RETROLENTAL FIBROPLASIA

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Retrolental fibroplasia, an ocular condition occurring in prematurely born infants, begins as an overgrowth of the developing retinal vessels which invade the vitreous and so give rise to retinal detachment and a retrolental fibrous membrane which characterize the final stages of the disease.

It was first described as a clinical entity by Terry in 1942, and subsequently there was a striking increase in the number of cases reported from all over the world, until it became the commonest cause of blindness in children, particularly in America where it was responsible for one third of all cases of blindness prior to school age.

Clinical Course

The clinical course of retrolental fibroplasia may be most simply described under three main headings:—The acute phase; the period of regression, and the cicatricial phase.

THE ACUTE PHASE

The initial changes of retrolental fibroplasia are usually noticed during the first month after birth but they may be easily overlooked unless careful and repeated examinations of the fundi with full pupillary mydriasis are made. The rate of progression may be rapid or insidious, but activity has usually subsided by the sixth month when it is followed by organization and distortion of the intraocular contents. The active phase of retrolental fibroplasia may be divided into five clinical stages (Owens, 1955).

STAGE 1

This stage is characterized by a well marked dilatation and tortuosity of the retinal vessels with new vessel formation in localized areas at the periphery of the fundus.

STAGE 2

The vascular changes of Stage 1 are closely followed by a peripheral retinal oedema manifesting itself as a greyish white area which although initially involving only an isolated sector may

extend rapidly to involve the whole circumference of the peripheral fundus.

STAGE 3

The retinal oedema is closely associated with progressive development of newly formed vessels within the retina, which eventually break through the internal limiting membrane to invade the vitreous. Scattered retinal haemorrhages and a localized peripheral retinal detachment are also usually present but at this stage an almost complete spontaneous remission may still occur.

STAGE 4

Further extension of the retinal oedema and neovascularization with a progressive retinal detachment involving half the retina.

STAGE 5

Complete retinal detachment.

PERIOD OF REGRESSION AND THE CICATRICIAL PHASE

Spontaneous regression is characteristic of the condition and may occur from any of the above stages. The degree of residual ocular changes, however, will depend upon the stage of the ocular changes reached when the phase of regression supervenes. The clinical picture associated with the terminal cicatricial phase will, therefore, range from a fundus appearing normal ophthalmoscopically to a complete retinal detachment covered anteriorly by a dense white retrolental membrane which completely obscures the red reflex of the fundus. Both eyes usually show approximately the same degree of involvement although on occasions the condition may be markedly more advanced in one eye than the other.

The Pathology of Retrolental Fibroplasia

The earliest histological change consists of an excessive proliferation in the inner layers of the retina of vasoformative tissue which breaks through the internal limiting membrane and invades the vitreous. The walls of the vessels formed from this angioblastic tissue are markedly

FIG. 1.—Shows localized area of retinal folding and detachment.

FIG. 2.—Shows retina completely detached and folded behind the lens.

permeable, and protein transudates pass into both vitreous and retina which becomes oedematous, folded and eventually shallowly detached (Fig. 1). Organization in both vitreous and retina progressively occurs and the resultant fibrous tissue on contracture accelerates and augments the retinal detachment. A dense lamina of fibrovascular tissue, interposed between the folded degenerate retina and the lens, is thus eventually formed (Fig. 2).

Aetiology

Although prematurity was immediately recognized to be an essential feature of the condition, the nature of the stimulus initiating the abnormal vascular obliteration remained for several years the subject of much discussion, and a variety of factors, both local and general, associated with prematurity were inevitably incriminated and equally inevitably discarded.

A study of the reported cases revealed that the incidence of retrolental fibroplasia appeared to vary inversely with the birth weight (being most common when the latter was less than three pounds) but a most puzzling feature of the condition was the extreme variability of the distribution for not only did the incidence vary markedly between different countries and different towns but it also showed a wide variation between individual hospitals and clinics in the same town. Comprehensive surveys carried out in many countries failed to reveal any relationship between maternal factors and the development of the retinopathy, and it was eventually generally concluded that it was prematurity itself and not the cause of the prematurity which was aetiological most significant. It was also apparent that the only factor which could be considered as a possible aetiological agent was that which could be directly correlated with the initial appearance of the disease.

Several workers had observed that the retinopathy was largely restricted to those institutions possessing special facilities for the care of premature babies, and further studies revealed the important fact that there was a marked correlation between the incidence of the disease and the increased use of oxygen. It also became apparent that premature baby units differed greatly in their use of oxygen and that these differences were closely followed by variations in the incidence of retinal changes. Although clinical evidence that increased oxygen causes a vasoconstriction in the retinal vessels of both adults and premature babies had already been published (Rosenthal, 1939 and Cusick *et al.*, 1940) it was not until 1951 that a definite association between oxygen administration and retrolental fibroplasia was demon-

FIG. 3.—Control kitten, 1 day old. Normal developing retina. There are three vascular complexes, maximum out-growth 6 mm. Proliferation most dense at periphery. (Compare Fig. 4.) Injected Indian ink. Mounted flat x 9.

FIG. 4.—Effect of 5 days 70-80 per cent. O₂. The retinal vessels have been obliterated leaving the hyaloid system intact. x 19.

strated by Campbell, 1951; Crosse, 1951; Szwedczyk, 1951.

Although the aetiological importance of oxygen administration thereafter was increasingly stressed (Patz *et al.*, 1952; Jefferson, 1952), a spirited controversy as to its exact role in the retinopathy ensued and two apparently conflicting theories

eventually emerged; some observers averring that retrolental fibroplasia was due to a relative anoxia whilst another school of thought considered that hyperoxia was the responsible agent. In an attempt to clarify this aetiological problem, Ashton *et al.*, 1953, 1954, carried out an extensive experimental investigation of the influence of varying concentrations of oxygen upon the developing retinal vasculature in the kitten. This vascular system is not only comparable to that in man anatomically but the degree of retinal vascularization in the full term kitten at birth and in the ensuing three weeks is also comparable in extent and maturity to that obtained in the premature baby.

The results obtained in these experiments were of unusual interest for they conclusively demonstrated that high concentrations of oxygen (60-80 per cent.) at atmospheric pressure were able to obliterate completely the growing vessels in the developing retina of the kitten (Figs. 3 and 4). This effect was found to be directly proportional to the degree of immaturity of the retinal vasculature, to the duration of the exposure to oxygen and to the degree of the oxygen concentration. When the animal was transferred from the oxygen chamber to air, however, revascularization commenced from the disc region, but this new vessel formation was grossly disordered in character and by the eighteenth day following the transfer of the kitten from the oxygen chamber to air, numerous vascular proliferations extended into the vitreous as loops or small glomerular tufts (Fig. 5).

Histologically there was evidence of an intense angioblastic activity in the inner layers of the retina with extension of vasoformative tissue and vessels into the vitreous (Fig. 6). Thus a pathological process was produced which was almost exactly comparable to that obtaining in the early stages of retrolental fibroplasia. The failure of the retina to detach, however, prevented the experimental reproduction of the later stages of the disease. It will, nevertheless, be noted that in the light of Ashton's observations the two conflicting theories as to the role played by oxygen in the pathogenesis of retrolental fibroplasia may be reconciled, the basic injury of vascular obliteration being associated with the initial hyper-oxygenation whilst the secondary vascular proliferative phase is associated with the relative anoxia resulting from the removal of the infant to normal atmospheric conditions. In view of the difference between the later development of the animal and human lesions there is need for caution in interpreting the findings in animals in relation to the premature infant (a fact emphasized by Ashton,

FIG. 5.—Effect of 5 days 70-80 per cent. O_2 , followed by 18 days in air. Retinal revascularization is advancing from the disc where there is a profuse circular ingrowth of the vessels several layers in depth. The pattern of growth is completely abnormal and on the surface of the ingrowth there are corkscrew proliferations extending into the vitreous as fine arborizations or glomerular tufts. $\times 5$.

FIG. 6.—Section showing mass of endothelial cells erupting through internal limiting membrane. Haematoxylin and eosin. $\times 115$.

1954), since there are obviously different factors involved.

In spite of an increasing number of published clinical reports associating the administration of high concentrations of oxygen with the incidence of retrolental fibroplasia, there was still an insufficiency of adequately controlled and prolonged

clinical investigation to implicate oxygen definitely as the main aetiological agent in the condition. In 1955, however, the results were published of a detailed investigation initiated in England in 1951 by the Medical Research Council. During the 20 months of the enquiry the clinical histories of 1,095 premature babies of 4 lbs. birth weight or under, who survived at least 2 months, were analysed and formed the basis of this report.

It was found that 84 (7.7 per cent.) of these babies had evidence of retinopathy. In 39 of these 84 cases there was a subsequent regression or return to apparently normal fundi; in 45 the eyes were permanently affected. Analysis of the results emerging from the investigation enabled the Research Council to draw the following main conclusions:—

(a) The cause of prematurity and maternal factors other than vaginal bleeding had no apparent influence on the development of the disease.

(b) The use of oxygen predisposed to the development of retinopathy and the more prolonged the oxygen administration the greater was the incidence of retrolental fibroplasia.

(c) Curtailment and reduction of oxygen therapy did not influence the mortality rate of the premature infants.

A point of interest emerging from this investigation was that of 115 babies whose mothers had a history of bleeding during pregnancy 14.8 per cent. were affected with retinopathy. In the 976 cases not associated with maternal haemorrhage only 6.9 per cent. were affected, a statistically significant difference.

In this survey only data regarding the length of time the baby was in oxygen proved suitable for statistical analysis. This, however, revealed that of the 344 babies who received no oxygen none developed retrolental fibroplasia. Of 581 babies receiving oxygen over a period of less than five days, only two were affected, but there was a steeply rising incidence with increasing length of oxygen administration.

A most comprehensive survey specifically designed to investigate the role played by oxygen in the development of retrolental fibroplasia was then carried out by Kinsey and his collaborators (1956). This study comprised a total of 786 premature infants weighing 1,550 g. or less at birth and who had survived 48 hours.

These infants were divided into two groups: The small group comprising 68 infants received oxygen in concentrations of over 50 per cent. for 28 days (routine oxygen group), the remaining 718 infants, however, received added oxygen only if in the opinion of the paediatrician the clinical condition of the infant demanded it. The con-

centration of oxygen given in any case was restricted to a maximum of 50 per cent.

The results obtained from this controlled study were of great interest for they not only largely confirmed the findings of the Medical Research Council report, but they provided a firm foundation upon which to base the use of oxygen therapy in the management of the premature baby in the future. The most vital facts which emerged from this survey may be summarized as follows:—

(1) The mortality rates in the routine and curtailed oxygen groups did not differ significantly throughout the whole year of investigation.

(2) The incidence of cicatricial retrolental fibroplasia in the group of infants who received no added oxygen after entry into the study 48 hours after birth, was less than one per cent. (1/112); the one infant who developed the disease was known to have received 11 hours of oxygen prior to admission to the study.

(3) The incidence of the active stages of retrolental fibroplasia in the routine oxygen group was approximately twice that in the curtailed oxygen group, but the ratio of the cicatricial grades of the disease, was approximately three and a half times as great.

(4) The incidence of both active and cicatricial retrolental fibroplasia rose rapidly with increased duration of exposure to oxygen.

(5) The incidence of cicatricial retrolental fibroplasia was inversely related to birth weight but was not appreciably dependent upon gestational age.

(6) The incidence of the cicatricial form of disease for infants of single birth was only approximately one-third of that for infants of multiple birth.

(7) Spontaneous regression of retrolental fibroplasia from active stages 1 and 2 occurred in approximately 90 per cent. of the cases of infants of single birth. Regression was much less frequent from active stages 3, 4 and 5 from infants of single birth, and a relatively rare occurrence in infants of multiple birth from stage 2 upwards.

(8) The incidence of cicatricial retrolental fibroplasia was for the most part not dependent upon the percentage of oxygen administered.

Although the majority of these findings are in the main in accord with those reported in the ever increasing literature published on the subject, a controversial note is struck by the denial of any association between the incidence of retrolental fibroplasia and the concentration of oxygen administered.

The elucidation of this particular point is clearly of great importance and it has been investigated experimentally by Ashton *et al.* (1954), Patz (1955) and Hellström (1956). The

first group of workers using the kitten, found that the severity of the vaso-obliterative effect of oxygen was directly proportional to the oxygen concentration, but that concentrations below 35 per cent. had little or no effect. Patz (1955) found that in the rat, oxygen concentrations under 40 per cent. did not appreciably constrict or obliterate the retinal vessels at any age, although he is later quoted by Kinsey *et al.* (1956) as having demonstrated that oxygen, when given in concentrations of 35 per cent. to 40 per cent. for 10 days, produced typical retrolental fibroplasia lesions in one fourth of the animal experiments. In the mouse Hellström (1956) found that a concentration under 40 per cent. caused no detectable histological changes, although at 40 per cent. pathological changes could be demonstrated in a few cases. It would thus appear that oxygen in a concentration of under 40 per cent. is probably innocuous to normal immature animals, but that the margin of safety is a narrow one (Ashton, 1957).

Although caution must be used in interpreting these results they have been confirmed by Guy *et al.* (1956) who reported that no cases of cicatricial retrolental fibroplasia were observed in 81 infants who received oxygen only at times of clinical need, and then for as brief period as possible at concentrations of less than 40 per cent., and by Patz and his colleagues (1954) who have reported that of 60 premature babies receiving a maximum concentration of 40 per cent. oxygen only one showed a residual ocular lesion.

The evidence, however, is conflicting and in the light of our present knowledge it would appear wiser not to lay down any arbitrary maximal concentration for oxygen administration for premature infants, but rather to stress that its use should be restricted to the minimum amount consistent with the infant's well being.

Although it is now generally accepted that the direct relationship between oxygen administration and the incidence of retrolental fibroplasia has been proved beyond all reasonable doubt, sporadic cases have been reported in infants who have not received supplementary oxygen (Coxon, 1951; Bembridge *et al.*, 1952). The cause of such isolated cases and their relationship to the oxygen-induced form has not yet been explained but it may possibly be relevant that whilst the oxygen saturation of arterial blood is approximately 50 per cent. in utero, the arterial saturation after birth rises in a few hours to approximately 90 per cent. at room atmosphere. Capillary obliteration

and secondary proliferation might therefore theoretically develop from this relative increase in oxygen tension, and could explain the occurrence of the occasional cases of retrolental fibroplasia where no additional oxygen has been given. Such cases, however, represent a very insignificant proportion of the total and as Ashton (1955) has already pointed out, vasoproliferation in the fundus is by no means a specific reaction and theoretically could easily arise in any circumstances of severe retinal anoxia, infection or even of hormonal disturbance just as retinitis proliferans, a comparable process in the mature retina, may develop in a variety of unrelated retinal diseases such as central venous thrombosis, and diabetic retinopathy.

The evidence incriminating oxygen as the main agent in the genesis of retrolental fibroplasia is now incontrovertible, and the irreversible changes associated with the condition have been virtually eliminated since the dangers inherent in its administration to premature babies have become widely recognized. If in the future the use of oxygen is universally restricted, both in concentration and duration, to the absolute minimum necessary to meet the clinical needs of the infant, it is not too optimistic to claim that this tragic chapter in the history of therapeutics will be brought finally to a close.

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