STUDIES ON DEVELOPING RETINAL VESSELS*

III. ROLE OF SYMPATHETIC INNERVATION IN OXYGEN VASO-OBLITERATION

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THE oblitative effect of high concentrations of oxygen on developing retinal vessels was first demonstrated in the eye of the kitten by Indian ink injection (Ashton and others, 1953) and was later observed directly by using a limbal window technique (Ashton and Cook, 1954); it has since been shown in eyes of puppies and new-born rats by ink injection methods (Patz, 1954) and in new-born mice by sections (Gyllensten and Hellström, 1954).

The mechanism whereby oxygen exerts this oblitative effect, however, is still entirely unknown, but the sum of experimental evidence so far obtained strongly suggests:

(a) that the influence is exerted locally through the evolution or destruction of some factor or factors within the immature retina itself;

(b) that the effect is confined to the immature retina by reason of its peculiar metabolism;

(c) that the retina is vulnerable to hyperoxia through its structural and functional relationships to the choroid.

Before this hypothesis is further explored, it is necessary to exclude the possibility that vaso-obliteration, in its immediate or delayed phases or both, may be controlled by a central mechanism involving the sympathetic nervous system.

In previous papers the effect of an adrenergic blocking agent had been reported, but the results were equivocal. Thus, in an ink-injection experiment, the administration of Priscol (2-benzyl-imidazoline hydrochloride) did not appear to influence oxygen vaso-obliteration (Ashton and others, 1954); whereas, by direct observation, obliterated vessels were seen to re-open slowly after the injection of Priscol (Ashton and Cook, 1954). In any case the results would be difficult to interpret, for Priscol is not sufficiently selective for our purposes, since it has a number of side actions—such as histamine-like and acetylcholine-like effects (Ahlquist and others, 1947).

Patz (1955) found no evidence of sympathetic control of vaso-obliteration in his recent experimental work on new-born puppies, which had been placed in high oxygen concentrations after section of the right vago-sympathetic trunk (? site of section); nor was the pattern of the subsequent vasoproliferation in air modified in any way. These experiments, however,

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are open to the minor objection that no time was allowed to elapse after the section of the sympathetic chain for degenerative changes to occur: if the section had been pre-ganglionic, the tissues would have remained innervated by post-ganglionic elements.

This paper reports the results of experiments to determine, by Indian ink injection and direct observation, the effect on vaso-obliteration of adrenergic blockade with Dibenamine (N, N-dibenzyl-chloroethylamine)—a selective drug acting directly upon effector cells to prevent excitatory responses to epinephrine or Sympathin E (Nickerson and Goodman, 1947); and of bilateral section of the cervical sympathetic trunk with extirpation of the superior cervical ganglia, with and without allowing a period for degenerative changes to develop.

Experimental Findings

INFLUENCE OF DIBENAMINE

(a) *By Direct Observation*

Experiment 100.—A limbal window was inserted into the left eye of a kitten (12 days old), which had previously been subjected to 70-80 per cent. oxygen for 6 hrs, in order to obtain the delayed oxygen effect (Ashton and Cook, 1954). After allowing an interval for recovery from any traumatic effect, the animal was placed in an oxygen chamber and the retinal vessels observed by direct vision. Total obliteration of the vessels was then induced with 90 per cent. oxygen and the animal was returned to air to allow the vessels to re-open.

Dibenamine 5 mg. in physiological saline (25 mg./kg.) was then injected intravenously and the animal was returned to 90 per cent. oxygen after 30 minutes. Total vaso-obliteration occurred, as above, in 8 minutes, and the vessels re-opened normally on return to air. A repeat experiment gave identical results.

Conclusion.—Intravenous Dibenamine in the concentrations used appeared to have no modifying effect on the vaso-obliterative action of oxygen (delayed phase).

INFLUENCE OF SYMPATHECTOMY

(a) *By Direct Observation*

Experiments 64, 66, and 67.—A limbal window was inserted into the left eye of each of three kittens (12 days old) upon which a bilateral cervical sympathectomy had been performed 1 hr previously. After an interval of 30 minutes the kittens were placed in an oxygen chamber and the effect of 90 per cent. oxygen on the retinal vessels was then observed by direct vision. Vasoconstriction and obliteration of the capillaries occurred within a few minutes.

Experiment 63.—A limbal window was inserted into the left eye of a kitten (12 days old) after the animal had been exposed to 70-80 per cent. oxygen for 7 hrs. A bilateral cervical sympathectomy was then performed. The retinal capillaries showed no evidence of immediate re-opening after the sympathectomy, but after an initial latent period of 30 minutes they gradually became patent. The vessels could thereafter be opened and closed by alternating exposure to air and oxygen.

Conclusion.—Acute or chronic bilateral cervical sympathectomy had no apparent effect upon the immediate or delayed phases of oxygen vaso-obliteration.

(b) *By Indian Ink Injection*

Experiment 104.—A bilateral cervical sympathectomy was performed by Dr. N. Ambache on one kitten (4 days old) under Nembutal anaesthesia, whilst two litter-

mates served as controls. After allowing 8 days for degeneration of the sympathetic nerve supply, the mother cat and all three kittens were placed in 70-80 per cent. oxygen for 5 days, after which the kittens were killed and injected with Indian ink *via* the left ventricle. The eyes were then removed and opened transversely, and the retinae were examined under a dissecting microscope. All six retinae showed almost total vaso-obliteration, and no significant differences were discernible between the control and sympathectomized litter-mates.

Conclusion.—The experiment showed that cervical sympathectomy, even after allowing a period for degenerative changes to develop in the sympathetic chain, had no modifying effect on oxygen vaso-obliteration.

Summary

These experiments have shown that the vaso-obliterative effect of oxygen on immature retinal vessels is uninfluenced, in either its immediate or its delayed phases, by cervical sympathectomy. Nor was the delayed phase modified by adrenergic blockade with Dibenamine.

The findings are in full agreement with those of Patz (1955), and appear to show that sympathetic innervation is not directly or indirectly concerned in the mechanism of oxygen vaso-obliteration.

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REFERENCES

- AHLQUIST, R. P., HUGGINS, R. A., and WOODBURY, R. A. (1947). *J. Pharmacol.*, **89**, 271.
 ASHTON, N., and COOK, C. (1954). *British Journal of Ophthalmology*, **38**, 433.
 ——— WARD, B., and SERPELL, G. (1953). *Ibid.*, **37**, 513.
 ——— (1954). *Ibid.*, **38**, 397.
 GYLLENSTEN, L. J., and HELLSTRÖM, B. E. (1954). *Acta paediat. (Uppsala)*, **43**, Suppl. 100, p. 131.
 NICKERSON, M., and GOODMAN, L. S. (1947). *J. Pharmacol.*, **89**, 167.
 PATZ, A. (1954). *Amer. J. Ophthal.*, **38**, 291.
 ——— (1955). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **59**, 25.