RETINAL VASCULARIZATION IN HEALTH AND DISEASE

PROCTOR AWARD LECTURE OF THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

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It was my intention to speak today on the whole problem of new vessel formation in the eye, but owing to several new observations made in my department just before I left, which I would like to report to you, it will be necessary to confine my remarks to vessel growth in the retina.

The nature of the stimuli which excite and direct the growth of blood vessels into the retina, in both normal and abnormal circumstances, is as yet unknown, but as a direct result of laboratory studies of retrolental fibroplasia we have been inundated with a mass of new and apparently isolated facts. It is imperative to arrange this knowledge in some sort of order, and a few broad generalizations appear to be justified on the data at present available, but they should not be regarded as rigid conclusions until the facts are incontrovertible, and that cannot at present be claimed. I present them to show the direction in which our experimental results are leading us and to provide working hypotheses to knit scattered observations together as a guide, and possibly a stimulus, to future research.

NORMAL RETINAL VASCULARIZATION

The mode of development of the human retinal circulation has been known for many years and need not be described here, but there is one feature which until recently has not been recorded. It has always been taught that the retinal vessels bud out as fully formed capillaries from the central retinal artery at the disc, where it is continuous with the hyaloid artery during the fourth month of intrauterine life; one bud appears from the upper side and one from the lower side, which then grow out into the nerve-fiber layer of the retina (fig. 1).

The feature which has only recently been appreciated, however, is that these vascular buds are preceded and accompanied by clusters of undifferentiated cells (Ashton, 1954[a]), presumably mesenchymal elements derived from the vessel wall. They may readily be identified with PAS stain as they contain PAS-positive granules—identified as glycogen (Serpell, 1954)—which are absent in endothelial cells. They always lie at the periphery of the advancing vessels as a spearhead of the ingrowth.

Whether these mesenchymal cells are responsible for the formation of the whole retinal vasculature, or only those elements, such as muscle and connective tissue which cannot derive from endothelium is not known with certainty. It is interesting that in retrolental fibroplasia wherein the blood vessels proliferate abnormally, these cells are similarly affected, and may play an important role in the subsequent formation of fibrous bands in the vitreous.

Fig. 1 (Ashton). Injected retina from a 20-week fetus viewed from one side. Above and below the hyaloid artery, vessels may be seen budding into the retina. (×20.)

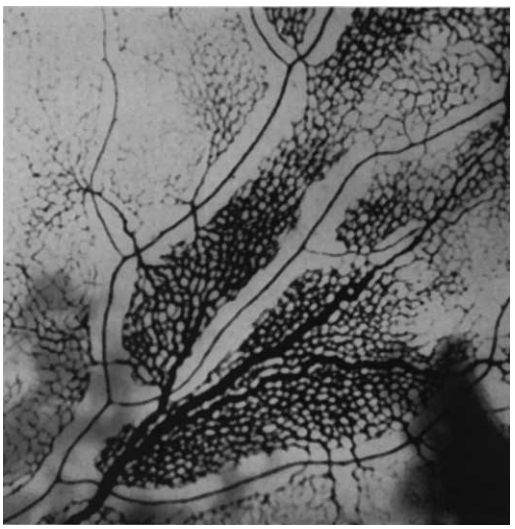

Fig. 2 (Ashton). Injected retina from a one-day-old kitten, showing capillary development from the veins, which occurs predominantly from the side of the vein remote from the artery. There is a capillary-free zone around the arteries. (×33.)

The comparatively recent studies of Michaelson (1948 a and b), particularly in man, the rat, and cat, by providing new observations and by emphasizing old ones have been of great value in indicating the general principles involved in normal retinal vascularization. He showed that the formation of retinal capillaries is pre-eminently a function of the retinal veins and that if a vein and artery are close to each other, growth takes place predominantly from the side of the vein remote from the neighboring artery (fig. 2). He pointed out the capillary-free zone existing around the arteries, both in the immature and in the mature retina (fig. 3), a feature previously depicted by Leber (1903).

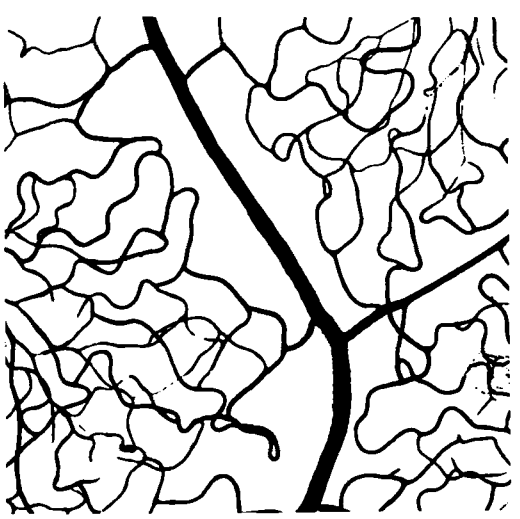

Fig. 3 (Ashton). Adult human retina injected with India ink to show the capillary-free zone around the artery. (×105.)

To Michaelson these anatomic facts were clearly associated with each other and suggested to him the presence in the retina of a vasoformative factor, possibly biochemical in nature, which was present in gradients of concentration differing in arterial and venous neighborhoods. He did not speculate further upon the nature of this factor, but quite clearly the pattern of vascular growth very strongly suggests its possible association with the level of oxygen tension within the tissues.

Indeed, the only adequate explanation of all the observed features of vessel growth and architecture in the normal retina is that a vasoformative factor—simple or complex—arises in areas of lower oxygen tension, but not in areas of higher oxygen tension. Thus it becomes apparent why vessels invade the developing retina at the 100-mm. stage as the choroid fails to meet its increased oxygen requirements; why growth is predominantly on the venous side; why there is a peri-arterial capillary-free zone; and why vessels never transgress, despite the absence of an anatomic barrier, the macula, the outer layers, or the periphery of the retina which are adequately oxygenated from the choriocapillaris.

These conclusions, however, are no more than speculative deductions from anatomic observations and I shall now consider experimental work which more fully explores the hypothesis.

Experimental studies

The idea that vascular morphogenesis in the retina may be related to oxygen was first expressed in the literature by Campbell

(1951), who tested the hypothesis by placing one-day-old rats in a low-pressure environment, and made the important observation that the capillary-free zone around the arteries became significantly narrower than in control animals. The converse of this finding, that raised oxygen tensions lead to widening of the capillary-free zone, we demonstrated (fig. 4) later when investigating the effect of hyperoxia on the retina of the kitten (Ashton et al., 1954).

There would thus appear to be two clearly defined processes in retinal vascular growth; one of inhibition, as evidenced by *vaso-obliteration* occurring in high oxygen concentrations, and one of stimulation, as evidenced by *vasoproliferation* occurring in low oxygen concentrations. The two processes, however, are not perfect mirror images of each other, for whereas in vasoproliferation both the normal and abnormal forms appear to be due to a similar mechanism, vaso-obliteration cannot be regarded simply as an extension of the normal periarterial capillary-free zone, for this is a region into which vessels have never grown and cannot, therefore, have been obliterated. Thus vaso-obliteration probably does not exist as a normal mechanism.

Since the data relating to these two processes are extremely intricate I shall consider them separately.

1. Vaso-obliteration

That oxygen in high concentrations can produce a partial or total obliteration of the retinal vessels in the immature eye was discovered about four years ago in experiments on the kitten (Ashton et al., 1953) and much has been learned about the phenomenon since that time. It commences as a marked constriction of the arteries and arterioles; the arterioles and arterial side of the capillary circulation are the first vessels to obliterate; this is followed by disappearance of the whole capillary bed; then the main arteries and finally the main veins close, leaving an apparently avascular retina.

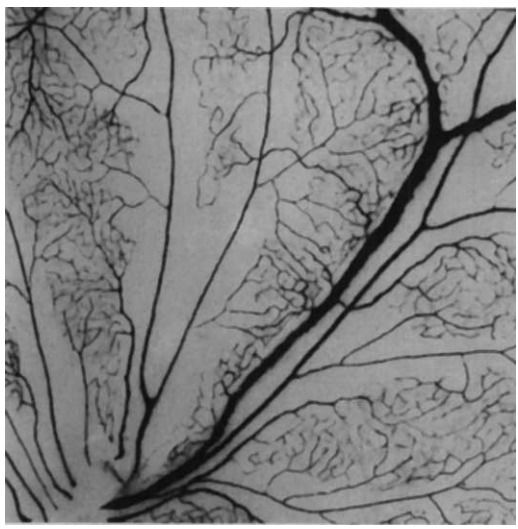

Fig. 4 (Ashton). Injected retina from an 18-day-old kitten subjected to hyperoxia. Vaso-obliteration is in its early stages and is seen to begin as a widening of the peri-arterial capillary-free zone. (×33.)

Injected specimens show that in general this process begins peripherally and spreads posteriorly, the disc region being the most resistant and the last area to be completely obliterated. It should be realized, however, that injected specimens do not reveal the degree of closure of the vessels in life, but only their ability to re-open when injected. This distinction is important, because it means that vaso-obliteration can only be studied accurately by direct observation in the living animal.

This phenomenon is confined to the growing retinal vessels, occurring neither in the other vessels of the eye nor in those of other organs (Ashton et al., 1954; Patz, 1954); nor in growing vessels as observed in the rabbit cornea (Ashton and Cook, 1954; Michaelson et al., 1954), nor in the rabbit's ear-chamber (Ashton and Cook, 1954); nor in chick embryos; nor in cat or rat embryos (Ashton, 1954b). Nor indeed does it occur in the retina itself, when it becomes detached from the choroid.

As shown by injections, the severity of the vaso-obliterative effect of oxygen is inversely proportional to the maturity of the

TABLE 1

SUMMARY OF EXPERIMENT

Group	Age (days)	Oxygen Exposure (days)	Air (days)	Vasoproliferation
A.	1	4	10	In 15-day-old retina
B.	10	15	10	In 35-day-old retina

retinal vessels and, once the circulation is fully established and the normal vascular architecture attained, oxygen fails to produce significant obliterative changes. Oxygen thus has no structural effect on the vessels of the adult cat, and recent experiments suggest that this is due, at least in part, to a change in the retinal metabolism.

It was possible, for instance, by exposing kittens of differing ages to varying periods of oxygen, to obtain, on transfer to air, vasoproliferations in retinas of an age normally sensitive to oxygen, and vasoproliferations in retinas of an age normally insensitive to oxygen (table 1). Re-oxygenation showed that obliteration of these abnormal proliferations occurred only in the first group. This demonstrates in a rather striking way that vaso-obliteration may be the outcome of an interaction between oxygen and retinal metabolism and not a peculiar reaction of growing retinal vessels themselves (Ashton, 1956).

Vaso-obliteration occurs in two phases, *immediate* and *delayed*. An *immediate* effect, consisting of severe constriction of the large vessels with obliteration of the capillaries, develops after five minutes' exposure to hyperoxia. The vessels then dilate again after about 10 minutes and so remain, although in continuous oxygen, for about six hours when the *delayed* effect comes into operation. This results in a gradual total vaso-obliteration and once it is achieved the circulation may be either opened or closed, in each case in about five minutes, by alternating air and oxygen. But after longer periods the process gradually becomes irreversible and at the end of three days the vessels seem to have largely disappeared although their remnants can be made out in flat preparations and in sections. The time relationships of these changes suggest that oxygen is inhibiting or poisoning an enzyme system vitally concerned in the maintenance of the vessels' patency.

In considering the possible mechanisms involved one could first postulate the elaboration of a vasoconstrictor substance. It would, however, be difficult to imagine upon what cells in such a primitive vascular system it could act, especially since known vasoconstrictors do not obliterate growing retinal vessels, nor is sympathetic innervation concerned in the mechanism (Patz, 1955; Cook and Ashton, 1955). Furthermore, extracts of retinas in which vaso-obliteration had been induced (extracts prepared in high ambient concentrations of oxygen) have been found to have no effect when injected via the vitreous onto normal retinas in direct-observation experiments on the living animal (Ashton and Pedler, 1957). Nor did such extracts show any evidence of a smooth muscle stimulant as tested against preparations of rat colon in two experiments (Dr. N. Ambache kindly carried out these tests on the extract with which he was provided).

Secondly one could postulate the *removal of a vasodilator substance* inherent in the vasoformative process. It is noteworthy, however, that for growing vessels to be obliterated by hyperoxia it is essential for them to be actually within the retinal tissue; developing vessels within the vitreous, on the iris, or in the cornea are not affected in this way. If oxygen produced vaso-obliteration merely by neutralizing a vasoformative substance it is hard to understand why it should be so remarkably selec-

tive. It is a difficult question to investigate and we have no conclusive evidence either to deny or to support the possibility.

Thirdly, one must consider that the vessels may close through *external pressure.* An increase of intraocular pressure as a result of hyperoxia has been excluded, but could the process of vaso-obliteration be partly or wholly due to swelling of the cells surrounding the blood stream?

Although it is known that endothelial cells have the property of swelling when subjected to irritating stimuli (Krogh, 1929), we can probably exonerate them here as oxygen vaso-obliteration does not occur in growing vessels outside the retina. Swelling of the retinal tissue, however, remains a possibility, and, in considering one of the ways in which this might theoretically occur, we were led to some new and interesting findings. The hypothesis upon which our experiments were based was as follows.

Until recently it has been the orthodox view that the cells of the body are in osmotic equilibrium with their extracellular environment, that is, their contents are isotonic with the blood plasma. It would now appear that this is the exception rather than the rule (Bartley et al., 1954); in fact it has been estimated that the osmotic pressure of the cell fluids is normally 50 to 100 percent greater than that of the extracellular fluid (Robinson, 1950). If these findings are substantiated, the idea of the osmotic equilibrium being governed solely by the physical properties of cell membranes would no longer be tenable, and it would be necessary to postulate that the water content of the cell, and therefore the cell size, is dependent upon some dynamic process involving a continuous supply of energy.

That this concept of osmoregulation may be correct is suggested, for instance, by the ability of some cells of the renal tubules to maintain a normal internal environment despite the variable tonicity of the urine which bathes them. In fact, this consideration led Robinson (1950) to investigate the behaviour of tissue slices cut from the kidneys of normal adult rats. By measuring the oxygen consumption and the amount of water in the tissues under varying conditions, he found that respiration was more important than the osmotic pressure of the external media in determining the amount of water in the cells. When respiration was inhibited by cyanide, water passed into the cells. In short, the energy for the transport of water across the cell membrane was in this case derived from cell respiration. It is interesting to note in his experiments that the imbibition of water was a rapid process, being almost complete in two minutes and then maintained for several hours.

It has been suggested that this steady-state exchange depends on energy-driven "pumps" located in the mitochondria, as these structures when isolated from the cell can be shown to do osmotic work by moving substances against concentration gradients (Bartley et al., 1954). Although there is not complete agreement on the existence of these pumping mechanisms, it having been denied that the cell is significantly hypertonic, and claimed that cellular swelling is isosmotic in nature (Mudge, 1956), the cardinal point that tissue cells swell when placed in an environment where the metabolism is inhibited is not in question.

Some years ago Trowell (1946) showed that liver cells when subjected to anoxia increased in size due to the passage of water into the cells. This process he described as "intracellular edema," although in this instance he did not attribute it to osmotic absorption.

Returning now to the retina, it will be recalled that it has the highest rate of respiration of any tissue (Warburg, 1927) and a higher rate of glycolysis in air than most other tissues. As early as 1924 it had been suggested by Warburg et al., that the various layers of the retina possessed their own peculiar metabolism, some of the cells being responsible for the high glycolytic activity, while the others were almost completely

oxidative in character. This suggestion was later strongly supported by other workers (Sjöstrand, 1953; Strominger and Lowry, 1955; Lowry et al., 1956).

In both monkey and rabbit, it would appear that the rod and cone layer is predominantly concerned with oxidative metabolism while the inner layers, especially of avascular retinas, as in the rabbit, are predominantly glycolytic in activity. Now the immature retina, at a stage when oxygen vaso-obliteration may be obtained, differs from the mature retina in the important respect that retinal vascularization is still developing, so that it is reasonable to suppose that the metabolism of the inner layers of such a retina may be predominantly glycolytic. Indeed, we have already deduced from our experiments that the immature retina probably has a metabolism differing from that in the mature retina.

If such is the case it would follow that fluid exchanges through the walls of the inner retinal cells—and, therefore, the cell size—might be dependent upon energy derived, not from respiration, but from glycolysis. With these considerations in mind we argued that if swelling of the cells is an important factor in the obliteration of retinal vessels by oxygen, then the inhibition of glycolysis by known enzyme poisons might also lead to vaso-obliteration.

We are, therefore, investigating the action of sodium fluoride which is known to arrest glycolysis by inhibiting enolase through displacing magnesium from the enzyme, and it has been shown that this inhibition occurs particularly in retinal tissue (Dickens and Greville, 1932; Holmes, 1940; Kerly and Bourne, 1940; Lenti, 1940).

By directly observing the developing vessels in the retina of the kitten through a limbal window, we found that sodium fluoride in isotonic solution, when injected into the vitreous, produced vaso-obliteration in a few minutes and in the same order of vessel closure as that seen on exposure to hyperoxia. As in the case of oxygen, this effect is apparently confined to the vessels of the immature retina and experiments on the adult retina and on extraocular vessels have so far been negative.

The first change noted after introducing the fluoride was a remarkable engorgement of the veins, which, as in the oxygen effect, were the last to close. These observations appear inconsistent with a closure from external compression, for one would expect vessels with the lower pressure to close first. It was most interesting to find, however, that their engorgement is associated with a compression of the veins in the disc region which could well be due to an increased tension within the retina from intracellular edema (fig. 5). The vessels rapidly reopened when hypertonic solutions of salt or sucrose were injected into the vitreous, which supports the notion that vessel closure may be due to swelling of the cellular environment. An exactly similar result may be obtained with isotonic solutions of iodoacetic acid.

These experiments are still in their very early stages and are being reported in detail elsewhere (Ashton et al., 1957) but it is of interest to know that oxygen vaso-obliteration can be so closely mimicked by other drugs and it is tempting to believe that the two processes share a common mechanism. Although there is little evidence that this is so, I think we have some indication that oxygen vaso-obliteration, as seen in the immature retina, may be due, not to active vasoconstriction or to removal of a vasodilator, but to a passive closure from swelling of the retinal environment; a swelling which theoretically could result from the inhibition by oxygen of some enzyme system upon which glycolysis depends.

As far as I am aware, this concept is a new one, but I introduce it with the important reservation that at present we have practically no direct evidence that swelling actually occurs in the retinal tissue after fluoride or oxygen exposure. Nor have we yet shown that the hypothetical considera-

Fig. 5 (Ashton). Retina showing the fluoride effect on the retinal vessels in the disc region. The disc and hyaloid artery may be seen on the extreme left of the picture. Note that the optic nerve fibers stand out distinctly, the arteries and capillaries are largely obliterated, while the vein is markedly engorged and constricted as it enters the disc. (×94.)

tions which led us to devise these experiments, namely the inhibition of glycolysis with a breakdown in osmoregulation, are in fact those operating in the fluoride effect. However, if future work substantiates this concept, it will not only have considerably clarified the enigma of the action of oxygen on the immature retina, but it will have uncovered a pathologic process which I feel sure would be important in interpreting disease pictures in the retina.

2. Vasoproliferation

It will be recalled that when a kitten is returned to air after several days in high oxygen, the obliterated vessels are unable to re-open to any satisfactory extent, and new vessels then invade the retina and extend into the vitreous. Similar proliferations have been obtained by other workers in newborn mice, ratlings, kittens, and puppies (Patz et al., 1953; Patz, 1954; Gyllensten and Hellström, 1954). These workers, and others interested in the problem of retrolental fibroplasia, have sought to explain these vascular proliferations in terms of oxygen poisoning leading to inactivation of oxidative enzymes, particularly of succinic dehydrogenase; that is, they have postulated that the proliferations are caused by an anoxia which is histotoxic in type.

On the other hand, I have always believed that the vasoproliferative reaction results purely from obliteration of the vessels and is not in itself directly concerned with oxygen exposure. This distinction is

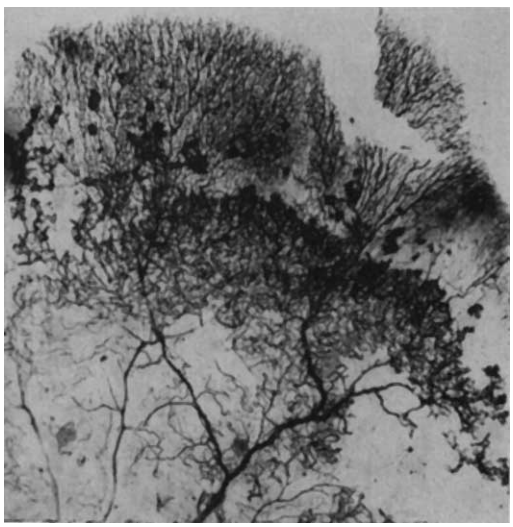

Fig. 6 (Ashton). Injected retina showing the type of vasoproliferation obtained in a more mature kitten when oxygen vaso-obliteration is only peripheral. The subsequent growth of vessels is similarly located. (×23.)

of some importance in understanding the general phenomenon of vasoproliferation in the eye, and, although the evidence is not yet conclusive one way or the other, my contention is supported by a number of facts.

First, as shown by our direct-observation experiments, the effect of oxygen is rapidly reversible at a stage when the vessels are still able to re-open; it becomes irreversible only when closure of the vessels has been maintained for so long that the vessel walls have become adherent or have been absorbed. In other words the action of oxygen appears to be only inhibitory and confined to the actual period of exposure. On this evidence it would appear doubtful whether oxygen at atmospheric pressure can give rise to enzyme-poisoning which persists on transfer to air. It will be recalled that in our experiments where kittens were allowed to survive for a year or two after total oxygen vaso-obliteration with reformation of the whole retinal vasculature, there was apparently no permanent impairment of vision although the vascular pattern was abnormal.

Secondly, vasoproliferation is always proportionate to the degree of vaso-obliteration and arises from those vessels immediately adjacent to the obliterated areas. Thus, in the youngest animals where obliteration is total, vasoproliferation recommences from the disc; in semimature animals where closure is partial, vessel growth occurs from the unobliterated vessels in the posterior fundus; and in more mature animals where obliteration is only peripheral, the subsequent vasoproliferation is similarly confined (fig. 6).

Thirdly, when irreversible vaso-obliteration is prevented, vasoproliferation does not occur, although the animal be exposed to the same concentration and period of hyperoxia as in the standard experiment. For instance, permanent closure of vessels can be prevented by administering anticoagulants which prevent the vessel walls adhering (not, incidentally, a very reliable method), or by re-opening the vessels periodically by giving the oxygen intermittently, that is by returning the animal to air for one hour after every period of five hours' exposure to oxygen. In both cases transfer to air does not produce vasoproliferation. Hence an essential factor determining the abnormal growth of vessels appears to be obliteration of the retinal vessels, and since they do not proliferate in oxygen but only on transfer to air, it follows that hypoxic conditions are also required.

Taking all these facts into consideration it is reasonable to conclude that the factor which stimulates the growth of vessels in the retina is formed in hypoxic tissue, and it is logical to speculate that it probably derives from the products of anaerobic metabolism. It is as though the mechanism of vessel-formation were especially designed to ensure the drainage of these products, and at the same time to replace the relatively wasteful process of anaerobic glycolysis by the more productive one of aerobic oxidation.

It might be expected that conditions of generalized anoxia, as result from low oxygen-tensions in the blood, from anemia or cardiac failure, could directly initiate retinal neovascularization. This is the mechanism

which has been advanced to explain those cases of retrolental fibroplasia which had not received supplemental oxygen. There is, however, little convincing experimental evidence to support this view. Kittens, ratlings, and newborn mice have been exposed to low ambient concentrations of oxygen for long periods (Ashton et al., 1954; Patz, 1955; Gyllensten and Hellström, 1955) but abnormal retinal vasoproliferations have not been produced. The important point here, I believe, is that although the necessary degree of hypoxia may be produced in the tissues, the efficiency of the circulation itself is not impaired, so that the vasoformative factor rapidly drains away and fails to accumulate to an active level.

From studies on the immature retina there are thus three basic requirements for the stimulation of vessel growth, and each of these is essential:

1. The presence of living cells to ensure an active metabolism.

2. A low oxygen tension to promote anaerobic metabolism.

3. A poor venous drainage to permit the accumulation of anaerobic metabolites, wherein the vasoformative factor probably lies.

In the mature retina, however, it is not easy to arrive at such clear-cut conclusions, because as already deduced the metabolic processes apparently differ. In fact, judging by the rapidity with which blindness follows occlusion of the central retinal artery the inner layers of the retina at least must have become largely dependent upon aerobic metabolism. Theoretically it would therefore follow that the vasoformative factor should be less readily elaborated in the mature than in the immature retina. That this is true, at least in certain circumstances, can be demonstrated simply by detaching the retina in experimental animals.

In the immature retina this procedure results in a profuse proliferation of vessels both outward to form a plexus of vessels on the under surface of the retina and inward to form vascular tufts in the vitreous.

In the mature animal detachment is not followed by new-vessel formation. It is, therefore, clear that the vasoformative stimulus is much less readily evoked in the adult animal.

Vasoproliferation in ocular disease

Nevertheless, as is well known, new-vessel proliferations are common features of several retinal diseases, so that the facility for elaborating the stimulus cannot be entirely lost, and it may be shown that the same basic requirements are as essential for vascular growth in the mature as in the immature retina. In contrast to the immature retina, however, *intraretinal* neovascularization in the mature retina is a rarity, although new-channel formation through obliteration and dilatation of pre-existing capillaries is common and has been misinterpreted as neovascularization. The vast majority of new-vessel formations arising from the adult retina extend almost immediately into the vitreous, either as delicate fronds of new vessels or in association with dense fibrous tissue.

In human eye disease, Klien (1938) based her classification of retinitis proliferans upon these two types. In Type I, exudations or hemorrhages into the vitreous of inflammatory or traumatic origin are followed by connective tissue proliferation and lastly by vascular ingrowth. Here it may be suggested that the vasoformative factor arises from the living cells carried into the vitreous, namely fibroblasts, which proliferating in an avascular tissue give rise to the necessary accumulation of anaerobic metabolites. Indeed, it is clear from histologic studies that the vascular component in this type of retinitis proliferans is proportional to the cellular content, and where the exudate is predominantly fibrinous there may be only a few tenuous vessels and sometimes even none.

In Klien's Type II retinitis proliferans there is a primary formation of new vessels with a secondary production of delicate con-

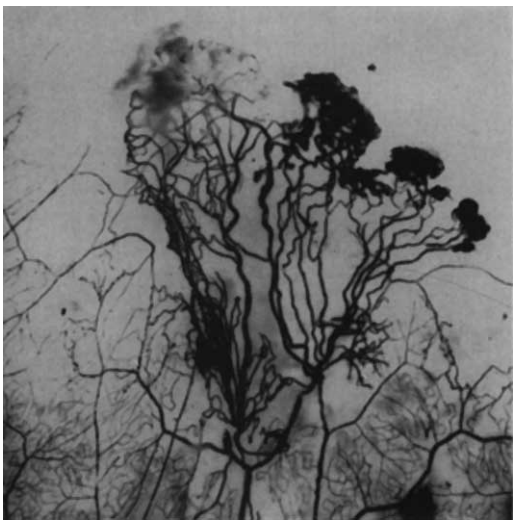

Fig. 7 (Ashton). Injected human retina from a case of Eales's disease showing that the intravitreal vasoproliferations are associated with vaso-obliteration in the underlying retina. (×13.)

nective tissue. This is the type of proliferating retinitis seen typically in diabetes and occlusion of the central retinal vein, although Type I may also occur. In pathologic specimens I have found that these intravitreal proliferations are always associated with underlying areas in the retina of obliterated capillaries or obstructed veins (fig. 7). Here it may be suggested that the vasoformative factor is elaborated in the hypoxic retinal tissue, and, failing to drain away, seeps into the vitreous where it reaches a concentration sufficient to stimulate the vessels to grow inward. They are exactly comparable to the glomerular tufts seen in experimental and natural retrolental fibroplasia and, similarly, may disappear when the stimulus has been expended or removed.

The concept of a preformed factor diffusing through the vitreous is applicable also to the problem of neovascularization of the iris. It is certainly not without significance that new vessels on the iris so frequently follow the development of retinal disease, wherein the pattern of vascular involvement provides the conditions for production of the vasoformative factor. Examples are: diabetic retinopathy, venous occlusion, Eales's disease, retinal detachment, and retrolental fibroplasia. In all these diseases the vasoformative factor may be elaborated either in the hypoxic retina or by fibroblasts in the vitreous, and be carried forward to stimulate the growth of vessels anteriorly.

In central venous occlusion, Redmond Smith (1954) has made the interesting observation that neovascularization at the disc tends to prevent vascularization at the filtration angles, which suggests that if the vasoformative factor is drained away by the intravitreal vessels, it cannot accumulate in sufficient quantity to reach the vessels in the anterior chamber.

These arguments could be even further elaborated, but sufficient examples have been quoted to justify the hope that the time may not be far distant when the mechanism of vaso-obliteration will be understood and the nature of the vasoformative factor identified. It is no exaggeration to prophesy that this knowledge should certainly provide new approaches in interpretation, and possibly new lines in treatment, of vascular diseases of the eye.

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BIOGRAPHICAL DATA

Norman Ashton, M.R.C.P., M.R.C.S.

Norman Ashton was born in London, England, on September 11, 1913. His adolescence was spent in the search for an outlet for his quite unusually varied talents. Eventually—and fortunately for ophthalmology—in 1933 he entered King's College, London, as a medical student and received his clinical training in the Westminster Hospital. As a medical student he is chiefly remembered for his artistic tendencies; and today the walls of the school are hung with a series of cartoons of his teachers of such merit and so delightfully scurrilous that their preservation was deemed necessary; today his paintings in oils are seen on the walls of his unique house in the 13th century Cloisters of Westminster Abbey as well as in the Institute of Ophthalmology, and are regularly exhibited in the art galleries of London. Moreover, during his graduate days he wrote—and the writing included the lyrics and the music—the annual pantomime that formed the social culmination of each academic year. Incidentally, or so it seemed, he graduated in medicine; and thereafter, apparently being found indispensible to the life of the hospital and its medical community, he completed an elaborate graduate training, acting for successive periods as an intern in the casualty department, in surgery and medicine, as well as in the departments of pediatrics, dermatology, and venereology, to become eventually the Senior Resident Medical Officer of the hospital, and finally, in 1939, a pathologist.

The Second World War then started and, in 1941, when England was expecting invasion, he went to that dangerous corner, the southeast coast of Kent, as blood-transfusion officer and pathologist; but as the