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Vaso-obliteration and Retrolental Fibroplasia[1]

Although it is now common knowledge that retrolental fibroplasia (RLF) is due to the toxic effects of oxygen, its pathogenesis having been first demonstrated over 17 years ago (Ashton *et al.* 1953), two misconceptions about its mode of action still persist. First, it is not uncommonly said that oxygen causes RLF by injuring the nervous tissue of the retina, whereas there is in fact no evidence that hyperoxia at normal atmospheric pressure has any direct deleterious effect upon the human retina. Secondly, one frequently reads in otherwise well-informed articles that oxygen causes RLF by producing vasoconstriction of the immature vessels: this is a most misleading half-truth, for vasoconstriction alone will not result in RLF unless it progresses to irreversible closure of the vessels and consequent destruction of the vascular bed. It is this unique phenomenon, originally called 'vaso-obliteration' by Ashton *et al.* (1953, 1954), which is fundamental to the pathogenesis of RLF, and which was first demonstrated in kittens, in which the stage of retinal vascular development at birth is comparable to that of the premature baby. High concentrations of oxygen administered continuously for three days resulted in total destruction of the developing retinal vessels, a process which has been shown to develop as a gross exaggeration of the normal process of capillary retraction. No other vessels in the eye were destroyed in this way. On return to air there followed a profuse and disordered ingrowth of new vessels into the retina and vitreous, which in the infant results in retinal detachment and the formation of a fibrous mass behind the lens. This retinal vasoproliferation is a nonspecific response to vaso-obliteration and is not itself directly due to oxygen.

[1]This paper is dedicated to Professor Dr Josef Böck on the occasion of his 70th birthday

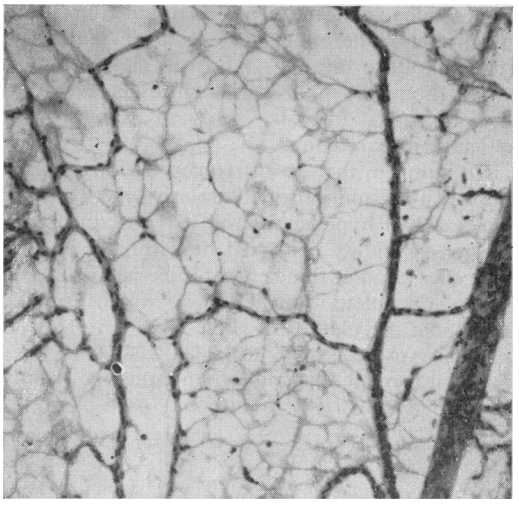

Fig 1 *Retina of premature infant subjected to 90 days' oxygen. Severe retraction has resulted in obliteration of the capillary bed, of which only a delicate basement membrane skeleton remains. Attenuated main vessels and an arteriovenous shunt may be seen. Digest preparation: PAS-hæmatoxylin stain.* × *100*

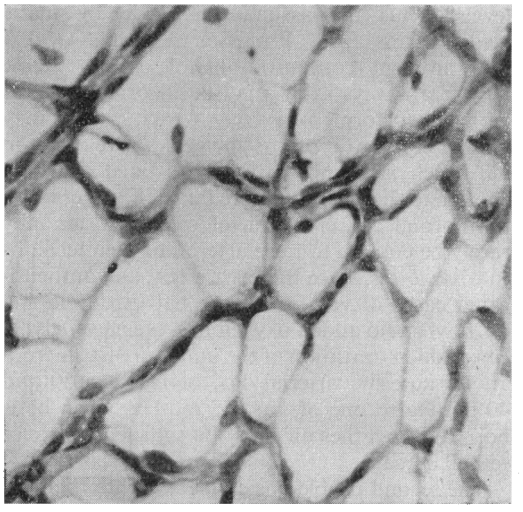

Fig 2 *Retina of premature infant subjected to oxygen therapy showing a slight increase in the normal process of capillary retraction. Digest preparation: hæmatoxylin and eosin.* × *330*

Having emphasized these basic points in pathogenesis we will now consider two aspects of vaso-obliteration: (1) Its demonstration in the premature infant and its possible relationship to the degree of immaturity and oxygen dosage. (2) Its prevention in the experimental animal.

Vaso-obliteration in the Retina of the Premature Infant

In 1965 we had the opportunity, through the courtesy of the late Dr M Dawkins, of examining retinal digests from premature infants who had been exposed to ambient hyperoxia, ranging from 50% to 80% oxygen for about 90 days. These specimens showed an obliterative process identical with that found in animal experiments. There was severe capillary retraction with migration of endothelium, leaving behind only a delicate

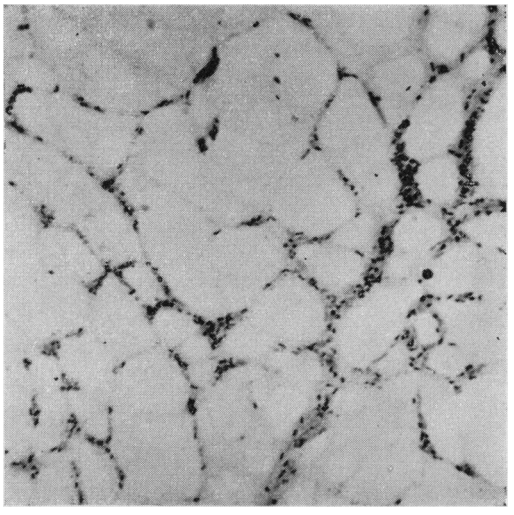

Fig 3 *Retina of premature infant subjected to oxygen therapy showing a marked degree of capillary retraction with migration and breakdown of endothelial cells. Digest preparation: hæmatoxylin and eosin.* × *130*

skeleton of basement membrane with numerous arteriovenous shunts in the obliterating capillary bed (Fig 1).

More recently, through the courtesy of Professor J P M Tizard and Mr A S Mushin, we have been examining retinas from babies treated in the Neonatal Research Unit at the Hammersmith Hospital, London, whose condition had necessitated oxygen administration and who had failed to survive. The degree of capillary retraction in digest preparations was assessed semi-quantitatively and put into one of 4 groups (i.e. normal, slight increase (Fig 2), definite increase, marked increase (Fig 3)). These groupings were then matched against duration of exposure to oxygen, maximum Pao_2 recorded, and birth weight.

Table 1
Relationship between retinal vaso-obliteration, exposure to oxygen and birth weight

Capillary retraction	*Case*	*O_2 exposure (hours)*	*Maximum $Pa\,o_2$ (mmHg)*	*Birth Weight (g)*
Normal	9	23	65	2,480
	15	20	—	3,100
	8	4	45	1,190
Mean		15·7	55	2,255
Slight increase	16	22	55	1,450
	17	15	40	1,430
	14	11	—	980
	1	36	—	1,940
	3	3	60	950
Mean		17·6	51·7	1,350
Definite increase	7	11		1,300
	12	40	65	1,630
	13	12	200	1,020
	11	33	144	1,240
	10	19	230	1,200
	4	72	—	1,220
	5	29	77	1,010
	6	28	156	1,160
Mean		30·5	145·3	1,225
Marked increase	2	40	—	890

It was found (Table 1 & Fig 4) that increasing grades of capillary retraction were associated with both progressively longer periods in oxygen and the degree of prematurity as measured by the birth weight. Furthermore, a combination of low birth weight and prolonged exposure to oxygen appears to be associated with a decidedly greater risk of pathological vaso-obliteration than pertains when the birth weight is not so low and the exposure to oxygen short. These findings, based as they are on a very small number of cases, are necessarily inconclusive, though they are in line with the clinical views of, amongst others, Kinsey (1956) and Patz (1965) and the evidence obtained from animal experiments (Ashton 1954, Ashton *et al.* 1954).

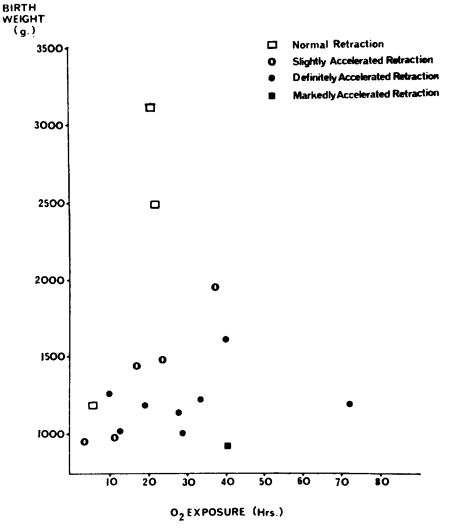

Fig 4 *Relationship of retinal vaso-obliteration to birth weight and duration of exposure to oxygen*

Vaso-obliteration is also shown to be related to the oxygen tension in the arterial blood (Fig 5) when comparison is made with maximum recorded Pao_2 levels in each case. However, 2 of the 6 cases with definite evidence of oxygen toxicity had Pao_2 levels of less than 90 mmHg. Such findings immediately pose the question whether the recorded figures truly represent the highest Pao_2 levels attained and underline the need for frequent and regular estimations. Nevertheless, none of the maximum Pao_2 readings in the babies with evidence of abnormal capillary retraction was below the corresponding values in those with a normal or trivial increase

in degree of retraction. In view of these findings, which are in line with the clinical observation that high Pao_2 levels may be associated with the later development of RLF (Roberton *et al.* 1968), it is with considerable interest that we await the results of the multi-centre study of a similar nature being undertaken by Kinsey and Patz in the USA (Patz 1970).

Experimental Prevention of Vaso-obliteration due to Oxygen

It was shown some years ago that, given the same degree of immaturity of vessels and the same level of hyperoxia, the transition from the first phase of vasoconstriction into the second phase of vaso-obliteration is dependent upon the duration of oxygen exposure. For instance, in the retina of the kitten (1–7 days old) exposed to continuous hyperoxia (80–90% at 1 atmosphere), complete constrictive closure of the retinal vasculature takes 6–8 hours to develop and is largely reversible in a matter of minutes on return to air; vasoproliferation does not then ensue. On the other hand, if the closure is maintained by continuous hyperoxia for 36 hours, complete destruction of the vessels occurs, and vasoproliferation on return to air is an invariable sequel.

Since the irreversible destructive effect of continuous hyperoxia takes so long to develop, it would seem possible that if oxygen and air were administered intermittently, in such a way that each exposure to oxygen was well within the period of the reversible effect (i.e. less than 6 hours) and each period in air sufficiently prolonged to permit re-opening of the vessels, destruction of the vascular bed might be entirely prevented.

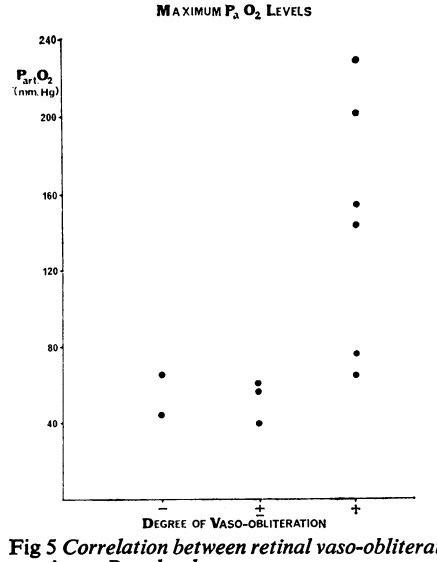

Fig 5 *Correlation between retinal vaso-obliteration and maximum Pao_2 levels*

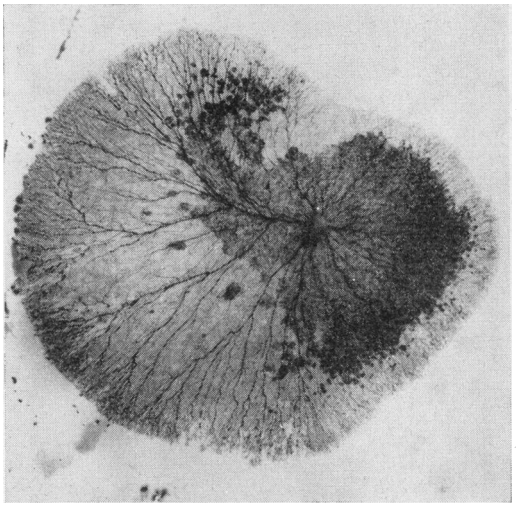

Fig 6 *Retina of 10-day-old kitten showing the effect of 72 hours continuous exposure to 80–90% oxygen, followed by air survival. There is a profuse and abnormal growth of vessels into the retina and vitreous (compare Fig 7). Indian ink injected.* ×4·5

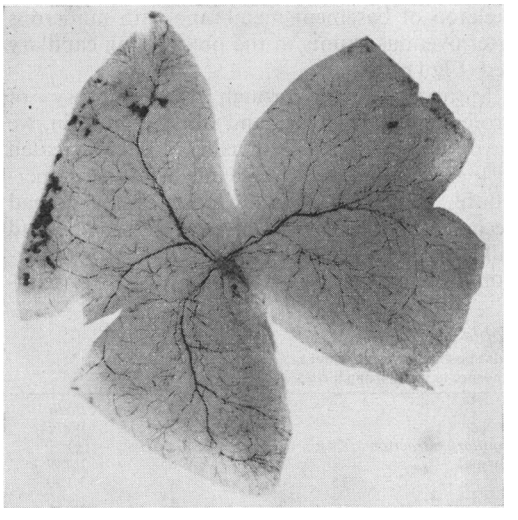

Fig 7 *Retina of 10-day-old kitten showing the effect of 72 hours exposure to 80–90% oxygen, but administered intermittently 1 hour oxygen/ ½hour air, followed by air survival. The appearances are normal (compare Fig 6). Indian ink injected.* ×2·5

With this in mind we have recently investigated the possibility that oxygen given intermittently, rather than continuously, might obviate its toxic effects (Ashton *et al.* 1971).

Kittens of 5–11 days old were exposed to 80–90% oxygen for a total period of 72 hours, but at the end of each hour the animals were returned to normal air for periods of either ½ or 1 hour. These animals were compared with litter

mates receiving an equivalent total dosage of oxygen given continuously.

It was found, as in the original experiments, that continuous exposure to oxygen for 72 hours caused complete obliteration of the retinal vessels, followed on return to air by marked vasoproliferation into the retina and vitreous (Fig 6). Interrupting the oxygen administration by intervals of 1 hour in air for each hour in oxygen, however, allowed the vessels to remain open and neither vaso-obliteration nor vasoproliferation were seen. These periods in oxygen did not appear, therefore, to have a cumulative effect. We then tried shorter periods of ½ hour intervals and again found either no or very minor degrees of vessel closure (Fig 7). Except for one minute focus in one eye of 3 animals allowed to survive, there was again no sign of vascular outgrowth into the vitreous, after 18 days survival (Table 2).

Table 2
Response of neonate kitten retinas to intermittent oxygen
All kittens exposed to 80–90% O_2 for 72 hours

Experiment	*Vaso-obliteration*	*Vasoproliferation*
Continuous O_2	+++	+++
Intermittent O_2 (1 h O_2: 1 h air)	—	—
Intermittent O_2 (1 h O_2: ½ h air)	±	—

It would be of interest to carry out further experiments to investigate the minimum air intervals required to protect the retinal vessels against lower concentrations of oxygen and to do this in animals of less sensitive age groups, and so simulate more closely the conditions obtaining in oxygen therapy of premature infants. For future work it should be relatively simple to devise an incubator wherein oxygen could be automatically and completely replaced by air at programmed intervals.

Since animal experiments can only be an approximate guide, it is a matter of speculation whether our experimental results have any application to the management of oxygen therapy in prematurity; it would, perhaps, seem unlikely that hypoxic infants could survive repeated intervals in air. Our findings are sufficient, however, to establish the principle that intermittent as opposed to continuous oxygen can prevent permanent injury to the growing retinal vessels.

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Retinal Photography in Premature Infants: *Forme Fruste* Retrolental Fibroplasia

In 1967, Patz stated that careful observation of the retinal vessels for spasm in premature infants receiving oxygen therapy might replace the need for direct monitoring of arterial oxygen tension (Pao_2). This suggestion induced us at the Hammersmith Hospital, London, to study the retinal changes of such infants objectively by photographic recording (Bulpitt & Baum 1969). In fact it proved impossible to photograph the retinal vessels in the most immature, because the persistence of the tunica vasculosa lentis (*see* Fig 1), a constant feature until 32 weeks of gestation, obscured any clear view of the retina. However, after 32 weeks satisfactory photographs were obtained. We studied 6 infants who were recovering from the respiratory distress syndrome but were still having Pao_2 measurements taken. We explained the procedure fully to the parents and obtained their permission. Photographs were taken with each infant breathing first room air and then 100% oxygen by face mask for 15 minutes. The Pao_2 was measured on each occasion. Vascular landmarks were then matched on the transparencies, and the vessel diameters measured at multiple sites.

All vessels constricted with elevation of the Pao_2. Moreover, pooling all the results, there was a significant relationship between the degree of constriction and the height of the Pao_2. However, when films taken at high Pao_2 were considered in isolation, it was not possible to

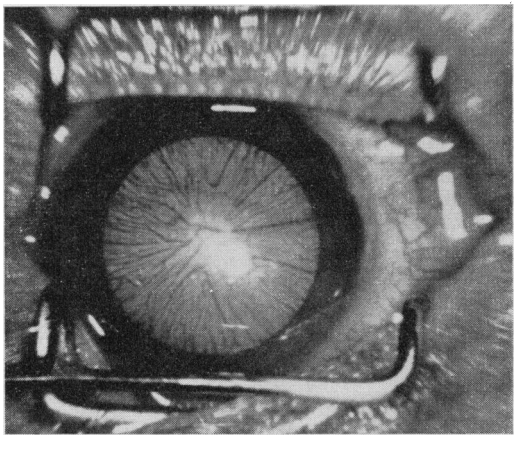

Fig 1 *Tunica vasculosa lentis in a premature infant of 29 weeks gestation (right eye: photograph taken* post mortem)