Some observations about retinal vascular-neuronal interrelationships

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SUMMARY The relationship between the intraretinal vessels of the human fundus and the surrounding neuronal tissue is discussed with regard to various disease states. Present evidence suggests that primary retinal neuronal death does not lead to secondary retinal capillary death. Primary retinal capillary non-perfusion generally leads to concomitant retinal neuronal degeneration, but if the occlusion takes place over a long period of time the surrounding neural retina may survive. It is suggested that many retinal degenerative changes, including retinal detachment, are due to primary retinal vascular alterations.

Just as the present often neglects the past, so it is likely that the future will neglect the present. Let me record for those who some day chance to peruse these words that their knowledge of the retinal circulation is in good part due to the bedrock of scientific information initiated and developed by Norman Ashton and his students. Those of us fortunate enough to work with 'The Prof' will scarce forget the wisdom and industry which he brought to the task of uncovering our ignorance of the retinal blood vessels and their relationship with the surrounding tissue. Remember, as you so glibly use the terms blood-retinal barrier, retinal ischaemia, retinal neovascularisation, that in good part the struggle for knowledge was directed from a room on the third floor of the Institute of Ophthalmology in Judd Street—Norman Ashton's room.

In this presentation I should like to explore some facets of the interrelationship of the neural retina and its circulation.

What do we know about the relationship of the retinal blood vessels and the surrounding neural elements? We assume that the retinal vessels exist to nourish the surrounding tissue and to remove waste products. We should not forget that many animals with excellent vision have no vessels within their retina. We know that the retinal capillary wall is impermeable to certain substances which other capillaries in the body allow to percolate into surrounding tissue. This is the blood-retinal barrier akin to the blood-brain barrier (Ashton, 1965;

Cunha-Vaz, 1976). A variety of transport mechanisms exist to allow necessary amino acids, carbohydrates, and lipids to traverse the retinal capillary endothelium, but the subject has not been fully explored (Futerman, 1976; Graymore, 1970). As an example, for glucose there seems to be a selective transport system which allows D- but not L-glucose to enter the retina (Dollery *et al.*, 1971).

We know that retinal ischaemia causes profound alterations in the surrounding neural tissue (Ashton *et al.*, 1966). Recently, we have learned that the initial alteration is in a process known as axoplasmic flow.

Unlike most other vessels in the body, those of the retina control blood flow locally without sympathetic control, but rather by an internal mechanism known as autoregulation—we don't know the exact way in which this works. We know much about retinal vessels, a good deal more than was known 25 years ago and undoubtedly a good deal less than will be known 25 years hence. Let us now explore areas where information is scant or where the questions that are the first step to learning have rarely been asked.

What do you imagine happens to the retinal circulation when the surrounding retinal neurons die? Here we consider only those situations where the retinal neuronal death is *not* secondary to prior retinal vascular embarrassment or death—situations such as inner retinal degeneration secondary to optic nerve disease or primary affections such as the various gangliosidoses. Most ophthalmologists or ophthalmic pathologists that I have queried about the subject either have no idea or feel that,

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if the neurons are dead, then there should be concomitant vascular death. It turns out that in man, though the inner retinal layers can totally disappear, the retinal circulation may remain physiologically (as determined by fluorescein angiography) and anatomically intact (Henkind *et al.*, 1970; Kurz *et al.*, 1971). Similarly, in animal experiments where the optic nerve was transected and the inner retina degenerated, the retinal circulation remained 'normal' (Henkind *et al.*, 1975). Recently, similar findings have been noted for the vasculature of the optic nerve head in experimental animals (Henkind *et al.*, 1977; Quigley and Anderson, 1977). From the limited data at present available, and because there is lack of contrary evidence, I conclude that *retinal vascular degeneration does not necessarily follow retinal neural degeneration*. The same situation may also apply to the brain.

If the above is correct, then the state of the retinal neural tissue cannot be judged by finding a normal fluorescein angiogram, nor can the presence of an apparently normal retinal 'digest' preparation tell us anything about the past health of the retina. It is interesting that the blood-retinal barrier maintains its integrity even in the absence of inner retinal neural structures (i.e., the presence of a normal fluorescein angiogram years after complete blindness in patients with ischaemic optic atrophy secondary to giant cell arteritis). On the other hand new retinal vessels developing from the pre-existing retinal vascular bed are characterised by the absence of a blood-retinal barrier (Henkind and Wise, 1974). Perhaps, as suggested by experimental work dealing with the development of the blood-brain barrier (Svengaard *et al.*, 1975), normal retinal neuronal tissue is necessary for the development of the blood-retinal barrier but not for its maintenance once it has developed.

At this point you may ask, So what? So far everything considered has almost no clinical importance. Who cares that *capillaries of the central nervous system may survive after neuronal death*? One can't bring the neurons back, and for all practical purposes the tissue is dead. Perhaps some day we will learn the secret of regeneration of central nervous system neurons. After all, our amphibian ancestors can do this with seeming ease. Is it not reassuring that a blood supply will be there waiting to provide nutrition?

What is the meaning of dead retinal vessels? In reality I am less concerned with what happens to vessels when neurons die than with the converse situation in which one finds absence of capillaries or other small vessels in the retina by fluorescein angiography or acellular capillaries on retinal digestion. Are such vascular alterations primary or

secondary? The answer seems to be primary, for we don't have good examples of simple secondary retinal vascular degeneration unless there has been antecedent severe retinal disease such as infection or inflammation. Possibly there is secondary retinal vessel degeneration in some cases of retinitis pigmentosa and related disorders. If true, this has important implications in the study of human disease. For example, the question was recently raised, 'Which is primarily involved in Leber disease, the vascular system or the nerve fibres?' (Nikoskelainen *et al.*, 1977). For in Leber's hereditary optic atrophy both neuronal damage and retinal vascular abnormalities, including capillary loss, were noted. I feel that the capillary alterations are a primary event, for neuronal changes do not generally lead to secondary vascular damage (or do they?).

That mysterious process called ageing is another subject which should be considered with regard to the previous statements. Is there any evidence that the neural retina (or the nervous tissue of the brain) degenerates with age? Too little is known, but I'm unaware of any degenerative alterations in such tissue that can be called age specific—*except* for those that are associated with primary vascular changes. Cogan (1963) noted that in the aged he found the capillaries of the retinal periphery had become acellular and, presumably, functionless. My hypothesis is that such vascular changes are primary and that they are the cause of the peripheral retinal conditions so commonly seen with increasing age. Significantly, most retinal tears occur in retinal areas where the retinal capillary bed is absent; the absence of capillaries around retinal tears is a primary and not a secondary event. Gass (1972) wrote, 'Alterations in the retinal vascular pattern may be evident in the immediate vicinity of the hole as well as in distant areas of retinal degeneration—particularly lattice degeneration, where much of the capillary bed is occluded'. I shall go out on a limb and predict that the future will show that the vitreous has been much overplayed as a key factor in the development of retinal degeneration and detachments. Rather, a diseased retinal circulation will prove to be the culprit, with vitreous changes occurring simply as a secondary phenomenon. Straatsma and Allen (1960) have postulated as much for lattice retinal degeneration, but I would extend this to many other retinal degenerative changes—students, beware that this concept is opposite to much current speculation about retinal detachments; see Tolentino *et al.* (1976).

Let us consider the case of glaucoma. Here I speak of that broad constellation of diseases in which the intraocular pressure is apparently too high for proper function of the retinal neurons,

which first are functionally embarrassed (reversible scotomas) and later die (absolute field defects). What is the initial pathology? Theories of primary neural, primary glial, or primary vascular alterations have all been considered in the pathogenesis of visual field loss in the glaucomas (Henkind, 1976). As postulated above, if one finds vascular alterations in the retina and/or the optic nerve head, they are unlikely to be secondary to neuronal or glial loss. Indeed one finds absence of capillaries both in the retina and in the optic nerve head in glaucoma, and I think this absence signifies that the primary pathogenetic feature of glaucoma damage is loss of capillaries with secondary neural and glial degeneration.

Can retinal blood vessels die and the retina survive?

Are there any human situations where the retinal blood vessels disappear or lose their function and yet the retinal neurons maintain their function? In acute retinal arteriolar occlusion there surely is rapid death of the surrounding neural elements. In vein occlusion there can be a marked abnormality of vascular perfusion, but as long as the capillary bed maintains its integrity the retina will continue to function. In diabetes of long standing we occasionally find, on fluorescein angiography and later by retinal digestion, substantial areas of posterior pole capillary non-perfusion in which the patient is unaware of a field defect, though defects may be demonstrated by static perimetry, and in which vision remains good. Perhaps in some instances where the retinal capillaries close down slowly over months or years, the surrounding retinal tissue can maintain its viability either by an anaerobic metabolic pathway or because of sufficient nutriment and gas exchange from the underlying choroid or from surrounding patent retinal vessels. If this proves correct, this is obviously an argument in favour of those who might deny the role of primary retinal vascular degeneration as a cause of retinal neuronal damage in conditions such as glaucoma and retinal hole formation—for these, too, are chronic situations.

All we may say is that, at least in certain situations, retinal capillary non-perfusion or closure does not always lead to death of surrounding retinal neural and glial tissue.

Discussion

I at present believe that the retinal circulation is responsible for much of the mischief that befalls our retina. I was taught that every day perhaps millions of the neurons of my central nervous system degenerate because of an inexorable process of neuronal ageing and that eventually my brain will atrophy. Perhaps it already has. However, from my

observations upon the retina, as fair a piece of central nervous tissue as exists anywhere, central nervous system tissue does not simply age and atrophy. The weakest link in our biological system is our blood vessels. They are subjected to tremendous stresses and strains nearly every living moment. They carry all sorts of metabolically active products and they are conduits for our internally produced waste products. It is no wonder that they degenerate. However, they probably degenerate on their own and perhaps independent of alterations in the surrounding tissue, at least in the central nervous system.

Were it not an invited contribution, this article would possibly have received less tolerant editorial scrutiny and perhaps have been found lacking in 'fact'. However, as one reasonably well versed in the past literature, I have found much substantial fact now reduced to mere fiction. Hopefully, this contribution will lead one to seek the truth. For example, would it not be worthwhile examining the fundi of aged animals to see what retinal vascular changes occur and to see if one could correlate them with neuronal alterations? Certainly in primates one should be able to examine the interrelationship between vitreous and retinal vascular changes. What happens to the vitreous in patients with complete central retinal artery occlusion? The best I can hope for is that some readers will open their minds to consider possibilities hitherto hidden.

Conclusions

Retinal neuronal death does not lead, a priori, to retinal capillary death. Where one finds retinal capillary non-perfusion or acellular capillaries, one generally finds concomitant retinal neural degeneration. Acute retinal arteriolar occlusion almost always leads to retinal neuronal degeneration. Slow retinal capillary occlusion, taking months or years, as in diabetes mellitus, may not necessarily lead to destruction of surrounding retinal neural tissue, though it may lead to neuronal dysfunction. Retinal degenerative changes, including most instances of retinal detachment, are due to underlying, primary retinal vascular alteration.

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