Intertissue vascular relationships in the fundus of the eye

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This report describes the vascular relationships between vitreous and retina, between retina and choroid, and between choroid and sclera, and indicates their importance in the understanding of certain pathological and clinical processes.

If one includes the developing as well as the definitive eye, there is a vascular or nutritional relationship between the vitreous and the retina, between the retina and the choroid, and between the choroid and the sclera, which is of some importance in the understanding of certain pathological processes. It is the purpose of this report to describe these vascular relationships and to indicate briefly the pathological and clinical processes which may result from their disturbance. The latter will be reported more fully elsewhere.1

Vitreous and retina

In the developing eye the primary vitreous can be seen in the 6.5 mm. stage as a series of fibers apparently originating essentially from the retina and stretching between it and the posterior lens capsule. This shortly thereafter becomes vascularized by the hyaloid system which, besides filling the space between the retina and the lens, forms a distinct vascular membrane around the latter's surface. The involution of the primary vitreous begins at about the 60 mm. stage and is well advanced at the 100 mm. stage, when from the hyaloid artery at the optic disc begins the budding of vessels which pass into the retina (Fig. 1).

Posterior persistent hyperplastic primary vitreous

This, which probably represents a lesser degree of retinal fold, consists of persisting attachment of the primary vitreous fibers to the retina at one or more places, with resulting progressive changes in the retina such as retinal holes and elevation. Weve2 and others indicated that it could be hereditary, transmitted as a recessive trait, possibly sex linked, as the majority appear in males. This condition is described here as posterior persistent hyperplastic primary vitreous, because developmentally it is a posterior manifestation of persistent hyperplastic primary vitreous as described by Reese,3 and clinically both manifestations may appear in the same eye or in the same patient, as will be shown. Fig. 2 illustrates this condition when the posterior manifestation alone is present.

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From theoretical considerations it could be assumed that some cases of persistent hyperplastic primary vitreous involving the fibrovascular sheath of the lens as described by Reese would also show these changes which we have described as posterior persistent hyperplastic primary vitreous. Clinically, of course, it is not usually possible to see this because of the anterior opacity. The observation of a family in which a member had anterior hyperplastic primary vitreous, in one eye, while two other members, a brother and the mother's brother, had bilateral posterior hyperplastic primary vitreous, clinically proves this possibility. Confirmation of this by pathological studies is given by Manschott, who had the opportunity to examine the globe histologically in 14 cases of persistent hyperplastic primary vitreous. In all of these cases he found evidence of fibers or bands of the primary vitreous remaining attached to the retina (Fig. 3). In some cases the retina had already been detached by the pull of the adhesion.
Fig. 3. Sections of eyes with persistent hyperplastic primary vitreous (anterior). A, Tissue extending between retina and retrolental membrane. B, Vitreal membrane attached to retina. (From Manschot, W. A.: Arch. Ophth. 59: 188, 1958.)

It seems possible that the increased oxygen content in the vitreous made available by the accession of new vessels into the retina at the 100 mm. stage is of significance with regard to the normal involution of the hyaloid system. This possibility is supported by the following facts. In cases of severe posterior persistent primary vitreous there is frequently an obvious diminution of retinal vessels. At today's session Dr. Patz has shown that if the newborn mouse is exposed to 85 per cent oxygen, with consequent narrowing or obliteration of the retinal vessels, there is a persistence of the hyaloid system. It is not suggested that oxygen tension is the primary factor in the involution of the primary vitreous; it appears to be an auxiliary factor. The vitreous and retina may be considered to be a single morphogenetic area in which the inductor evoking involution of the vitreous (or the lack of that evoking its evolution) has an activity parallel to that inducing the development of the retina. The resulting fall and rise of cellular activity in the vitreous and retina result in the removal or growth of vessels in these tissues, respectively. It is at what may be described as a tertiary level that oxygen concentration may play its supporting interlinking role. The level is described as tertiary on the basis that inductor activity and cellular growth are the primary and secondary levels, respectively.

Vitreal new vessels

These grow from the retinal vessels and are present usually only in such conditions as central venous thrombosis, diabetic retinopathy, and Eale's disease. All of these diseases have three characteristics in common: there is new vessel growth within the retina, there is a degree of venous obstruction, and the capillary disturbance is so widespread as to suggest the probability of a low oxygen content in the vitreous. If it can be assumed that intraretinal new vessel formation is the result of the accumulation in the retina of a substance that promotes the growth of vessels, it is not difficult to assume that this substance can diffuse into the vitreous and from there attract the new vessels. The oxygen tension in the normal vitreous of the cat is 53 mm. Hg, but it can be reduced to 28 mm. Hg should the oxygen in the ambient air be reduced to 15 per cent. The vitreal oxygen is derived from the retinal capillaries, and it is easy to understand that this oxygen will be reduced should the retinal capillaries be grossly affected, as they are in the diseases mentioned. The vitreal hypoxia may be a further factor in permitting the growth of vessels from the retina into the vitreous. The degree of hypoxia and the amount of vessel growth-stimulating factor are probably critical, because one does not find vitreous vessels if the venous obstruction...
is confined to a branch of the central retinal vein. The subject of vitreal new vessels has been thoroughly discussed by Ashton.  

**Choroid and retina**

In the definitive human eye the choriocapillaris is responsible for the nutritional supply of the retina in the following situations: (1) the outer part of the retina consisting of the rod and cone layer, the outer nuclear layer, and a portion of the outer molecular layer; (2) the foveal area where there are no retinal vessels, (3) the periphery of the retina where there are no retinal vessels (Fig. 4).

This interplay of choroidal and retinal circulation is peculiar to certain mammals. In the porcupine and the Australian fruit bat, for example, the choroid supplies practically all the nutrition; in the eel there is no choroid and the retina is self sufficient.

It would appear that the choriocapillaris is capable of supplying the nutritional needs of the outer retina to a distance of about 120 μ. Bruch's membrane, besides acting as a semipermeable membrane controlling this process, also physically prevents the accession of new vessels into the retina from the choroid as would be expected in other circumstances should the retina require extra nutrition. On the other hand, if the retina is separated from the choroid, new vessels may grow deeply into the retina or below it.

The circle of Zinn supplies the choroidal system, sends branches to the central artery in the optic nerve referred to by Wybar as uveoretinal vessels (Fig. 5), and in 20 per cent of eyes sends a branch or branches directly into the retina called cilioretinal vessels.

**Closure of retinal artery**

When there is a closure of the central retinal artery, it might be expected that the choriocapillaris would respond by attempting to increase its retinal responsibilities. This was shown by Neumann. Closure of a branch of the retinal artery resulted in a dilatation of the choroidal vessels strictly confined to the sector of the fundus affected (Fig. 6).

It is not possible to know to what extent this reaction succeeds in helping
visual recovery in such cases. It is not certain to what extent the choriocapillaris can be therapeutically helped in its nutritional effort. The problem is to find a means whereby the nutritional responsi-

bilities can be extended from 120 to 300 μ. The diffusion of oxygen into a viable tissue is limited by utilization to a definite distance, and the distance to the inner retina layers may be too great even with extremely high oxygen tensions. The retina has a remarkably high rate of oxygen utilization—higher than any other tissue.10 It would appear that experimental evidence must be obtained regarding the distance that oxygen under circumstances of increased pressure can be passed into the retina before consideration is given to time required or the importance of other deficiencies in clinical trials. The experimental setup would involve the placing of an oxygen electrode progressively deeper from the internal limiting membrane of an appropriate experimental animal under normal atmospheric and hyperbaric conditions.

Closure of retinal vein

This is a problem similar to that indicated in closure of the retinal artery. There is both clinical and histological evidence that the choroidal vessels may react to closure of the retinal vein by sending new vessels into the retina, a process that implies some local destruction of Bruch’s membrane (Fig. 7).11,12

Fig. 5. Anastomosis between central retinal artery and short posterior ciliary arteries at lamina cribrosa. (From Wybar, K. C.: Brit. J. Ophth. 40: 65, 1956.)

Fig. 6. Case of branch occlusion of retinal artery showing at (2) affected edematous area of retina with gross dilatation of the vessels of the adjacent choroid and at (1) normal retina and choroid, the separation between them being an artifact. (From Neumann, E.: Brit. J. Ophth. 46: 357, 1962.)
Macular disease

The problem of intertissue vascular pathology is in no part of the eye more clearly exemplified than at the fovea. The retina here is about 100 μ in thickness, and obtains its nutrition partly from the choriocapillaris and partly from the retinal capillaries surrounding the fovea which itself is free from capillaries. The functions of these choroidal and retinal capillaries are obviously most delicately balanced and compensatory in order to maintain the nutrition of the important foveal cells. There are certain conditions in which this balance is upset. From theoretical considerations the initial lesion in macular disease may be in the choriocapillaris, the capillary limbus around the fovea, or in the neural and supporting tissue of the macula, as in disciform degeneration.

Senility. In senility there may be intrusion of capillaries from the foveal vascular limbus into the normally capillary-free zone. This presumably represents an effort to supplant a diminished nutritional supply from the choriocapillaris (Fig. 8).

High myopia. In this condition there is frequently choroidal atrophy, especially in the region of the macula. With the loss or partial loss of nutrition from the choroid, new retinal vessels may invade the fovea. Rupture of these new vessels may give rise to the dreaded foveal hemorrhage of myopia. The condition is probably similar to the capillary intrusion already noted above as found in senility, where, too, foveal hemorrhage, although smaller and more superficial, may occur.

Disciform degeneration. In this condition degenerative processes take place in the deeper layers of the retina, probably the result of a disturbance of Bruch's membrane. The vascular response is from both the choroidal and retinal circulation,
the former being shown in Fig. 9. There is a local dilatation of all the choroidal vessels (at first considered to be an angioma in this case) and a break in the membrane of Bruch has allowed the passage of a new vessel, attracted to the grossly disturbed retina. The retinal vascular response is shown clinically when a vessel can be seen passing backward out of sight, obviously on its way to the choroidal system of vessels.

**Senile macular disease.** In this condition there is apparently essentially a defect of the retinal capillaries around the fovea which can be observed clinically and histologically (Fig. 10). The choriocapillaris in published reports is apparently anatomically normal, although this does not preclude a physiological incompetence associated with age.

The vascular relationship of these conditions to one another is schematically indicated in Fig. 11. The delicate balance of retinal and choroidal vascular function may be upset by choroidal atrophy, age, and sclerosis. The extranutritional effort required is expressed by new vessel formation. This is confined to the retinal system unless there is a break in the membrane of Bruch. It would appear that a choriocapillaris deficiency can be more adequately met by a retinal compensation than can a retinal deficiency be met by a choroidal compensation, the latter being dependent on the membrane of Bruch.

**Choroid and sclera**

The *developing eye*. Ida Mann does not mention any interrelationship between the developing choroid and sclera. The following observations by Berson suggest that the nutrition of the developing sclera is at least partially dependent on the choroidal vascular system. Four groups, each containing four adult female rats and one adult male rat, were placed in four cages. Each day the females were tested by a vaginal smear in order to check for pregnancy. In this way it was possible to obtain a series of rat fetuses in

![Fig. 10. Flat trypan preparation of the retina of a patient clinically observed to have senile macular degeneration in an advanced stage. The foveal area shows considerable enlargement, capillary acellularity, and numerous intercapillary strands. (From Kornzweig, A. L., Elizsoph, I., and Feldstein, M.: Bull. New York Acad. Med. 40: 116, 1964, published by The New York Academy of Medicine, New York, N. Y.)](image-url)

![Fig. 11. Scheme showing normal macula with indications of probable sites of vascular changes in senility, myopia, senile macular degeneration, and disciform degeneration. The choriocapillaris is indicated by a row of circles, while the perifoveal vascular limbus is indicated by two vascular cross sections.](image-url)
known stages of development. There were thus available sections of fetal eyes from the 14th to the 21st day, and of eyes from 1 to 20 days after birth. The fetal and newborn eyes were stained with eosin and azan. As the findings have been published by Berson, it is necessary here only to summarize them.

14th day: No evidence of choroid or sclera.

15th day: Sinusoids representing early chorio-capillaris at equator only.

17th day: Mesenchymal cell condensation opposite the sinusoids. These are the earliest scleral cells.

19th day: These cells now spindle shaped with axis parallel to choroid (Fig. 12).

20th day: With azan a blue staining is clearly seen in the elongated cells which are now becoming arranged as lamellae.

21st day: The sclera is more demarcated as a separate tissue.

1st day after birth: Choroidal vessels not limited to a single layer.

The scleral development then begins at the equator from which it progresses anteriorly and posteriorly. The initial stage and each successive one are locally preceded by the formation of choroidal sinusoids and capillaries.

The definitive eye. In view of these findings Berman and Zauberman,16 in a report to be published shortly, performed a series of experiments in order to determine whether the adult sclera was at all dependent on the choroid for its nutrition. On the basis of preliminary experiments with rabbits, it was found that intravenously injected radioactive sulfate was taken very rapidly into the sclera. In five minutes, considerable radioactivity was detected in the sclera, very little of which due to sulfate was incorporated into mucopolysaccharides. Using cats it was found that the choroid could be detached from the sclera by injecting silicone between both tissues, the other eye remaining as a control. Radioactive sulfate was then administered and after five minutes the animal was killed and both eyes enucleated. Radioactivity was measured in pieces of sclera from the detached and nondetached areas of the eye operated upon and from the intact eye. This radioactivity is a measure of the total amount of free sulfate in the sclera. Bound sulfate accounted for less than 5 per cent of the total radioactivity and was considered negligible. The radioactivity in the eyes operated upon and not operated upon was nearly the same, and there was very little difference in the radioactivity found in the detached as compared to the intact portions of the operated eye. It would appear that in the definitive eye of the cat the choroid does not contribute to the nutrition of the sclera. If one is permitted to combine the results in the developing eye of the rat and the definitive eye of the cat as described above, it would appear that a temporary dependence during development is replaced by an independent local vascular supply similar to the temporary dependence of the retina during development on the choroid.

REFERENCES


References not cited in text
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