EDITORIALS

TOLERANCE – WILL IT END IN TEARS?

'Some good meaning, mystical, marvellous physicians, or favoured ladies with knowledge inherent, say the bane will prove the best antidote, and hence advise the forbidden leaves to be eaten, both as a preventive and cure to the external disease.'

The quotation above is taken from a paper that described the use of oral tolerance in the treatment of contact dermatitis induced by poison oak and ivy and is probably the first description in the literature of its use to abrogate clinical disease.[1] Subsequent investigators managed to substantially reduce their skin reactivity to these plants by long-term ingestion of small but progressively increasing doses of them taken orally. Tolerance is the state of specific immunological unresponsiveness induced by the prior administration of antigen, most often by the mucosal route (oral, aerosol). It has an important physiological role since mucosal surfaces are constantly exposed to a wide variety of environmental antigens derived from food, but hypersensitivity reactions to dietary constituents are rare.[2] The mechanisms whereby systemic immune unresponsiveness coexists with active mucosal responses, shown through the presence of antigen-specific secretory IgA antibodies, has been a matter of great scientific curiosity over the last 25 years and the cellular and molecular mechanisms underlying this phenomenon have been slowly unravelled.[3] Additional interest has been stimulated by the realisation that such hypo-responsiveness may also be of therapeutic value in autoimmune disease (where an appropriate antigen(s) can be identified), in the development of oral vaccines, in the control of transplant rejection and in the modulation of unwanted immediate and delayed type hypersensitivity reactions.[3,4]

Tolerance has been shown to occur in most experimental animals. The actual mechanisms involved in its induction are still not precisely known but probably comprise active T cell suppression, functional clonal anergy or possibly clonal deletion of the relevant antigen-specific cells.[5,6] In experimental autoimmune disease tolerance induced by administering antigen either by oral or nasal routes has been shown to suppress (partially or totally) experimental allergic encephalomyelitis (EAE), uveoretinitis (EAU) and adjuvant- and collagen-induced arthritis, all with remarkably uniform results.[4] This has led to both open and placebo-controlled, randomised clinical trials in patients with multiple sclerosis,[7] rheumatoid arthritis,[8] and uveoretinitis. These human studies have not been completely convincing, although good results in selected patients with multiple sclerosis were reported, as well as short-term complete remission in some patients with rheumatoid arthritis. However, the optimum dose, treatment regime and type of vehicle have not been determined and there remains the problem that in experimental animals at least, tolerance is best induced prior to induction of disease, although some effect has been noted in chronic relapsing EAE where disease is already present.[9]

Two principal concerns pertinent to the treatment of patients with autoimmune diseases are the possibility of exacerbating pre-existing disease and the effects of inducing tolerance in patients who are already on immunosuppressive drugs. These concerns are addressed by a paper in this issue of *Eye* by Kreutzer *et al.* They report the effects of combining standard immunosuppressive therapy (cyclosporin A) and nasal tolerisation with retinal proteins in EAU after the induction of disease. They show that this is effective in delaying disease onset and in reducing disease severity even when the cyclosporin was subsequent stopped. The extrapolation of these data to human studies would seem to hold promise for patients with uveoretinitis.

Further studies of the effects of tolerance in human autoimmune disease are clearly warranted. These will need to address the optimal types and forms of relevant antigen, the best antigen delivery systems, such as covalent linkage to cholera toxin B subunit,[10] and which mucosal surface is the most

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 cytokines[9] and potent angiogenic factors[10] 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-