Editorial: The retinal cotton-wool spot

The retinal cotton-wool spot has for many years excited the interest of ophthalmologists and histopathologists alike, and together they have defined through decades of careful work its clinical features, its associated diseases, and its structure and ultrastructure and have sought to explain its pathogenesis.

Familiar to generations of students of ophthalmology, the cytoid body has been the structure of dominant interest in the histology of cotton-wool spots, and indeed it can now be seen that the elucidation of the ultrastructure of this body, a century after its first description, was the turning point from the period of purely descriptive morphology to the more dynamic concepts of today.

Cytoid bodies were first described by Heymann in 1856 (in collaboration with Zenker in a case of Bright’s disease) and were thought to be degenerate ganglion cells, a view with which Virchow (1856) agreed. Müller (1858), however, claimed that they were swollen varicose nerve fibres, and this was subsequently proved by Leber (1915); so that over 60 years ago it was suspected that varicose nerve fibres were basic components of the cotton-wool spot. Unfortunately, subsequent work tended to confuse rather than clarify this issue, it being suggested that cytoid bodies were ‘moulded exudates’ or ‘non-specific deposits of acellular origin’, the outer zone being precipitated ground substance and the inner zone fibrin or fibrinoid material. A further suggestion was that they represented glial degeneration (Verhoeff, 1921).

A return to the correct line of thought, however, was provided by Wolter (1959) when by silver staining of the retina he again showed cytoid bodies as terminal swellings of interrupted nerve fibres, and he pointed out their location on the distal stump in connection with the ganglion cell, whereas the proximal axon soon became atrophic. He also emphasised that the damage causing the interruption may be of any kind—a cut, compression, or ischaemia, for example. This was soon followed by a study of the pathology of cotton-wool spots and cytoid bodies in hypertensive retinopathy (Ashton and Harry, 1963), wherein it was established that the cotton-wool spot was causally related to focal ischaemia from arteriolar occlusion. The presence of localised axonal swellings in the affected zone was demonstrated and cytoid bodies proved to be sited at terminal axonal bulbs, which, in agreement with Wolter (1959), were thought to correspond to the bulbs of injured nerve fibres as described by Cajal (1913), who believed them to represent a combined process of degeneration and regeneration.

Further advances were made by Ashton and Harry (1963), who showed for the first time that the swollen nerve fibre of the cotton-wool spot contained aggregations of mitochondria, dense bodies, vesicles, and granules and that the fully formed cytoid body additionally contained a ‘pseudonucleus’ consisting of an electron-dense mass of ill-defined particles, probably deriving from degenerate elements in the axonal bulb. The nature of the cytoid body now seemed clear, but the pathogenesis of the cotton-wool spot itself was still obscure, although focal ischaemia was almost certainly involved.

It was then found that cotton-wool spots could be produced experimentally by emboli, by injecting either latex spheres (Gay et al., 1964) or glass ballotini (Ashton and Henkind, 1965) into the carotid artery. These findings led to an extensive clinicopathological study in which cotton-wool spots were produced in the pig’s retina by similar injections of glass ballotini, thus providing perfect experimental conditions for correlating the clinical evolution of the lesions with their ultrastructural changes as seen in suitably fixed material (Dollery et al., 1966; Shakib and Ashton, 1966). Their crucial finding in the present context was that the injured axons in the ischaemic area rapidly became swollen, and after a few hours those swollen axons at the periphery of the lesion became packed with mitochondria, dense bodies, and membranous whorls; a break then occurred in the axon, and the distal stump attached to the ganglion cell formed a bulb-like swelling (‘torpedo’ formation) which developed into a cytoid body, while the proximal fibre atrophied. The swollen axons in the centre of the lesion did not develop this aggregation of organelles, only those axons at its periphery. These authors concluded that axons from irreparably injured ganglion cells within the ischaemic zone underwent complete degeneration, whereas axons of unaffected or surviving ganglion cells developed the ‘torpedoes’.

The fundamental question arose as to the origin of the massive aggregates of mitochondria and other organelles within the terminal axonal swellings, and it seemed likely that proliferation beyond the normal turnover of organelles had taken place. It was well established at that time that mitochondria, for instance, can replicate (De Robertis and Bleichmar, 1962), but whether they could proliferate...
locally at the axon terminal was not clear. Shakib and Ashton (1966) considered axonal flow as a possible explanation of the organelle aggregation, although such an entity in the retinal axons had still to be generally recognised (Taylor and Weis, 1965, in mouse; Rahmann, 1968; McEwen and Grafstein, 1968; Elam and Agranoff, 1971a, b, in goldfish; Hendrickson, 1969, in the monkey; Cuenod and Schonbach, 1971, in the pigeon; and Karlsson and Sjöstrand, 1968, in the rabbit).

There were, however, reports of similar axonal reactions in crush injuries of the sciatic nerve of guinea-pigs by Webster (1962), who suggested that the accumulations arose through migration and proliferation of the pre-existing mitochondria, and in transected spinal cords of rats by Schlote (1964), who concluded that they were 'formed at the place where they are found and do not represent the result of damming the axoplasm or migration of organelles only'. On the other hand Friede (1964) believed that the accumulation of substances in an axon swelling did not inherently indicate a changed rate of production by the nerve cell and could result from a confined local shift of axoplasm. It had also been known for some years that organelle flow within axons was bidirectional (Hughes, 1953; Miani, 1964; Lasek, 1967), and Zelena (1968), in demonstrating this in an isolated segment of sciatic nerve, concluded that these particles shifted towards the fibre ends and were deposited there, although he could not exclude a local proliferation of mitochondria by division or segmentation. Shakib and Ashton (1966) interpreted their own findings as more in favour of a proliferation of organelles within the axonal bulb, but in a later paper it was further suggested that organelles of the ganglion cells might migrate into the axonal swellings and later proliferate at these sites (Ashton, 1970). Thus the main unsolved question remaining at that time was not the nature of the cotton-wool spot but the source of the axoplasmic organelles in the terminal swellings. Subsequently, research into the whole problem of axonal transport developed rapidly, as was well shown in the review by Jeffrey and Austin (1973) and in the Editorial recently published in this journal. Within this work the interesting view was expressed by Martinez and Friede (1970), again in a study of transected sciatic nerves, that the local formation of organelles in the axon stump is unlikely, since the magnitude of the increased density of organelles would necessarily imply an enormous multiplication of mitochondria, which would be inconsistent with the finding of a relatively small uptake of labelled amino-acids into swollen axons. They were in favour of an active redistribution of axoplasmic organelles towards the axon stump.

Axonal flow, as followed by labelled leucine with autoradiography or scintillation counting, is also now receiving attention in ocular conditions, especially as regards the effects of raised or lowered intraocular pressure on flow from the retinal ganglion cells to the lateral geniculate nucleus (Anderson and Hendrickson, 1974) or to the optic nerve (Levy, 1974; Minckler et al., 1976).

It is only very recently, however, that the role of axonal flow has again been considered in the case of cotton-wool spots. Beginning from purely clinical studies of fundi with retinal vascular occlusion McLeod (1975) deduced that axonal ischaemia in the retina results in the interruption of both orthograde and retrograde axon flow and that the dense white opacity of the cotton-wool spot is due to the aggregation of organelles on either side of the lesion; while centrally the ganglion cells become necrotic. He subsequently described, in terms of axoplasmic transport, the clinical manifestations of occlusion of the central retinal and posterior ciliary arterioles (McLeod, 1976). Since neither axonal flow nor organelles nor ganglion cells are ophthalmoscopically visible, these views could be regarded only as interesting speculations based on circumstantial evidence interpreted in the light of microscopic studies in the literature, but the experimental work reported in the present issue (McLeod et al., 1977) goes far to confirm them.

By occluding retinal arterioles of the pig with laser photocoagulation, both at the same time and after introducing labelled leucine into the vitreous, these co-workers have traced orthograde and retrograde axonal flow by autoradiography to the swollen axon terminals on both sides of the infarcts, and they have demonstrated by electron microscopy the accumulated organelles within them and the fundamental importance of the interruption of normal axonal flow. No evidence of atrophy of the distal axon was provided. The authors stress that, although ischaemia is the common cause of these lesions, they may develop from any other injury resulting in such axonal disruption, and they are not, therefore, to be regarded as synonymous with micro-infarction. This broader view of the pathogenesis of cotton-wool spots was also advocated by Ashton (1970).

There are, of course, dangers in interpreting these pathological lesions purely in terms of interrupted physiological flow, especially in circumstances as gross as ischaemia, wherein the ensuing chemical, physical, and bioelectrical disturbances might well be factors in determining the aggregation and proliferation of organelles; for instance, Shakib and Ashton (1966) found such aggregations also in intact fibres in the ischaemic zone. Nevertheless,
this excellent work will surely stimulate further research into the role of axonal flow in neuroretinal disease, and it provides an instructive example of how new light can still be brought to bear on an old problem simply by informed clinical observation and deduction, backed by experimental confirmation, even in a field as fully explored as the ocular fundus.

References