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Letters to the editor

Vascular factors in diabetic neuropathy: comment

Dear Sir,

In the conclusions of their review article Tesfaye et al. [1] noted that studies of animal models of diabetes and of patients with diabetic neuropathy had increased the amount of information about the disorder. While pointing out that microvascular changes are involved they noted that "... there is still a large gap in our knowledge about how these changes are initiated".

May I emphasise that while the blood vascular system provides the conduits through which the blood circulates, the delivery of oxygen and metabolic requirements to the tissues occurs only through capillaries. For that reason persistently impaired capillary blood flow is absolutely incompatible with normal tissue function.

But it is unlikely that the contribution of impaired blood flow to the pathogenesis of diabetic neuropathy will be understood if the role of the blood itself is disregarded. It is equally unlikely that observations on arterial events will help to explain problems of flow at capillary level. Most capillaries are devoid of reactive elements and they are not capable of dilating because they are invested in type 2 collagen. Many are smaller than the diameter of erythrocytes and for that reason cells must change shape to pass along small capillaries.

Earlier this year I drew attention to unpublished work which showed that the type of erythrocyte changes which occur in human diabetes are not the same as those in streptozotocin-induced diabetic rats [2]. Streptozotocin causes a time-related echinocytosis, while in both insulin-dependent and non-insulin-dependent human diabetes erythrocytes are predominantly flat cells. These changes are easily seen by scanning electron microscopic examination of immediately fixed blood, processed according to a published technique [3].

What seems important is that although the changed erythrocytes are morphologically dissimilar, they have the same adverse effect on capillary blood flow. This may lead to capillary occlusion resulting in localised necrosis. Evidently this may be followed by re-canalisation on one or more occasions with the formation of layers of basement membrane. Tesfaye et al. [1] considered that the re-duplication of basement membrane ".. may be the result of episodes of increased endothelial cell turnover," but Vracko [4] considered the layered basement membrane to be the outcome of episodes of endothelial cell death. Schoefl [5] described the mechanism of re-canalisation as the result of endothelial cells becoming motile and forming an endothelial tube within the existing tube of basement membrane. The cells then laid down a new basement membrane. Thus, the basement membrane layers may provide evidence of previous episodes of capillary occlusion.

By shifting the emphasis from blood vessels to blood cells, a basis is provided for understanding the mechanism by which gammalinolenic acid (GLA) prevents the worsening of nerve dysfunction or improved nerve conduction velocity. The beneficial effects of GLA supplementation have been described [6, 7]. In man, dietary supplements such as evening primrose oil which are rich in GLA, enhance prostaglandin E_1 (PGE_1) formation. By means of a spin-labelling technique PGE_1 has been shown to increase the fluidity of the erythrocyte membrane lipid bilayer [8] and the associated improvement in deformability was demonstrated by a filtration system [9].

As Horrobin [10] has pointed out, in both animal models of diabetes and in humans with diabetes, changes in the fatty acid composition of blood components are consistent with a decline in the efficiency of 6-desaturation and a resulting reduction in the capacity to convert cis-linoleic acid to GLA. This enzyme block at delta-6-desaturase may be circumvented by dietary supplementation with evening primrose oil which provides GLA.

Although haemorheological abnormalities of the erythrocytes of patients with diabetes have been reported by several authors, if anticoagulated blood or washed erythrocytes were used, then the relevance of the results to the in vivo condition is questionable as such procedures change erythrocyte morphology [11, 12].

While Tesfaye et al. [1] considered that "Multiple factors are likely to be the source of all diabetic complications," it seems probable that impaired flow properties of the blood will play a major role. The effects of such rheological changes will be compounded in the eye where intraocular pressure provides an additional hazard for retinal blood flow. In the kidney, the haemoconcentrating effect of glomerular filtration will enhance the effects of any haemorheological abnormalities in pre-glomerular blood. Such changes may influence blood flow in the peritubular plexus adversely and thus impair tubular eithelial cell function. While other factors may have significant roles in the development of the complications of diabetes, they may not be as easy to demonstrate or to correct as the changes in the blood.

Yours sincerely,
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Response from the authors

Dear Sir,

We are most interested in the comments of Dr. L. O. Simpson regarding the importance of intracapillary blood constituents and endothelial cells in the damaging effects of capillary disease in diabetic nerve. We would agree with the opinion that this is probably just as important as the abnormal haemodynamics in the vessels supplying the nerve. In the original studies of sural nerve biopsies where capillary endothelial changes were noted [1–3] many of the vessels showed debris which was undoubtedly of cellular nature with fibrin and in some instances small plugs of deactivated platelets. However, we would agree that the haemodynamic factors within the nerve are extremely difficult to assess in vivo. We would suggest that there is an urgent need for relatively non-invasive methods of measuring nerve blood flow, perhaps as simple as nerve oxygen tension to study the varying effects of the metabolic state and the influence of drugs known to affect nerve blood flow in animals.

Yours sincerely,

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The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG-vaccination

Dear Sir,

Several studies in the diabetes-prone nonobese diabetic (NOD) mouse have shown that even one single injection of either complete Freund's adjuvant (CFA) [1] or BCG-vaccine [2] given at an early age prevented the development of diabetes in this animal model. The mechanism has been indicated to be due to a non-specific stimulation of natural suppressor activity. Recently, Shehadeh et al. [3] reported that CFA and BCG vaccine modulated the development of diabetes mellitus in NOD mice. Furthermore in an open clinical trial in 17 newly-diagnosed insulin-dependent diabetes mellitus (IDDM) patients intracutaneous administration of 0.1 ml BCG-vaccine (1 mg/ml) led to a clinical remission more frequently when compared to non-treated control subjects. Based on these indications several large-scale placebo-controlled trials have been started in diabetic humans including children with primary prevention in healthy children as a goal.

In Sweden, since 1 July 1977 we have continuously registered all childhood-onset diabetic cases with a level of ascertainment close to 99 % [4]. Before 1975 all newborn babies in Sweden were offered BCG-vaccination (using the dose given above) in the first month of life and the coverage of this vaccination programme was almost complete [5, 6]. Due to side effects, in some cases severe complications, this policy was stopped on 1 April 1975. Since then only high-risk groups such as immigrant children or children with a close relative with tuberculosis have been vaccinated. In 1976 only 0.6 % were vaccinated [5] and between 1976–1980 less than 2 % were vacci-

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