STUDIES ON DEVELOPING RETINAL VESSELS*

II. INFLUENCE OF RETINAL DETACHMENT ON OXYGEN VASO-OBSTRUCTION

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By direct observation, it was recently shown that the obliterative action of high concentrations of oxygen on the ingrowing vessels of the kitten retina may be prevented by retinal detachment (Ashton and Cook, 1954). The obliterated vessels re-open as soon as detachment begins, indicating that close apposition between retina and choroid is necessary for the obliterative phenomenon to operate. Since it is known that vaso-obstruction is also dependent upon the concentration of oxygen, it would appear that, once the retina detaches, effective levels of oxygen no longer reach this tissue.

The maximum period, however, for which the vessels of the detached retina were observed in hyperoxia was $12\frac{1}{2}$ hours, and the question remained whether a longer period of exposure might not be required for oxygen to diffuse across the subretinal space and reach the retina in sufficient concentration. In this paper experiments are reported which show that retinal detachment prevents the vaso-obstructive effect of oxygen even when high concentrations are continuously maintained for 4 days. Survival in air after such detachment and exposure is followed by proliferative changes which are difficult to interpret in view of our findings on the effect of detachment alone (Ashton and Cook, 1955).

Experimental Findings

Experiment 76.—One mother cat and three kittens (k1, k2, and k3) 4 days old.

Plan.—Through a needle withdraw enough vitreous from the right eye of each anaesthetized kitten to induce retinal detachment. Left eye to remain as control. Then put mother and litter into 70-80 per cent. oxygen for 4 days. Then kill all the kittens to demonstrate:

(a) Effect of 4 days' 70-80 per cent. oxygen at 8 days old (left eyes).

(b) Effect of 4 days' 70-80 per cent. oxygen at 8 days old with retinal detachment (right eyes).

Results (both eyes injected Indian ink)

(a) *k1 left.*—Total obliteration of temporal complexes but nasal complex only partially obliterated. (This animal was found to have pulmonary collapse and cardiac enlargement; these findings may explain why a total obliteration was not obtained).

k2 left.—Total obliteration of retinal vessels.

k3 left.—Total obliteration of retinal vessels.

(b) *k1 right.*—Extensive retinal detachment. Small vitreous haemorrhage. In the detached retina the vessels were engorged and fully patent; there was no abnormal vaso-proliferation. In a small area between the temporal complexes where the retina was attached,

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there was a zone of total vaso-obliteration, and there was some degree of capillary obliteration around the disc.

k2 right.—Folded detachment on temporal side, total vaso-obliteration except in the detached fold where there were two main vessels leading to an engorged capillary bed. No abnormal vasoproliferation.

k3 right.—Detachment of whole temporal retina. On the nasal side the retinal vessels were completely obliterated, and there were a few scattered haemorrhages. On the other hand the temporal complexes were almost fully patent and the large vessels were dilated and tortuous over the folded areas. No abnormal vasoproliferation (Fig. 1).

Conclusions.—This experiment showed that retinal detachment could prevent the vaso-oblitative effect of oxygen, even when hyperoxia was continuously maintained for 4 days.

FIG. 1.—Exp. 76, k3 right, 8 days old. After detachment of the temporal half of the retina, the kitten was exposed to 70-80 per cent. oxygen for 4 days. On the attached nasal side (right of picture) the retinal vessels have been completely obliterated, but on the detached temporal side (left of picture) the vascular complexes have remained fully patent. $\times 5.33$.

Experiment 82.—One mother cat and two kittens (k1, k2) 7 days old.

Plan.—Procedure as in Experiment 76, but allow k1 to survive in air for 18 days and k2 for 28 days to demonstrate:

(a) Effect of 4 days' 70-80 per cent. oxygen followed by 18 days' air at 29 days old (k1 left) and by 28 days' air at 39 days old (k2 left).

(b) As above with retinal detachment (right eyes).

Results (both eyes injected Indian ink)

(a) *k1 left.*—No normal complexes present. Profuse, roughly circular ingrowth of vessels at the disc consisting of intraretinal and intravitreal networks, 4 $\times$ 5 mm. in diameter (Fig. 2, opposite).

k2 left.—No normal complexes present, usual ingrowth of vessels. The intravitreal glomerular network was roughly circular 4 mm. diameter, whereas the intraretinal network extended further to the nasal side. Maximum outgrowth 4 mm. Total diameter 7 mm.

FIG. 2.—Exp. 82, k1 left, 29 days old, control. The usual type of dense retinal and intravitreal vasoproliferation is seen around the disc in a kitten exposed to 70-80 per cent. oxygen for 4 days and then allowed to survive in air for 18 days. No normal complexes were present (cf. Fig. 4). $\times 19$.

(b) *k1 right*.—Anteriorly retina irregularly detached and posteriorly mostly *in situ*. No evidence of vaso-obliteration, normal three complexes present, densely proliferating, particularly at upper temporal periphery—maximum outgrowth 8 mm. No intravitreal proliferations but the retinal vessels extended deeply into the retina and in many areas had completely penetrated it to form a polygonal network on its under surface. This down-growth was particularly marked at the temporal periphery (Fig. 3).

FIG. 3.—Exp. 82, k1 right, 29 days old. After retinal detachment the kitten was exposed to 70-80 per cent. oxygen for 4 days and then allowed to survive in air for 18 days. A posterior view of the retina shows vessels extending through to form a network on its under surface. No intravitreal vessels were seen in this case. $\times 15$.

k2 right.—Generalized folded detachment but the retina appeared most closely in apposition over the tapetum. The whole vascular network was fully open and the main vessels were normal in distribution, but the capillary pattern was irregular and markedly proliferative. Over the whole surface there were intravitreal proliferations of the glomerular and loop type, and these were particularly in evidence where the retina was freely detached. In this detached portion vessels had proliferated through the retina towards the choroid and emerged on the subretinal surface, particularly in the lower temporal quadrant, where they had formed a coarse plexus of finely intertwining vessels (Figs 4, 5 and 6, opposite).

Conclusions.—This experiment confirmed the previous experiment, that retinal detachment prevents oxygen vaso-obliteration. Both kittens showed that detachment permits the retinal vessels to extend deeply towards the subretinal surface to form a plexus in a normally avascular area. The absence of intravitreal vessels in *k1* and their presence in *k2* is difficult to explain without a knowledge of the extent of detachment at the time of oxygen exposure.

Discussion

The first experiment (76) confirms our previous observations that retinal detachment prevents the vaso-obliterative action of oxygen, and it shows in addition that even though a degree of ambient hyperoxia, which normally leads to total vaso-obliteration, be continuously maintained for 4 days it is without effect on the vessels in a detached area, whereas the vessels in an attached portion of retina obliterate completely in the usual way (Exp. 76, *k1*, *k2*, *k3*, right). We, therefore, believe that effective concentrations of oxygen are unable, either through inadequate diffusion or impaired transfer, to reach the detached retina, although the unlikely possibility that there may be differences in reactivity to oxygen between the attached and detached retina cannot be excluded.

The second experiment (82) in which the retina was detached before oxygen exposure, and the animals then allowed to survive in air for periods of 18 days and 28 days respectively, showed a marked proliferation of vessels outwards through the detached retina to form a dense polygonal network on its outer surface. In only one animal, however, (*k2 right*) was there intravitreal proliferation; this occurred over the whole surface of the retina and was particularly in evidence where the retina was freely detached.

The control eyes showed the dense intravitreal proliferation which constantly follows complete vaso-obliteration, and, as usual, there were no penetrating vessels on the outer surface.

From the first experiment and from previous studies it had been expected that survival in air after oxygen exposure might lead to vasoproliferation from those portions of the retina which remained attached in oxygen, whereas no proliferation was expected to occur in detached areas where the preliminary phase of vaso-obliteration had been prevented.

However, in the actual experiment (Exp. 82 quoted above), the results were not so straightforward as anticipated and although the detached retina behaved entirely differently from the attached retina, the findings are difficult to interpret for two reasons. First, one has no knowledge of the extent or site of detachment during the actual period of oxygen exposure. Thus in

FIG. 4.—Exp. 82, k2 right, 39 days old. After retinal detachment the kitten was exposed to 70-80 per cent. oxygen for 4 days and then allowed to survive in air for 28 days. There was a generalized folded detachment and over the whole surface of the retina new vessels had proliferated into the vitreous—see also Fig. 5. Vessels also extended through the retina (cf. Fig. 6). $\times 5.33$.

Fig. 5.—High-power view of Fig. 4. Disc region shows glomerular tufts and loops of vessels extending into the vitreous. $\times 11$.

FIG. 6.—Posterior view of Fig. 4. Vessels have penetrated the retina to form a polygonal plexus of finely intertwining vessels on its under surface. $\times 25$.

one animal (Exp. 82, k2 right) the retina was found to be totally detached at *post-mortem* examination, but may have been only partially detached in oxygen. Secondly, it was found in another series of experiments that detachment itself, without oxygen exposure, can give rise to abnormal vasoproliferation both outwards through the retina and inwards into the vitreous (Ashton and Cook, 1955).

Hence it is not possible to determine to what extent the varying degrees of vasoproliferation obtained in our second experiment were due to oxygen vaso-obliteration, to the modification of vaso-obliteration by detachment, or to detachment alone.

Summary

(1) Experiments are reported which show that detachment of the developing retina prevents the vaso-oblitative action of oxygen even though a normally effective ambient concentration is maintained for as long as 4 days.

(2) Survival in air after such detachment and exposure leads to vasoproliferative changes which cannot be distinguished from those found in detachment alone. These findings are discussed.

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