RETROLENTAL FIBROPLASIA.

A clinical and experimental survey
during the five years (1948 - 1952)
in the City of Edinburgh.

BY

JAMES DOUGLAS KERR, M.B., Ch.B., D.C.H.

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SECTION 1.

INTRODUCTION.
INTRODUCTION.

T.L. Terry (1942), in the United States of America, first described an alarming condition of blindness affecting babies of low birth weight. He called the condition RETROLENTAL FIBROPLASIA. At that time the condition was relatively uncommon and, generally speaking, the average medical man was not altogether surprised to read of a new hazard affecting the prematurely-born infant. However, from that date cases appeared with quite frightening regularity in the United States of America. It was realised that this condition of blindness had a tragic implication on the family unit, and if it was not checked it might well become a social problem for which a satisfactory solution would be difficult. The after-care and education of blind children was already a large enough burden.

Naturally, with the advent of a new condition, search began to be made of earlier records. As this proceeded new cases came to light and it was found that in 1938, the incidence of what was now recognised as retrolental fibroplasia occurring among babies in the Boston Lying-In Hospital with a birth weight of 4 lbs. and under, was 18% (Zacharias 1952). Although the condition was not known by the name of retrolental fibroplasia, cases resembling it were described in the earlier
It seemed in Britain that we were to escape this tragic occurrence. However, it was not to be, for in 1948 the first case under the title of retrolental fibroplasia was shown at the Royal Society of Medicine by Galloway. It is interesting to note that Franklin (1949) described retrolental fibroplasia as "a rare disease in and around London". Moffat (1950) found, out of 119 cases of blindness in Sunshine Homes in England, twelve were definite cases of retrolental fibroplasia and two were doubtful cases. It appears that the years 1946-1947 marked the initial record of cases in this country (Crosse and Evans 1952). From that date onwards the incidence has gradually increased. As interest throughout the world increased reports began to come in from other countries. As in the United States of America, once the condition had been defined reviews of the national literature and of existing cases of blindness were undertaken to determine the earliest true appearance of retrolental fibroplasia.

Reports of investigations and opinions as to the possible aetiology became increasingly numerous. Although opinions differed widely, all groups had two common objectives, namely the
understanding and prevention of retrolental fibroplasia.

The first recorded case of the condition in Edinburgh was in 1948. At the beginning of 1952, it was decided to survey all babies who were born and resident in the city during the previous four years, provided that their birth weight was 4 lbs. or under. All babies of a similar weight group born during 1952 were to be examined at frequent intervals up till the age of six months. It was hoped that a clearer understanding of the disease might be achieved by the adoption of such measures.
SECTION 2.

REVIEW OF THE LITERATURE.
4.

A REVIEW OF THE LITERATURE.

As the incidence of the disease rapidly increased in the United States of America, so also did reports of the condition quickly follow one another. It is not surprising, therefore, to find that the greatest volume of literature is American in origin.

1. PATHOLOGY.

When Terry in 1942 first described the condition of infant blindness, there existed considerable confusion as to the exact nature of the condition. Terry thought the condition was related to the hyaloid system including the tunica vasculosa lentis. The hyaloid system, which is the primitive blood supply to the inner eye, normally disappears before birth. Terry felt that the condition arose out of a stimulation by some unknown factor on this primitive blood supply, whereby it persisted after birth. However, it is now generally accepted that persistence of the tunica vasculosa lentis and retrolental fibroplasia are two quite separate conditions and in no way related.

The anaemia of prematurity was suggested by Unsworth (1948) as the stimulus to pathological changes. He described vessel changes, pre-retinal haemorrhages and leakage of blood into the vitreous, followed by organisation of the haemorrhages by
vascularisation from the retinal vessels. All these changes he ascribed to a pre-existing abnormality of the vitreous.

Wolff (1950) described the pathology as being due to a "noxious stimulus" which reached the embryo in its formation, affecting primarily the retina which remained non-attached in part or in whole. Fluid gathered under the retina producing real detachment, which gradually became total. This gave rise to a mild uveitis which was responsible for the retrolental membrane.

Reese and Blodi (1951) found 15% of their cases of retrolental fibroplasia had skin haemangiomas. They concluded from their experience that the eye condition was a manifestation of a generalised angioblastic process. The early changes consisted of vascular dilation of the retinal vessels, exudation into the vitreous, and haemorrhage. Spontaneous regression could occur in the early stages, but once neovascularisation and exudation were established, spontaneous regression was rare.

Laupus and Bousquet (1951) stated that a very definite sequence of events took place. The stages they described were as follows:-
6.

(a) Pre-retinal haemorrhages.
(b) Extension of the haemorrhages into the vitreous.
(c) Organisation of the haemorrhages.
(d) Subsequent retinal detachment.
(e) Formation of a retrolental membrane.

Bembridge and Jackson in 1951 studied nine eyes enucleated in the late stages of retrolental fibroplasia and regarded the disease as inflammatory in origin but could not deduce the cause of the irritation from the histology.

The great drawback to an accurate description of the pathology was the fact that these children, apart from the blindness, generally remained quite well, hence few opportunities arose for the examination of the eyes in the early stages. The diagnosis was seldom in doubt and enucleation of the eyes was not indicated. One had, therefore, to depend on death intervening in order to provide specimens of eyes in the so-called acute phase of the disease. To all interested in this vastly important subject the report of Reese, Blodi and Locke (1952) on the pathology of the early stages of retrolental fibroplasia must indeed be very welcome. They showed the pathological process to commence in the nerve fibre layer of retina at the equatorial region. The process then advanced by bursting via the internal limiting membrane, into the
vitreous proper. Hence followed transudation and haemorrhage. There was organisation of this tissue followed by fibrosis, contraction and retinal detachment. The end-result was the classical retrolental membrane. They also suggested that the vitreous was the source of a positive taxis which attracted new blood vessels from the retina. This latter description will be described in detail, with diagrams, in a further section.

2. **ONSET OF THE DISEASE.**

It has not yet been definitely agreed whether the disease is pre-natal or post-natal in origin. Krause (1946) maintained that there was a frequent association of cerebral and somatic defects with ocular disease and that retrolental fibroplasia was only part of a wider failure to develop the anterior part of the central nervous system - the so-called "encephalo-ophthalmic dysplasia". Krause further stated that the factors causing the disease were ante-natal in time. Rychener (1949) stated that recent investigations seemed to indicate that the membrane arose from the retina behind the ciliary body and was present before birth but tended to increase in size post-natally. Terry, in his pioneer work, and Reese (1949) thought the basic lesion was a persistence of the tunica vasculosa lentis, and that the disease was essentially ante-
natal in origin. On the other hand, Locke (1951) and Owens and Owens (1949) reported that on examination of a large group of premature infants who died at or soon after birth, there was no evidence of retrolental fibroplasia.

In a masterly description of the pathology of early retrolental fibroplasia, Reese, Blodi and Locke (1952) stated on microscopic examination of 458 eyes of still-born and new-born infants, the occurrence of a lesion absolutely identical with the early stages of retrolental fibroplasia was observed in two sets of eyes. On this finding they concluded that the matrix of the condition may be present at birth, but that it is the exception rather than the rule.

It is unfortunate that all observers of the early stages of this condition are not in agreement as to the exact commencement of the disease. The main difficulty is lack of uniformity in the knowledge of the appearance of the normal fundus in the prematurely-born infant. Owens and Owens (1950) stated that the earliest signs of retrolental fibroplasia appeared at the age of four weeks. The retinal vessels dilated, then followed swelling and infiltration of the retina. The vitreous became cloudy. Localised bands arose from areas of proliferative retinitis and extended into the
vitreous. This was followed by extensive retinal detachment and formation of a complete retrolental membrane by fusion of the vitreous bands and peripheral folds of detached retina. The complete retrolental membrane was usually formed by the time the baby was four months old. By the time the classical membrane had formed, secondary features due to intraocular fibrosis had made their appearance. These features include microphthalmos, shallow anterior chamber and possibly glaucoma. Tyner (1951) stated clearly that factors such as a flat grey appearance at the periphery, large retinal veins and isolated retinal haemorrhages were not, in fact, indicative of the presence of retrolental fibroplasia. While he agreed that a "cloudy vitreous" was observed in the early stages of the disease, he issued a warning that many infants have a mucous-like protective film over the cornea which produces an impression of hazy ocular media.

Guy, Dancis and Lanman (1953) described three features which they regarded as abnormalities of the premature fundus. The so-called vitreous haze, myopia - requiring a minus correction of one or more diopters on the ophthalmoscope, and dilatation and tortuosity of the retinal vessels, were regarded as being suggestive of the initial signs of the disease.
They stated that these abnormalities can be detected in the first two weeks of life. However, if these signs were present it did not follow that the child would develop retrolental fibroplasia. In their series of 77 infants demonstrating these early abnormalities, only 12 developed advanced signs of the condition. Krause (1946) was of the opinion that the condition could occur unilaterally. Some observers have stated that they have seen a membrane in one eye, while the other eye appeared quite normal on examination. This was perhaps due to the fact that degrees of severity existed not only in different children, but also in the two eyes of the same infant. Degrees of severity varied from small retinal folds, patches of choroido-retinal atrophy and retinal scarring, to the fully-developed retrolental membrane. In other infants, the eyes appeared quite normal to outward appearances. Unsworth (1949) reported that it was generally accepted that both eyes were involved in retrolental fibroplasia.

It is generally agreed that 60% of cases showing early retrolental fibroplasia undergo spontaneous regression with no serious residual damage (Owens 1951). Szewczyk (1952) thinks that spontaneous regression may take place at any stage short of severe retinal detachment.
3. **DIFFERENTIAL DIAGNOSIS.**

Perhaps the most important conditions from which retrolental fibroplasia must be differentiated are retinoblastoma and pseudoglioma. The former is important because early enucleation is indicated, the latter because under this heading cases of retrolental fibroplasia might well have passed in years gone by. As already stated, Terry (1942) regarded retrolental fibroplasia as arising from the remnants of the tunica vasculosa lentis. However, persistence and hyperplasia of the primary vitreous (tunica vasculosa lentis) is a real condition, although the incidence is low (Reese and Blodi 1951). The features of this later condition are:— it is unilateral; the involved eye is smaller than the fellow eye; the opaque tissue behind the lens is densest in the central portion and fades in the periphery where the long ciliary processes can be seen. If the opaque tissue at the back of the lens is sufficiently thin around the periphery to permit a view of the interior of the eye, a persistent hyaloid artery can usually be seen.

Other conditions from which retrolental fibroplasia should be differentiated include retinitis proliferans and angiomatous retinae. Bousquet and Laupus (1952) considered that the so-called congenital retinal folds were in actual fact degrees of retrolental fibroplasia.
4. **INCIDENCE.**

Reese and Blodi (1949) pointed out that retro-lental fibroplasia was the most common cause of infant blindness in the United States of America over the previous ten years. Many reports continue to appear, some showing an increase in the cases of this form of blindness, others showing a sudden decrease. In some large cities it has appeared in one hospital and not in another. This curious uneven distribution makes an accurate estimation of the incidence very difficult. Krause (1950) stated that in the Chicago Hospital the incidence was 7% from 1937 till 1946, when it rose sharply to reach almost 40% in 1949. Since that time it has been declining.

The incidence in Britain is still very much lower than it is in the United States of America (Crosse 1951). Bembridge et al (1952) in a British report regarded retrolental fibroplasia as the largest single cause of blindness.

From other countries evidence is accumulating which suggests that the incidence is rising. In Vancouver, Canada, 15 cases had appeared since 1948 (Mallek and Spohn 1950). LeLong et al (1951) reported an incidence of 6.8% in Paris. Ryan (1952), in Australia, stated that there were no cases before 1948, while for the following three years it reached 17% of all babies of a birth weight of 3 lbs. 5 ozs.
and under. Bjelkhagen (1952) discovered 38 cases in babies of birth weight 4 lbs. 14 ozs. or under in Sweden. Von Winning (1952) stated that 30 cases of retrolental fibroplasia were known to have occurred in the Netherlands.

With the increased facilities for the management of the premature infant at birth, the question is naturally asked "Is the whole appearance of this condition not really in fact due to the saving of more premature babies?" Kinsey and Zacharias (1949) showed that in the Boston Lying-In Hospital the survival rate of prematurely-born infants was not significantly increased in the past sixteen years. Crosse and Evans (1952) showed in the Sorrento Premature Baby Unit in Birmingham that the survival of babies with a birth weight of 2-3 lbs at the age of six months was 37% for the years 1946 - 1948. During the years 1949 - 1950 the survival rate at six months of a group of infants of similar birth weight was 37.7%, while in 1950 - 1951 it was 44.5%.

5. **ASSOCIATION WITH PREMATURITY.**

Most observers are agreed that this form of blindness is confined almost exclusively to premature infants of low birth weight. Chace (1950) found no evidence of the disease in 1,024 full-time infants. King (1950) reported that in a series of
236 cases of retrolental fibroplasia, all infants weighed less than 5 lbs. at birth, and 84% weighed less than 4 lbs. at birth. Kinsey (1950) suggested that when the disease attacked a new premature infant unit, it affected the smaller babies first and then subsequently attacked the heavier babies. Griffiths (1951) stated that the incidence rose as the birth weight decreased. An interesting feature of the various reports has been that some investigators stated that the crucial time for the development of the condition was between 3 - 4 lbs. irrespective of the birth weight. Unsworth (1951) found that 29% of his cases weighed less than 3 lbs. at birth and 10% were in the 3 - 4 lbs. group. However, the condition is not unknown in full-time infants (King 1950). In Britain, Cole (1950) described the occurrence of retrolental fibroplasia in a full-time infant (6 lbs. 12 ozs.) who had died from gastro-enteritis, but had multiple congenital deformities.

6. **SEX RATIO.**

Bakwin (1946) described 150 cases of the condition and found that 95 were males. Kinsey and Zacharias (1949) found in their survey 14% were males and 9.2% were females. Ryan (1952) in an Australian report found the incidence equal. Speert, Blodi and Reese (1950) analysed 104 cases of retrolental fibroplasia with reference to sex incidence.
They found the ratio approximately equal.

7. **AETIOLOGY.**

Many and varied are the theories postulated as to the aetiology of retrolental fibroplasia. For ease of description, the various factors will be discussed under the following three main headings:

(a) Factors acting on the mother during pregnancy.

(b) Factors acting at the delivery.

(c) Factors acting after the birth of the infant.

**FACTORS ACTING ON THE MOTHER DURING PREGNANCY.**

**X-RAYS OF CHEST AND ABDOMEN.**

Although it was thought that X-ray might be a factor, no relationship has been found with regard to X-ray examination of the mother and the appearance of retrolental fibroplasia (Unsworth 1949).

**INFECTIONS AND MEDICATION OF THE MOTHER.**

Mann (1946) advanced the hypothesis that the primary cause of retrolental fibroplasia was a maternal upset, probably non-specific in nature but specific in time. Ingalls (1948a), however, attributed the initial stimulus to a systemic insult to the foetus during or after the second trimester of pregnancy. He listed various factors which might produce this insult and among them he recorded intercurrent infection in the mother. Hepner, Krause and Nardin (1950) found no evidence in their
series of cases to suggest that specific infection, or the use of sulphonamides in the mother pre-natally, played any part in the production of the eye condition in the infant.

Naturally, the possible role that rubella played in the condition was carefully investigated. No obvious relationship was found, although Speert, Blodi and Reese (1950) reported two cases in which the mother suffered from rubella at the third month of pregnancy. Toxaemia of pregnancy along with other causes of prematurity itself have been investigated, without throwing any light on the possible aetiology. It has also been suggested that the mother might well suffer from a sub-clinical infection of toxoplasmosis in the pregnancy (Bjelkhagen 1952) and, if this was the case, the infection might cross the placental barrier and attack the child. It was well known that toxoplasmosis produced retinal changes in the form of a chorioretinitis, but there was little to support the view that toxoplasmosis had any bearing on the aetiology of retrolental fibroplasia.

**VAGINAL BLEEDING — ANTE-PARTUM HAEMORRHAGE.**

Ingalls (1948a) suggested that bleeding was an important feature in the production of sublethal oxygen lack, which in turn might be the stimulus to the commencement of the disease, while Reese (1949)
found that 30 - 35% of his cases gave a history of vaginal bleeding in the mother during pregnancy. Gilger (1949) found no evidence to suggest antenatal bleeding played any part in the production of retrolental fibroplasia. Kinsey and Zacharias (1949) stated that it appeared no more often in premature children who developed retrolental fibroplasia than in those who did not.

**Diet and Vitamins.**

Following the experimental work of Warkany and Schraffenberger (1946) on rats, they concluded that pregnant mother rats deprived of Vitamin A gave birth to an offspring with an eye condition similar to retrolental fibroplasia. This work was repeated by Jackson and Kinsey (1946), and while they corroborated Warkany and Schraffenberger's results, they expressed extreme doubt if actually the Vitamin A level ever fell so low in humans as to cause retrolental fibroplasia in the offspring. Gilger (1949) concluded that Vitamin A played no part in the aetiology of the disease. No observations appear to have been made on any other vitamin deficiency in the mother as being a possible causative factor. Most observers, e.g. Platou (1951), failed to find any correlation between an inadequate diet in the mother and the development of retrolental fibroplasia in the infant.

**The Rhesus Factor.**

Most observers are agreed that the Rhesus blood
group of the mother plays no part, e.g. Krause (1951).

OTHER FACTORS.

Kinsey and Zacharias (1949) showed that 19.7% of the cases occurred in multiparae, while 9.5% was the incidence in primiparae. Speert, Blodi and Reese (1950) stated that parity of the mother was of no significance.

The relation to plural pregnancies has received considerable attention. Fleming (1950) at The Royal Society of Medicine presented monovular twins each blind in both eyes, due to retrolental fibroplasia. Crosse (1950) examined 4,000 premature infants and found four cases of the disease. Of the four cases, two were binovular twins. Speert, Blodi and Reese suggested that when both members of a set of twins were affected they were usually monovular. When only one of the twins developed the disease, they were usually binovular, and these workers gave the example of triplets in which two infants who shared a common placenta developed the condition, while the third child with a separate placenta remained normal.

FACTORS ACTING AT THE BIRTH.

CAUSE OF THE PREMATURE BIRTH.

Kinsey and Zacharias (1949) investigated the numerous causes of prematurity, such as plural pregnancies, toxaemia of pregnancy, placenta praevia,
both from the point of view as factors causing the early birth, and as possible aetiological pointers in the production of retrolental fibroplasia. They, and most investigators concluded, that it was the prematurity itself that was the significant factor in the production of retrolental fibroplasia, and that the many causes of the prematurity were not apparently causative agents of the disease.

**ANAESTHETIC USED IN LABOUR.**

No definite relationship has been found between the administration of an anaesthetic during the labour and the incidence of the disease (Unsworth 1949).

**LENGTH OF LABOUR, PRESENTATION OF THE INFANT AND METHOD OF DELIVERY.**

Unsworth also stated that these factors had no bearing on the ultimate appearance of the eye condition.

**ABNORMALITIES OF THE PLACENTA.**

Ingalls (1948a) considered abnormalities of the placenta as one of the causative factors in the production of retrolental fibroplasia, although many others, e.g. Speert, Blodi and Reese (1950), found no such evidence.

**FACTORS ACTING ON THE INFANT.**

It is in this group that the majority of the observers have sought the final answer to the problem.
As indicated previously, many workers considered the disease to commence ante-natally, but most agreed that it was what happened to the infant in the early weeks of life that determined if the disease would actually appear.

**STATE OF THE BABY AT BIRTH.**

Szewczyk (1952) made perhaps a deep observation when he recorded that a baby blue at birth was a potentially seriously injured child. Ryan (1952) could find no relationship, however, between the state of the baby at birth and the subsequent development of retrolental fibroplasia.

**THE ROLE OF LIGHT.**

It was to be expected that the effect of light falling on an immature retina might bring about chemical alterations that would lead to pathological changes, but Hepner, Krause and Davis (1949) covered the eyes of a group of five prematurely-born infants from birth till the age of 35 - 60 days. On examination at the end of that time, they found four cases of retrolental fibroplasia. Locke and Reese (1952) carried out a very well-controlled experiment along similar lines and they concluded that the instillation of mydriatics, premature exposure of the eyes to light and handling of the premature babies for routine ophthalmoscopic examination were not factors in the production of the disease.
RELATION TO SKIN HAEMANGIOMAS.

Haemangiomas of the skin are said to occur in 1 - 2% of full-time infants and from 3 - 10% of premature infants (Hess, Mohr and Bartelme 1934). Reese and Blodi (1951) found that skin haemangiomas occurred in 15% of their cases of retrolental fibroplasia. They pointed out that only 20% of such skin lesions were present at birth and the remaining 80% appeared in the first six weeks of life. Most of these haemangiomas seemed to grow for the first six months of life, and then regressed till they gradually faded by the end of the first year. These two workers suggested that the pathological development of retrolental fibroplasia was that of an angiomatous process in the vitreous, and the many new vascular channels were identical histologically with these associated with haemangioma. Both the skin lesion and the eye condition underwent an active phase in which progressive changes took place, a subsequent regressive period, and finally a stage of cicatrization, with the time factors concerned in the various phases of the two conditions roughly comparable.

BLOOD TRANSFUSIONS.

Unsworth (1948) regarded retrolental fibroplasia as post-natal in origin and predisposed to, if not actually caused by, the anaemia of prematurity. Mallek and Spohn (1950) reported that all 13 of
their cases of retrolental fibroplasia received early and repeated transfusions of pooled blood. Hepner and Krause (1952) also felt there existed a relationship between large blood transfusions for the anaemia of prematurity and retrolental fibroplasia. On the other hand, Exline and Harrington (1951) found in their group that of the 50% of premature infants requiring transfusions, none developed the disease.

**FEEDING.**

Since the majority of these small infants spend much of their early life in hospital, the commencement of feeding varies according to the routine adopted by the various maternity units. Generally speaking, most units withhold feeding till the child "demands it" - possibly about the third day. Many groups of observers stated that the initial withholding of food played no part in the aetiology of retrolental fibroplasia, e.g. LaMotte and Tyner (1950). Heath (1950), however, advocated early feeding because he considered that the retinal disease became manifest only because of a nutritional imbalance falsely created. Hepner and Krause (1952) pointed out that cow's milk has four times the sodium and twice the chloride and seven times the phosphorous content of human milk. They stressed the fact that early feeding with cow's milk mixtures might result in an electrolyte retention and imbalance. This, in turn, would result in generalised oedema which would also
be manifest in the retina. The retinal oedema then might well proceed to the further stages of retrolental fibroplasia. In proof of this they cited that in Sweden, where breast milk was used extensively for feeding premature infants, few cases of the disease had appeared, but when the condition did appear, it was found that the first four cases of retrolental fibroplasia had been fed on cow's milk. However, Coxon (1951) and Crosse (1951) reported cases of the condition in infants who were totally fed on breast milk.

**VITAMINS AND IRON.**

Clifford and Weller (1948) tested 42 premature infants for Vitamin A absorption after oral ingestion. Only three out of the group showed good absorptive powers. They found that retrolental fibroplasia was not prevented by daily oral administration of large doses of Vitamin A. Intramuscular injections failed to prevent the disease in one case. Bain (1952) found similar results in the use of Vitamin A as a preventive measure. On the basis that Vitamin A and iron increased the requirements of Vitamin E, Kinsey and Zacharias (1949) showed that supplementary Vitamin A and iron in the diet of premature infants could be correlated positively with an increase in the incidence of retrolental fibroplasia. Hepner, Krause
and Davis (1949) also cast suspicion on high potency multi-vitamin preparations. Reese and Blodi (1951) stated that the pharmacological action of Vitamin E as an anti-oxidant could have a beneficial influence on the metabolism of the retina. Kinsey and Chisholm (1951) showed the average plasma level of Vitamin E in infants at birth to be 0.6 mgms. per cent. Thus, these infants did not appear to have any Vitamin E deficiency at all. These workers reported that when the multi-vitamins and iron were excluded from the diet the incidence of retrolental fibroplasia remained the same. LaMotte, Tyner and Scheie (1952) treated 17 cases of retrolental fibroplasia in the early stages with Vitamin E in the form of alpha-tocopherol acetate. The results were as follows:

(a) 9 became blind in both eyes.
(b) 3 became blind in one eye.
(c) 5 had normal vision in one or both eyes.
(d) 10 of these cases developed the disease while receiving Vitamin E as a preventive measure.

ANOXIA AND OXYGEN.

It is logical to assume that anoxia and oxygen are so closely related that they cannot really be considered apart. As previously recorded, Szewczyk stated that a baby blue at birth was a potentially seriously injured child. Ingalls (1948a) stated
that lack of oxygen was the most important mechanism leading to damage of vascular tissue, and in another communication (1948b) suggested that sublethal anoxia was the cause of retrolental fibroplasia. Kinsey and Zacharias (1949) observed that their cases of retrolental fibroplasia remained on an average in oxygen incubators for a longer period than the ones showing no sign of the disease. Reporting on 27 cases in Melbourne, Campbell (1951) suggested intensive oxygen therapy as a possible cause of the disease.

One factor was obvious to all observers, viz. that practically all these small infants required oxygen therapy at birth. Many workers held that oxygen itself was the sole cause of the condition. They pointed out that the disease only made its appearance with the advent of more efficient methods of oxygen administration. This probably explained why the disease might appear in one hospital centre and not in another. Thus, the disease would tend not to occur in some hospitals where intensive and efficient oxygen therapy was not given. Crosse and Evans (1952) showed that in the Sorrento Premature Baby Unit (Birmingham) the increase in incidence of retrolental fibroplasia coincided with free oxygen therapy and the disease disappeared on reduction of the concentration and duration of oxygen therapy. They gave minimal doses of oxygen for the shortest
possible duration and gradually "weaned" the infant back to normal oxygen concentration. Szewczyk (1952) considered retrolental fibroplasia a terminal stage of an "anoxic retinopathy" — induced by retinal oxygen deficiency during a period of life when vascularisation of the retina was taking place. The retina utilises oxygen at a higher rate than any other tissue in the body. Szewczyk further showed that babies suddenly taken out of an oxygen atmosphere of 54 - 84% concentration and placed in a concentration of 25% exhibited the early signs of retrolental fibroplasia. In addition, he considered that if an early case of the disease was placed in oxygen at 45% concentration and gradually weaned slowly back to atmospheric conditions, it would show spontaneous regression or even complete cure. Huggert (1953) observed 130 premature infants. He noted that the retinal vessels narrowed during the giving of oxygen. He also noted vascular dilatation and peripheral oedema in most cases when the oxygen was stopped. In other cases he observed dilatation and oedema when the infant was still in oxygen. The infants who received no oxygen therapy showed dilatation and peripheral oedema just after birth. Of these treated with oxygen, two developed retrolental fibroplasia. Patz, Hoeck and de la Cruz (1953) divided a group of 76 infants of birth weight less than 3½ lbs. into two groups. The
first group were given continuous oxygen at 65 - 70% concentration for 4 - 7 weeks. The second group were given continuous oxygen at 40% concentration for 1 - 14 days. It was found that 25% of the first group developed advanced signs of retrolental fibroplasia. In the second group no infants developed the advanced signs of the disease, but 6% showed dilatation and tortuosity of the retinal vessels with oedema, haemorrhage, and cloudy vitreous. Long (1952) stated that in his Premature Baby Unit oxygen was used for all babies continuously till moved to a graduate nursery at the weight of 5 lbs. Many babies remained in oxygen for 60 - 90 days. Eight cases were recorded in the year, but none showed eye changes while in oxygen or before discharge from hospital. He issued a warning not to lay the blame at the door of oxygen therapy without more substantial evidence. There are instances of retrolental fibroplasia in babies who have had no oxygen therapy at all, e.g. Bembridge et al (1952).

INFECTION.

It will be readily admitted that the sudden appearance of the condition, its gradual spread, its peculiar geographic distribution and its variation in severity, suggest that a virus infection may be a possible aetiological factor. The literature, as yet, is lacking on any such information.
RELATION TO OTHER ABNORMALITIES.

The question of the relationship with skin haemangiomas has already been discussed.

Krause (1946) maintained there was a frequent association of cerebral and somatic defects with ocular disease. He considered that retrolental fibroplasia was only a part of a wider failure to develop the anterior part of the central nervous system.

Ingalls (1948a), writing on the condition "congenital encephalo-ophthalmic dysplasia", stated that three main processes were at work:

(a) variable ocular abnormalities including retrolental fibroplasia;
(b) structural and dissociated malformations of the cerebrum;
(c) single or multiple haemangiomas of the skin.

These features might arise together or singly, depending at what stage the host received the anoxic insult. Thus, three apparently unrelated conditions of retrolental fibroplasia, cerebral palsy (with or without mental retardation) and skin haemangiomas would make their appearance.

Cole (1950) illustrating a case of retrolental fibroplasia in a full-term infant, demonstrated coincident multiple congenital abnormalities. Szewczyk (1952) in describing his anoxic retinopathy expressed the belief that changes akin to that happening in the eye took place in other tissues.
Depending at what stage of development the brain was at, the infant might subsequently exhibit features of cerebral palsy and or mental retardation. Bjelkhagen (1952) found in 38 cases in Sweden 14 were mentally retarded, 11 mentally normal, and in the rest the mental state was uncertain.

8. TREATMENT AND PREVENTION.

Treatment when the condition has reached the final cicatrical stage is obviously useless. No medical therapy at this stage has been found to be of any value. It was thought when the disease appeared in its terminal phase, that if the retro-lental membrane was removed the child might regain some vision. When it was realised that the membrane consisted of detached retina this form of treatment was discontinued. Most surgical attempts at such a procedure proved quite unsatisfactory (Reese and Blodi 1951). X-ray therapy of the eyes proved equally unsuccessful (Reese 1949 and Unsworth 1949). The role of Vitamin E in the form of alpha-tocopherol acetate as a preventive and as a measure of treatment has virtually been discontinued. Although LaMotte, Tyner and Scheie (1952) agreed that the results were discouraging, they believed that it was justifiable to continue its use till something more promising became available.

It was to be expected that sooner or later the
adrenocorticotrophic hormone (A.C.T.H.) or cortisone would be tried in the treatment of this condition. The rationale for their use could be summarised as follows:

(a) There was good evidence to suggest that retrolental fibroplasia was possibly a disease of the blood vessels characterised by dilatation of the existing blood channels and by their proliferation into the vitreous. It was known that induced hyperadrenalism inhibited the growth of mesenchymal cells and that cortisone specifically prohibited the growth of capillaries. It seemed reasonable to expect that A.C.T.H. might halt the vascular overgrowth which marked the beginning of retrolental fibroplasia.

(b) There was evidence of hyperadrenalism in the last trimester of pregnancy, caused probably by the formation of A.C.T.H. and adrenal cortical steroids in the placenta. It was conceivable that these hormones might be necessary for the normal development of the foetus, and that premature separation from the maternal hormonal environment had a deleterious effect.

It has been suggested that the dosage required
is 20 - 25 mgms. daily for 14 days. The side effects appear to be cessation of growth, tachycardia and glycosuria. The possibility of bringing about an electrolyte imbalance was a very real one. Hepner and Krause (1952) considered that A.C.T.H. might exert a temporary effect on the eye condition by its diuretic action on the water and salt metabolism of the premature infant. Scheie et al (1951) treated five cases with A.C.T.H. and had encouraging results. Bembridge et al (1952) treated six cases, and the A.C.T.H. appeared to restrain the disease. Fitzgerald et al (1951) treated three cases with dubious results. Laupus (1951), Woods (1950 and 1951), and Lanman, Guy and Dancis (1952) all concluded that A.C.T.H. was quite ineffective in the treatment of retrolental fibroplasia. Reese, Blodi et al (1952) while originally holding high hopes for the value of A.C.T.H. concluded, "on the basis of our results in the 1951 series and with the comparison of these cases with control cases we conclude that A.C.T.H. has no effect on the course of the disease". In a report by a similar group of workers (1951), they emphasised the dangers of treatment to the infant, if extended beyond two weeks. Locke and Silverman (1951) reported six deaths in 33 infants given A.C.T.H. for retrolental fibroplasia. They stressed the dangers of prolonged treatment.
Lastly, perhaps should be included the fact that Szewczyk (1952) claimed to have treated early cases of retrolental fibroplasia by replacing them in minimal concentrations of oxygen and weaning them slowly to normal conditions. He also stated that the disease could be prevented by the adoption of such measures in the first place.
METHOD OF STUDY

At the start of the year 1900 it was decided to carry out a field survey into the question of infantile diarrhoea. Many difficulties had to be faced as to the possible means of carrying out such a project.

Edinburgh being a teaching and hospital-based institution for a wide area, was more interested in the health of Scotland and England. It was thought that a follow-up of all premature babies born in the town would give valuable results. Premature babies were divided into groups and then returned home to their own locality. It was then decided to visit the investigating in private homes who were in Edinburgh and who remained resident within the city boundaries. It had to be decided on which group of premature babies to include in the survey. It was generally agreed that the definition of a premature baby, being any patient with a birth weight of 1 1/2 lb. or under, was best in the series of investigation. In the report the work of the Department of Medicine in the Public Health Department of Edinburgh, before the middle of 1900, was recorded according to the series of
At the start of the year 1952 it was decided to carry out a field survey into the question of retrolental fibroplasia. Many problems had to be faced as to the possible means of carrying-out such a project.

Edinburgh being a teaching and hospital centre provided medical facilities for a vast area, even stretching to the border of Scotland and England. To attempt a follow-up of all premature babies born in Edinburgh would have been quite out of the question. The population was continually changing and mothers, as already stated, came from afar to have their confinement in hospital and then returned home to their own locality. It was thus decided to limit the investigation to premature babies who were born in Edinburgh and who remained resident within the city boundary. It had to be decided on which group of premature children to include in the survey. It is generally accepted that the definition of a prematurely-born infant is "any infant with a birth weight of 5 1/2 lbs. or under, irrespective of the period of gestation". In the register of notifications of births to the Public Health Department of Edinburgh, before the middle of 1949 prematurity was recorded according to the period of
gestation. The estimation of the period of gestation in many cases was quite inaccurate, thus to attain any statistical accuracy was indeed a difficult problem. For this reason, in 1949 the Department commenced to record prematurity on the now familiar lines, based on birth weight. As will be seen from the figures illustrated in a subsequent section, to attempt to follow-up every premature baby would be virtually impossible, and in the light of present knowledge quite unnecessary. While admitting that cases of retrolental fibroplasia might exist in the upper birth weight group, it was a well-established fact that the disease was confined in the vast majority of cases to babies who weighed approximately 4 lbs. and under at birth. For this reason, it was decided to confine the examination to all babies with a birth weight of 4 lbs. or under.

To summarise, this was to be a survey "of all prematurely-born children with a birth weight of 4 lbs. and under, irrespective of the period of gestation, provided they were born in Edinburgh and were resident within the city boundaries."

However, in order to get a correct conception of the true incidence of retrolental fibroplasia, it was necessary to get some data on every premature baby born and resident in Edinburgh. The information
gathered on this large group consisted of: hospital in which born, period of gestation, sex, birth weight, presence of any congenital or visual abnormality. This further information was required to produce a back-cloth to the specialised scene that was to comprise the main survey. It was next established that no cases of retrolental fibroplasia were noted prior to the year 1948. Thus, it was felt that the investigation should comprise the years 1948 - 1952 inclusive. It was necessary, therefore, to review in retrospect the four years up to the start of 1952. To this end, a questionnaire was drawn up including the many relevant questions. The mothers of all these children with a birth weight of 4 lbs. and under were interviewed and the questionnaire completed as fully as possible. If the baby was born in hospital the ante-natal, obstetric and baby records were carefully examined and much further valuable information acquired. Any suspect or fully-developed case of retrolental fibroplasia was examined at the special clinic set up for this purpose. The examination consisted of weighing, measuring, eye examination and complete physical check-up. An estimation was made of the child's intelligence. A routine X-ray of the skull was carried out in each case. Further similar examinations were carried out on the same children
where the circumstances indicated.

In the babies born during 1952, a different sequence of events took place. There are four main maternity hospitals in Edinburgh, which will be referred to as Hospitals A, B, C and D. All babies in this group were examined as soon as their general condition would permit. Repeat examinations were made at four-weekly periods. If any abnormality was noticed, they were examined at more frequent intervals. The eyes were dilated by a mixture containing 1% homatropine hydrobromide and 1% paredrine hydrobromide. It was found that the pupils dilated completely in 30 - 45 minutes. The use of general anaesthesia in such fragile babies was not to be recommended. However, it was quite amazing to find the "anaesthetic effect" produced by a bottle of 5% glucose water, especially on the babies over a month old, and it was found that in practically every case the eyes opened wide and remained open as long as the glucose water was administered. This enabled an excellent view of the fundus, including the far periphery, to be obtained.

Each week a group of 6 - 8 mothers and babies were brought to the clinic by special transport, which also returned them home at the conclusion of the examination. Thus, it was possible to examine
each baby at a regular monthly interval up to the age of six months. The babies who showed no abnormal ocular signs up till the age of four months were not examined at the age of five months, but were finally checked again at the sixth month. Any baby showing abnormalities at these routine examinations was re-examined within the week under a general anaesthetic. The affected babies were followed-up at much shorter intervals till it was felt that any process that was in progress had either subsided or reached an inactive stage. The routine examination was exactly as already described, with the exception that routine X-rays of the skull were not carried out unless indicated. After each visit a letter was sent to the mother, giving the results of the examination and also the next date at which she was due to return with her infant for further follow-up. The week prior to the visit, each mother was visited personally to ensure that everything was in order for the next examination. The same questionnaire was completed on each baby during the year. As before, if the baby was born in hospital, the ante-natal, obstetric and infant records were carefully analysed in order to complete the story. The survey form consisted of 5 pages, and was set out as follows:-
SURVEY of all babies 4 lbs. birth weight or under - irrespective of period of gestation - born between January 1948 and December 1952.

(A) GENERAL

(1) Mother:

Age ___

Number of previous pregnancies -
Sex & Birth Weight & Period of Gestation:
(If stillborn, dead or premature, state cause if known)

(i)
(ii)
(iii)
(iv)
(v)
(vi)

Health of these children now, with special reference to eyesight and mentality -

(i)
(ii)
(iii)
(iv)
(v)
(vi)

Mother's previous medical history of significance.
Any history of blindness in family?

(2) Father:

Age ___

Employment _______________________

Previous medical history of significance.
Any history of blindness in family?

(3) Housing Conditions:

Type of House _______________________
Number of Rooms ________
Number of Occupants ________
Sanitation _______________________

_________________________
(B) **ANTE-NATAL HISTORY.**

(1) Has mother ever been X-rayed?
   If so, how often?

(2) Had she any illness at all in pregnancy,
   no matter how slight?

(3) Did doctor ever attend her during pregnancy?
   If so, what for and at what stage?

(4) Did doctor ever prescribe any M & B,
   penicillin or antibiotic in any form at all?
   If so, what for, in what form, and for how long?

(5) Did mother ever have German Measles or any
    rashes at all, no matter how slight?

(6) Were there any features of toxaemia of
    pregnancy?

(7) Was the mother's diet to all intents and
    purposes adequate in the pregnancy?

(8) Did she take Vitamins A & D?
    If so, in what form, how often, and for how long?
    Dose?

(9) Did she take iron?
    If so, in what form, how often, how much,
    and for how long?

(10) What was her occupation during pregnancy?

(11) WR & Kahn of the mother, if possible?

(12) Blood group of mother, if possible?

(13) Rh. blood group of mother?

(14) Was she vaccinated in pregnancy?

(15) Was any evidence of vaginal bleeding?
    If so, when?
(C) **INTRA-NATAL HISTORY**

(1) Was child born at home or in hospital?  
   If hospital, which one?

(2) Period of gestation?

(3) Reason for premature birth, e.g.  
   Caesarean Section because of toxaemia,  
   placenta praevia, insufficient uterine  
   contractions in multiple pregnancy.

(4) Anaesthetic used in labour?  
   If so, state type.

(5) Length of labour?

(6) Method of delivery, e.g.  
   breech, vertex, forceps, etc?

(7) Was cord abnormally placed?

(D) **THE INFANT**

(1) State of baby at birth, e.g. normal,  
   cyanosed, pallid and collapsed, yellow?

(2) Did baby need oxygen at birth, and for  
   how long?

(3) Did mucus require to be extracted?

(4) Did baby cry quickly?

(5) Were any congenital defects noted at birth?

(6) Were the eyes sticky?

(7) Were the eyes treated or bathed at all  
   after birth?  If so, with what?

(8) Illumination of the room in which baby  
   was born?

(9) Heating in the room in which baby was born?

(10) Did baby need an incubator, and for  
     how long?
(11) Did baby need any form of stimulus at all?  
If so, what?

(12) How was baby fed - at first, then later?

(13) Were there any birth marks, e.g.  
haemangiomas (excluding post-natal  
staining)?

(14) Did baby have any infections of the newborn  
at all - even colds?

(15) Was baby needed to be seen by a doctor in  
the first six months of life?  
If so, what for?

(16) Was any form at all of medication given to  
the baby in the first six months of life?  
If so, state what.

(17) When did baby start vitamin supplements?  
In what form and how much?

(18) Did baby take these vitamins?  
If not, was anything given in their place?

(19) Was baby vaccinated?  
If so, at what age?  
Did it take?  
Any undue reaction?

(20) Was baby immunised against diphtheria?  
If so, at what age?

(21) Was baby immunised against whooping cough?  
If so, at what age?

(22) Was there any illness at all in the house  
in the first six months of life?  
If so, state its nature?

(23) Were any of the following noted? --  
(a) Nystagmus  
(b) Squint  
(c) Photophobia  
(d) Microphthalmos  
(e) Foetal blue iris  
(f) Defective vision -  
If one or  
other of  
these noted,  
state if  
unilateral  
or  
bilateral.
(24) State as near as possible when baby was able to do the following:—
(a) Follow a light
(b) Balance head
(c) Smile
(d) Sit up
(e) Talk
(f) Stand
(g) Walk
(h) Cut first tooth
(i) Cut complete set of teeth

(25) What is the impression created by the child's intelligence and mental development?

(26) Are there any signs or symptoms of neurological involvement?

(27) Have any congenital defects ever been noted?

(28) Has child ever been in hospital or attended as an out-patient? If so, what hospital and for what reason, and when?
SECTION 4.

RESULTS OF INVESTIGATION WITH DISCUSSION.
RESULTS OF INVESTIGATION WITH DISCUSSION.

During the five year period, 23 true cases of retrolental fibroplasia were observed. One child of that group, born in 1951 died while under treatment with cortisone and another infant in the same year, while not showing actual membrane formation, exhibited extensive eye changes. For ease of description this latter infant will be classified with the fully-developed cases of the disease. In 1952, the eyes of three of the total cases of retrolental fibroplasia were observed to undergo spontaneous regression. In the same year, a further five cases showed retinal changes in some ways suggestive of the disease, but they are not included under the true cases of the condition.

1. PATHOLOGY.

The greatest drawback to clarification in the early years was the lack of material to examine and study in the acute stages of the disease. This was due mainly to the failure to diagnose the condition till it had reached the stage of membrane formation and gross retinal detachment. However, material started to be collected as a result of the routine examination of the fundi and the careful interpretation of the eye sections of any baby who died/
died during the acute stages of retrolental fibroplasia. The outstanding report of Reese, Blodi & Locke (1952) on the early histopathology of retrolental fibroplasia, however, helped to clear up the confusion and most observers now accept that the disease pursues a definite pathological sequence.

The disease commences in the equatorial region of the nerve fibre layer of the retina. A few nests of endothelial cells gather in the nerve fibre layer at this point. (Fig. 1). Over the same area this layer shows thickening due to an increase of glial cells. The internal limiting membrane, however, appears intact. The endothelial nests become quite numerous and commence to canalize (Fig. 2). Near the affected area is oedema of the nerve fibre layer. The internal limiting membrane remains intact. Thus is present a pathological process as yet confined to the equatorial region of the nerve fibre layer of the retina. Now numerous budding capillaries burst through the internal limiting membrane (Fig. 3) in an almost "angiomatous" manner. Masses of angiomatous tissue creep along the surface of the retina and then invade the vitreous proper. Haemorrhage and transudation takes place from these new vessels and fibrous tissue makes/
Fig. 1: The initial stage showing nests of endothelial cells in the nerve fibre layer of the retina at the equatorial region.

Fig. 2: Thickening of the nerve fibre layer due to an increase of glial cells. The cells of the endothelial nests are beginning to canalise.
Fig. 3: Numerous budding capillaries have broken through the internal limiting membrane.

Fig. 4: A large mass of vascular tissue along the surface of the retina, which is in folds.
Fig. 5: Connective tissue with many blood vessels internal to the folded retina. New formed blood vessels are seen sprouting inwards from the retrolental mass.

(Figures 1 - 5)

DIAGRAMMATIC ILLUSTRATIONS OF THE PATHOLOGICAL PROCESS IN RETROLENTAL FIBROPLASIA

(After Reese, Blodi and Locke, 1952)
makes its appearance, pulling on the retina and throwing it into folds. (Fig. 4). Finally there is formation of extensive connective tissue containing many blood vessels internal to the folded retina. Newly formed blood vessels sprout inwards. The peripheral retina appears normal save for some thickening of the nerve fibre layer (Fig. 5).

Thus results a globe undergoing a severe process of fibrosis. Reese and Blodi (1951) noted also an inflammatory process of the uveal tract in 18% of the cases examined. In some cases these inflammatory cells seemed only to involve the choroid, while in others the cells were even noted in the vitreous. They concluded that the uveitis preceded the neovascularization and that the same noxious agent provoked both reactions.

During this survey only one child died showing any evidence of retrolental fibroplasia. This child by the age of three months had developed bilateral retrolental membranes. It was then decided that he should be admitted to hospital to undergo treatment with cortisone. Unfortunately death took place during treatment. No other obvious abnormality was noted on post-mortem examination, apart from the eye condition.

Examination/
Fig. 6: Male, age 4 months. Sections of both eyes of the baby who died while under treatment with cortisone.
Examination of the eyes showed the following features. (Hospital Pathological Report) -

*Left eye.* Postero-inferiorly there is a large retinal detachment upon the surface of which new formed vessels may be seen. Many vascular and fibrous strands extend from the detached area to the posterior surface of the lens. The new formed vessels appear to be empty. A few haemorrhages are present in the retina.

**Horizontal sections.** The cornea, corneo-iridic angle, iris and lens appear normal. On one side is a focus of inflammatory cells in the ciliary body. Posteriorly the retina is detached and thrown into complicated convolutions. In this area extensive haemorrhage has occurred on the retinal surface and numerous new formed blood vessels and organising fibrous strands may be seen extending into the vitreous in company with irregular masses of vasoformative tissue. A subretinal exudate containing fibrinous fibres and macrophages is present. Elsewhere the retina shows focal aggregations of proliferating endothelial cells and diffuse hyperplasia of glial cells in the stratum opticum - a reaction which diminishes in intensity as the ora serrata is approached. The retina is not detached/
detached anteriorly so that there is no separation at the pars plana. In the peri-ocular tissue on one side of the globe there is an undulating vessel which appears to have been replaced by a solid cord of endothelial cells; this appearance was seen in only one section. P.A.S. staining shows dense aggregations of positive staining granules in these areas where endothelial proliferation is most intense, but not in the areas of new vessel formation. The sclera and optic nerve are normal.

Right eye. Situated posteriorly and to the nasal side there is a folded retinal detachment covered with extensive haemorrhages. Small haemorrhages are present elsewhere. An extensive net of new formed vessels with fibrinous strands extends into the vitreous and is adherent to the adjacent retina and posterior surface of the lens.

**Horizontal sections.** The cornea, corneo-iridic angle and lens are normal. There is some albuminous exudate in the anterior chamber and the iris shows an increased cellularity. On one side there is early elongation of the ciliary epithelium. Posteriorly there is a folded detachment of the retina which extends almost to the ora serrata but does not involve the pars plana. A subretinal exudate, containing distended macrophages is present. Within the folded retina/
retina there is a focal and diffuse proliferation of glial and endothelial cells which have extended through the internal limiting membrane to form masses of vasoformative tissue on the retinal surface. From this area new vessels and strands of fibrin and fibroblasts extend into the vitreous. Elsewhere the retina shows glial and endothelial cell proliferation in the stratum opticum and there are small turrets of fibrin attached to the internal limiting membrane. The sclera and optic nerve are normal."

It appears, therefore, that the main features of the pathology of the condition are as follows:--

(a) Endothelial and glial cell proliferation.
(b) New vessel formation.
(c) Haemorrhage and transudation arising from these new vessels.
(d) Some evidence of uveal inflammation.
(e) Fibrous organisation of the exudate.
(f) Resulting retinal detachment and a process of gross intra-ocular fibrosis.

It should be re-emphasised, that all cases do not proceed to these final end-results. The process can stop short at any stage and show regression either to the apparently normal state or leave "scars" to show evidence of past abnormalities.
2. CLINICAL FEATURES.

(a) General features.

(i) Early signs. It is unfortunate that there are no obvious early outward signs of the progressing ocular condition. Without routine ophthalmoscopic examination, signs do not appear until gross damage has taken place within the eye. As a general rule, the child was brought for examination on account of one or both of two reasons. The parents might state that the child did not appear to see or even to follow a light. On the other hand, they might have noticed that "the pupil was white" in colour. This was observed as a rule between 4½ and 6 months of age. On examination this state of affairs might be confined to one eye, but more often both eyes were involved. On shining a light into the affected eye or eyes there could no longer be detected the presence of the familiar "red reflex". However, it was possible in some cases to produce a red reflex on one side while the other showed a greyish white reflection. At this stage the child might show some degree of photophobia and nystagmus.

(ii) Late signs. As a general rule the late signs were mostly due to the presence of extensive intra-ocular fibrosis. It was most striking how
these children sat and rubbed almost incessantly at the eyes. Indeed many of the children went further than merely rubbing the eyes. They took a finger and pushed it hard into the eye socket. This action was obviously much more distracting to the mother than it was to the child. Photophobia was present to some degree in the majority of cases, while a searching nystagmus was often evident. The eye sockets became sunken and microphthalmos appeared as the fibrotic process continued. When one eye was affected more than the other, the microphthalmos became all the more pronounced. (Fig. 7A). As a rule some degree of squint was usually present.

In many cases the iris became "tacked down" in parts to the anterior surface of the lens producing posterior synechiae. Atrophy of the iris was seen in some cases, but none showed persistence of the so-called foetal blue colour. In one case there was bilateral corneal opacities produced presumably by the existence of a shallow anterior chamber, which permitted the lens and iris to come forward till contact was made with the corneal surface. Although glaucoma was quoted as an important sequela, it has not been observed as yet in this series. Characteristically in the fully-developed cases a greyish/
Fig. 7A: Female, age 1 year. Showing bilateral retrolental membranes. The left eye shows microphthalmos, squint and posterior synechia.

Fig. 7B: Female, age 1 year. The right eye showing a complete retrolental membrane.
greyish white mass was observed in the pupil of one or both eyes (Fig. 7B). It might appear as a complete curtain lying deep behind the lens or the mass might only be visible by careful examination with direct light far round on the nasal or temporal sides. The association with other abnormalities and mental retardation will be discussed at a later stage.

3. **DIAGNOSIS.**

Ophthalmoscopic findings.

(i) **Early signs.** Before attempting to detect early pathological changes in the premature fundus, it was necessary to study in detail just what represented the normal picture. An excellent view of the fundus was obtained on examination using a mydriatic, but without the use of a general anaesthetic. The disc, as a rule, showed distinct pallor, while the vessels were well defined. The central portion of the fundus was orange pink in colour. However, as the periphery of the fundal field was approached, this reddish colour gave way to a grey-green appearance (Fig. 8). This is a normal finding present in the majority of premature babies as well as in some full time babies, and unless this fundamental point is appreciated much confusion and erroneous conclusions will be arrived at in the early/
Fig. 8: Drawing of the normal fundus. The dark area at the temporal periphery is greyish green in appearance.

Fig. 9: Female, age 5 weeks. Drawing of the right fundus. Dilated and tortuous vessels running towards a greyish white mass at the temporal periphery.
early diagnosis of the condition. Just when this grey-green appearance of the peripheral retina disappears is not known, although it could still be observed in some cases on final examination at six months of age.

To understand the changes that were unfolded by ophthalmoscopic examination two fundamental basic facts must be kept in mind. These essential facts are, that the retina owes its colour to contact with the pigment epithelium, and by its very transparency is illuminated by the vascular choroid which lies behind it. Thus, if detachment does take place or oedema supervenes the affected part of retina will lose its orange tinge and become greyish white in colour. In a similar manner the retinal blood vessels appear as orange coloured channels, because they lie in close contact with the retina. Should for any reason these vessels proceed forward into the vitreous, they would lose their reddish appearance and become almost black in colour. Thus the interpretation of the abnormal features is all the more easily understood.

While many observers stated that the earliest possible sign of retrolental fibroplasia was cloudy ocular media - the so-called "vitreous haze" - in this series it has only been observed in one case which, this/
this apart, never showed any other abnormality of the fundus. However, in this series it was the practice not to carry out routine examinations until the general condition of the baby had improved enough to permit the handling necessary for such a procedure.

Four weeks of age was the earliest period at which any baby in the survey showed definite signs of retrolental fibroplasia (Case 23). At that time the right fundus showed very noticeably dilated and tortuous vessels running towards a greyish white area at the temporal periphery (Fig. 9). The left fundus showed a flat solid looking detachment of the retina temporally with very appreciably dilated and tortuous vessels (Fig. 10). For the next five weeks, although examined weekly, there was no appreciable change in either eye. After three weeks, the vessel changes in the right fundus became less noticeable, but there was a flat detachment of the retina at the temporal periphery with an area of pigmentary disturbance. The left fundus showed only a greyish appearance at the upper lateral aspect. No abnormal vessels were noted. Three weeks later, under general anaesthesia, both fundi were quite normal except for a slight exaggeration of the "normal" greyish appearance at the periphery. The/
Fig. 10: Female, age 5 weeks. Drawing of the left fundus. A flat solid-looking detachment of the retina at the superior temporal periphery with dilated and tortuous vessels.

Fig. 11: Female, age 3 months. Drawing of the right fundus. Dilated vessels running forward in the vitreous towards a greyish mass of tissue. The main vessel bends forward into the vitreous.
The vessels were normal. A final check at the age of six months showed both fundi to be well within the limits of normal.

Thus here was a baby showing the typical early signs of retrolental fibroplasia, viz. well dilated and tortuous vessels running towards a whitish area of retinal oedema or early detachment at the extreme periphery. The condition remained much the same till three months of age when spontaneous regression occurred, with the restoration of the normal state of the eye by the age of six months.

A second infant (Case 21) was examined four weeks after birth and both fundi were found to be quite normal. At two months of age the ophthalmoscopic appearance was still normal. By the age of three months, however, the right fundus showed vessels running forward in the vitreous towards a greyish mass of tissue. It was observed at the same time that one large vessel bent forward into the vitreous (Fig. 11). The left fundus showed a greyish appearance towards the temporal periphery. Two weeks later, the appearance in the right eye was unchanged. In the left eye, there appeared to be a flat solid looking detachment of the retina at the periphery with convoluted vessels. The vitreous appeared clear. At the age of five months/
months the changes in the right eye were reduced in intensity, although similar in character. The left eye showed no abnormality except a greyish discolouration on the lateral side at the extreme periphery. Four weeks later, in the right fundus the vessel running towards the region of the former grey mass was now almost normal in calibre. This vessel showed a "ghost vessel" effect at the site of the former bending into the vitreous. It also appeared to have receded from the vitreous (Fig. 12). At the age of eight months, the right fundus still showed a vessel running to the temporal side with a "kink" in it, but the vessel now appeared in the same plane as the retina. A large area temporal to the disc appeared pale pinkish white in colour and had a "frothy" appearance. The left fundus showed a similar change temporal to the disc, although less marked. (Fig. 13). A final check at the age of nine months showed no abnormalities other than the pale appearance of both fundi.

Once again these were typical early signs of retrolental fibroplasia. It was interesting to observe that these changes did not make their appearance till the age of three months. Spontaneous regression took place, although the fundi were by no means normal at the age of five months/
Fig. 12: Female, 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.

Fig. 13: Female, age 8 months. Drawing of the right fundus. The main vessel is now in the same plane as the retina. A large area temporal to the disc is pale pinkish white in colour giving a "frothy" appearance.
months.

A further baby (case 22) showed other features of the early stages of the disease. This small baby was born at home and was never admitted to hospital. At the first routine examination at the age of four weeks, the right fundus showed a small retinal haemorrhage near the disc with vitreous opacities on the nasal side. A red mass was seen in the vitreous of the left eye at the nasal periphery with thin brown processes extending further into the vitreous. Further vitreous opacities were observed on the temporal side in the left fundus, with a superficial haemorrhage temporal to the disc. Otherwise, the retinal vessels appeared to be within the range of normal. One week later, in the right eye, a superficial retinal haemorrhage temporal to the disc was observed along with dark brown streaky opacities medially in the anterior vitreous. The left fundus showed a superficial retinal haemorrhage temporal to the disc, with numerous streaky opacities laterally in the anterior vitreous. There was a greyish white area at the inferior nasal region with some streaky opacities in the anterior vitreous (Fig. 14). In a further three weeks, the right fundus appeared to be quite normal and the vitreous was clear. The vitreous of/
Fig. 14: Female, 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.

Fig. 15: Female, age 2 months. Drawing of the left fundus. An area of choroido-retinal atrophy and old haemorrhage at the inferior nasal region with some pigmentary change.
Fig. 16: Female, age 4 months. Drawing of the left fundus. An area of choroido-retinal atrophy with streaks of pigmentary change at the inferior nasal region.

Fig. 17: Female, age 3 months. Drawing of the right fundus. Two large haemorrhages on the temporal side of the disc.
of the left eye was clear, but at the inferior nasal region there was a greyish white area of choroido-retinal atrophy with some pigmentedary change (Fig. 15). At this area there was also evidence of an old haemorrhage. At the age of four months, the right fundus appeared quite normal, while the left one showed an area of choroido-retinal atrophy with streaks of pigmentedary change at the inferior nasal periphery (Fig. 16).

Here was another baby showing bilateral signs of early retrolental fibroplasia. It differed from the previous two cases in that tortuosity and dilatation of the retinal vessels were not noted, although they might well have existed in the weeks prior to the first routine examination.

Before proceeding to discuss the details of the terminal stages of the disease, it should be mentioned again that five babies other than the true cases of the disease, had abnormal features observed on routine examination with the ophthalmoscope, but all subsequently regressed to the normal state. It was felt that these hardly justified inclusion as definite cases of retrolental fibroplasia. It might well be that in actual fact they did represent early stages of the disease, but at a time when accurate accounts of the incidence and progress of the condition/
condition were of prime importance, it was felt that they should be considered under a separate heading.

Doubtful Cases of Retrolental Fibroplasia.

Case A. At the age of three weeks, the fundi were pronounced to be quite normal. One month later, the periphery of the right fundus appeared greyish in colour, and the retinal veins rather full. The left fundus showed no abnormality. Within the next six weeks both eyes showed numerous retinal haemorrhages. The right eye in particular showed two large haemorrhages on the temporal side of the disc (Fig. 17). More haemorrhages continued to appear in both eyes while under observation, but by the age of six months no obvious abnormality was noted in either eye.

Case B. At four weeks of age, both eyes showed dilated retinal veins, but apart from this no other abnormal feature was recorded. Unfortunately the baby died of suffocation under rather strange circumstances and as a result a police investigation followed. From the point of view of this survey, it was unfortunate that notification of death was not received till shortly after the baby had been cremated.

Case/
Case C. On first examination at the age of four weeks, both fundi showed dilated vessels in the lower temporal area running towards a greyish white area. It was felt at the time that this was a case of early retrolental fibroplasia. Three weeks later, both fundi showed generalised pallor, while two small retinal haemorrhages were observed in the left eye. No further changes took place under close observation. At the age of six months, the right fundus was quite normal, while the left showed no evidence of the haemorrhages, but there was some diffuse choroidal-retinal degenerative changes below and nasally from the disc.

Case D. Both fundi were regarded as being within the limits of normal on the first examination at the age of four weeks. One month later the right fundus showed a greyish white area laterally, like a large tear or defect in the retina. The left eye showed a greyish white area at the temporal periphery, but the vessels appeared quite normal. At a subsequent examination four weeks later, a brownish red opacity at the site of the retinal defect was noted in the right fundus. In a further four weeks, both eyes were quite normal save for some slight diffuse choroidal atrophy temporally in each case.

Case/
Case E. At the first examination four weeks after birth, the right fundus showed a greyish green appearance of the retina in the upper and outer quadrants, which looked like an infiltration beneath the retina. There was no actual detachment. The left fundus appeared normal. At the next follow-up four weeks later, both fundi were quite normal save for a greyish area at the temporal periphery in each eye.

(ii) Late signs. Broadly speaking these can be divided into two main groups.

(a) Those who showed the presence of a retrolental mass in one or both eyes.

(b) Those in whom there was no membrane formation, but obvious abnormalities were observed on examination with the ophthalmoscope.

Dealing with group (a) first, a baby at the age of three months (Case 5) was noticed to have a right greyish white mass at the temporal periphery, with a few strands running into the vitreous at this region. The left fundus showed a greyish white mass laterally at the periphery. Running from the region of the ciliary body down into the anterior vitreous, was a soft mass brownish-red in colour (Fig. 18). Over the next few weeks the right eye condition appeared to deteriorate, while the state of left eye remained unchanged. Three weeks later, the right/
Fig. 18: Female, 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 softish mass brownish red in colour.

Fig. 19: Female, age 4 months. Drawing of the right fundus. Vascularised folds occupying most of the lateral half of the vitreous body.
right fundus showed vascularised folds occupying most of the lateral half of the vitreous body. A good red reflex was present nasally, but there was a greyish area above and laterally (Fig. 19). The striking feature was that the left fundus was now completely normal. The vitreous was quite clear. At the age of six months, the grey mass in the right vitreous had increased and no red reflex was now present. The left fundus remained quite normal. At the age of nine months, a complete retrolental membrane was present in the right eye. There was a thin area just lateral to the centre through which retinal vessels could be seen (Fig. 20). There was nothing abnormal to note in the left fundus except a greyish discolouration at the extreme temporal periphery with some pigmentary change.

This was an interesting case. It showed the bilateral nature of the disease. It also showed the power and ability of spontaneous regression. At one stage extensive changes were taking place in the left eye, yet the whole process resolved itself, leaving a minimum of pathological change.

The changes that took place in the left eye were in many ways similar to the sequence of events that existed in Case 22 (Fig. 14).

A further infant (Case 7) was noted at the age of/
Fig. 20: Female, age 9 months. Drawing of the right fundus. A complete retrolental membrane with a window through which retinal vessels can be seen.

Fig. 21: Male, age 18 months. Drawing of the left fundus. Fibrous tissue in the anterior vitreous with scattered pigmentary change on the temporal side.
of two months to have tortuous vessels, but no haemorrhages were observed. By the age of four months, a mass of tissue was noted in the right eye occupying the lateral part of the anterior vitreous, with a large dilated vessel running forward to it from an area of localised detachment of the retina. This right eye also showed diffuse choroido-retinal degenerative changes at the upper temporal periphery. The left eye showed a mass of soft looking tissue in the lower anterior vitreous, with vessels running to it from the retina. The child was then treated with a six weeks course of cortisone.

Two months after the previous examination, the right eye showed marked improvement and no abnormality was noted, save for a flat greyish area at the extreme lateral periphery. The left eye condition was worse. The mass of tissue now occupied most of the lower vitreous and also extended up and laterally.

At the age of eighteen months, the right eye appeared quite normal. The left fundus showed a mass of fibrous tissue which occupied most of the medial half of the vitreous. Vessels were seen quite clearly, even by naked eye, cruising over the surface of this mass. On the temporal side was normal retina with scattered pigmentary change (Fig. 21).

Again/
Fig. 22: Male, age 7 months. Drawing of the left fundus. A fold running from the temporal side of a malformed disc with a vessel looping forward in the fold. Then appears a gap followed by an area of pigmentary change. At the temporal periphery is a greyish white area.
Again the bilateral nature of the disease was evident. As in Case 5, regression took place in one eye only. The part that cortisone played in this case will be more fully discussed under the section on treatment. The final end-result was as before, the formation of a retrolental mass of fibrous tissue.

One child (Case 6) clearly illustrated the fact that all cases of retrolental fibroplasia do not progress to membrane formation. This case developed before the commencement of this survey, therefore the details of the early stages of the disease were not known. The left fundus showed a fold running from the temporal side of a malformed disc, with a vessel looping forward into the fold. Then came a gap followed by an area of pigmentary change. At the temporal periphery was a greyish white area (Fig. 22). The right fundus showed no fold, but at the periphery was a greyish white region surrounded by an area of pigmentary change.

Table I shows to what extent the eyes of the 23 cases of retrolental fibroplasia were involved. The degree of partial vision retained varied from the appreciation of light to being able to recognise an object at a distance.
TABLE 1.

Summary of eye findings in 23 cases of Retrolental Fibroplasia.

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>VISION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>23</td>
<td>13</td>
</tr>
</tbody>
</table>

Having described in detail the pathology, clinical features and ophthalmoscopic findings, it is desirable to try and correlate the various features.

Correlation of pathology, clinical features and ophthalmological findings.

While the initial pathological reaction of endothelial cell proliferation, increase of glial cells and oedema of the nerve fibre layer of the retina is taking place (Figs. 1 & 2), dilatation and tortuosity of the retinal vessels (Figs. 9 & 10) passing perhaps to a greyish white area at the periphery, is seen with the ophthalmoscope. This area is due to oedema of the nerve fibre layer or to early retinal detachment. As the disease progresses, the budding new capillaries burst through the internal limiting membrane (Fig. 3). Transudation and haemorrhage results from these new vessels as they sprout into the vitreous. This gives/
gives rise to reddish brown masses or opacities in
the anterior vitreous (Figs. 14 & 18). As a result
of this, and possibly in conjunction with some degree
of uveal irritation, organisation of the exudate
follows, with subsequent retinal detachment (Fig. 5).
As the fibrosis increases, the eye shrinks and a
whitish mass is seen lying behind the lens (Figs.
7A & 7B). The lens and iris may become adherent
to form posterior synechiae. The membrane as a
rule shows vessels across its surface and may be
complete (Fig. 20) or occupy only a part of the
vitreous body (Fig. 21).

The whole process may stop short at any stage
leaving as evidence areas of choroido-retinal
atrophy with pigmentary change (Fig. 16). An
intermediate stage between this and membrane
formation may result, as shown by the evidence of a
retinal fold attached to a malformed disc and passing
laterally to an area of choroido-retinal atrophy
surrounded by pigmentary change (Fig. 22).

4. DIFFERENTIAL DIAGNOSIS.

Although there are numerous conditions that can
be considered in the differential diagnosis of
retrolental fibroplasia, three of them warrant
special attention.

(a)
(a) **Retinal glioma.** This is a highly malignant tumour which affects infants in the first few years of life. It affects all classes of baby, whether full-time or premature. It may in some cases be bilateral. It is yellow in colour, and because of the yellow colour of the pupil the child is brought for examination.

(b) **Persistence of the tunica vasculosa lentis.** This has already been dealt with under the section on the review of the literature (P.11). It is really a form of pseudoglioma.

(c) **Pseudoglioma.** The most common of this group is the infantile metastatic uveitis. It may affect one or both eyes and produces a yellow-white appearance behind the lens. It can affect full-time or prematurely born children. Although examples of the first two conditions were not encountered during this survey, it was interesting to observe, on perusal of the various eye department records, the notes on a male child born at 40 weeks gestation and weighing 7 lbs. 2 ozs. The mother stated that the child "seemed to have something in its pupil". At one month of age, the child was examined and the report read as follows:— "The right cornea is bright. White mass visible in the pupil. The left cornea is hazy. The condition unlikely/
unlikely to be gliomatous because of the extensive formation at the age of 17 days. Also unlikely to be due to retrolental fibroplasia as the baby is not premature? metastatic uveitis." Three weeks later the diagnosis of uveitis was confirmed. In a further ten days, it was noticed that the left eye was beginning to shrink. Four months later, the child showed bilateral phthisis bulbi.

This case is recorded to illustrate how a "whitish mass" in the vitreous presented a three sided differential diagnosis. It cannot help being felt that ten years ago this would have just been a case of glioma or pseudoglioma. On the other hand, if the case had been one of retrolental fibroplasia ten years ago what would have been the diagnosis?

5. INCIDENCE OF RETROLENTAL FIBROPLASIA.

TABLE 2.

Relationship of main features of all premature babies born and resident in Edinburgh 1948-1952.

<table>
<thead>
<tr>
<th>Years</th>
<th>Birth Weight 5½ lbs. and under</th>
<th>Birth Weight 4 lbs. and under</th>
<th>True Cases of Retrolental Fibroplasia</th>
<th>Babies Showing Cerebral Palsy</th>
<th>Babies Showing Other Congenital Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>217</td>
<td>52</td>
<td>2</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>1949</td>
<td>180</td>
<td>54</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td>280</td>
<td>57</td>
<td>4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>1951</td>
<td>291</td>
<td>51</td>
<td>8</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>1952</td>
<td>289</td>
<td>46</td>
<td>5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>1257</td>
<td>240</td>
<td>23</td>
<td>11</td>
<td>51</td>
</tr>
</tbody>
</table>

* One child died while under treatment.

** Three showed spontaneous regression of the eye condition.

During/
During the period 1948-52, 1,257 premature infants were born to parents resident in Edinburgh, and 23 or 1.83% showed definite evidence of retrolental fibroplasia. Details for the five years under review are given in Table 2. Under the heading "other congenital defects" are included conditions such as mongolism, congenital heart disease, cleft palate and various limb deformities. The number of premature infants with cerebral palsy are shown separately, because there appears to be some relationship between this and retrolental fibroplasia, as will be discussed later.

During 1952 there were five definite cases of retrolental fibroplasia, three of which underwent spontaneous regression. This meant that 1.7% of all premature children born in Edinburgh or 10.8% of these with an approximate birth weight of 4 lbs. and under suffered from the disease. It may be that the proportions were even greater, because five other infants showed on examination early retinal changes, subsequently resolving, which might have represented the mildest form of the disease. These "doubtful cases" are considered again later, but if accepted as instances of the disease then the incidence of retrolental fibroplasia in 1952, would be as high as 3.4% of all premature infants and 21.6%
GRAPH.

21.6% of those with a birth weight of 4 lbs. and under.

It is difficult to compare the figures of 1952 with those of the previous four years, not only because the numbers are small, but because no routine ophthalmoscopic examination was carried out in these earlier years. When the established cases of retrolental fibroplasia are considered, however, it would seem as shown in the accompanying graph, that 1951 was the peak year for the period under review.

The fact that the incidence of retrolental fibroplasia reached a peak in 1951 was in no way related to an increased survival rate of the small babies. As shown in Table 2 (P. 80) the survival rate of babies with a birth weight of 4 lbs. and under has remained almost constant during the five years period.

6. **ASSOCIATION WITH PREMATURITY.**

Since the definition of prematurity for this survey was based on the birth weight, there were no cases of retrolental fibroplasia observed in full time babies. Indeed over the whole series, only three had a birth weight of over 4 lbs. and they surpassed this level by a matter of only a few ounces. On the other hand one baby, although weighing/
weighing 3 lbs. 12 ozs. at birth, was claimed to have been born at full-term. In Table 3 is shown the relationship of birth weight to the period of gestation in 191 babies. In a further 33 cases there was no record of the period of gestation, so they are excluded from the Table. A similar relationship is shown in Table 4 for the 23 definite cases that occurred during 1948-52. It will be observed that these figures total up to 247, while the original number in the survey of babies of 4 lbs. and under was stated to be 240 (Table 2). The remaining seven babies were over 4 lbs. but under 4½ lbs. Three of them were cases of retrolental fibroplasia, while the other four were included because they belonged to a set of twins, and in each case one partner was under 4 lbs. at birth.

**TABLE 3.**

Relation of Birth Weight to period of gestation in 191 cases.
(excluded are 23 definite cases of retrolental fibroplasia and 33 cases where there was no record of period of gestation).

<table>
<thead>
<tr>
<th>Weights</th>
<th>Under 28 weeks</th>
<th>28-32 weeks</th>
<th>32-36 weeks</th>
<th>36 weeks and over</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 3 lbs.</td>
<td>1</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>3-3½ lbs.</td>
<td>2</td>
<td>15</td>
<td>21</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>3½-4 lbs.</td>
<td>2</td>
<td>10</td>
<td>56</td>
<td>25</td>
<td>93</td>
</tr>
<tr>
<td>4 lbs. and over</td>
<td>-</td>
<td>1</td>
<td>14</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>41</td>
<td>98</td>
<td>47</td>
<td>191</td>
</tr>
</tbody>
</table>

**TABLE 4/**
TABLE 4.

Relation of Birth and period of gestation
to 23 definite cases of Retrolental Fibroplasia.

<table>
<thead>
<tr>
<th>Weights</th>
<th>Under 28 weeks</th>
<th>28-32 weeks</th>
<th>32-36 weeks</th>
<th>36 weeks and over</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 3 lbs.</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>3-3½ lbs.</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>3½-4 lbs.</td>
<td>-</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>4 lbs. and over</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>

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.

7. SEX RATIO.

There was no evidence of any sex preference. Twelve of the established cases of retrolental fibroplasia in the five years period were males, and eleven were females.

8. RELATIONSHIP TO PHYSICAL DEVELOPMENT.

Apart from any manifestations of cerebral palsy and/or mental retardation it was estimated how each of the 20 fully developed cases of the condition was/
was progressing from a general physical point of view (Table 5). As already stated, one child died while under treatment with cortisone. The measurements of two of the remaining 19 were not available. In each case the measurements were expressed as a percentage of normal (Nelson 1950). As will be noted, there was a wide variation in the attempt to catch up on their full-time counterparts.

**TABLE 5.**

Physical Growth of 17 fully-developed cases of retrolental fibroplasia (expressed as percentages of normal).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at examination</th>
<th>Birth Weight</th>
<th>Weight</th>
<th>Height</th>
<th>Head Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>9 months</td>
<td>48.3</td>
<td>86.6</td>
<td>95.1</td>
<td>96.1</td>
</tr>
<tr>
<td>1</td>
<td>1 yr. 2 mths.</td>
<td>46.7</td>
<td>69.2</td>
<td>93.2</td>
<td>93.9</td>
</tr>
<tr>
<td>6</td>
<td>1 &quot; 8 &quot;</td>
<td>43.3</td>
<td>97.2</td>
<td>97.3</td>
<td>98.6</td>
</tr>
<tr>
<td>7</td>
<td>1 &quot; 8 &quot;</td>
<td>41.7</td>
<td>79.5</td>
<td>95.8</td>
<td>98.8</td>
</tr>
<tr>
<td>3</td>
<td>1 &quot; 9 &quot;</td>
<td>50.8</td>
<td>101.9</td>
<td>98.8</td>
<td>98.8</td>
</tr>
<tr>
<td>11</td>
<td>1 &quot; 10 &quot;</td>
<td>33.3</td>
<td>86.5</td>
<td>94.5</td>
<td>82.6</td>
</tr>
<tr>
<td>2</td>
<td>3 years</td>
<td>48.3</td>
<td>114.5</td>
<td>104.4</td>
<td>99.0</td>
</tr>
<tr>
<td>4</td>
<td>3 &quot; 3 &quot;</td>
<td>50.8</td>
<td>84.8</td>
<td>94.7</td>
<td>92.7</td>
</tr>
<tr>
<td>10</td>
<td>4 &quot; 1 &quot;</td>
<td>46.3</td>
<td>74.9</td>
<td>89.8</td>
<td>92.9</td>
</tr>
<tr>
<td>8</td>
<td>4 &quot; 2 &quot;</td>
<td>57.1</td>
<td>92.3</td>
<td>99.4</td>
<td>101.9</td>
</tr>
<tr>
<td>9</td>
<td>4 &quot; 5 &quot;</td>
<td>56.7</td>
<td>82.0</td>
<td>100.0</td>
<td>93.5</td>
</tr>
<tr>
<td>15</td>
<td>1 yr. 1 mth.</td>
<td>47.3</td>
<td>79.5</td>
<td>99.2</td>
<td>98.3</td>
</tr>
<tr>
<td>14</td>
<td>2 &quot; 2 &quot;</td>
<td>33.8</td>
<td>73.2</td>
<td>90.6</td>
<td>96.1</td>
</tr>
<tr>
<td>17</td>
<td>2 &quot; 8 &quot;</td>
<td>31.2</td>
<td>70.5</td>
<td>94.1</td>
<td>93.7</td>
</tr>
<tr>
<td>18</td>
<td>2 &quot; 9 &quot;</td>
<td>38.0</td>
<td>86.3</td>
<td>92.4</td>
<td>95.1</td>
</tr>
<tr>
<td>16</td>
<td>2 &quot; 11 &quot;</td>
<td>27.0</td>
<td>84.8</td>
<td>96.1</td>
<td>94.5</td>
</tr>
<tr>
<td>13</td>
<td>3 &quot; 5 &quot;</td>
<td>40.5</td>
<td>83.1</td>
<td>91.6</td>
<td>95.0</td>
</tr>
</tbody>
</table>

While /
While dealing with physical development it is perhaps of interest to record at this stage, the results collected on all the premature babies of birth weight 4 lbs. and under routinely examined during 1952.

**TABLE 6.**

The Average increase in weight of normal premature babies (expressed as percentage of normal) during first six months of life.

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALES</strong></td>
<td>51.3</td>
<td>70.6</td>
<td>85.9</td>
</tr>
<tr>
<td><strong>FEMALES</strong></td>
<td>48.6</td>
<td>65.3</td>
<td>76.9</td>
</tr>
</tbody>
</table>

From Table 6 it will be seen that the male was slightly heavier at birth, and made a bigger attempt to catch up on the baby born at term, in the first six months of life, than did the female.

**TABLE 7/**
TABLE 7.

Increase in height and head circumference (expressed as percentage of normal) of normal premature babies during first six months of life.

<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Head Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>85.9</td>
<td>87.1</td>
</tr>
<tr>
<td>3 months</td>
<td>90.6</td>
<td>92.4</td>
</tr>
<tr>
<td>6 months</td>
<td>94.6</td>
<td>95.7</td>
</tr>
<tr>
<td>Birth</td>
<td>81.5</td>
<td>84.7</td>
</tr>
<tr>
<td>3 months</td>
<td>87.1</td>
<td>90.0</td>
</tr>
<tr>
<td>6 months</td>
<td>90.8</td>
<td>94.2</td>
</tr>
</tbody>
</table>

The figures in Table 7 show that the male was slightly bigger at birth, but both male and female made an approximately equal attempt to catch up on their full-time counterparts in the first six months of life.

9. AETIOLOGY.

INFECTIONS IN THE MOTHER. This question will be dealt with more fully when anoxia and oxygen are considered. However, it should be stated that no cases of maternal rubella were recorded during the pregnancies/
pregnancies. In case the mother harboured a subclinical infection of toxoplasmosis, the fully-developed cases of the condition were X-rayed in order to see if any evidence of cerebral calcification existed in the skulls. All X-rays were completely negative.

**DIET AND VITAMINS.**

It was estimated that 25 mothers received an inadequate diet during the pregnancy. Two of these mothers produced babies who subsequently developed retrolental fibroplasia. One hundred and sixty-eight mothers claimed to have taken some form of vitamins A, D and C during the pregnancy and of these, 20 of their children developed the disease.

**RHESUS FACTOR.**

In this survey 32 babies were born of mothers who were Rh negative. Of this group, only two developed the disease. In neither of these cases were antibodies present in the mothers' sera and in both babies the Coombs test was negative. It would appear that this is not an aetiological factor.

**OTHER FACTORS.**

There appeared to be no relationship with the parity of the mother and retrolental fibroplasia. Approximately 50% of the cases of the disease resulted/
resulted from first pregnancies.

Relation to plural pregnancies. During the whole survey 38 twin pregnancies were observed, and six of these showed retrolental fibroplasia in one member of the pair only. Two members of the six sets of twins affected by the condition were stillbirths. It was interesting to note that one of these stillbirths was a mongol. Perhaps more interesting was the fact that in one set of twins, the babies were regarded as being uniovular. These twins fortunately were born in 1952, and it was possible to observe the condition develop to its full stage in one twin (Case 5), while the other was examined just as regularly, but never at any time displayed signs suggestive of retrolental fibroplasia. It has been stated that if the twins were binovular, only the eyes of one infant might be affected, while if they were uniovular, the eyes of both partners were involved. It appears that the condition may exist in one or both twins irrespective of whether they are uniovular or binovular.

LENGTH OF LABOUR AND METHOD OF DELIVERY.

Six cases of retrolental fibroplasia were observed where the labour had lasted under five hours, six after a labour lasting 5-10 hours, and seven after labours of 1-20 hours. In one case the labour lasted/
lasted for over 20 hours. Two cases that subsequently developed the disease were delivered by caesarean section. The length of labour was not known in the remaining case. Over the whole survey 167 babies had a normal vertex presentation and of these, 14 developed retrolental fibroplasia. Seven of the cases had a breech presentation. No obvious connection was apparent between these factors and the production of the condition.

**RELATION TO SKIN HAEMANGIOMAS.**

Approximately 11% of the total babies surveyed showed the presence of skin haemangiomas. Only one of the true cases of the condition (Case 5) showed the presence of these birth marks. Case E, which was one of the five doubtful cases of retrolental fibroplasia observed during 1952, showed no less than ten skin haemangiomas. They were situated as follows: 2 right leg, 1 right axilla, 1 base of the neck, 1 right parotid region, 1 anterior chest wall, 1 lower right eyelid, 1 right palm, 1 behind the right ear. A final one was situated actually in the substance of the right breast (Figs. 23 & 24). The characteristic blood spot was in the situation of the right nipple. The whole right breast was more prominent than the left. It could be concluded from/
Fig. 23: Female, age 6 months. Photograph showing multiple haemangiomas. One is noted below the right eye and on the anterior chest wall. The right breast contains a haemangioma. Note the darker appearance of the right nipple in comparison with the left.
Fig. 24: Female, age 6 months. Photograph showing multiple haemangiomas. One on the right parotid region, right axilla, right thigh and anterior chest wall. The right breast contains a haemangioma. Note the general enlargement of the right breast due to the haemangioma.
from these findings that skin haemangiomas were no more common in babies who developed the condition, than in those who showed immunity from the disease.

**DIET AND VITAMINS IN THE CHILD.**

It has been suggested that the condition may be precipitated by the feeding of a baby on a high electrolyte diet such as cow's milk. There was no such evidence in this series. In fact, two children who developed the disease were entirely breast fed. More than 50% of the cases were breast fed for a period and no correlation was found between the change from breast to artificial feeding, and the onset of the disease. Various artificial feeds were used such as Nestlé's, Carnation milk and Cow's milk mixtures. All babies were started on vitamins while still in hospital. Each hospital used its own form and dosage of vitamins A, D and C. It was recorded that 190 babies received vitamins A, D and C in some form during the first six months of life, and of these, 21 developed retrolental fibroplasia. The nature of feeding does not seem to be concerned in the production of the disease. Certainly lack of vitamin A was not a factor, while it was difficult to comment on the possibility of excessive amounts of that vitamin being instrumental in the appearance of the disease, since 80% of the total babies surveyed/
surveyed received regular supplements during the first six months of life.

ANTIBIOTICS AND SULPHONAMIDES.

Only three mothers whose babies were later affected with retrolental fibroplasia received one or other of these forms of therapy. Sixty per cent of the babies who developed the disease received either one or both of these drugs in their early life.

ANOXIA AND OXYGEN.

Anoxia and oxygen are so closely inter-related that it would be quite wrong to study them under separate headings. Before attempting to assess the role played by these factors it was essential to know what facilities were available for the handling of the prematurely born infant. There are four main maternity hospitals in Edinburgh. They will be referred to as Hospitals A, B, C and D. Hospital "A" is further subdivided into four separate units, which will be referred to as Wards 1, 2, 3 and 4.
TABLE 8.
Place of Birth of all premature babies in the survey (1948-1952).

<table>
<thead>
<tr>
<th>Degree of Retrolental Fibroplasia</th>
<th>Home</th>
<th>Nursing Home</th>
<th>Hosp &quot;A&quot;</th>
<th>Hosp &quot;B&quot;</th>
<th>Hosp &quot;C&quot;</th>
<th>Hosp &quot;D&quot;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Signs ..</td>
<td>22</td>
<td>7</td>
<td>75</td>
<td>40</td>
<td>46</td>
<td>29</td>
<td>219</td>
</tr>
<tr>
<td>True cases fully developed</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>6</td>
<td>-</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>True cases spontaneous regression (1952 only)</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Doubtful cases spontaneous regression (1952 only)</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>7</td>
<td>89</td>
<td>48</td>
<td>46</td>
<td>34</td>
<td>247</td>
</tr>
</tbody>
</table>

The results shown in the Table are indeed quite surprising. No cases even suggestive of the condition had appeared from 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 practically the second highest out of the four main hospitals. From this revealing fact the question was naturally raised, why did Hospital "C" appear to remain immune from the disease/
disease?

The management of the infants at the four main centres had obviously to be compared. Table 9 shows the management of these babies in the four hospitals. Leaving the question of oxygen therapy to the last, it will be noted that the temperature was maintained at a level of 80° - 90°F, while the humidity was kept at 65 - 75%. It should also be mentioned here that the incidence of the disease between the four wards in Hospital "A" showed quite a wide variation. In each case feeding was "on demand" with an average of three days and a maximum of five days, before it was commenced. Each hospital had its own artificial feed of choice, e.g. Hospital "D" favoured Carnation Milk, Hospital "A", Nestlé's Milk, but all units sooner or later, if breast milk was not available, used National Dried Milk or Liquid Cow's Milk mixtures. Vitamins were started as a rule by the tenth day, although Ward 1, Hospital "A", claimed to commence these supplements at the end of the third week. All babies were moved, as a rule, to a cooler nursery at a weight of approximately 4½ lbs., although in Hospital "C" it appeared that the procedure was carried out in two stages, i.e. when the child reached 4 lbs. and again at the weight of 5 lbs. Four of the units gave routine administration of iron, as a rule commencing at/
TABLE 9.
The Management of the Premature Baby
in the Hospital Units.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Oxygen How Given</th>
<th>Concentration of Oxygen</th>
<th>Carbon Dioxide Oxygen Mixture</th>
<th>Temperature in Degrees Fahrenheit</th>
<th>Feeding Commenced</th>
<th>Type of Feeding</th>
<th>Vitamins A and D Commenced</th>
<th>Vitamin C Commenced</th>
<th>How Oxygen Therapy is Stopped</th>
<th>Bathing Commenced</th>
<th>To Cooler Nursery</th>
<th>Iron Administration Commenced</th>
<th>Discharged</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. WARD 1</td>
<td>Plastic Tent over head and chest</td>
<td>72%</td>
<td>None</td>
<td>82°</td>
<td>Third day as a rule</td>
<td>Breast or Nestle's then National Oat Milk</td>
<td>End of third week</td>
<td>&quot;Abyd&quot;</td>
<td>End of third week</td>
<td>&quot;Abyd&quot;</td>
<td>—</td>
<td>—</td>
<td>AT 4 lbs 8 ozs</td>
</tr>
<tr>
<td>A. WARD 2</td>
<td>&quot;</td>
<td>65%</td>
<td>None</td>
<td>82°</td>
<td>On demand (3-5 days)</td>
<td>Nestle's on 3rd day</td>
<td>5th day</td>
<td>&quot;Abyd&quot;</td>
<td>5th day</td>
<td>&quot;Abyd&quot;</td>
<td>As soon as possible but oxygen then given for quantities in every hour</td>
<td>AT 4 lbs 12 ozs</td>
<td>AT 4 lbs 12 ozs</td>
</tr>
<tr>
<td>A. WARD 3</td>
<td>&quot;</td>
<td>65%</td>
<td>None</td>
<td>80°</td>
<td>On demand (3-5 days)</td>
<td>Breast or Nestle's</td>
<td>7-10 days</td>
<td>&quot;Abyd&quot;</td>
<td>7-10 days</td>
<td>&quot;Abyd&quot;</td>
<td>AT 4 lbs 12 ozs</td>
<td>AT 4 lbs 12 ozs</td>
<td>AT 6 weeks of age</td>
</tr>
<tr>
<td>A. WARD 4</td>
<td>&quot;</td>
<td>59%</td>
<td>None</td>
<td>80°</td>
<td>On demand (3-5 days)</td>
<td>Nestle's then National Oat Milk</td>
<td>7th day</td>
<td>&quot;Abyd&quot;</td>
<td>7th day</td>
<td>&quot;Abyd&quot;</td>
<td>AT 4 lbs 12 ozs</td>
<td>AT 4 lbs 12 ozs</td>
<td>AT 6 weeks of age</td>
</tr>
<tr>
<td>B. OXENAIRNE INCUBATOR</td>
<td>68%</td>
<td>None</td>
<td>90°</td>
<td>On demand (3-5 days)</td>
<td>Breast or National Oat Milk</td>
<td>7th day</td>
<td>&quot;Abyd&quot;</td>
<td>7th day</td>
<td>&quot;Abyd&quot;</td>
<td>When condition remains good after feed out of incubator</td>
<td>—</td>
<td>—</td>
<td>None given routinely</td>
</tr>
<tr>
<td>C. PLASTIC INCUBATOR</td>
<td>78.4%</td>
<td>Minutes hourly for first few days</td>
<td>90°</td>
<td>On demand (3-5 days)</td>
<td>Breast milk</td>
<td>3rd day</td>
<td>&quot;Abyd&quot;</td>
<td>3rd day</td>
<td>&quot;Abyd&quot;</td>
<td>For short periods then completely</td>
<td>AT</td>
<td>AT 6 weeks of age if hematocrit level indicates it</td>
<td>Not till 5-5½ lbs</td>
</tr>
<tr>
<td>D. PLASTIC INCUBATOR</td>
<td>65.8%</td>
<td>Minutes hourly for first few days</td>
<td>85°</td>
<td>On demand (3-5 days)</td>
<td>Breast or Carnation Milk</td>
<td>3rd day</td>
<td>&quot;Abyd&quot;</td>
<td>3rd day</td>
<td>&quot;Abyd&quot;</td>
<td>Stopped for increasing periods after feeds</td>
<td>AT</td>
<td>AT</td>
<td>5 lbs</td>
</tr>
</tbody>
</table>
at six weeks of age. The remaining units only gave it, if indicated by the haemoglobin level. In practically all cases the baby was not discharged till a weight of 5-5½ lbs. was attained. Certain features, such as the nursing of the babies in a naked state and the administration on one or more occasions of a Vitamin K preparation, were common to all centres. Wards 3 and 4 of Hospital "A" used an oesophageal tube for the feeding of the smallest babies in place of the more widely used Belcroy feeder.

Thus far, differences in the technique of management of premature infants in the units were slight and apparently of little significance.

**ADMINISTRATION OF OXYGEN.**

Hospital "A" was opened in March, 1939. The small babies were nursed in incubator rooms, as they are nowadays. However, oxygen was not piped into the rooms at that time, but was supplied by means of an ordinary oxygen cylinder, which stood at the side of the cot. No flow meters were in use at that time, so the oxygen was bubbled through water and administered by the means of a funnel in the early stages, and later by the use of a plastic hood. The rate of flow was judged by the flow of the bubbles. A few years later oxygen was supplied by pipes from a common/
Fig. 25: The administration of oxygen in Hospital "A".
Fig. 26: The administration of oxygen in Hospital "B".
common pool. Fig. 25 shows the method now adopted for the administration of oxygen. It is piped in from the wall, passed through water and then into the roof of a plastic hood which fits over the child. The normal rate of flow used, produced a concentration within the tent of 60 - 70% of oxygen. Prior to the sampling of the concentrations, some babies were receiving between 70-80% of oxygen. This method was adopted in each of the four wards of Hospital "A". It was claimed that the use of routine oxygen was discontinued as soon as possible. All wards of Hospital "A" claimed to reduce the baby slowly from the high concentrations to the normal conditions.

At Hospital "B" the infants were all nursed in oxygenaire incubators, while oxygen was fed in from a cylinder at the side of the incubator (Fig. 26). The concentration of oxygen in the incubator at their normal rate of flow was found to average 68%. The baby as soon as possible was fed out of the incubator and the oxygen was discontinued as soon as the state of the baby remained good during feeding.

At Hospital "C" the baby was nursed in an incubator room. The baby was placed in a plastic "incubator" and oxygen was fed in from a cylinder at the side of the cot. It should be pointed out that although the baby appeared clothed in Fig. 27, all infants/
Fig. 27: The administration of oxygen in Hospital "C".
Fig. 28: The administration of oxygen in Hospital "D".
infants were actually nursed quite naked. At the usual rate of flow, a concentration of 78.4% oxygen was attained in the incubator. For five minutes in every hour the baby was given a mixture of carbon dioxide and oxygen, then the routine oxygen was re-started. The routine use of oxygen was stopped as soon as possible, this being done by gradually increasing the periods of time without oxygen. In many cases the hourly use of carbon dioxide and oxygen was maintained for a further length of time.

At Hospital "D" the babies were nursed in a special incubator room. Oxygen was supplied from a cylinder and administered to the baby by the top half of an incubator which was placed over the infant in the cot (Fig. 28). The concentration of oxygen attained in this "tent" proved to be 65.8%. As in Hospital "C", a carbon dioxide-oxygen mixture was given for five minutes in every hour over the first few days. The routine use of oxygen was always discontinued slowly, by withholding it for progressively longer periods after a feed.

It would appear broadly speaking, that there were no basic differences in the method of supplying the new-born infant with oxygen. All units claimed to "wean" the baby gradually from the oxygen enriched atmosphere. However, it must be admitted that/
that merely withholding oxygen for increasing periods of time and then replacing the baby back into the high oxygen atmosphere, hardly constituted systematic "weaning". Indeed, this procedure might be harmful to a baby as yet unstable to any sudden changes of environment. On closer examination of individual cases, it was noted in many instances that this method was carried out along with a gradual decrease in the flow of oxygen. Presuming, therefore, that the babies were subjected to similar concentrations under like circumstances, it would be necessary to investigate the exact duration of such therapy. On examination of the hospital records over the last five years, many times the report "Baby put on continuous oxygen" was observed. This in many cases constituted the last entry regarding the administration of oxygen. Perhaps this is hardly the time or place, but a plea must earnestly be put forward for keeping more precise records of the early life of infants with special regard to the prematurely born baby. Much work has yet to be done on the question of prematurity as a whole, and without accurate observations the problem will continue to be a matter of considerable uncertainty. Table 10 illustrates the part oxygen played in the management of the early life of the premature/
107.

premature babies investigated.

**TABLE 10.**

Administration of oxygen and its relation to the cases of retrolental fibroplasia.

<table>
<thead>
<tr>
<th>Degree of Retrolental Fibroplasia</th>
<th>Period of Oxygen Treatment</th>
<th>Total</th>
<th>No Oxygen Treatment</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>True cases: fully developed...</td>
<td>3 weeks and over</td>
<td>20</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2-3 wks.</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 1 week</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Time not known</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>True cases: Spontaneous Regression (1952 only)</td>
<td>3 weeks and over</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Doubtful cases: Spontaneous Regression (1952 only)</td>
<td>2-3 wks.</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No signs ...</td>
<td>75</td>
<td>130</td>
<td>33</td>
<td>163</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>156</td>
<td>34</td>
<td>190</td>
</tr>
</tbody>
</table>

One fact became obvious, viz. that 63% of the babies of the whole group were known to have received oxygen. A further 23% had no record of having been given any oxygen, yet in actual fact probably the majority did receive such therapy for varying lengths of time. All the fully-developed cases of retrolental fibroplasia, and four out of the five doubtful cases/
cases were submitted to such treatment. Two out of the three babies who were definite cases of the disease, but showed spontaneous regression, received continuous oxygen therapy. The evidence indicated that oxygen was a primary etiological factor. The following proportions were calculated:

(1) Proportion receiving oxygen among the true cases of retrolental fibroplasia

\[ \frac{22}{23} = 0.9565 \]

(2) Proportion receiving oxygen among the remaining cases

\[ \frac{134}{167} = 0.8024 \]

The difference between the proportions, while considerable, is not statistically significant.

Looking more carefully at the length of time these infants were submitted to this form of treatment, it was indeed unfortunate that the accurate period of exposure was known only in eight of the true cases of the disease. Nevertheless, it was interesting to observe that these periods were relatively long. Although the known durations were too few to draw statistical conclusions, it might be stated that the average period of oxygen therapy – for those instances where it could be determined – was 3.4 weeks for cases of retrolental fibroplasia and 2.4 weeks for non-affected cases. This appeared to be an observation of some value.

It is important to remark that over the whole series/
series only one infant from Hospital "C" was recorded as having received oxygen for three weeks or over. It is possible, that this factor alone was responsible for the so-called immunity of this hospital, since all other hospitals showed an even distribution of cases of the disease. It was realised only too well that the evidence was not conclusive, but such as it was, it gave a more than useful pointer in the direction, that the prolonged administration of oxygen should be considered as one of the main factors in the causation of the disease. Since the concentrations to which these infants were subjected appeared virtually equal in all centres, and all claimed to have weaned the babies in a similar manner from the oxygen tents, it must be concluded that the length of exposure was the variable factor.

Just as all the loose ends appeared to be getting tied up, it was observed that one of the true cases of the condition (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 up under spontaneous regression. This would seem to indicate that while oxygen no doubt was vitally important/
important, it was not necessarily the basic factor producing the disease. Other factors must be looked for which might play their part in this intricate mechanism. In this series, one other factor stood out quite prominently, namely the presence of anoxia. In Table 11 are listed the 23 true cases of retrolental fibroplasia. The Table contains information relative to -

(a) Factors acting on the mother, which might produce some anoxic insult to the foetus.
(b) Factors acting at the birth which might produce anoxia in the newborn infant.
(c) Factors acting on the child in the neonatal period which might cause an anoxic state.

TABLE 11./
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Ante-natal Period (Mother)</th>
<th>Birth</th>
<th>Neonatal Period (Child)</th>
<th>Total Anoxic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Illness in Pregnancy</td>
<td>True or Apparent Toxaemia</td>
<td>Vaginal Bleeding</td>
<td>Other Anoxic Factors</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>+</td>
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<td>+</td>
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<td>12</td>
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<td>13</td>
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<td>+</td>
<td></td>
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<td>14</td>
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<td>15</td>
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<td></td>
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<td>17</td>
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<td>18</td>
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<td></td>
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<td>19</td>
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<td>20</td>
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<td>21</td>
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<td>22</td>
<td>+</td>
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<tr>
<td>23</td>
<td>+</td>
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</tr>
<tr>
<td>x23</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>6224</td>
<td>57</td>
<td>89</td>
<td>56</td>
<td>202</td>
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* Cases of Retrolental Fibroplasia.

* Normal Cases.

* Indicates presence.
In the ante-natal period under the heading of "other anoxic factors" were 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 an anaesthetic was included because of the possible effect it might have in depressing the respiration of the mother and child. 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 in removing a 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.

In the ante-natal period, any of these anoxaemia-producing factors acting singly or together might cause a serious anoxic effect on the foetus at a particular stage of its development. As stated by Szewczyk (1952), anything that depressed the respiration of the mother or child, such as anaesthetics, should be carefully watched. It should be observed that 17 of the mothers of the 23 cases of retrolental fibroplasia received anaesthetics at birth, such as nitrous oxide, chloroform/
chloroform, pentothal or cyclopropane. Szewczyk also stated, that a baby blue at birth was a potentially seriously injured child. It will be noted that 16 out of the 23 cases were in poor condition at birth. The prolonged or sudden removal from high oxygen concentrations might also produce detrimental effects in the newborn infant. Unsworth (1948) felt the condition was associated with anaemia. This was closely linked with the suggestion of Mallek and Spohn (1950) to the effect that a correlation existed between retrolental fibroplasia and the giving of blood transfusions. It seemed, however, the fact that the baby needed a transfusion, was more important than its actual administration.

It was interesting to note that only five babies in the whole series required transfusions and of these, three developed the full condition.

It would appear that anoxia might play quite an important part in the production of the disease. From the comparison of the 23 true cases of retrolental fibroplasia with the 224 "normal" cases (Table 11), it was calculated that the average number of so-called anoxic insults in these infants who developed the disease was 4.30, while in the other group the average number was 2.65.

Examples/
Examples of the degree of anoxia to which the child was subjected are illustrated by the following brief case records:-

Case 8. Male - Birth weight 4 lbs. 4 ozs. Born 7/1/49.

(a) Mother - Age 27 years. Gestation 33 weeks.
   Two previous female children, full time, both alive and well. Normal pregnancy till 4/1/49 then had a fairly severe vaginal haemorrhage, which required admission to hospital. The bleeding continued so Caesarean section for placenta praevia was carried out on 7/1/49.
   Anaesthetics used - cyclopropane, nitrous oxide and oxygen.


(c) Eyes - Nystagmus, bilateral squint and photophobia noted at the age of five months.

(d) General Condition - normal mentally and physically.
Case 7. Male - Birth weight 3 lbs. 2 ozs.

(a) Mother - Age 31 years.
One previous female child, full time, alive and well. Suffered from chronic anaemia. Large antepartum haemorrhage one week before admission. Anaesthetics used - pudendal nerve block and chloroform.
Length of labour 3 hours 40 minutes.
Breech extraction - prolapse of the cord.

(b) Child - Condition very poor at birth - very poor lung expansion. Severe colour changes. Put on continuous oxygen, with carbon dioxide and oxygen mixture for five minutes in every hour. Loose stools 12/5/51 - given chloromycetin. Infection in the right sub-mandibular gland 18/5/51.

(c) Eyes - Tortuous, retinal vessels noted 10/7/51. Both eyes extensively involved 11/9/51. Given a six weeks course of systemic cortisone. One eye improved - other deteriorated 7/11/51.

(d) General Condition - subnormal mentally.
Cerebral spastic diplegia.

The recurring appearance of anoxia was noted in an article by Bembridge et al (1952) where they described six cases of retrolental fibroplasia treated/
treated with the adrenocorticotrophic hormone. (ACTH)

"Case 1. Thirty-eight year old mother who had severe toxaemia of pregnancy superimposed on chronic renal disease".

"Case 2. The neonatal period was complicated by bronchopneumonia which responded to penicillin and streptomycin".

"Case 3. The mother had severe toxaemia a week before the child was born".

"Case 5. She had toxaemia of pregnancy and surgical induction was performed for this. Normal labour followed. An upper respiratory infection in the child was treated by chemotherapy".

"Case 6. The infant had an attack of vomiting and abdominal distension which responded to chemotherapy".

**Mental Retardation and Cerebral Palsy.**

Ingalls (1948a) writing on congenital encephalophthalmic dysplasia suggested that lack of oxygen was the most important mechanism leading to damage of 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 resulted in such conditions as cerebral palsy and mental retardation/
retardation. If anoxia did play a part, it would seem illogical to assume that the eye alone should always be the site of attack. In this series no fewer than five cases of retrolental fibroplasia were typical examples of cerebral spastic diplegia. This was approximately 50% of the total cases of cerebral palsy noted in the investigation of all premature infants during the five year period. Seven of the 20 fully developed cases (Table 2) were considered to be subnormal mentally, even allowing for the obvious handicap of blindness.

Agreement, therefore, can be expressed with the views of Szewczyk (1952) who stated that retrolental fibroplasia was an anoxic retinopathy and that similar changes could be found in other vital tissues, with the production of such conditions as cerebral palsy and mental retardation, and of Patz, Hoeck and de la Cruz (1952), who observed that the fully-developed cases of retrolental fibroplasia were submitted to prolonged periods of oxygen therapy.

It now becomes necessary to try and correlate these two main factors. During this survey the condition was noted to appear in one member of each of six sets of twins. In two of these sets, the other partner was recorded as a stillbirth. It was interesting to observe that one of the two stillbirths was/
was a mongol. The remaining four sets of twins continued to thrive, although one partner subsequently died while under treatment with cortisone. It is now necessary to examine in more detail the case histories of these four sets of twins.

Case 5.

(1) Mother. Age 31 years. Period of gestation 35 weeks. On a strict duodenal ulcer diet during pregnancy. Phlebitis at the fifth month of pregnancy. Rash four weeks prior to delivery. Thought to be due to taking sedatives. Severe pre-eclamptic toxaemia.

(2) Child. Length of labour 2 hours 40 minutes. A uniovular twin pregnancy.

1st twin (male) Vertex presentation. Very limp at birth and a lot of mucus present.

Weight 3 lbs. 10 ozs.

2nd twin (male) Vertex presentation.

Condition satisfactory at birth. Weight 4 lbs. 12 ozs.

(3) Treatment and results.

1st twin. Put on continuous oxygen therapy for three weeks. On being taken out of the incubator at that time, he suddenly became limp and collapsed. He was put back into oxygen for a further week, then gradually/
gradually weaned slowly to normal conditions. The child showed pronounced bilateral signs of retrolental fibroplasia. One eye showed spontaneous regression, while the other went on to complete membrane formation.

2nd twin. This baby was put on continuous oxygen for 3–4 days and gradually weaned to normal conditions. This child was examined at least every 3–4 weeks till the age of six months and at no time was any abnormality noted in either eye.

Case 19.

(1) Mother. Age 27 years. Period of gestation 32 weeks. The mother remained quite fit and well during the pregnancy.

(2) Child. Length of labour 4 hours 40 minutes. A binovular twin pregnancy. Anaesthetic used only for twin two.

1st twin (female) Vertex presentation. Fairly good condition at birth. Weight 3 lbs. 3½ ozs.

2nd twin (female) Assisted breech delivery. Limp at birth. Weight 3 lbs. 3 ozs.

(3) Treatment and results.

1st twin was treated on continuous oxygen for/
for six days when it was suddenly discontinued. No signs suggestive of retrolental fibroplasia were noted in the eyes of this child.

2nd twin also treated on continuous oxygen and although the exact time of discontinuing this therapy was not known, she was still receiving oxygen at 12 days of life. At this time it was recorded that the oxygen was being discontinued for short periods. This child developed bilateral retrolental membranes.

Case 12.

(1) Mother. Age 31 years. Period of gestation 32 weeks. Severe pre-eclamptic toxaemia in the pregnancy.

(2) Child. Length of labour 2 hours 15 minutes. A binovular twin pregnancy. Surgical induction for severe toxaemia. Anaesthetic used for the assisted breech.

1st twin (male) Vertex presentation. Fairly good immediately at birth but then had a severe colour change due to inhalation of vomit. Weight 4 lbs. 3 ozs.

2nd twin (male) Assisted breech delivery. Poor condition at birth with attacks of cyanosis. Weight 4 lbs. 6 ozs.
(3) Treatment and results.

1st twin. The child was given continuous oxygen therapy. There was no record of the exact length of period the child was thus exposed. The baby was given a course of cortisone but died at the age of four months while under treatment. Extensive bilateral retrolental fibroplasia was present.

2nd twin was put on continuous oxygen therapy. There was no record to indicate when this treatment was discontinued. This child was examined once only and at that time the mother stated that some doubt was expressed regarding the condition of one eye. She was so upset over the death of the other twin that she refused to have this baby further examined. This child can see very well and there is no outward evidence of any abnormality.

Case 3.

(1) Mother. Age 28 years. Period of gestation 33 weeks. Had symptoms of toxaemia of pregnancy.

(2) Child. Length of labour six hours.

Artificial rupture of the membranes. A binovular/
122.

binovular twin pregnancy. Anaesthetic used in both cases.

1st twin (male) Assisted breech delivery.
Feeble condition at birth but cried quite well. Had one severe colour change.
Weight 3 lbs. 13 ozs.

2nd twin (female) Vertex presentation.
Feeble condition at birth, but cried quite well. Colour always remained good.
Weight 4 lbs. 3 ozs.

(3) Treatment and results.

1st twin. Put on continuous oxygen therapy for three weeks, then discontinued. At the age of four months was found to have bilateral retrolental membranes.

2nd twin. Also put on continuous oxygen, but there was no exact record when this treatment was discontinued. No evidence was found to indicate the presence of retrolental fibroplasia.

To summarise the main factors in these case records, the existence of the pre-eclampsia in the mother of Case 5 will be noted. The pregnancy was stated to be uniovular which would appear to disprove the theory that when only one twin was affected the pregnancy was always binovular. On the other/
other hand if both partners were affected the pregnancy was uniovular. It will be observed that the smaller child was affected and was in much the poorer state at birth. The first twin was subjected to oxygen therapy for a total of four weeks, in comparison with a period of four days in the other baby. The second twin was examined at regular intervals and at no time showed any abnormal features in the eye.

In Case 19 a binovular pregnancy, an anaesthetic was used only in the case of the second twin. Once again the smaller twin was affected, although the weights were virtually equal at birth. Once again the affected twin was in the poorer state at birth and she received oxygen therapy for at least twice the period of the other member. It may be of importance, in an negative sense, that the oxygen was discontinued suddenly in the non-affected child, while the baby that subsequently developed the disease was gradually weaned from its oxygen enriched atmosphere.

In Case 12 the mother had severe toxaemia that necessitated the surgical induction of labour. Once again the smaller twin was affected, but at birth the non-affected baby was in the poorer state. The affected twin had, however, a severe colour change/
change just after birth. Both members had continuous oxygen therapy although the exact length of time was not recorded. While it was known that one baby developed the condition, it might rightly or wrongly be supposed that the second baby did in actual fact have the disease, but it subsequently underwent spontaneous regression. However, there were no records to justify this suggestion.

In Case 3 the mother exhibited symptoms suggestive of the toxaemia of pregnancy, which necessitated the surgical induction of labour. An anaesthetic was used in both cases. Once again the smaller partner was attacked. Both children were in feeble condition at birth, while the affected twin showed one severe colour change, the colour of the other twin always remained good. Both babies received continuous oxygen therapy and it was known that the affected child was maintained in this environment for three weeks.

Thus it would appear that one twin may be involved only, irrespective of the fact that they are uniovular or binovular. It is suggested that when one partner is involved, the smaller baby as a rule is affected. Evidence seems to indicate that the more anoxic of the two infants, is potentially the one more likely to develop the disease. It is extremely/
extremely likely that long exposure to an oxygen enriched atmosphere is a fundamental factor in the production of retrolental fibroplasia.

To correlate the features of anoxia and prolonged oxygen therapy, would merely be to postulate a theory. However, it may be possible that the following state of affairs exists. Anoxia may well be the initial stimulus to the commencement of the disease. If the child receives no oxygen, the premature retina, and in fact all the developing tissues will have to fight for their very existence. In the vast majority of cases the body can accomplish this fact, but not without changes occurring in the eye to indicate the presence of the disease. The majority of such babies may show early signs of retrolental fibroplasia with subsequent spontaneous regression. This would explain the appearance of a case in this series and also in the series of Bembridge et al (1952), who received no oxygen therapy of any kind. It would be unwise to assume that the body can always overcome such a process. It might well be that some of these non-oxygenated cases proceed to develop a retrolental membrane, and it is equally possible that prior to the worldwide appreciation of the disease, many of these eye changes might have escaped under the diagnosis of glioma or pseudoglioma.
pseudoglioma.

It is possible that if the baby is submitted to prolonged oxygen therapy while the eye condition is progressing, this additional factor may actually further activate the process, with the subsequent appearance of the fully-developed case of retrolental fibroplasia.

It is difficult to visualise how the mere submission of an infant to a high concentration of oxygen, followed by the sudden removal to normal conditions, can produce the disease. This statement is made on the following observations:

Hospital "A" was opened ten years before the first recorded case of the condition and oxygen was given at an unknown rate judged only by the "flow of bubbles". It was very likely that these infants received as high, if not a higher concentration of oxygen than did babies in later years, where the supply of oxygen was recorded by flow meters. A few years later oxygen was piped into the incubator rooms and the facilities for giving prolonged therapy were greatly improved. Of no small importance was the fact that Hospital "C" appeared to produce a higher concentration of oxygen than most of the other units, yet no cases were known to have come from this hospital.

The/
The possible effects produced by the sudden removal from high oxygen concentrations is a matter for experimental study. Attempts have been made, as described in the next section, to demonstrate the correlation between the sudden removal from an oxygen enriched environment and the production of retrolental fibroplasia.

10. **TREATMENT.**

Active treatment was attempted in two cases. In both cases they were given a systemic course of cortisone. The following are the case records of the babies:-

**Case 12.**

Male. Date of Birth 13/12/51. Birth weight 4 lbs. 3 ozs. First of twins (other a male - birth weight 4 lbs. 6 ozs.). The hospital records state -

1. 3. 52: Quite a well made baby in general good health. The right eye appears smaller than the left. Bilateral retrolental fibroplasia.

4. 3. 52: Systemic cortisone therapy begun. 25 mgms. per day, with potassium chloride ½ gram daily.

7. 3. 52: Appearance of scrotal oedema with a weight gain of 4 ozs. Cortisone withheld. Serum sodium - 300 mgms.% Potassium 37 mgms.% Chlorides 630 mgms.%
9. 3. 52: A right inguinal hernia appeared and was reduced with difficulty.

14. 3. 52: Cortisone recommenced 20 mgms. per day orally in divided doses. Blood pressure 100/60.

18. 3. 52: Weight gain 3 ozs. Blood pressure 115/75.

21. 3. 52: Blood pressure 100/60. Serum sodium 315 mgms.%, Potassium 24.5 mgms.%

24. 3. 52: Cortisone withheld for two days because of weight gain.

26. 3. 52: Cortisone 5 mgms. three times per day recommenced.

1. 4. 52: Gain of 4 ozs. Cortisone withheld.

4. 4. 52: Serum sodium 338 mgms.%, serum chlorides 650 mgms.% Cortisone recommenced. The child died suddenly without any preceding signs of ill health.

Post-mortem Report.

Apart from the eye condition only one other abnormality was noted. The lungs showed an occasional scattered subpleural haemorrhage. Microscopic examination of the lungs showed no evidence of any infective condition, nor of oedema. Microscopy of all other organs showed no histological abnormality.

Comment.

There was no histological abnormality to account/
account for death, leaving the assumption that death was in some manner related to the administration of cortisone".


11. 9. 51: Right eye. A mass of tissue in the lateral part of the anterior vitreous with a large dilated vessel running forward to it from an area of localised detachment of the retina. Diffuse choroido-retinal degenerative changes at the temporal periphery.

Left eye. A mass of soft looking tissue in the lower anterior vitreous, with vessels running to it from the retina.

The child was given a six weeks course of systemic cortisone along similar lines to that described under Case 12.

7. 11. 51: Right eye. Marked improvement: nothing to be seen except a flat greyish area at the extreme lateral periphery.

Left eye. Condition worse: the mass of tissue now occupies most of the lower vitreous and also extends up and laterally.

24. 11. 52: Right eye. Vitreous clear. Fundus shows nothing abnormal apart from being rather pale towards the extreme periphery.

Left/
Left eye. Fibrous tissue in the anterior vitreous with scattered pigmentary change on the temporal side of the fundus.

11. 2. 53: General examination showed the child to be of subnormal intelligence and to exhibit the features of cerebral spastic diplegia.

Comment.

It would appear from the right eye that the therapy had produced a beneficial result. However, it was observed that the left eye actually deteriorated during treatment. Realising that retrolental fibroplasia was a self limiting disease, it was concluded that the cortisone played no beneficial therapeutic part in the progress of the disease.

Although only two cases were given cortisone therapy its use was discontinued for two reasons. First and foremost there was the unexplained death in Case 12, followed by the apparent lack of value in the treatment of Case 7.

11. PREVENTION.

While perhaps it is unwise to suggest that the disease can be prevented it is felt that the tragic end-results can, to a large extent, be reduced to minimal residual damage.

If prematurity could be eliminated the disease would/
would rapidly disappear. Careful ante-natal supervision, adequate diet, vitamins and rest, relief from anxiety and the prevention of inter-current infection, are all factors which if given the consideration they merit, may help in bringing about a decrease in the incidence of prematurity and, therefore, in the number of cases of retrolental fibroplasia.

The indications and carrying out of an artificial induction of labour, should be very carefully considered and postponed, where possible, till the last moment. The unnecessary use of analgesics and anaesthetics in the pregnant mother should be avoided. The administration of oxygen therapy to the new born infant should be confined only to cases in whom its use is clearly indicated. It seems quite unnecessary for such large oxygen concentrations to be attained in the tents. A concentration of 40-50% is quite adequate and this can be roughly estimated by suppying the baby with just sufficient oxygen to avoid the appearance of cyanosis. This state of affairs is the optimum, for it is realised that the baby in utero is in a constant state of subclinical anoxia. Most important of all the oxygen must be discontinued as soon as possible. It appears unreasonable to imagine/
imagine that a baby requires oxygen therapy for as long as six weeks, which was the time noted in a number of cases in this survey. It is also logical to suggest that when oxygen has been given, the baby should be gradually acclimatised to its normal environment. To merely withhold oxygen for increasing periods of time hardly constitutes correct weaning. The flow of oxygen should be gradually reduced until the baby is in normal atmospheric conditions.

Towards the later half of 1952, most centres restricted oxygen therapy to the cases that required it, and it was given in minimal amounts for the shortest possible duration. Since that time, no new fully-developed case with membrane formation has been observed in Edinburgh.
SECTION 5.

EXPERIMENTAL STUDIES.
EXPERIMENTAL STUDIES.

INTRODUCTION.

As the search for the main aetiological factors in retrolental fibroplasia intensified, investigators found one feature common to all cases, namely that the infants with the disease required and, in actual fact, received oxygen therapy for varying lengths of time. Convincing evidence showed that the disease only appeared with the advent of more efficient methods of giving oxygen therapy. Szewczyk (1952) stated that the disease could be produced by taking an infant suddenly from an oxygen enriched atmosphere and placing it in normal oxygen concentrations. He further proved, that if the early signs of retrolental fibroplasia became evident under these normal conditions the disease would regress if the child was replaced in oxygen and after a time gradually weaned to normal atmospheric conditions. It was obvious that some attempt should be made to try and prove or disprove experimentally, the truth of these statements. It was essential, before taking any steps on the experimental side, to review in some detail any such attempts to produce artificially, the lesions typical of retrolental fibroplasia.

REVIEW/
REVIEW OF THE LITERATURE.

Pride of place in any form of experimental work must without doubt go to the person who appears to prove a point, using the human being as the subject of study. Szewczyk (1951) reported that he was able to induce early retrolental fibroplasia in seven premature infants by removing them at varying intervals in early neonatal life from incubators containing a 50% oxygen concentration, to conditions containing an oxygen concentration of 22%. These early signs were described as vessel dilatation, neovascularisation, haemorrhage and progressive peripheral retinal detachment. In 1952, he obtained similar results by removing 19 premature infants suddenly from their high oxygen concentration incubators. When they were replaced in oxygen all infants showed dramatic improvement within 24 hours, and had returned to normal in 3-4 days.

It was interesting to read of the work carried out by Smith, et al (1932). They observed the histological changes in the lungs of rats exposed for long periods to oxygen. Only a few died from acute poisoning. The lung changes consisted of hyperplasia and hypertrophy of the alveolar cells. There was also perivascular oedema, thickening and hyaline changes of the arterial walls. The latter changes/
changes began in the smallest vessels, but eventually the larger arteries were similarly affected. They noted that rats under a month old showed no clinical signs. The severity of the reaction increased with age, as did the mortality rate.

Warkany and Schraffenberger (1946) stated that they produced in rats, eye defects that closely resembled the lesions found in retrolental fibroplasia. These defects were produced in the offsprings of rats given a Vitamin A deficient diet. The abnormalities included: absence of the anterior chamber, iris and ciliary body; failure of vitreous formation with the development of connective tissue in its place; eversion of the retina and retinal disorganisation. Jackson and Kinsey (1946) confirmed these results but doubted if vitamin A in human beings ever fell to a comparably low level.

Callison and Orent-Keiles (1951) reported that in the offsprings of mother rats deficient in vitamin E, the eyes showed defects suggestive of retrolental fibroplasia. The defects in their cases were small eyeballs, unopened eyelids, opaque white membranes and large blood clots behind the pupil.

Campbell (1951) observed that when new-born rats were subjected to low oxygen tension, capillary budding occurred from the retinal veins.

Gyllensten/
Gyllensten and Hellstrom (1952) placed full-term new-born mice in a sealed box with a continuous flow of oxygen, which was interrupted every 48 hours. This procedure was continued for 1-3 weeks. The following abnormalities were noted in the eyes of the mice:

(a) Haemorrhages into the vitreous, behind the iris and into the anterior chamber.
(b) Hyperplasia of the tunica vasculosa lentis.
(c) Detachment of the optical retina from the pigment layer with multiple retinal folding.

They concluded that these features were very similar to the changes noted in retrolental fibroplasia.

Ingalls, Tedeschi and Helpern (1952) described experiments on inducing anoxia in pregnant mice whereby they produced the condition known as "open eye" in the offspring. They pointed out that mice in common with many other animals were born with adherent eyelids. The external ocular defect that justified the name of "open eye" was a defective formation, or a separation of the eyelids, permitting direct inspection of the cornea and globe. With the understanding that the palpebral defect was merely/
merely one manifestation of a more complex ocular disorder, the whole process was referred to as "open eye". By subjecting pregnant mice to anoxic insults at various stages of pregnancy, they were able to produce many cases of "open eye". They stated that there were remarkable similarities in "open eye" to the retinal vascular disorder, retrolental fibroplasia.

Hepner (1952) gave repeated blood transfusions to a group of kittens and the signs of vascular engorgement and hyperplasia of the iris, tunica vasculosa lentis, and retinal separation which he thereby produced, were regarded as being similar to the early stages of retrolental fibroplasia.

Experimental studies were, therefore, undertaken in an attempt to ascertain the possible role of anoxia and oxygen in producing ocular disease in albino rats.  

**METHOD OF STUDY.**

It was essential to try and produce as near as possible the conditions under which the premature infant was placed at birth. A room heated to a temperature of 72-80°F. was chosen, being illuminated by two normal sized windows. The albino rat was chosen as the animal for the experiment, as such rats had a relatively short gestation, produced moderately large litters and anatomically the ocular apparatus was/
Fig. 29: The experimental and control incubators.

Fig. 30: The experimental incubator with oxygen from a cylinder bubbled through a bottle of water.
was in many ways similar to that of the human eye.

The aims of the experiment were to observe the effects of high oxygen concentrations on the animals, and to note clinically the changes produced by taking the rats suddenly from their oxygen enriched atmosphere and placing them in normal atmospheric conditions.

Two old type wooden incubators were set up side by side as shown in Fig. (29). Oxygen was administered continuously into one incubator. The oxygen passed via a normal flow meter and was also bubbled through a bottle containing water (Fig. 30). The rate of flow of the oxygen was regulated in order that a concentration of 70% was produced in the experimental incubator. In order to ensure that the concentration of oxygen remained constant inside the incubator, repeated samples of the air were taken and the percentage estimated by the Peters and Van Slyke method. The second incubator was used to maintain the animals under similar conditions, but no oxygen was given. Inside each incubator was placed a small cage containing the animals (Fig. 31). In the experimental incubator the rubber tubing from the oxygen cylinder was fixed into the roof of the cage. The grill cover in the front of the experimental incubator was closed/
Fig. 31: Showing the small cage containing the rats. The tube supplying the oxygen enters at the top of the cage. A lid is placed on top of the cage and the incubator closed.

Fig. 32: Method of holding the older rat for examination.
closed, while the one in front of the control incubator was opened.

Before commencing the experiments, rats of various age and size were examined clinically with the ophthalmoscope in order to establish a good technique in handling the animals. Normally, the pupil of the adult rat's eye was a virtual pinpoint, but two drops of 2% homatropine hydrobromide in each eye produced full dilatation in 3-5 minutes. The adult rat was held firmly on a table, gripping it just behind the ears (Fig. 32). The smaller animals were held firmly in the left hand and the eyelids held apart by the thumb and forefinger of the right hand (Fig. 33). It was thus possible to examine in detail the fundi of these animals. The picture observed in the albino rat's eye differed from the human eye in that the fundus gave a pale white appearance with the retinal vessels standing out in bold relief and there was no evidence of a disc or disc margins, but it was possible to see the main retinal vessels dip into a common point where the disc actually would be situated. The presence of a shallow anterior chamber was also noted.

It was found that the average length of pregnancy of the rat was 21 days. A litter as a rule/
Fig. 33: Method of holding the younger rat for examination.

Fig. 34: The unopened eye of a ten-day old rat.
rule contained approximately seven animals.

DETAILS OF THE EXPERIMENT.

Repeated experiments were carried out in samples of rats representing the following groups:

Group 1. A pregnant mother rat approximately five days short of term was placed in each of the incubators. One mother was subjected to an oxygen concentration of 70%, while the other acted as a control. From the date of delivery till a further seven days had passed, the mother rats and litters were maintained under the above described conditions. At the end of that time they were taken out of the incubators suddenly and placed in atmospheric conditions.

Group 2. A litter delivered by Caesarean section, was divided into two groups, one being placed with a foster mother in the oxygen incubator, the other with a foster mother in the control incubator. Within 24 hours in each case, the foster mother had eaten the new-born litter. The experiment was, therefore, repeated but instead of providing the litter with foster mothers, each half litter was placed on a layer of cotton wool and submitted to the conditions just described. After 24 hours the animals were taken from the incubators and put into room conditions for a further 12 hours.

No/
No feeding had taken place. All rats were then killed and histological sections of the eyes were prepared.

**Group 3.** A new-born litter was taken and divided into two groups. The first group was subjected to a high oxygen concentration, while the second group acted as a control. Seven days later both groups were placed suddenly in normal conditions.

**Group 4.** A group of rats were subjected to exactly the same procedure as already described under Group 1. When the experimental and control animals of the litters reached 30 days of life they were again replaced in their original conditions, namely one group in oxygen and the other in the control incubator. These groups were kept in this state for a further period of three days and suddenly removed once more to normal conditions. The eyes were examined clinically eight to twelve hours later and some rats were killed for section. Further examinations of the surviving rats took place at regular intervals until two months of age.

**Group 5.** A new-born litter was taken and placed in a bell jar into which was passed a mixture of nitrogen 95% and carbon dioxide 5%. This was continued till extreme cyanosis almost to the point of death, resulted. The litter was then divided into/
into two groups. One group was placed in the experimental incubator with a high oxygen concentration, the other in the control incubator, for a period of seven days. At the end of seven days both groups were suddenly removed from the incubators.

**Group 6.** A new-born litter was taken and placed in a bell jar into which was passed a mixture of nitrogen 95% and carbon dioxide 5%. While the rate of flow of this mixture in the previous group was 8 litres per minute, in this case it was regulated to 4 litres per minute, but maintained for four hours. The further procedure was identical with that already described in Group 5.

In Groups 1, 3, 5 and 6 some animals were killed and histological sections made of the eyes, 48 hours after removal from the incubators. The eyes of the surviving rats were examined regularly by the ophthalmoscope from the date of opening of the eyelids, till the age of two months. Some rats were killed at frequent intervals in order to prepare histological eye sections.

**FINDINGS.**

Certain findings were common to all groups. The rat was born with closely adherent eyelids (Fig. 34). It was quite striking how almost to the/
the day - on the fifteenth post-natal day - the eyelids started to separate. In every case the eyes were open by or on the seventeenth day of life. On examination of the eyes with the ophthalmoscope at this time, it was surprising to find the vitreous full of vessels. This produced an effect as if looking at a Christmas tree through a window, with the tree placed close up against the window. By daily examination, it was possible to observe that this effect had almost completely disappeared by the 27th day of life, although few strands of vessels were still able to be seen for a further few days. It was obvious that it was the tunica vasculosa lentis that was seen. The tunica vasculosa lentis in babies was almost completely absorbed by the time of birth. Thus in theory, the eye of a rat at 25 days old was more immature than the most premature baby's eye. It was also logical to assume, that if retrolental fibroplasia was entirely due to the effect of oxygen on an immature eye, then it could reasonably be expected that abnormalities would appear more readily in the very immature eye of the rat.

In order to make the histological sections of the eyes, the animals were decapitated and the globe removed by blunt dissection. As the age increased so/
so also did the size and hardness of the lens. It was striking how in a month-old rat the lens practically filled the whole globe. Due to the very brittle nature of the lens, it was not surprising that in the sections of older rats much retinal folding was observed. The younger the rat the more perfect the section appeared.

Apart from these common features, the findings in the various groups were as follows:

Group 1. No abnormalities were ever noted on clinical examination. One section gave the appearance of oedema of the nerve fibre layer of the retina. However, despite numerous repetitions of this experiment, no such evidence was again observed.

Group 2. The sections proved very satisfactory and were normal in every respect.

Group 3. One rat at the age of 23 days showed bilateral white membranes. These proved to be lens opacities. In two different eyes of separate rats, large haemorrhages were seen as if lying just behind the lens, and one eyeball appeared very small at enucleation. These haemorrhages were evident before the disappearance of the tunica vasculosa lentis, so it was concluded that the haemorrhages resulted from the vessels of the tunica vasculosa lentis. These abnormalities were noted in rats belonging to the control group and at no time/
time were they subjected to oxygen therapy.

Group 4. As already stated, the tunica vasculosa lentis of the baby was almost completely absorbed by birth. Thus in theory, the rat's eye at the time of disappearance of the tunica vasculosa lentis (25-30 days) was at a comparable stage of development with that of the premature baby's eye at birth. This was the reason, therefore, for placing this further group of rats in oxygen at the age of 30 days. No abnormalities were noted on clinical examination of the eyes. The histological sections showed no features suggestive of retrolental fibroplasia.

Groups 5 and 6. In the group subjected to anoxia no abnormalities were ever noted. In the group made anoxic and then placed in oxygen, no abnormal clinical signs were observed, but in one histological section there appeared to be a proliferation of cells, on one side, of the ganglion cell layer of the retina. It was felt that this might be due to an obliquity of the section at this point (Fig. 36). Subsequent sections failed to reproduce this state of affairs.

Finally, during the whole series of experiments, only two of the rat mothers were noted to exhibit pathological changes. In both cases these changes were/
Fig. 35: Section of the eye of a twenty-day old rat, showing many vessels in the vitreous and at the posterior surface of the lens. (x 25)

Fig. 36: Section of the eye of a twenty-day old rat showing increased cellularity of the ganglion cell layer. There are also vessels in the vitreous and at the posterior surface of the lens. (x 95)
were confined to the respiratory system. One of the mothers belonged to Group 1, and after death was found to have extensive bilateral pulmonary oedema. The second mother belonged to Group 3, and prior to death developed generalised lung crepitations quite audible by placing the rat next to the ear. The cause of death was concluded to be extensive bronchopneumonia.

DISCUSSION - WITH SUMMARY AND CONCLUSIONS.

The object of the experimental work was to try and produce artificially, ocular signs similar to those found in retrolental fibroplasia.

The rats were subjected to a concentration of 70% of oxygen for varying periods, then suddenly removed to normal atmospheric conditions. Before actual experiments were conducted on these rats, an attempt was made to determine the normal ophthalmoscopic appearance of their eyes. From these observations the following four characteristics emerged:

1. The pupils dilated quickly and completely with the use of 2% Homatropine hydrobromide drops.
2. Examination of the fundi was very satisfactory.
3. Being albino rats, the fundus was white and no disc was apparent although its position could be localised by the convergence of the clearly defined retinal vessels.
4. The anterior chamber was shallow.

The following were noted in all groups:—
1. The rats were born with closely adherent eyelids, and practically to the day they opened on the 17th day of life.
2. As soon as the eyes were open and examined with the ophthalmoscope, it was noted that the vitreous was full of vessels producing a "Christmas tree like" effect - the tunica vasculosa lentis. This disappeared almost completely by the 27th day of life, although a few fibrils could still be observed in the vitreous for a further few days. Oxygen and anoxia had no effect on the involution of the tunica vasculosa lentis.
3. The animals were killed by decapitation and the eyes removed by blunt dissection. In the young rats the sections were excellent. As the age of the animal increased, the lens became larger till it almost completely filled the globe. With increasing age the lens became more brittle, so it was not surprising to find degrees of retinal folding in many of the histological sections.

In the groups subjected to oxygen the following were noted:-

1/
1. At no time was any vascular abnormality (such as dilatation, tortuosity, haemorrhage or neovascularisation) observed in any of the groups.

2. In one set of eyes of Group 1 there was an appearance of oedema of the nerve fibre layer of the retina. However, numerous repeated experiments failed to reproduce this appearance.

3. In Groups 5 and 6 there was a suggestion in one eye section of an increased cellularity of the ganglion cell layer of the retina. It was felt that perhaps this was due to obliquity of the section at that point. Numerous repetitions of this experiment failed to produce similar results.

In the control group the following were noted:

1. One rat in Group 3 showed bilateral white membranes that proved to be lens opacities.
2. In two different eyes of separate animals in Group 3, large haemorrhages were noted lying behind the lens. It was concluded that these resulted from the breakdown of the vessels of the tunica vasculosa lentis.
3. At enucleation in one case an eyeball was found to be much smaller than that of its neighbour/
neighbour.

In the group of mother rats subjected to oxygen the following were noted:

1. One mother of Group 1 showed extensive bilateral pulmonary oedema.
2. One mother of Group 3 showed extensive bilateral bronchopneumonia.

No direct evidence was produced to show that the sudden removal from an oxygen enriched atmosphere to normal conditions provided the initial stimulus to the process of retrolental fibroplasia. Callison and Orent-Keiles (1951) in their rat experiments stated that small eyeballs, opaque white membranes and large blood clots behind the pupil, were suggestive of retrolental fibroplasia. Each of these findings were noted in the control groups of the present experiments, but in no way could they possibly be related to retrolental fibroplasia.

Gyllensten and Hellstrom (1952) in their mice experiments described haemorrhages into the vitreous, hyperplasia of the tunica vasculosa lentis, detachment of the optical retina from the pigment layer with multiple retinal folding, all of which they stated, were suggestive of retrolental fibroplasia.

From the observations made during the present experiments/
experiments, it could not help being felt that many of these features were actually "normal abnormalities" and quite unrelated to the process of retrolental fibroplasia.

Of the two rat mothers who died, the one that showed bilateral pulmonary oedema was subjected to oxygen for a longer period than any other rat in the series of experiments. Haldane and Priestley (1935) commenting on experiments by Lorrain Smith in 1899 on the appearance of lung oedema in animals produced by oxygen at pressure, stated "It is evident from these observations that when oxygen is used for therapeutic purposes the percentage ought not to be increased more than is really necessary". It is, therefore, logical to assume that similar changes might well take place in other tissues such as the retina. This might indicate that prolonged exposure to high oxygen concentrations is an important aetiological factor.
SECTION 6.

SUMMARY AND CONCLUSIONS.
SUMMARY AND CONCLUSIONS.

The complex nature of retrolental fibroplasia, a condition first described by Terry (1942) in the United States of America, is indicated by the review of the literature. Practically all observers, however, are agreed that the disease is essentially one that affects the prematurely born infant.

A survey was undertaken in Edinburgh to review all babies with a birth weight of 4 lbs. and under, born and resident in the city during the years 1948-1952. During 1952, each baby of that weight group was examined as soon as possible after birth and subsequently at monthly intervals, till the age of six months. The infant was weighed, measured, and examined physically at each examination. Routine examinations of the fundi were carried out without general anaesthesia, but the pupils of the infant's eyes were dilated with a solution of 1% pareddrine hydrobromide and 1% homatropine hydrobromide. If any ocular abnormality was noted, the baby's eyes were re-examined under general anaesthesia, and the infant was followed up at more frequent intervals. The already fully-developed cases were examined in a similar manner on one or more occasions, as indicated.

The pathological process in retrolental fibroplasia starts at the equatorial region of the
retinal nerve fibre layer. Nests of endothelial cells gather in this layer, which becomes thickened due to oedema and to an increase of glial cells. Neovascularisation, transudation and haemorrhage then follow, and the vitreous is invaded. Fibrosis, contraction and retinal detachment may result with the formation of a retrolental membrane. All cases, however, did not progress to this stage of gross intracocular fibrosis.

Early clinical features were conspicuous by their absence. Loss of the "red reflex" was often the first clinical manifestation, though the earliest sign noticed by the parents was the inability of the infant to follow a light.

The classical features appeared later and consisted of white masses of tissue in the vitreous, nystagmus, photophobia, squint, microphthalmos and posterior synechiae. The anterior chamber was shallow and corneal opacities occurred. The continued rubbing of the eyes by the infant was characteristic.

During the 1952 survey, the early changes observed by the ophthalmoscope consisted of dilatation and tortuosity of the retinal vessels, with greyish white peripheral areas of oedema or early detachment. Extensive vitreous haemorrhages were also evident. The ability of the process to
undergo spontaneous regression was clearly demonstrated. The late signs showed a wide variation, such as fully-developed vascularised folds in the vitreous, retinal folds, peripheral pale areas, and areas of pigmentary disturbance.

Of the 23 cases of retrolental fibroplasia noted during 1948-1952, thirteen finally had no vision, seven had partial vision, and three, while showing early signs of the disease, subsequently underwent spontaneous regression with the development of normal vision. The disease was always bilateral, although one eye could be affected to a greater extent than the other eye. Four to twelve weeks of age was the time of onset of the disease, in this survey.

Over the five years period, 1.83% of all premature infants within the city were affected with retrolental fibroplasia. During 1952, there were five definite cases, three of which subsequently showed spontaneous regression. This meant that 1.7% of all premature babies and 10.8% of those with a birth weight of approximately 4 lbs. and under were affected with the disease. There were five other doubtful cases of the condition which, if accepted as instances of the disease, would then give an incidence of retrolental fibroplasia as high as 3.4% of all premature infants, and 21.6% of
those with a birth weight of 4 lbs. and under. The incidence reached a peak in 1951, but this was not related to an increased survival rate of babies of smaller birth weight.

Of the 23 cases of the disease, twenty had a birth weight of 4 lbs. and under, while three exceeded this level only by a few ounces. All infants with one exception had apparently a gestational period of 36 weeks or under. The disease became more prevalent as the gestational period shortened and the birth weight decreased.

The sex ratio of the infants who developed retrolental fibroplasia was approximately equal; 12 were males and 11 were females.

The appearance of retrolental fibroplasia was unrelated to the parity of the mother. Fifty percent of the infants who developed the disease were born as a result of a first pregnancy. Thirty-eight twin pregnancies were investigated during the survey and in six of these, one partner in each case showed evidence of retrolental fibroplasia. In a set of twins where one partner was affected, the pregnancy was claimed to be uniovular, while the remaining five sets were binovular twins. The affected twin was the smaller and lighter at birth, in each case.

The following maternal factors were unrelated to the production of retrolental fibroplasia:
rubella, toxoplasmosis, Rhesus blood factor, diet and vitamins.

The length of labour, presentation of the infant, and method of delivery had no influence on the development of the disease.

The general management of the premature infant, the diet and the administration of vitamins, did not appear to be aetiological factors.

It was found that skin haemangiomas occurred no more frequently in the infants who developed the disease, than in those who remained unaffected.

There was no evidence in this survey to suggest that the giving of antibiotics to the mother or child played any part in the subsequent development of retrolental fibroplasia.

Of the 23 cases who developed the disease, 22 received continuous oxygen therapy for varying lengths of time in their early life. The affected babies appeared to be kept in this false environment for longer periods than did the infants who showed no evidence of the condition. During the whole survey, only one baby (from Hospital "C") was recorded as having received oxygen for three weeks or more. This hospital had no cases of retrolental fibroplasia, while all the other hospitals showed an identical incidence of the disease. This seemed unrelated to the concentration of oxygen given to these infants,
because Hospital "C" attained as high concentrations in the oxygen tents as did the other units. All units claimed to have weaned the babies slowly from their oxygen enriched atmospheres.

The presence of anoxia was prominent in the cases who developed retrolental fibroplasia. After analysing all the factors that might have produced an anoxic state in the foetus or new-born infant, it was found that the affected babies received on an average almost twice the number of these "insults" than did the infants who showed no signs of the disease. If anoxia was a factor in the production of retrolental fibroplasia, it would be expected that the affected infants might show features other than the eye condition.

In this series, five infants showed typical features of cerebral spastic diplegia. Four out of these five infants were considered to be subnormal mentally, as were three of the remaining eighteen cases of retrolental fibroplasia.

Further evidence of the part played by anoxia was demonstrated by an infant who was born at home and developed bilateral signs of retrolental fibroplasia. This infant received no oxygen therapy.

The theory is postulated that anoxia may be the initial stimulus to the commencement of the pathological process. If no oxygen is given, the
infant, in the vast majority of cases, will overcome the condition and spontaneous regression will occur, though some cases will undoubtedly progress to membrane formation. In past years, these cases might well have been diagnosed as instances of glioma or pseudoglioma.

Prolonged administration of oxygen to infants with the matrix of the disease already present, may result in severe changes, which the baby will be unable to overcome and so the classical appearance of a retrolental membrane will result.

Only two infants in this series of 23 cases were treated with cortisone. One child died while under treatment, and the other infant appeared to derive little benefit from the therapy. From the experience in these two cases, and adverse reports in the literature, the use of cortisone in the treatment of retrolental fibroplasia was discontinued in Edinburgh.

It was felt that the incidence of the disease might be reduced by the adoption of the following measures:

(a) The prevention and avoidance of all factors that may predispose to a premature delivery.

(b) The prevention and avoidance of all factors that may produce an anoxic state in the foetus or new-born infant.
(c) The administration of continuous oxygen therapy should be restricted to cases where it is indicated, and it should always be given in minimal amounts for the shortest possible duration. Weaning to normal atmospheric conditions should be done gradually.

To carry out the suggestions put forward in (a) and (b) is very much more difficult than the restriction of oxygen therapy. By the end of 1952, most of the Edinburgh units had adopted the policy of restricted use of oxygen, and since that time, no new fully-developed case of retrolental fibroplasia has been observed in the city.

From the experimental studies, there was no evidence to suggest that the sudden removal from an oxygen enriched atmosphere was the causative factor in the production of retrolental fibroplasia.
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APPENDIX ONE

Summary of the 23 cases of Retrolental Fibroplasia

CASE 1 (Male) Hospital A.
Gestation: 30 weeks. Birth weight: 3 lbs. 8 ozs.
Ante-natal (mother): severe respiratory infection; antepartum haemorrhage.
Neonatal (child): oxygen therapy; blood transfusion; severe bronchitis.
Present state: no vision; cerebral spastic diplegia; subnormal mentally.

CASE 2 (Male) Hospital D.
Gestation: 31 weeks. Birth weight: 3 lbs. 10 ozs.
Ante-natal (mother): toxaemia of pregnancy; antepartum haemorrhage.
Natal: vertex presentation; anaesthetic used; duration of labour, 1 hr. 30 mins. State of baby: poor.
Neonatal (child): oxygen therapy; septic spots.
Present state: no vision; other systems normal.

CASE 3 (Male) Twin. Hospital D.
Natal: breech presentation; anaesthetic used; duration of labour, 6 hrs. State of baby: feeble.
Neonatal (child): oxygen therapy.
Present state: no vision; subnormal mentally.

CASE 4 (Male) Hospital D.
Ante-natal (mother): uneventful.
Neonatal (child): oxygen therapy; chest infection; septic spots.
Present state: partial vision; other systems normal.

CASE 5 (Male) Twin. Hospital B.
Gestation: 35 weeks. Birth weight: 3 lbs. 10 ozs.
Ante-natal (mother): ulcer diet; phlebitis; severe toxaemia of pregnancy; rash.
Natal: vertex presentation; anaesthetic used; duration of labour, 2 hrs. 40 mins. State of baby: poor.
Neonatal (child): oxygen therapy; upper respiratory infection; haemangioma chest wall.
Present state: partial vision; other systems normal.
CASE 6 (Male) Hospital B.
Gestation: 29 weeks. Birth weight: 3 lbs. 4 ozs.
Ante-natal (mother): recurrent vaginal bleeding.
Natal: vertex presentation; anaesthetic used; duration of labour, 9 hrs. 27 mins. State of baby: fairly good.
Neonatal (child): oxygen therapy; recurrent colour changes; pneumonia; septic spots.
Present state: partial vision; cerebral spastic diplegia.

CASE 7 (Male) Hospital B.
Gestation: 28 weeks. Birth weight: 3 lbs. 2 ozs.
Ante-natal (mother): chronic anaemia; antepartum haemorrhage.
Natal: breech presentation; anaesthetic used; prolapse of cord; duration of labour, 3 hrs. 40 mins.
State of baby: poor.
Neonatal (child): oxygen therapy; severe colour changes; infection of the submandibular gland; given a six weeks course of cortisone.
Present state: partial vision; subnormal mentally; cerebral spastic diplegia.

CASE 8 (Male) Hospital A.
Gestation: 33 weeks. Birth weight: 4 lbs. 4 ozs.
Natal: placenta praevia; caesarean section; anaesthetic used. State of baby: poor.
Neonatal (child): oxygen therapy; severe colour change; generalised septic spots; septic umbilicus; blood transfusion.
Present state: no vision; other systems normal.

CASE 9 (Male) Hospital D.
Ante-natal (mother): recurrent boils; severe antepartum haemorrhage.
Natal: breech presentation; duration of labour, 10 hrs. 10 mins. State of baby: fair.
Neonatal (child): oxygen therapy; chest infection.
Present state: no vision; subnormal mentally.

CASE 10 (Male) Hospital B.
Gestation: 30 weeks. Birth weight: 3 lbs. 7½ ozs.
Ante-natal (mother): respiratory infection.
Natal: vertex presentation; anaesthetic used; duration of labour, 18 hrs. 40 mins. State of baby: poor.
Neonatal (child): oxygen therapy.
Present state: no vision; cerebral spastic diplegia; subnormal mentally.
CASE 11 (Male) Hospital A.
Ante-natal (mother): headaches; swelling of the ankles.
Natal: vertex presentation; anaesthetic used; duration of labour, 8 hrs. State of baby: good.
Neonatal (child): oxygen therapy.
Present state: partial vision; subnormal mentally.

CASE 12 (Male) Twin. Hospital A.
Gestation: 32 weeks. Birth weight: 4 lbs. 3 ozs.
Neonatal (child): oxygen therapy; severe colour change; generalised septic spots; given a course of cortisone; died while under treatment.

CASE 13 (Female) Hospital B.
Gestation: 30 weeks. Birth weight: 3 lbs.
Ante-natal (mother): uneventful.
Neonatal (child): oxygen therapy; jaundice; marked loss of weight; deformity of left foot; skin pustules; septic umbilicus.
Present state: no vision; cerebral spastic diplegia; subnormal mentally.

CASE 14 (Female) Hospital A.
Ante-natal (mother): cardiac case; died of cardiac failure shortly after the birth.
Natal: vertex presentation; duration of labour, 6 hrs; placenta very unhealthy with numerous infarcts and areas of calcification. State of baby: good.
Neonatal (child): oxygen therapy; colour change; pustules on the face.
Present state: no vision; other systems normal.

CASE 15 (Female) Hospital A.
Gestation: 33 weeks. Birth weight: 3 lbs. 8 ozs.
Ante-natal (mother): severe upper respiratory tract infection.
Neonatal (child): oxygen therapy; jaundice.
Present state: no vision; other systems normal.
CASE 16 (Female) Hospital A.
Ante-natal (mother): uneventful.
Neonatal (child): oxygen therapy; colour changes; anaemia.
Present state: no vision; other systems normal.

CASE 17 (Female) Hospital B.
Ante-natal (mother): leg infection; antepartum haemorrhage.
Natal: Breech presentation; anaesthetic used; duration of labour, 126 hrs. 25 mins. State of baby: poor.
Neonatal (child): oxygen therapy; respiratory infection; anaemia; blood transfusion.
Present state: partial vision; other systems normal.

CASE 18 (Female) Hospital A.
Gestation: 34 weeks. Birth weight: under 3 lbs.
Ante-natal (mother): influenza; fulminating toxaemia of pregnancy.
Natal: caesarean section; anaesthetic used.
State of baby: good.
Neonatal (child): oxygen therapy; recurrent cyanotic attacks; pustules on the face.
Present state: no vision; other systems normal.

CASE 19 (Female) Twin. Hospital A.
Gestation: 32 weeks. Birth weight: 3 lbs. 3 ozs.
Ante-natal (mother): uneventful.
Natal: breech presentation; anaesthetic used; duration of labour, 4 hrs. 40 mins. State of baby: poor.
Neonatal (child): oxygen therapy.
Present state: no vision; other systems normal.

CASE 20 (Female) Twin. Hospital A.
Ante-natal (mother): urinary infection; toxaemia of pregnancy.
Natal: vertex presentation; anaesthetic used; duration of labour, 4 hrs. State of baby: good.
Neonatal (child): oxygen therapy.
Present state: no vision; other systems normal.
CASE 21 (Female). Hospital A.
Gestation: 29 weeks. Birth weight: 3 lbs. 8½ ozs.
Ante-natal (mother): asthma; thrombosis in the leg; antepartum haemorrhage.
Natal: vertex presentation; anaesthetic used; duration of labour, 5 hrs. State of baby: poor.
Neonatal (child): oxygen therapy; infection of the jaw.
Present state: normal vision; other systems normal.

CASE 22 (Female). Home.
Gestation: over 36 weeks. Birth weight: 3 lbs. 12 ozs.
Ante-natal (mother): persistent nausea.
Natal: vertex presentation; anaesthetic used; duration of labour, 10 hrs. 20 mins. State of baby: poor.
Neonatal (child): no oxygen therapy.
Present state: normal vision; other systems normal.

CASE 23 (Female). Twin. Hospital A.
Ante-natal (mother): persistent nausea; anaemia.
Natal: breech presentation; anaesthetic used; forceps delivery; duration of labour, 12 hrs. 20 mins.
State of baby: poor.
Neonatal (child): oxygen therapy; pyrexia of unknown origin.
Present state: normal vision; other systems normal.
Summary of the 5 doubtful cases of Retrolental Fibroplasia

CASE A (Female) Hospital A.
Ante-natal (mother): anaemia; antepartum haemorrhage.
Natal: vertex presentation; duration of labour, 13 hrs. 20 mins.
State of baby: poor.
Neonatal (child): oxygen therapy.
Present state: normal vision; other systems normal.

CASE B (Female) Hospital B.
Gestation: 30 weeks. Birth weight: 3 lbs. 6 ozs.
Ante-natal (mother): uneventful.
Natal: vertex presentation; anaesthetic used;
duration of labour, 3 hrs. 30 mins.
State of baby: good.
Neonatal (child): oxygen therapy; died of suffocation.

CASE C (Male) Hospital B.
Gestation: over 36 weeks. Birth weight: 3 lbs. 12 ozs.
Ante-natal (mother): anaemia; antepartum haemorrhage.
Natal: Placenta praevia; caesarean section;
aeesthetic used.
State of baby: poor.
Neonatal (child): no oxygen therapy; abscess on back.
Present state: normal vision; other systems normal.

CASE D (Female) Hospital A.
Natal: caesarean section; anaesthetic used.
State of baby: poor.
Neonatal (child): oxygen therapy; chest infection.
Present state: normal vision; other systems normal.

CASE E (Female) Hospital D.
Gestation: under 28 weeks. Birth weight: 3 lbs. 10 ozs.
Ante-natal (mother): antepartum haemorrhage (recurrant).
Natal: vertex presentation; anaesthetic used;
duration of labour, 13 hrs. 10 mins.
State of baby: poor.
Neonatal (child): oxygen therapy; ten skin haemangiomas.
Present state: normal vision; other systems normal.