

introduced into the vitreous.<sup>11</sup> All of the techniques for maintaining asepsis in the operating room are directed towards preventing such an event from occurring, but non-postoperative forms of endophthalmitis are exempt from these precautions. The third and perhaps most important issue affecting visual outcome is the time lapse between the onset of symptoms and clinical diagnoses and the initiation of aggressive appropriate therapy. Paradoxically, time is the only factor over which the clinician has a small measure of control. The faintest suspicion that the patient is developing endophthalmitis should lead to the immediate institution of a standardised diagnostic and treatment protocol such as the one described by Okhravi and colleagues in this issue.

Admittedly, there are still questions regarding the standard of therapeutic care. Are systemic antibiotics really necessary for the treatment of endophthalmitis? Has the question of when to do a vitrectomy been definitively answered? In spite of the results of the Endophthalmitis Vitrectomy Study<sup>12</sup> these grey areas of clinical judgment continue to weigh heavily on clinicians. Perhaps it is the complex nature of endophthalmitis itself that prevents a standard protocol from being devised that can consistently produce a satisfactory visual outcome in this group of patients that are so difficult to treat. Unfortunately, even in the best of hands the results are still frustrating and the ideal treatment for endophthalmitis remains elusive.

JOHN P WHITCHER

Francis I Proctor Foundation for Research in Ophthalmology, Box 0944, University of California San Francisco, San Francisco, CA 94143-0944, USA

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## Oral administration of antigen in the treatment of eye disease

Feeding antigens to experimental animals can result in oral tolerance, a peripheral immunological non-responsiveness induced by the processing of exogenous antigen through gut associated lymphoid tissue.<sup>1</sup> Oral administration of autoantigen has been shown to ameliorate disease in a number of rodent models of organ specific autoimmune conditions including experimental autoimmune uveoretinitis (EAU),<sup>1-5</sup> experimental autoimmune encephalomyelitis (EAE),<sup>6</sup> experimental granulomatous colitis,<sup>7</sup> and experimental autoimmune thyroiditis.<sup>8</sup> Because antigen feeding protocols have been shown to be effective even in sensitised recipients with established disease, induction of oral tolerance represents a novel potential strategy for the treatment of human autoimmune disease, allergy and possibly graft rejection.

The mechanisms involved in induction and maintenance of oral tolerance depend critically upon antigen dosage.<sup>1-3</sup> Immunisation with high doses of antigen leads to energy of antigen reactive cells, whereas lower antigen doses induce a form of immune deviation or active suppression. Anergy reflects the situation in which antigen reactive cells are generated but are functionally inactive: the molecular mechanisms involved are uncertain. Immune deviation operates through induction of a population of transforming growth factor beta (TGF- $\beta$ ) secreting regulatory T cells (Th3 cells) which down regulate immune responses, and by a general skewing towards a Th2 immune response with production of immunomodulatory cytokines IL-4 and IL-10. In most experimental systems, oral tolerance can be augmented by covalent coupling of antigen to the mucosa binding cholera toxin B subunit, which appears to have a strong adjuvant effect,<sup>9</sup> or by concomitant administration of IL-2.<sup>5</sup> As with anterior chamber associated

immune deviation (ACAID),<sup>10</sup> an intact spleen is necessary for the induction of oral tolerance to ocular antigen.<sup>4</sup> A detailed review of potential pathways to tolerance in autoimmune eye disease has recently been provided by Rizzo and Caspi.<sup>11</sup>

In 1996, Niederkorn and his colleagues demonstrated that oral administration of donor type antigen halved the incidence of murine corneal allograft rejection across multiple major and minor histocompatibility antigen mismatches.<sup>12</sup> Antigen was administered in the form of tissue cultured, immortalised corneal epithelial and endothelial cells or freshly isolated keratinocytes of donor phenotype. In this issue of the *BJO* (p 778), the same group shows that conjugation of cultured corneal cells to the cholera toxin B subunit significantly enhances the efficacy of the regimen in prolonging graft survival, with a single oral dose of antigen reducing the incidence of corneal graft rejection by 36%. Multiple oral doses decrease the incidence of rejection by over 90%. Initiating antigen feeding on the day of corneal transplantation is very effective but oral administration of conjugated corneal cells can be delayed for up to 7 days after corneal transplantation and still produce a significant (albeit lesser) effect. Interestingly, administration of exogenous IL-2 has no augmentative effect but, as expected, recipient splenectomy abolishes induction of oral tolerance.

The majority of reported studies on oral administration of antigen have been performed in rodent models. The question on everyone's lips is, of course, will oral immunisation work in humans? In one clinical trial, patients with multiple sclerosis fed bovine myelin suffered fewer relapses and demonstrated significantly fewer blood borne antigen reactive T cells<sup>13</sup> and more TGF- $\beta$  secreting T cells<sup>14</sup> than

did patients fed placebo, although the authors urged caution in interpreting the results because differences in clinical indices of disease activity did not reach statistical significance. In a trial of oral administration of avian collagen type II for rheumatoid arthritis, treated patients showed significant clinical improvement compared with controls.<sup>15</sup> Oral administration of a dust mite extract to asthmatic patients sensitive to this allergen resulted in improvement in a variety of objective measures of disease status.<sup>16</sup> Trials of oral administration of uveitogenic retinal antigen preparations in patients suffering from recurrent uveitis have recently been reported and are tentatively supportive of this approach.<sup>17</sup> Overall, the available evidence indicates that oral tolerance may be a useful therapeutic option in some clinical situations.

Assuming oral administration of antigen does tolerise in the clinical setting, what might constitute a clinically applicable protocol in the context of human corneal transplantation, and is such a protocol actually necessary? The second question is straightforward; corneal graft rejection is the major cause of corneal graft failure in large, longitudinal clinical studies and is a particularly important cause of graft loss in patients with a history of inflammatory eye disease.<sup>18</sup> A non-toxic, non-pharmacological alternative or adjunct to existing immunosuppressive drugs for the prevention of corneal graft rejection would be of major interest. How could feeding of donor corneal antigen be accomplished in practice? The use of immortalised residual corneal epithelial and endothelial cells from a specific donor would be cumbersome and logistically difficult. The ethical use of keratinocytes harvested from corneal donor skin would require extension of current donor consent procedures and presupposes that all important tolerising epitopes relevant to the cornea are represented in skin. Although the work of Niederkorn and his colleagues strongly implicates major and/or minor histocompatibility complex antigens as the polymorphisms of importance in oral administration of antigen for experimental corneal transplantation, every reader will be aware of the controversy that has surrounded the role of HLA matching for clinical corneal transplantation. Whether synthetic major histocompatibility complex allopeptides<sup>19</sup> could be used as a source of antigen for inducing oral tolerance to corneal grafts is unclear, but possibly worthy of further experimentation. Such a regimen would, however, require HLA typing of donor and recipient so that appropriate tolerising peptides could be selected for oral administration.

K A WILLIAMS

Department of Ophthalmology,  
Flinders University of South Australia,  
Adelaide, South Australia

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