

effective in inducing tolerance. A large-scale, clinical trial of feeding bovine retinal proteins to patients with posterior uveitis at NIH is due to report in the near future. However, oral administration requires huge amounts of purified protein, which is unlikely to be economically viable on a large scale. Furthermore, using proteins derived from the neural tissue of cows in the UK is unlikely to be acceptable to patients for the foreseeable future. However, recombinant antigens can be made and the smaller but equally effective doses required for nasal tolerisation would seem to be relevant and certainly hold promise for the future. Intriguingly, in experimental models, it has been shown that tolerance may be induced by giving the antigen in tear drops at an equivalent dose to the nasal route,¹¹ and it may well be that we will be able to offer our patients therapy in the form of eye drops before too long.

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CLINICOPATHOLOGICAL CORRELATIONS PROVIDE NEW INSIGHTS INTO THE PATHOGENESIS OF AGE-RELATED MACULAR DEGENERATION

The neovascular form of age-related macular degeneration (AMD) poses an important clinical dilemma for ophthalmologists, as the only proven treatment modality – laser photocoagulation – has been largely ineffective in preventing visual loss in the majority of patients suffering from this disease.^{1,2} Histopathological studies in this condition seek clues to its aetiology in the hope that better understanding will allow the development of alternative and more effective treatment strategies. These studies have shown that the most characteristic feature of neovascular AMD is the accumulation of debris, notably drusen, basal laminar deposit (abnormal material located between the plasma membrane and basal lamina of the retinal pigment epithelium (RPE)) and basal linear deposit (material located between the basal lamina of the RPE and the inner collagenous zone of Bruch's membrane).^{3–5} It has been hypothesised that these deposits obstruct the normal transfer of oxygen and metabolites from the

choriocapillaris to the outer retina, with the prevailing tissue hypoxia causing the release of angiogenic factors which provoke the growth of what are termed choroidal neovascular membranes (CNV).⁶ A number of investigators have observed collections of macrophages and multinucleated giant cells in close proximity to the outer layer of Bruch's membrane at locations where the diffuse debris is present.^{6–8} It has been suggested that these inflammatory cells have been recruited to remove the debris and in the process of so doing, damage Bruch's membrane. The interaction of the inflammatory cells with RPE cells creates the conditions for the release of pro-inflammatory cytokines⁹ and potent angiogenic factors¹⁰ which set the scene for continuing inflammation and neovascularisation. The damaged Bruch's membrane is then easily breached by the new vessels.

In this issue of *Eye*, Sarks *et al.*, using material derived from two patients with preclinical neovas-

cular macular degeneration, examine the early cellular events associated with the formation of choroidal neovascular membranes and the subsequent invasion of the sub-pigment epithelial space by the neovascular complex.¹¹ Based on their histopathological observations they argue that the separation of the outer layers of Bruch's membrane from the choroid by membranous debris and soft drusen is a crucial event in the pathogenesis of neovascular AMD. This separation could potentially cause oxygen concentrations to fall in the outer retina, resulting in the release of diffusible angiogenic factors which paradoxically would reach the choroid in highest concentrations where the RPE is still attached to Bruch's membrane. In support of this hypothesis, Sarks *et al.* show that erosion of Bruch's membrane by choroidal neovascular complexes often commences beneath small hard drusen which anchor the RPE to Bruch's membrane. They also provide compelling evidence to show that separation of RPE from Bruch's membrane by diffuse debris is an important prerequisite for the next step which is the spread of the neovascular complex in the sub-pigment epithelial space.

Sarks *et al.* also attempt to elucidate some of the hitherto unexplained angiographic features that are commonly noted in clinically recognisable neovascular AMD. They observe that the growing vascular tips of the CNV, which extend approximately 100 μm beyond the main membrane, lack pericyte cover and are capped with fibrin and a thick basement-membrane-like material. They suggest that these tips would leak fluid more readily and would correspond to the scalloped edges which are often seen on angiography. They also note that the RPE overlying the edge of the membrane is hyperpigmented and multilayered, which would account for the dark halo of blocked fluorescence so often noticed around the CNV on angiography.¹²

Understanding the causation and mechanism of disease is a vital part in the strategy for the development of new and potentially more effective treatments. Nowhere will this be more important than in the management of macular degeneration, which is responsible for visual handicap in what is estimated conservatively to be approximately 16 million individuals worldwide. Clinicopathological correlations using tissues derived from patients with different morphological types of neovascular AMD are essential for furthering our understanding of the

aetiology and pathogenesis of this complex visual disorder.

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