THE RETINOPATHY OF PREMATURITY

BY

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(RECEIVED FOR PUBLICATION JUNE 8, 1954)

When the condition of retrolental fibroplasia was first described by Terry (1942) in the United States of America it was then only recognized in the advanced state of a cicatricial mass or membrane behind the lens. It is now appreciated, however, that the earliest pathological changes occur in the nerve fibre layer of the retina, which first of all becomes thickened as a result of oedema, transudation and haemorrhage then follow, with subsequent neovascularization and invasion of the vitreous. In cases which do not regress the process ultimately goes on to fibrosis, with detachment of the retina and the formation of a retrolental membrane. In 1950 Heath therefore suggested that the process could best be described as a retinopathy of premature birth.

The first case to be recorded in Edinburgh was in 1948, one more case occurring in that year, four being recorded in 1949, four in 1950, and eight in 1951.

In 1952 we began an examination of premature infants born in the City of Edinburgh.

Clinical

In order to ensure that, as far as was possible, we would be able to follow up the future development of these premature infants we limited our enquiry to premature babies weighing 4 lb. or less at birth whose parents lived in Edinburgh.

We also recalled for examination all babies satisfying the above criteria who had been born in Edinburgh during the years 1948–52. During 1952 each baby was examined as soon after birth as his general condition would permit. On the average, this was possible at about 2 weeks of age, and thereafter the infants were examined at monthly intervals until the age of 6 months.

Ophthalmoscopic Examination. Routine examinations of the fundi were normally carried out without general anaesthesia, the pupils of the infants' eyes being dilated with a solution of 1% paredrine hydrobromide and 1% homatropine hydrobromide. If any ocular abnormality was noted, or if there was

any difficulty in obtaining a clear view of the fundi, the baby's eyes were re-examined under general anaesthesia.

General Examination and Investigation. General examination included reference to the following factors:—

IN THE MOTHER. Parity, plural pregnancies, rubella, toxoplasmosis, rhesus factor, diet, antibiotic therapy, length of labour, presentation of the infant, and method of delivery.

IN THE INFANT. Birth weight, degree of immaturity, general management, diet, skin haemangioma, and antibiotic therapy.

In view of the controversy regarding the possible role played by anoxaemia or by hyper-oxygenation, particular attention was paid to the current practice in hospitals in Edinburgh when giving oxygen to premature babies.

During the period 1948–1952, 1,257 premature infants weighing $5\frac{1}{2}$ lb. or less were born to parents living in Edinburgh; of these babies, 240 weighed 4 lb. or under. Thirteen infants developed diplegia, of whom five also had retrolental fibroplasia. Fifty-one showed other congenital defects such as mongolism, cleft palate, and various limb deformities (Table 1). During this five-year period 20

TABLE 1
RELATIONSHIP OF MAIN FEATURES OF ALL PREMATURE BABIES BORN AND RESIDENT IN EDINBURGH (1948–52)

Year	Birth Weight $5\frac{1}{2}$ lb. and Under	Birth Weight 4 lb. and Under	True Cases of Retro- lental Fibroplasia (all under $4\frac{1}{2}$ lb.)	Babies Showing Cerebral Palsy	Babies Showing Other Congenital Defects
1948	217	52	2	3	15
1949	180	34	4	2	6
1950	280	57	4	2	7
1951	291	51	8*	2	13
1952	289	46	5†	2	10
Total	1,257	240	23	13	51

* One child died while under treatment.

† Three showed spontaneous regression of the eye condition.

fully developed cases of retrolental fibroplasia came under our observation. There were, in addition,

three infants (Cases 21, 22, and 23) who, although exhibiting definite signs of the disease, subsequently showed spontaneous regression of the ocular disturbance.

Five further babies are not included. They exhibited doubtful abnormal features on routine ophthalmoscopic examination consisting mainly of small retinal haemorrhages and fullness of the retinal vessels without real tortuosity. All subsequently returned to the normal state and it was hardly considered justifiable to include them as definite cases of retrolental fibroplasia. The degree of visual impairment in the 23 cases reviewed in this survey is analysed in Table 2.

TABLE 2
SUMMARY OF EYE FINDINGS IN 23 CASES OF
RETROLENTAL FIBROPLASIA

No. of Cases	Vision		Spontaneous Regression to Normal
	None	Partial	
23	14	6	3

Results of the Investigation

Ophthalmoscopic Findings. Before describing the ocular findings, it is essential to emphasize that, without routine ophthalmoscopic examination, clinical signs do not appear until the eye has been grossly damaged.

It is also important to appreciate that, apart from the pallor of the optic discs which is seen in all babies, the majority of premature infants show a pale greyish-green appearance at the periphery of the fundus not unlike, at first glance, the appearance of a very early detachment of the retina. This appearance was also noted in a number of full-term infants.

The early ophthalmoscopic signs consisted, in most cases, of dilatation and tortuosity of the retinal vessels with an appearance, in certain areas at the periphery, resembling a flat, solid-looking detachment of the retina. These appearances were followed by proliferation of new vessels into the vitreous.

The late signs varied from pale areas, with pigmentary change, mainly at the periphery of the fundi, to retinal folds, or detachment of the retina, and the classical retrolental membrane.

Owens (1951) stated that 60% of cases of retrolental fibroplasia undergo spontaneous regression with no serious residual damage, while Szewczyk (1952) thinks that spontaneous regression may take place at any stage short of advanced retinal detach-

ment. Our own observations are in agreement with the latter statement.

The disease appears always to be bilateral although one eye can be affected to a greater extent than the other. The onset, in so far as clinical signs are concerned, appeared, in our series, usually at 4 weeks although it might be delayed until 12 weeks of age. This is in agreement with the observations of Owens and Owens (1950). The earliest time at which any baby in our survey exhibited definite signs of retrolental fibroplasia was 4 weeks of age. Early ophthalmoscopic examination of these premature infants, with subsequent regular follow-up examinations, revealed, as other authors have emphasized, the frequency of spontaneous regression.

The following records and photographed drawings illustrate some of the changes seen and the ability of the process to undergo spontaneous regression.

Relationship to Birth Weight and Maturity. Most observers have agreed that this form of blindness is confined to premature infants of low birth weight (Chace, Merritt and Bellows, 1950; King, 1950). Griffiths (1951) stated that the incidence rose as the birth rate decreased. In this series three exceeded a birth weight of 4 lb. and only by a few ounces. One infant, although weighing 3 lb. 12 oz. at birth, was claimed to have been born at full term.

In Table 3 is shown the relationship of birth

TABLE 3
RELATION OF BIRTH WEIGHT TO PERIOD OF GESTATION
IN 187 CASES

Weights	Under 28 Weeks	28-31 Weeks	32-35 Weeks	36 Weeks and Over	Total
Under 3 lb.	1	15	7	1	24
3 and under 3½ lb.	2	15	21	15	53
3½ and under 4 lb.	2	10	56	25	93
4 lb. and over	—	1	10	6	17
Total	5	41	94	47	187

Excluded are 23 definite cases of retrolental fibroplasia and 33 cases where there was no record of period of gestation.

weight to the period of gestation in 187 babies. In a further 33 cases there was no record of the period of gestation, and they are therefore excluded from Table 3. A similar relationship is shown in Table 4 for the 23 definite cases of retrolental fibroplasia that occurred during the period 1948-52.

From Tables 3 and 4 it will be observed that the susceptibility to retrolental fibroplasia increases as the period of gestation becomes shorter and as the birth weight decreases. This supports the general belief that retrolental fibroplasia is essentially a

disease of prematurity, and is more prone to affect the smallest of these babies.

TABLE 4

RELATION OF BIRTH WEIGHT AND PERIOD OF GESTATION IN 23 CASES OF RETROLENTAL FIBROPLASIA

Weights	Under 28 Weeks	28-31 Weeks	32-35 Weeks	36 Weeks and Over	Total
Under 3 lb.	3	3	1	—	7
3 and under 3½ lb.	—	4	1	—	5
3½ and under 4 lb.	—	4	3	1	8
4 lb. and over	—	1	2	—	3
Total	3	12	7	1	23

Sex Ratio. Speert, Blodi and Reese (1950) and Ryan (1952) found the sex incidence of cases of retrolental fibroplasia approximately equal. There was no evidence of any sex preference in our present survey. Twelve of the established cases of retrolental fibroplasia in the five-year period were boys and 11 were girls.

Negative Factors. No relationship was found between the development of retrolental fibroplasia and the following factors:—

IN THE MOTHER. Parity, plural pregnancies, rubella, toxoplasmosis, rhesus factor, diet, vitamins and antibiotic therapy, length of labour, presentation of the infant, method of delivery.

IN THE INFANT. General management, diet, vitamins, skin haemangiomas, and antibiotic therapy.

Oxygen. There are four main maternity hospitals in Edinburgh. They will be referred to as Hospitals A, B, C and D.

The results shown in Table 5 are of particular interest. No cases even suggestive of the condition occurred in Hospital C, while it will be noted that approximately 15% of the babies born in each of the remaining three hospitals showed signs in some way suggestive of retrolental fibroplasia. The number of small babies handled by Hospital C was almost

the second highest of the four main hospitals. The question therefore naturally arose as to why Hospital C should appear to remain immune from the disease.

Apart from the administration of oxygen, there was no significant basic difference in the management of these infants in the four main hospitals. In Hospital A the infant was nursed in an incubator room, and oxygen was supplied by means of a plastic tent that fitted over the head and shoulders. In Hospital B the infant was nursed in an oxyginaire incubator. In Hospital C the infant was nursed in an incubator room, and oxygen was supplied by means of a plastic tent in which the baby was placed. In Hospital D the infant was nursed in an incubator room and oxygen was supplied by means of a plastic tent which covered the whole body.

Random estimations of the oxygen concentrations attained in the tents showed that in hospitals A, B, and D the percentages were all high (over 60%), while in Hospital C the concentration was even higher (over 70%). All units claimed to have weaned the babies gradually from their oxygen-enriched atmosphere. Unfortunately in many cases the exact duration of oxygen therapy was not recorded.

All but one of the 23 cases of the disease received continuous oxygen therapy. The tendency was for these infants to have been submitted to this environment for long periods. On an average, the infants who developed the disease were kept in oxygen for seven to 10 days longer than those showing no signs of the condition.

In Hospital C, however, in which there were no cases of retrolental fibroplasia, only one infant was recorded as having received oxygen for as long a period as three weeks, the average period of oxygen therapy in this hospital being only five to seven days, although the concentration attained in the 'tents' was higher than in any other hospitals.

Our findings therefore agree with those of Kinsey and Zacharias (1949) and many others, who observed that their cases of retrolental fibroplasia remained, on an average, in oxygen incubators for a

TABLE 5
PLACE OF BIRTH OF ALL PREMATURE BABIES IN THE SURVEY (1948-52)

Degree of Retrolental Fibroplasia	Home	Nursing Home	Hospital A	Hospital B	Hospital C	Hospital D	Total
No signs	21	6	74	39	46	29	215
True cases fully developed	—	—	10	6	—	4	20
True cases of spontaneous regression (1952 only)	1	—	2	—	—	—	3
Doubtful cases of spontaneous regression (1952 only)	—	—	2	2	—	1	5
Total	22	6	88	47	46	34	243

TABLE 6
ANOXIC FACTORS IN 23 CASES OF RETROLENTAL FIBROPLASIA

Case No.	Illness in Pregnancy	True or Apparent Toxaemia	Vaginal Bleeding	Other Anoxic Factors	Total Factors	Anaesthetic Used	Baby in Poor State	Total Factors	Oxygen Given	Infection	Blood Transfusion	Total Factors	Total Anoxic Insults
1	+		+		2				+			3	5
2		+	+		2	+	+	2	+	+		2	6
3		+	+		1	+	+	2	+			1	4
4							+	1	+			2	3
5	+	+			2	+	+	1	+	+		2	6
6			+		1	+	+	2	+	+		2	4
7			+	+	2	+	+	1	+	+		2	6
8			+		1	+	+	2	+		+	3	6
9	+				2	+		2	+	+		2	4
10	+				1	+	+	1	+			2	4
11	+				1	+		1	+			1	3
12		+			1	+		1	+			1	4
13		+				+		1	+			1	3
14				+	1		+	1	+	+		2	3
15	+				1	+	+	1	+			1	3
16	+						+	2	+			1	3
17	+		+		2	+	+	2	+	+	+	3	7
18	+	+			2	+	+	2	+	+		2	6
19						+	+	2	+			1	3
20	+	+			2	+	+	1	+			2	4
21	+		+		2	+	+	2	+	+		2	6
22	+					+	+	2				1	4
23				+	1	+	+	2	+			1	2
*23	9	7	7	3	27	17	16	33	22	14	3	39	99
+220	55	88	54	—	197	92	69	161	134	92	2	228	586

* Cases of retrolental fibroplasia.

† Normal cases.

‡ Indicates anoxic factors.

longer period than the ones showing no sign of the disease.

Anoxia. There are instances of retrolental fibroplasia in babies who have had no oxygen therapy at all (Bembridge, Coxon, Houlton, Jackson and Smallpeice, 1952), and in our survey one of the babies who developed retrolental fibroplasia (Case 22) was never at any time subjected to any form of oxygen therapy. This child showed definite bilateral signs of the condition, which subsequently cleared spontaneously. This seems to indicate that while the administration of oxygen may well be an exacerbating factor it is not the essential basic cause of the disease.

In our series of cases, one other factor stood out quite prominently, namely the presence of anoxia. In Table 6 are listed the 23 true cases of retrolental fibroplasia. It also gives factors acting on the mother which might produce some anoxic insult to the foetus; factors acting at the birth which might produce anoxia in the newborn infant; and factors acting on the child in the neonatal period which might cause an anoxic state. Under the heading of 'other anoxic factors' are included such conditions as gross anaemia and cardiac failure. One mother died after the birth from heart failure, which had been apparent throughout the pregnancy. The use of oxygen was included for one or both of two reasons. The first of these reasons was that it might be toxic to the newborn infant if given in

excessive amounts for prolonged periods. On the other hand, an anoxic state might result from removing the baby suddenly from an oxygen-enriched atmosphere to normal room conditions.

Blood transfusion was included by virtue of its administration in cases of anaemia in the child.

From the comparison of the 23 true cases of retrolental fibroplasia with the 220 normal cases (Table 6) it was calculated that the average number of so-called anoxic insults in those infants who developed the disease was 4.3, while in the control group the average number was 2.66.

Ingalls (1948), writing on congenital encephalophthalmic dysplasia, suggested that lack of oxygen was the most important mechanism leading to damage to vascular tissues. Szewczyk (1952) described retrolental fibroplasia as an anoxic retinopathy. He also stated that changes might take place in other tissues, depending on the stage of development of the child at that time, and result in such conditions as cerebral palsy and mental retardation.

If anoxia does play a fundamental role it would seem illogical to assume that the eye alone should always be the site of attack. In this connexion it is of interest to note that no fewer than five of our cases of retrolental fibroplasia also developed cerebral spastic diplegia. This appears to be even more significant when one notes that there were only 11 cases of cerebral palsy among the 240 premature infants with a birth weight of 4 lb. and

FIG. 1.—Female (Case 23) age 4 weeks. Drawing of the right fundus. Dilated and tortuous vessels running towards a greyish white area at the temporal periphery.

FIG. 3.—Female (Case 21) age 3 months. Drawing of the right fundus. Dilated vessels running forward in the vitreous towards a greyish mass of tissue. One vessel bends forward into the vitreous.

FIG. 2.—Female (Case 23) age 4 weeks. Drawing of the left fundus. An appearance resembling a flat, solid-looking detachment of the retina at the superior temporal periphery with dilated and tortuous vessels. There was little change for a further five weeks when regression began. At 12 weeks both fundi were quite normal except for a slight grey appearance at the periphery. At six months both fundi were within normal limits.

FIG. 4.—Female (Case 21) age 6 months. Drawing of the right fundus. The main vessel is now almost normal in calibre. There is a 'ghost vessel' at the site of the former bending. The left eye showed a temporal flattish detachment of the retina which had returned to normal by the fifth month. A final examination at 9 months showed no abnormality except that both fundi appeared pale.

FIG. 5.—Female (Case 22) age 5 weeks. Drawing of the left fundus. A superficial haemorrhage temporal to the disc. Streaky opacities temporally in the anterior vitreous. A greyish white area at the inferior nasal region with some streaky opacities in the anterior vitreous

FIG. 7.—Male (Case 5) age 3 months. Drawing of the left fundus. A greyish white mass at the temporal periphery. Running from the region of the ciliary body down into the anterior vitreous is a soft, brownish red mass. At 4 months this fundus had greatly improved and appeared normal at 6 months. Examination at 9 months showed no abnormality except for a greyish discoloration at the extreme temporal periphery with slight pigmentary change.

FIG. 6.—Female (Case 22) age 4 months. Drawing of the left fundus. An area of choroido-retinal atrophy with streaks of pigmentary change at the inferior nasal region.

The right eye also showed haemorrhages and vitreous opacities at 4 weeks which had cleared by 8 weeks. It is noticeable that tortuous and dilated retinal vessels were not seen at any time, though they may have been present before the first examination at 4 weeks.

FIG. 8.—Male (Case 5) age 4 months. Drawing of the right fundus. Vascularized folds occupying most of the lateral half of the vitreous body.

At 6 months there was further progress and at 9 months a complete retrolental membrane was seen in this eye. This case is of particular interest since it demonstrates that spontaneous regression may occur even in a relatively advanced stage of the disease.

TABLE 7

INCIDENCE OF CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA IN SURVIVING PREMATURE BABIES BORN AND RESIDENT IN THE CITY OF EDINBURGH (1948-1952)

Birth Weight (lb.)	Number of Survivors	Cerebral Diplegia		Retrolental Fibroplasia		Infants with Both Cerebral Diplegia and Retrolental Fibroplasia	
		No. Cases	Incidence per 1,000	No. Cases	Incidence per 1,000	No. Cases	Incidence per 1,000
5½ and over 4	1,017	2	1·96	3	2·95	0	—
4 and under	240	11	45·83	17	70·82	5	20·83
Total	1,257	13	10·34	20*	15·91	5	3·97

* Three cases where the condition underwent spontaneous regression are excluded.

under who were examined in the present review (Table 7). In addition, seven of the 20 fully developed cases of retrolental fibroplasia were considered to be subnormal mentally. The association of retrolental fibroplasia with cerebral diplegia and mental retardation is discussed elsewhere (Ingram and Kerr, 1954), and has been referred to by Scott (1954) in a discussion on this subject.

The main problem seems to lie in assessing the parts played by anoxaemia and by oxygen in the aetiology of the retinopathy.

During our survey the condition was noted in one member of each of six sets of twins. In two of these sets the other partner was recorded as a stillbirth. The remaining four sets of twins continued to thrive, although one partner subsequently died while under treatment with cortisone. Summaries of the case histories of these four sets of twins may be of interest.

CASE 5. Severe maternal toxæmia; anaesthesia used at birth; uniovular twins.

First Twin. Boy, weight 3 lb. 10 oz. In continuous oxygen for two weeks; taken out but suddenly become limp and collapsed. Replaced for one week and gradually returned to normal conditions.

Pronounced bilateral eye changes with spontaneous regression in one eye and complete permanent membrane formation in the other.

Second Twin. Boy, 4 lb. 12 oz. Satisfactory at birth; oxygen for two days; never developed eye abnormalities.

CASE 19. Binovular twins; anaesthesia for second twin only.

First Twin. Girl, 3 lb. 3½ oz. Fairly satisfactory at birth. Oxygen for six days then suddenly discontinued. No abnormal eye signs.

Second Twin. Girl, 3 lb. 3 oz. Limp at birth. Oxygen for at least 12 days. Bilateral retrolental membranes.

CASE 12. Eclampsia; anaesthesia for delivery; binovular twins.

First Twin. Boy, 4 lb. 3 oz. Vertex presentation. Fairly satisfactory but inhaled vomit and had cyanotic

attack. Given oxygen for an unknown period; ocular condition treated with cortisone. Died at 4 months. Extensive retrolental fibroplasia.

Second Twin. Boy, 4 lb. 6 oz. Breech delivery. Had cyanotic attacks and given continuous oxygen; probably did not develop any eye abnormality and can now see well.

CASE 3. Eclampsia. Six-hour labour with anaesthesia. Binovular twins.

First Twin. Boy, 3 lb. 12 oz. Assisted breech delivery. Feeble at birth with severe cyanotic attack. Given continuous oxygen for unknown period. Bilateral retrolental membranes at 4 months.

Second Twin. Girl, 4 lb. 3 oz. Vertex presentation. Feeble but cried well. Good colour. Continuous oxygen for unknown period. No evidence of retrolental fibroplasia.

These cases show that one twin only may be involved whether they are uniovular or binovular. As might be expected, in each pair when one partner is involved, the smaller was affected. In addition, in each case, the more anoxic of the two infants, judged by the early post-natal state, was the one more likely to develop the disease.

It appears that anoxia and the prolonged administration of oxygen are the essential factors in the production of retrolental fibroplasia in small premature infants. It may well be that either of these two factors alone is capable of producing retrolental fibroplasia in varying degrees of severity. In this connexion it is of interest to note the recent experimental work of Ashton, Ward and Serpell (1953) upon kittens. They produced vascular proliferation in the vitreous resembling the changes in retrolental fibroplasia. They found that the developing retinal vessels of the kitten became obliterated if the animals were subjected to a continuous high concentration of oxygen. When, however, the kittens were returned to ordinary air the vessels grew again and formed an irregular, extensive growth proliferating into the vitreous. This was often preceded by haemorrhages. The degree of obliteration of the retinal vessels was directly proportional to the degree of im-

maturity of the retinal development, and the concentration of oxygen and the length of exposure to such an environment. A somewhat similar effect was produced if the kittens were subjected to low oxygen concentrations. These experimental findings gave strong support to the impressions created in our survey with regard to the part played by anoxia and the prolonged use of oxygen in the aetiology of retrolental fibroplasia.

The fact that the disease can occur in infants who have never been given oxygen, as in one of our cases, suggests that the administration of oxygen is not the only factor concerned. Ford (1952) has emphasized the importance of asphyxia at birth in the aetiology of spastic diplegia, though he points out the difficulties in evaluating this factor since many babies are deeply asphyxiated at birth without ill effects.

Our conclusion is, therefore, that this form of retinopathy in premature infants is probably part of a general cerebral disorder resulting primarily from anoxaemia. On the other hand, it appears that the administration of oxygen may well, by reproducing retinal vaso-constriction, aggravate the initial disturbance of angioblastic tissue, and may consequently be responsible for the high incidence of the condition in recent years. The duration

of oxygen administration seems to be a more important factor than the concentration.

We are indebted to Drs. W. G. Clark, H. E. Seiler and H. P. Tait for providing facilities for surveying premature infants born in Edinburgh, and to Dr. Nora Campbell for her help in the production of the drawings of the fundi. We are most grateful to Professor R. W. B. Ellis for his help and criticism in the preparation of this paper. We have finally to thank the Medical Research Council for a grant.

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