroplasia at birth, but nine developed it in post-natal life. The eyes of these infants were normal at birth.

Between the second and the fifth month of post-natal life the infants who developed retrolental fibroplasia began to show angiomatous dilatations of the retinal vessels with oedema of the retina. After a short time the retina became detached. At first the detachment was limited to the peripheral parts of the retina, but in course of time the folds of the detached retina coalesced and a total retinal detachment took place. Bands of fibrous tissue developed from the detached retina and extended into the vitreous.

In the final stage of a fully developed case of retrolental fibroplasia an opaque vascular membrane could be seen behind the lens. In the fully developed stage of the disease the eyes may be smaller than usual (microphthalmia), the anterior chamber is usually shallow, the iris is usually atrophic and may be bluish in colour (foetal blue colour), and the margins of the pupil are adherent to the lens (posterior synechiae). The infants may sometimes develop a secondary nystagmus. The eyes become blind. In some cases perception of light may be present.

These reports about the development of retrolental fibroplasia in premature infants are therefore of importance to paediatricians and obstetricians.

Is the disease prenatal in origin or is it post-natal? A number of observers are of the opinion that the disease of the eyes of premature infants is only one manifestation of a generalized maldevelopment (dysplasia) of the vascular and nervous tissues of the foetus in antenatal life. They point out that these infants usually

show other congenital defects—haemangiomas of the skin and retarded mental and physical development. These views are of great interest to obstetricians, who are now searching for all possible causes of the development of the disease in antenatal life. Virus infections, toxoplasmosis, and vitamin deficiencies during pregnancy have been put forward as likely agents.

The clinical observations of Owens and Owens, that this eye disease shows itself in post-natal life, have stimulated research by paediatricians. Vitamin-E deficiency with excess of vitamin A in the food of the premature infant is suggested by some as the cause of the onset of the disease.

The following two cases are reported because they show the typical manifestations of retrolental fibroplasia. The post-mortem pathological investigations of the first case may throw further light on the causation of the disease.

Case 1: Retrolental Fibroplasia in a Full-term Infant Associated with Multiple Congenital Deformities

Family History.—Both parents healthy. No family diseases. No consanguinity. Mother aged 32: group A, Rh-positive. Two previous pregnancies, both going to term: first baby died 36 hours after birth from pneumonia. Birth weight 8 lb. (3.6 kg.). Second baby, full-term infant of 8 lb. 11 oz. (3.9 kg.); now fit and normal, aged 6 years.

Pregnancy.—Mother was quite well until seventh month, then developed slight backache and oedema of the ankles, with moderate hydramnios.

Labour.—Medical induction on September 16, 1949, five days after expected delivery. Normal vertex delivery, placenta complete, membranes ragged. There were about 6 pints (3.4 litres) of amniotic fluid.

Birth Weight.—This was 6 lb. 12 oz. (3.1 kg.). The baby was vigorous, but had multiple congenital deformities: mild micrognathia, cleft soft palate, mild talipes equinovarus, and heart slightly enlarged to the right. No haemangiomas were found. No defect of the eyes noticed at birth, and there was no eye infection. The baby's progress was slow, as the cleft palate made feeding difficult.

At 5 Weeks.—Bilateral opacities in the eyes were first noticed by Dr. Helen Mackay. Examination of the eyes showed these to be retrolental (J. Minton). Head circumference was then $13\frac{1}{4}$ in. (35 cm.).

At 3½ Months.—Admitted to Queen Elizabeth Hospital for investigation. On examination: Restless puny baby, weighing 7 lb. 9 oz. (3.4 kg.), with micrognathia, cleft palate, and talipes. No haemangiomas of the skin. When put on her side she frequently arched her back and lay with her head retracted, and the legs tended to cross when she was picked up, but there was no true spasticity. She appeared to be mentally defective. The eyes showed bilateral retrolental opacities, intermittent nystagmus, and there was alternating concomitant convergent squint. No attempt was made to follow light.

Report of Examination of Eyes under an Anaesthetic, January 13, 1950 (J. Minton)

"Left Eye.—Optic disk pale. Retinal vessels small but otherwise normal. Small degenerate retinal areas were present around the disk. A whitish vascular mass was seen at the equator of the eye: this was situated between 3 and 6 o'clock. The mass was mobile, and when the eye was pushed inwards the vascular mass moved and covered the pupil. This vascular structure was thought to contain a part of the detached retina. **Right Eye.**—The optic disk could not be seen. A red reflex was present in the outer part of the eye. A vascular whitish mass was present behind the pupil from 1 to 7 o'clock. This was probably a

detached retina. There was no evidence of any lens opacities in either eye and there were no posterior synechiae."

The baby was then put on vitamin E, 3 mg. thrice daily, working up to 6 mg. thrice daily, over two weeks, but a few days after admission she developed gastro-enteritis, and on February 5 she died, aged 5 months.

Post-mortem Examination

Apart from the deformities previously mentioned, there were a patent ductus arteriosus, an unusually small spleen, and changes in the small intestine due to gastro-enteritis. The brain was small, the left cerebrum being slightly smaller than the right, and the optic tract was smaller than normal. The convolutions were entirely absent over both halves of the cerebrum.

The baby's eyes were removed and sent to the Institute of Ophthalmology, where they were examined by Dr. Norman Ashton, who reported as follows:

"Both eyes appear moderately microphthalmic. *Right Eye.*—There is a shadow crossing behind the lens from 11 o'clock to 5 o'clock. Total retinal detachment. *Vertical Section.*—The cornea, iris, and corneo-iridic angle show no abnormality. The lens is healthy. Situated immediately behind the lens, and especially to one side, there is a mass of fibroplastic tissue which is partially calcified. To this tissue the totally detached and degenerate retina

FIG. 1.—Case 1. The right eye (whole section) shows fibroplastic tissue situated immediately behind the lens. To this tissue a totally detached and degenerate retina is adherent. At one side the detachment has extended beyond the ora serrata, and on the other the detachment ends at the ora.

FIG. 2.—Case 1. The retinal detachment, including a part of the pars plana.

FIG. 3.—Case 1. Hypoplastic brain, showing almost complete agyria.

is adherent; on one side the detachment has extended beyond the ora serrata and has involved about half of the pars plana, while on the opposite side only a small portion of the pars plana is detached (Figs. 1 and 2). In some areas there is marked vascularization of the retrolental connective tissue. The choroid and ciliary body are normal and show no inflammatory reaction. The sclera shows no abnormality. There is early atrophy and gliosis in the optic nerve. *Left Eye, Horizontal Section.*—The condition of the left eye is exactly similar except that the detachment does not extend beyond the ora serrata.

"This case would appear to be a perfect example of the association between anomalies in the eyes and brain, as described by Krause (congenital encephalo-ophthalmic dysplasia). The cerebrum is markedly hypoplastic, and apart from the parieto-occipital sulcus it appears to be agyric." (Fig. 3.)

Comment on Case 1

In this case retrolental fibroplasia was found in a full-term infant, in association with other congenital abnormalities: (1) cleft soft palate, (2) patent ductus arteriosus, and (3) mental defect due to hypoplasia of the brain. There is no doubt that some unknown agents caused the maldevelopment of the brain, the soft palate, and the heart in the antenatal life of the infant. At the same time the development of the eyes was also affected. The mother carried the infant to full term, and at birth the eyes looked normal. The retrolental opacities appeared in post-natal life. These opacities were due to the formation of a vascular fibroplastic tissue, which included a degenerated detached retina. The detach-

ment of the retina in the right eye extended beyond the ora serrata and involved about half of the pars plana of the ciliary body.

Embryologists have shown that in the pars plana the clear and pigmented cells should unite between the third and fourth months of foetal life and that the union should be firm; the presence of the pars plana in the vascular fibroplastic tissue shows that the union did not take place in the right eye, and that the fibroplastic reaction started before the union could have been established. In the left eye the retinal detachment did not extend beyond the ora serrata. Evidently the vascular fibroplastic process started after the union of the pars plana was completed.

In November, 1949, the Section of Ophthalmology of the Royal Society of Medicine had a discussion on retrolental fibroplasia. Mr. Eugene Wolff demonstrated sections of an eye excised from a prematurely born infant. The infant was nine weeks premature, and weighed at birth 2½ lb. (1.1 kg.). The left eye of the infant was excised at the age of six months. Eugene Wolff's sections showed an appearance similar to our case.

The post-mortem findings of our case and the pathological report of the eyes suggest that the cause of retrolental fibroplasia should most probably be looked for in the intrauterine life of the foetus, and that premature birth may be the result of the same noxious influences.

Case 2: Retrolental Fibroplasia in a Premature Infant Now Aged 2 Years

Family History.—Both parents healthy. No family disease or blindness. No consanguinity. First child. No miscarriages.

Pregnancy.—Mother perfectly well throughout, but went into labour 14 weeks before expected date.

Labour.—Normal labour. Thirteen hours. Vertex delivery. Placenta unhealthy.

Birth Weight.—2 lb. 8 oz. (1.1 kg.). Baby cried well. Colour good. Kept in oxygen tent for 16 days. Gained steadily from fifth day onwards.

Feeding.—Expressed breast milk for six weeks, then half-cream National Dried Milk. No extra protein. At 6 weeks, orange juice 3 min. (0.18 ml.) and cod-liver oil 3 min. daily. No other vitamins given.

At 1 Month.—Discharge from both eyes for two weeks. Treated with penicillin eyedrops.

At 2 Months.—Discharged from maternity home weighing 5 lb. 1 oz. (2.4 kg.). No abnormality of eyes noticed at this time.

At 4 Months.—Mother first noticed "white mist" over the eyes, and that the baby did not follow objects with the eyes. She thought the baby had some perception of light, as she disliked bright sunlight.

At 9 Months.—Referred to one of us (J. M.) for investigations into cause of blindness. Posterior synechiae were then present with bilateral opacities behind the lens.

Investigations.—W.R., Kahn, and gonococcus complement-fixation tests negative in serum and C.S.F. Blood count, urine, and radiograph of skull were normal.

At 10 months the baby developed measles, without complications, and at 2 years of age she was admitted to Queen Elizabeth Hospital for investigation.

Milestones of the case are: first teeth at 11 months; patient did not sit up till 1 year old; at 2 years she walks well and talks a little.

Examination showed her to be a thin but healthy child who was blind. There were no haemangiomas of the skin, no clinical abnormality in the C.N.S., and no nystagmus. Intermittent alternating convergent squint was present.

Report of Examination of Eyes under an Anaesthetic (J. Minton)

"Both eyes are smaller than normal. Intraocular tension is normal. **Right Eye.**—Cornea clear and of normal dimensions. No keratic precipitates or opacities present. Very shallow anterior chamber. Iris atrophic at the pupillary margin. The rest of the iris has a normal pattern. Pupil irregular, with multiple small and large posterior synechiae adherent to the lens, which is clear: no opacities (Fig. 4). A grey mass is lying in the vitreous a good way behind the lens. This is most probably a detached retina. With an ophthalmoscope a yellowish light reflex can be obtained from the nasal side. Pressure on the temporal side of the globe causes a movement of the temporal part of the detached retina. **Left Eye.**—Cornea clear, normal dimensions. Shallow anterior chamber. Iris atrophic. The lens has no opacities. The pupil is irregular, and more dilated than the right. A number of posterior synechiae are adherent to the lens. A grey mass is present in the vitreous, a good way behind the lens. This mass is most probably a detached retina. With an ophthalmoscope a faint yellowish light reflex can be obtained from the centre of the detached retina."

FIG. 4.—Case 2. A drawing of the right eye, showing atrophic iris. The pupil is irregular, and posterior synechiae are adherent to the clear lens. A grey mass is lying in the vitreous.

Case 2 is a typical case of retrolental fibroplasia in a prematurely born infant without any other congenital abnormalities. She is not mentally retarded.

Incidence of the Disease

Retrolental fibroplasia seems to be more prevalent in the U.S.A. than here. Owens and Owens and Gilger found an incidence of 7% in prematurely born infants weighing 4½ lb. (2 kg.) or less at birth.

American and British investigations have shown that its incidence is inversely proportional to the birth weight of the premature infants. That explains the high figure of 23% in Boston (Terry, and Clifford and Weller) amongst premature infants weighing under 3 lb. (1.4 kg.) at birth.

In Great Britain Dr. Mary Cross has investigated 4,000 cases of premature births in the City of Birmingham. These cases were followed up to the age of 1 year. Only four cases of retrolental fibroplasia have been found among them. Dr. Mary Cross gave the following figures of its incidence: "0.1% of all prematurely born babies, 0.8% of babies under 4 lb. at birth, 4.2% of babies under 3 lb. at birth."

The latest reports from America are as follows: Hepner, Krause, and Davis followed up 66 cases of retrolental fibroplasia. All but 5 of 110 infants were prematurely born.

In Great Britain Mr. P. McG. Moffatt examined 119 blind children who are being cared for in the six Sunshine Homes. At the time of investigation (1949) he found 12 cases in which the diagnosis of retrolental fibroplasia could be made with reasonable certainty; two others were doubtful. Evidently the disease is not new in Great Britain, but it was not diagnosed.

Diagnosis

Until 1942, when Terry first described retrolental fibroplasia, infants who were found to have opacities in the eyes in the first few months of their lives were often thought to be suffering from congenital cataracts. It is very difficult to examine young infants, and a rapid examination of the eyes of a struggling child has led many paediatricians and ophthalmologists to diagnose opacities inside the eyes as congenital cataracts.

In view of the recent work on retrolental fibroplasia it seems essential that the eyes of such infants should be examined under a general anaesthetic. Only in this way can one distinguish an opacity in the lens from a vascular membrane in the vitreous.

The other conditions which must be considered are:

Glioma of Retina (Retinoblastoma).—This condition has no relation to the premature birth of the infant. The eye is normal in size, and there are no posterior synechiae. The condition is usually unilateral. The mass which lies in the vitreous behind the lens is usually yellowish. The tension of the eye may be raised.

Remains of Posterior Vascular Sheath (Hyperplasia of Primary Vitreous).—In this condition a persistent hyaloid artery with a cone of vascular connective tissue is found in the vitreous. The amount of hyperplastic tissue in the vitreous varies in different cases. This condition is present at birth and is usually unilateral.

Pseudoglioma.—This eye disease starts in much older children—at the age of 2 years. It usually follows a severe general infective disease (meningitis). The mass in the vitreous is the result of metastatic uveitis.

The general physician will find in the ophthalmic literature full descriptions of the clinical and pathological features of the last three eye diseases. Retrolental fibroplasia is not yet described in textbooks of ophthalmology.

Prognosis and Treatment

Local treatment of the eye by needling of the vascular membrane has been tried by a number of ophthalmic surgeons, but the results are unsatisfactory. Various forms of general treatment have also been tried. Owens and Owens have given to a group of prematurely born infants, in whom the disease was just becoming apparent, a water-miscible vitamin-E preparation. At the same time the intake of vitamin A and iron was reduced. They reported a retrogression of the disease of the eyes. These reports have not yet been confirmed by other observers.

Children suffering from this disease usually lose their vision. Some cases have perception of light. A large number of children are mentally retarded. The reports from U.S.A. show that at least 50% of these children are mentally backward.

Summary and Conclusions

Terry first described retrolental fibroplasia in 1942 amongst prematurely born infants in Boston, U.S.A. Since that date a large number of these cases have been reported in the U.S.A. In Great Britain, Dr. Mary Cross followed up 4,000 premature infants in the city of Birmingham. Four cases of retrolental fibroplasia were found among them. Mr. P. McG. Moffatt examined 119 blind children in the Sunshine Homes in Great Britain and found 12 cases of retrolental fibroplasia—7 girls and 5 boys. Prematurity varied from 12 to 8 weeks.

In this paper two cases of retrolental fibroplasia are reported from the Queen Elizabeth Hospital for Children,

London. The first infant was born at full term and weighed 6 lb. 12 oz. (3.1 kg.) at birth. This infant died from gastro-enteritis. The pathological appearances of the brain and eyes are described. The second case was typical. It is most probable that this eye disease is caused by some noxious agents during the intrauterine life of the foetus.

We wish to thank Dr. Helen Mackay and Dr. I. M. Anderson for referring the two cases to the Ophthalmic Department of the Hospital, Dr. B. Levin for the post-mortem report of Case 1, Dr. Peter Hansell for the photographs of the sections of the eyes, and Dr. Norman Ashton for the pathological reports and for his kind help and co-operation.

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From time to time the feasibility of health centres is discussed as a method of improving the facilities and therefore the standard of general practice, and it is often assumed that they must benefit the National Health Service. They face, however, two kinds of difficulties, it is pointed out in a recent *Manchester Guardian* article. One is purely financial: it is estimated that it would cost between three and five times as much to give a doctor proper equipment and accommodation, with the service of cleaners, clerks, and nurses, in a health centre, as it does at present for him to work in his own home assisted by his wife. The other is a matter of psychology: no one in fact knows to what extent the public will be prepared to use health centres. Few established practitioners would be willing to move into them, fearing that they would lose patients if they did; but on the other hand some doctors take quite the opposite view—that a health centre represents "unfair competition" with the home-based doctor. Clearly the only answer is to try opening just one or two centres as an experiment, to see what in fact happens, and it is this which is a particularly important aspect of the proposed opening of Darbishire House, Chorlton-on-Medlock, as an independent health centre in Manchester under the general control of the University. The five or six general practitioners who would take part all have N.H.S. lists of over 3,000, and would be guaranteed against any loss of income in the first seven years by a grant from the Rockefeller Foundation, which has offered £20,000 for this and other purposes, and £10,000 towards equipment. The building is to be converted and loaned by the Nuffield Provincial Hospitals Trust, which is prepared to put over £30,000 into the scheme.