Autoimmunity: molecular mimicry or bystander damage

The distinction between pathogen mediated and autoaggressive inflammation is becoming increasingly blurred. Current thoughts on the mechanisms of autoimmune disease broadly fall into two camps, not necessarily mutually exclusive. The molecular mimicry theory holds that tolerant self reactive T cells which have escaped deletion in the thymus generally ignore self antigens mostly as a result of factors such as low affinity of their receptors for antigen, and it is not until they are exposed to antigens from micro-organisms which have homology to self antigens that they receive a sufficiently strong stimulus to be activated. The alternative theory of bystander activation suggests that tissue damage induced by micro-organisms releases a variety of cytokines, not always the same set, which under appropriate circumstances activate self reactive T cells which happen to be in the vicinity as they travel through the tissues. Recently, evidence in support of the latter theory has been reported in a model of experimental diabetes mediated by Coxsackie B infection of pancreatic islet cells (Nature Medicine 1998;4:781–5). The requirement for local viral infection was also reported last year in a model of “immune mediated” keratitis, induced by transfer of herpes simplex specific T cells (Science 1998;279:1344–7). The involvement of micro-organisms and especially viruses in putative autoimmune diseases has long been suggested in several ophthalmological conditions, not least the many forms of uveitis, but evidence for viral material in these disorders is particularly elusive. As Benoist and Mathis state, however (Nature 1998;94:227–8), the notion that bystander damage mediated by cytokines may be a mechanism for disease allows the possibility of alternative therapeutic approaches not necessarily based on identification of the “autoantigen”.

Retinoblastoma management

The management of retinoblastoma has been revolutionised during recent years, according to Professor Brenda Galie who reviewed her work in this area when she delivered the Doyle Lecture at the Oxford Congress. With a combination of chemotherapy, cryotherapy, and the novel use of the immunosuppressive drug cyclosporin A to “trick” the tumour cells into allowing intracellular accumulation of the chemotherapeutic drugs, she has shown that many previously inoperable or unmanageable tumours can be induced into sufficient regression to allow more direct attack with cryotherapy or laser. Coordination of therapy at several different centres via telemedicine techniques on the internet has allowed the pooling of data for the management of this rare but devastating tumour between national centres worldwide in what Galie described as a virtual “World Retinoblastoma Institute”. Not only can textual data be transmitted but sufficiently highly resolved fundus images of tumours using a standardised wide angle camera allow consensus to be reached between several retinoblastoma experts for the best management of individual tumours. This approach is of course especially important for retinoblastoma where the correct management in individual cases is not always obvious. However, the model for disease management in rare conditions is clearly and application to other rare sight threatening conditions might be worth considering.

First Combined International Symposium on Ocular Immunology and Inflammation

The first combined meeting of various groups interested in ocular immunology and inflammation was held in Amsterdam (June 1998), bringing together among others the International Uveitis Study Group and the International Ocular Inflammation Society. This was heralded as a major initiative in forging links and developing a sense of integration, especially between the basic scientists and clinicians. The meeting had much to offer with several sessions dealing with mechanisms of inflammation and tolerance induction in experimental models and clinical conditions such as corneal graft rejection, ocular surface disease, and intraocular inflammation. Overviews of current management in AIDS related ocular inflammation, particularly in light of what is now known as “immune recovery uveitis” in patients receiving protease inhibitors for HIV disease, outlined present day approaches to this continually evolving set of conditions.

The need for a single international grouping dealing with all aspects of ocular inflammation was never better underlined than at this meeting and the organisers brought off a considerable feat in achieving this aim. In particular, such a meeting can act as a focus for developments in the understanding of disease mechanisms but probably more importantly mediates the dissemination of new and effective approaches to the management of these frequently blinding conditions.

Intraocular tissue plasminogen activator

Tissue plasminogen activator (tPA) is increasingly being recommended for use in clearing fibrinous deposits from the eye—for instance, for the management of non-resolving traumatic hyphaema and for post vitrectomy fibrinous reaction in patients with advanced proliferative diabetic retinopathy. Several experimental studies on the effects of tPA on neuronal viability, however, should indicate that some caution in the use of intraocular tPA may be advised (Current Biology 1998;8:274–7). Neuronal cell death is generally believed to result from excitotoxic factors such as glutamate especially if this amino acid is produced in excess and not cleared quickly enough from the perineural matrix. Studies in tPA knockout mice have shown that they are resistant to glutamate induced injury and it has been suggested that tPA produced by microglia is responsible in some way for excitotoxic neuronal cell death possible by activating matrix metalloproteinases. The effect seems to be critically dependent on the degradation of perineurial laminin which may have a protective role in preventing excitotoxic cell death. Clearly this would be lost if laminin is degraded.

Most of this work has been performed in the brain and it further emphasises the importance of microglia in CNS disease. Microglia are also prominent cells in the retina and it is equally likely that such processes might occur after intraocular injection of, by comparison, relatively high concentrations of tPA.

Evidence based screening

A recent editorial in the Journal of the Royal Society of Medicine (1998;91:347–9) suggested that in addition to evidence based medicine acting as the foundation of good clinical practice, there should also be “value for money” in promoting screening for disease. Several situations were highlighted which indicated that there might be little benefit from screening and indeed there may be positive harm induced by, for instance, a high rate of false positives in conditions such as breast cancer or false negatives in screening for cervical cancer. This issue is also highly relevant to screening in ophthalmology where one of the most important elements in a screening programme is a good correlation between sensitivity and specificity. Conditions that spring to mind in which difficulties may arise are glaucoma screening and screening for retinopathy of prematurity. Should there be some means of evaluating the effectiveness of screening procedures in practice in terms of disease outcomes?