The pathology of diabetic retinopathy

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Today's diabetes world is fast moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this instalment of *Tattersall's Tales*, Robert Tattersall follows the development of our understanding of retinopathy through the 20th century. He takes us through innovative pioneering studies to the present hopes for the future.

Before, and for a decade after, the introduction of insulin in 1922, every patient with retinopathy was middle aged or elderly and most had arteriosclerosis and/or hypertension. It was therefore natural to think that retinopathy was due to hardening of the arteries. During the 1930s young people whose lives had been saved by insulin began to present with retinal changes without hypertension or arteriosclerosis. It therefore seemed to some that retinopathy might be a specific complication. Nevertheless, it was a mysterious condition about which an editorial in the *British Medical Journal* in 1939 claimed:

> *'There is hardly an aspect of the problem on which any positive agreement has been reached.'*
> *(Editorial, British Medical Journal, 1939)*

Microaneurysms

Pioneering studies on the histology of the diabetic eye were done in the 1940s by Arthur James Ballantyne (1876–1954), Professor of Ophthalmology in Glasgow, and his assistant Arnold Lowenstein (1882–1952), who came to Glasgow from Prague. With a magnifying glass or low-power microscope on flat retinal preparations, they found circular bodies which appeared to be the same as the 'blood spots' seen through the ophthalmoscope. Serial sections showed that they were microaneurysms, not haemorrhages as previously thought (Ballantyne and Lowenstein, 1944).

The next steps were taken by Norman Ashton in London and Jonas Friedenwald in Baltimore. Norman Ashton (1913–2000) had been a general pathologist until 1948 when he was invited by the Institute of Ophthalmology to become Director of Pathology, a position he held for the next 30 years. Between 1949 and 1951, he made detailed investigations of the retinal vessels and stressed that microaneurysms originated from veins (Ashton, 1959). In one of his earliest publications, Ashton described the appearance of the retinal vasculature injected with Indian ink in a 71-year-old woman who had been living with diabetes for 26 years. Ashton wrote,

> *'The picture clearly shows some thousands of microaneurysms. Beading, localised dilatations and looping of the vessels and multiple haemorrhages can be seen. It is believed that it has not previously been realised how surprisingly numerous microaneurysms are and the picture is a depressing one for one wonders how it can ever be possible to reverse such a gross and widespread process by the administration of drugs or the control of diet.'*
> *(Ashton, 1950)*

Jonas Friedenwald (1897–1955), whose father and grandfather had both been professors of ophthalmology, showed that by treatment with periodic acid and staining with Schiff's reagent, very fine histological pictures of the retinal vascular system could be obtained. These showed large numbers of microaneurysms, 'like berries in a holly tree' (Friedenwald, 1953). He thought these developed from a persistent slow haemorrhage from a weakened area in the vessel wall with endothelial cells then growing out to surround the mini haemorrhage. His explanation of exudates was that the tear in the vessel wall was so small that it held back corpuscles while letting plasma leak out.

Proliferative retinopathy

The clue to the pathogenesis of proliferative retinopathy came unexpectedly from the study of a blinding disease in premature babies. In 1942, a Boston Professor of Ophthalmology, Theodore L Terry (1899–1946), noted an unusual cluster of five blind premature infants who each had an opaque membrane behind the lens, a condition later called retrolental fibroplasia (RLF; Terry, 1942). Reports flooded in and by the end of the epidemic, which lasted 10 years, more than 10 000 premature babies had become blind (Silverman, 1977; Jacobson and Feinstein, 1992). At first, it was thought that retrolental fibroplasia developed in intrauterine life, but in three premature infants, Terry found normal eyes at birth only for it to develop several months later. Over 50 different conditions were blamed, including premature exposure to light, vitamin deficiency and anoxia. In a presentation to ophthalmologists in 1944, Terry admitted knowing little of the care of premature infants but claimed that this 'new' disease could not be accounted for by any recent changes. What he did not know was that new incubators had been introduced that could deliver oxygen at high concentrations and that these were promoted as a way of reducing neonatal mortality. In 1951, Mary Crosse in Birmingham, England, and Fergus Campbell in Melbourne, Australia, suggested that the cause was excessively high concentrations of oxygen. Crosse found that 12 of 14 affected infants had been given oxygen continuously for more than 2 weeks via an oxygen tent or incubator rather than the face mask used in previous years. Campbell retrospectively contrasted infants at one

institution who received 40–60 % oxygen with those in two other institutions who received lower concentrations. The rates of RLF were 19 % and 7 %. Eventually, a randomised study in the USA in July 1953 confirmed that RLF occurred in 23 % of babies on high concentration oxygen compared with 7 % in those on restricted oxygen. Even after this result, many paediatricians were reluctant to accept that oxygen, which had an almost mystical reputation for doing good, could be harmful. They may have been partly right: in the controlled trials, a big problem was that the nurses were so convinced of the benefit of oxygen that they gave it surreptitiously to children who had been randomised to restricted oxygen.

'Nonperfused retina is not necessarily dead retina'

The theory that the developing retina liberates a chemical substance which stimulates vascularisation was first suggested in 1948 by the Scottish ophthalmologist Isaac C Michaelson (1903–1982; Michaelson, 1954). Michaelson worked in Glasgow with Ballantyne and Lowenstein before moving to Israel where he was head of ophthalmology at the Hadassah Hospital from 1954 to 1972. He injected Indian ink into the arterial system of the eye of human fetuses at autopsy and then teased out the retina to make flat preparations. One of his main findings was that the capillaries bud from the veins, away from the oxygen-laden arteries, leaving a zone free of capillaries (Patz, 1984). Later work showed that when animals were reared in an atmosphere with reduced oxygen content, the capillary-free zone became narrower. He studied the developing vasculature in kitten retinas and concluded that a 'chemical factor' was probably responsible for controlling the growth and development of the retinal vasculature and that it had the following characteristics.

- It was present in the extravascular tissue of the retina.
- Its concentration differed in arteriolar and venous neighbourhoods.
- It was probably biochemical in origin.
- It acted predominantly on the retinal veins.
- Its concentration determined the distance to which new vessel growth extended.

Noting that neovascularisation was also seen in diabetes, Eales disease and after retinal vein thrombosis, Michaelson commented that:

> *'If these cases can be considered as a group they can be seen to have two main features in common. The new vessels are associated nearly always with the retinal veins, and secondly, occurring late in these chronic diseases, they are probably a response to changes in the retinal and possibly vitreous metabolism… With this appreciation of the epigenesis of new-formed vessels in diabetes and other conditions comes an understanding of the function which those vessels are meant to serve. Just as the metabolic needs of the embryonic retinal tissue demand closer proximity of capillary vessel, so does the disturbed metabolism of certain retinal diseases call for the accession of vessels to insufficiently or non-vascularised situations, intraretinal, pre-retinal or vitreous.'*
> *(Michaelson, 1948)*

Further evidence that this was correct came from Norman Ashton's 1954 paper on retrolental fibroplasia. He put a cat and three kittens in an oxygen-enriched atmosphere of 70–80 % O_2 for 4 days. The initial effect was marked narrowing of the immature retinal vessels which Ashton called 'vaso-obliteration'. After the kittens had been returned to a normal atmosphere, blood vessels grew in a disorganised fashion with new capillaries budding out of the normal retinal area into the vitreous body. Ashton postulated that the retina served by the obliterated vessels became hypoxic and that, in response, 'a vasoformative factor' – similar to that proposed by Michaelson – was liberated (Ashton et al, 1954). In further work, Ashton emphasised the important role of capillary closure, which would later be visually confirmed by fluorescein angiography (Ashton, 1963).

Work in the last decade suggests that the 'vasoformative factor' is one or more growth factors including vascular endothelial growth factor (VEGF), protein kinase C-β and even erythropoetin. Blockers of these growth factors have been developed and there is hope that they will slow or prevent the progression of proliferative retinopathy in the same way that they do with age-related macular degeneration.

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