Editorial

Neovascularisation again

Since the original suggestion by Michaelson in 1948 that there is probably a substance in retina which can stimulate new vessel formation[1] and the publications from Ashton's laboratory explaining the preretinal neovascularisation in retinopathy of prematurity (ROP)[2] and the more remote neovascularisation of the iris in central retinal vein occlusion (CRVO)[3] in terms of retinal hypoxia, many experiments have been carried out in attempts to elucidate the mechanisms involved. The probability that the hypoxia theory is correct was much increased by the classical work of Laatikainen and Kohner,[4] who showed that neovascularisation occurred in CRVO only when retinal capillary closure could be identified by fluorescein angiography. Meanwhile the search for a substance to incriminate had already begun. Numerous clinical studies were carried out over the years, not to mention the rise of retinal ablation as a means of treatment for diabetic retinopathy[5] and neovascular glaucoma.[6]

One of the earliest substances to come under suspicion was lactic acid.[7] Intravitreal injections of lactic acid were given repeatedly to young kittens, of which 50% developed intravitreal vasoproliferation. Later attempts to confirm this by demonstrating excess lactic acid in the vitreous of kittens and rats whose retinas had been rendered ischaemic were unsuccessful,[8] and lactic acid seems to have been dropped. In 1978 Patz and coworkers[9] made the interesting observation that tumour cells introduced into rabbit vitreous produced neovascularisation only when in contact with vascularised retina and suggested that there may normally be an anti-neovascularising substance present in rabbit vitreous. It is worth mentioning that as well as studies on the subject of preretinal intravitreal and even iris new vessels interest was also being taken in subretinal neovascularisation, since this is just as important a field as the others and probably concerned with similar pathological processes. Miller and colleagues,[10] for example, thought that the retinal pigment epithelium might play a part in inhibiting new formed subretinal vessels, but, although there does not seem to be a convincing theory as to the causation of subretinal neovascularisation, nevertheless the possibility that the pigment epithelium has some sort of active role has continued to arouse interest.

There was something of a setback in 1977 when Kissun and Garner[11] were unable to prove that extracts of ischaemic kitten retina would induce excess neovascularisation in experimental corneal tunnels, but in 1980 Federman and coworkers[12] succeeded in inducing corneal vascularisation by retinal implants, and in 1982 Kissun and colleagues[13] found similar results in chorioallantoic membrane test beds using extracts of healthy adult cat retina. They proposed a low molecular weight angiogenic factor, which seems to be similar or possibly the same as the endothelial cell stimulating angiogenic factor (ESAF) which was originally described in tumour angiogenesis. They pointed out that, whereas clinically neovascularisation seems to occur only in response to retinal ischaemia, the angiogenic factor appears to be present in healthy retina. This puzzle can be explained by postulating that there is also an antivascularising substance present which is normally in equilibrium with ESAF. Neovascularisation in disease or regression of neovascularisation as a result of therapy may therefore be expressions of alterations in this balance rather than the production or reduction of a single substance. In 1986 Taylor and coworkers carried the story further when they demonstrated significant levels of an ESAF-like substance in the retinas of oxygen deprived kittens[14] and in 1988 increased levels in the vitreous humour.[15]

Parallel with these studies have been tissue culture experiments where the properties of retinal extracts can be studied in the laboratory in rather a precise and elegant manner. Wong and colleagues[16] have shown that tissue-culture media conditioned by extracts of retinal pigment epithelial cells stimulate the proliferation of retinal capillary endothelial cells as well as pericytes. However, in a paper in the *BJO* this month Singh and colleagues show that exactly the opposite effects are seen in tissue culture when the system is conditioned by vitreous from eyes which had been subjected to extensive retinal destruction by laser. This appears to be further evidence for the retina's balancing act between neovascularisation and vascular stability, and the authors proffer it as a possible explanation for the beneficial anti-neovascularising effect of retinal ablation.

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