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The Natural History of Proliferative Diabetic Retinopathy

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Proliferative diabetic retinopathy is the commonest sight-threatening lesion in type I, insulin dependent diabetes. Its natural history has been well described and has now been known for many years. In the Wisconsin epidemiological study of Klein *et al.*[1] proliferative retinopathy was uncommon in those under the age or 30 years at diabetes diagnosis, if the diabetes duration was under 10 years. Thereafter it rose rapidly, so that after 15–20 years diabetes duration some 60% had such sight-threatening lesions. After about 35 years duration of the disease the prevalence dropped, probably because by then many of the patients with the worst lesions had died. In the Joslin clinic study the chances of proliferative lesions developing in those who did not have it previously was 3%/year.[2] In the study reported from Switzerland[3] over a period of eight years 9% of insulin dependent patients without any retinopathy at the first examination developed proliferative lesions. If background retinopathy was present at the first examination 25% advanced to this sight-threatening lesion.

The Natural History of Proliferative Retinopathy

The exact cause of new vessel formation is not known. It is however always secondary to the presence of large areas of capillary non perfusion, usually associated with non perfusion of arterioles and venules. It is therefore not specific to diabetic retinopathy, but occurs in a number of other retinal vascular diseases characterised by vascular occlusion, such as sickle cell disease and retinal vein occlusion.

In diabetic patients there is usually a stage of pre-proliferative retinopathy when there are large areas of non perfusion but before new vessels develop. Pre-proliferative retinopathy can be recognised from characteristic lesions, such as multiple cotton wool spots, usually five or more in an eye, intraretinal microvascular abnormalities, venous abnormalities, such as beading, loop formation and reduplication, clusters of blot haemorrhages, and white lines, occluded vessels seen in the retina (Fig 1a and b).

New vessels arise from the optic disc or from the retinal periphery (Figs. 2 and 3). Their origin is usually a major vein, but they may occasionally arise from arteries. Disc vessels sometimes arise from the choroidal circulation, the development of these vessels has been described,[4] and only a brief summary is given here. Peripheral new vessels lie initially in the plane of the retina but soon pierce the internal limiting membrane, and with their accompanying mesenchyme are preretinal, forming adhesions with the overlying vitreous. While the vitreous is attached to the retina the new vessels are symptomless. However the presence of the new vessels leads to retraction of the vitreous, pulling the vascular mesenchyme forming epiretinal membrane forward. It is this pulling which leads to the complication of new vessels, such as vitreous haemorrhage (subhyaloid or intragel haemorrhage). The vessels with their fibrous tissue covering may be pulled, resulting in traction on the internal limiting membrane and the retina, causing distortion of vision. The fibroglial tissue proliferating on

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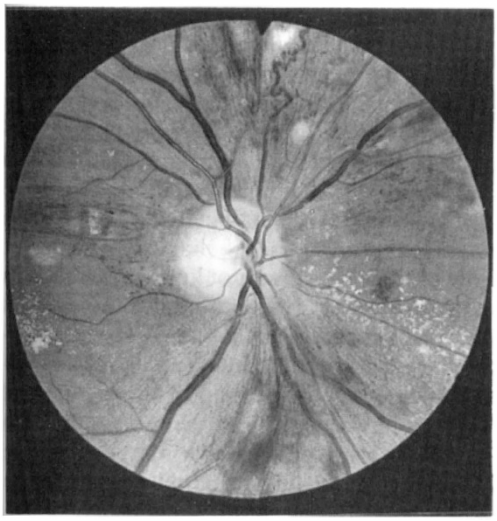

Fig. 1a. *From a colour photograph of R. disc of patient with pre-proliferative diabetic retinopathy. Note more than five cotton wool spots, dilated veins, venous loop with reduplication and multiple haemorrhages.*

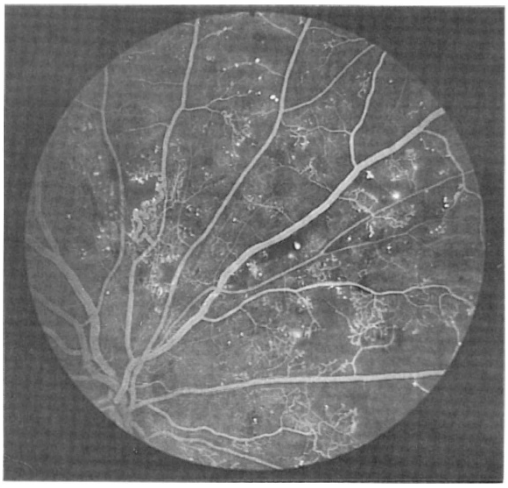

Fig. 1b. *Fluorescein angiogram of superior area of same eye as seen in Fig. 1a. Note venous reduplication and large areas of non perfusion.*

the posterior vitreous face tends initially to contract forming traction, and later detachment. Retinal detachment is always associated with some degree of visual loss, if the macula is involved the visual loss is profound. It must be remembered, that until tractional complications develop new vessels are symptomless. It should also be remembered that new vessels never develop in an otherwise healthy retina.

Disc vessels go through the same process, but their progression is usually more rapid. In a study performed at the Hammersmith Hospital, before photocoagulation became available out of 17 eyes with peripheral new vessel in only two did vision improve, in 10 it remained unchanged, and in five eyes it deteriorated over a 5-year period. Three of the five eyes became blind (Fig. 4). In contrast out of 21 eyes with disc vessels, two improved vision, six remained unchanged, and 13 deteriorated, eight of these to blindness (Fig. 5). The first lesion to cause visual loss is

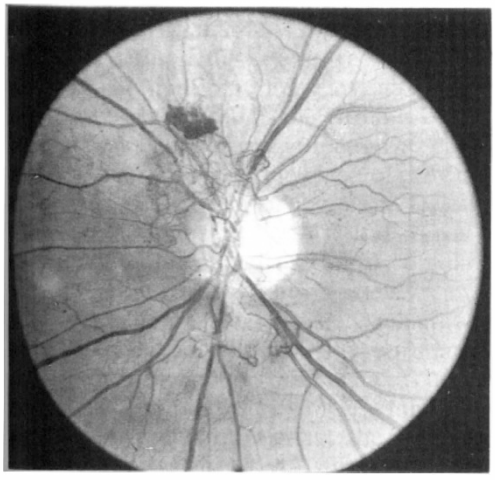

Fig. 2. *Disc new vessels with haemorrhage arising from the vessels.*

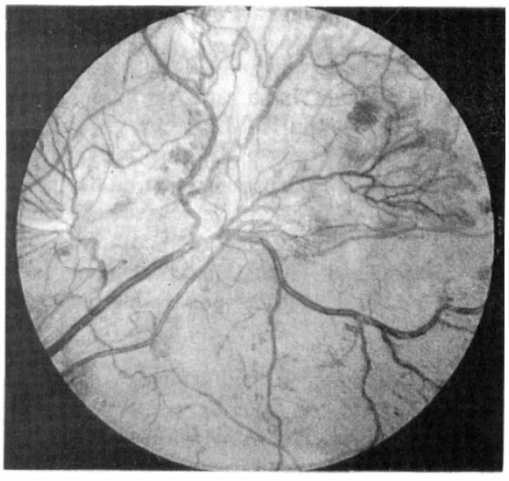

Fig. 3. *Peripheral new vessels with fibrous retinitis proliferans.*

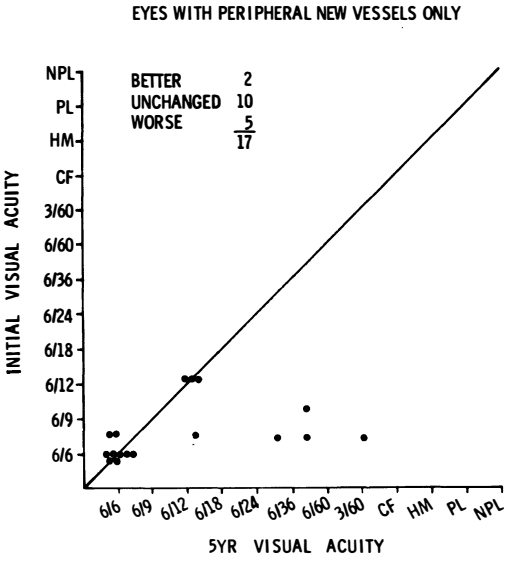

Fig. 4. *Graph showing initial and five-year visual acuity of eyes with peripheral new vessels only. Diagonal line is no change line. Each eye is represented by a black dot.*

usually vitreous haemorrhage. Though this may improve initially, Caird found that within one year of the first vitreous haemorrhage one-third of eyes were blind, and within three years one-third of patients were blind in both eyes.[5]

The visual prognosis for eyes with new vessels is poor. This is particularly so, when there are 'high risk' characteristics present, as described in the Diabetic Retinopathy Study.[6] These are disc vessels of more than minimal degree of severity, disc vessels with present or previous haemorrhage, and peripheral new vessels with haemorrhage.

Proliferative retinopathy responds well to photocoagulation, but it is essential that it be treated early and adequately, at a time when symptomless, before tractional complications have developed. This means, that new vessels have to be looked for when screening asymptomatic patients.

The Pathogenesis of Proliferative Retinopathy

As stated before, the cause of new vessel formation is not known. However in the last few years a considerable amount of work has been done which leads to better understanding of, at least, some of the steps in the formation of the new vessels. Most of this work comes from cell culture work, and from the study of growth factors.

In the normal retina the capillary wall consists of endothelial cells and pericytes, in a one to one relationship. Thus, there are more pericytes in the retina than in any other tissue in relation to the endothelial cells. The exact role of the pericytes is not known, but there is now increasing evidence that the pericytes have a controlling influence over the endothelial cells. Endothelin, a powerful vasoconstrictor peptide is secreted by the endothelial cells, but the receptors in the retina appear to be on the pericytes,[7] which may control the diameter of the retinal capillaries. Orlidge and d'Amore[8] showed, in elegant experiments, that cell multiplication is also controlled by pericytes, and for this control cell to cell contact is essential. Loss of pericytes led to endothelial cell proliferation in culture. This proliferation occurred even in co-culture with pericytes when direct contact between the cells was lost. In further experiments these authors also showed that activated transforming growth factor-β was the factor responsible for this growth inhibition.[9] Pericytes are lost early in diabetic retinopathy, and even

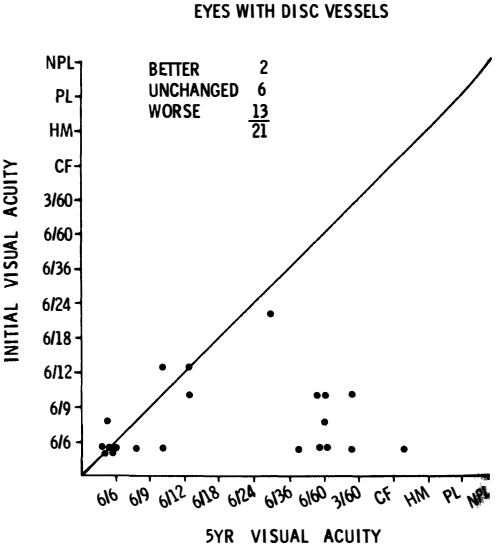

Fig. 5. *Graph showing initial and five-year visual acuity in eyes with disc new vessels. Annotation same as in Fig. 4.*

before they are lost, cell to cell contact may be lost by the increased thickness of the basement membrane. Thus changes such as capillary dilatation and microaneurysm formation may be explained by this alone. Indeed the controlling role of pericytes has further been emphasised by the studies in galactosaemic dogs, where aldose reductase inhibitors which prevented the loss of pericytes also delayed the development of microaneurysms.[10]

Why capillaries occlude is still not known, but abnormalities of the endothelial cells secondary to high glucose concentration in the blood is the most likely cause. New vessels arise from remaining relatively normal vessels. The first step in new vessel formation is dissolution of the extracellular matrix followed by cellular migration and proliferation, and finally the formation of a vascular lumen. The dissolution of the extracellular matrix is brought about by proteoglycans secreted by the endothelial cells. What causes cell migration and proliferation is not known, but basic fibroblast growth factor (bFGF) is stored in the extracellular matrix of endothelial cells. In cell culture work it has been shown, that as endothelial cells die FGF is released into the medium. This FGF has a proliferative effect, and may stimulate surrounding cells. The other growth factor of interest is Insulin like growth factor-1 (IGF-1), which has been shown by the Hammersmith group to be increased in serum in patients during active proliferation of retinal vessels, while normal in those with pre-proliferative retinopathy,[11] and reduced after photocoagulation.[12] IGF-1 has also been shown to be increased in the vitreous of diabetic patients undergoing vitrectomy,[13] but in these patients it may be the result of previous vitreous haemorrhage, or increased leakage from hyperpermeable vessels. IGF-1 has a chemotactic effect, and may thus stimulate migration and growth of new vessels.

In health there is a balance between growth promoting and growth inhibiting substances in the retina. In diabetes this balance is upset. It may well be that there are less inhibiting substances produced, or that the cells are more responsive to growth stimulating substances. This may be the case, as it has been shown that high glucose stimulates the cascade leading to activation of protein kinase-C. Protein kinase-C is at least one of the substances which enables the growth and multiplication of endothelial cells.[14]

There are still many steps missing in the understanding of the pathogenic mechanisms of diabetic retinopathy, but during the last decade much has been learnt about the molecular biology of endothelial cells and pericytes, and we can hope that a full answer will be forthcoming soon.

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