

MINI REVIEW

Endogenous posterior uveitis

The recent development of several animal models of endogenous uveitis has considerably advanced our understanding of the many clinical presentations of uveitis. For instance, it is now quite clear that, pathogenetically as well as clinically, anterior uveitis is a separate disorder from posterior uveitis. In contrast, despite the considerable heterogeneity of posterior uveitis syndromes, the evidence from experimental models suggests that each clinical entity may be a manifestation of one aspect of a common pathogenetic process which is represented by a limited set of uveoretinal responses to inflammatory stimuli.^{1,2}

Many factors combine to produce uveitis. In anterior uveitis, a genetic predisposition is highlighted by the link with the major histocompatibility complex (MHC) class I antigen, HLA-B27,³ while an association with infectious disease is suggested, particularly with regard to viral infection⁴ and more recently *Yersinia enterocolitidis*.⁵ Most inflammatory diseases of the posterior segment are of unknown aetiology, though some such as retinal vasculitis may be linked with systemic disease such as sarcoidosis, or they may occur as part of a well described clinical disorder such as Behçet's disease.⁶ Association with other diseases, however, does not equate with causation, and the lack of evidence implicating micro-organisms in most cases of endogenous posterior uveitis has led investigators to consider autoimmunity as a cause. Indeed, sympathetic ophthalmia, which represents one form of endogenous posterior uveitis, was probably the first autoimmune disease described.⁷

Even in this regard, however, the distinction between autoimmune disorders (or disturbances of immune regulation) and infectious disease is becoming blurred. Current hypotheses concerning the aetiology of autoimmune diseases include several variations on the theme of altered immune regulatory mechanisms induced by invading micro-organisms. Sequence homology between epitopes on foreign and self-antigens for instance, may be sufficient to initiate an autoimmune disease via cross-reacting anti-idiotypic T or B cells which persist long after the inciting micro-organisms have been eliminated. Molecular mimicry of this type has recently been demonstrated in experimental autoimmune uveitis induced by retinal antigen-related peptides bearing sequences which resemble peptides from certain viruses.⁸ All immune responses, including those against autoantigens, require the appropriate MHC haplotype for their induction, and this explains the genetic predisposition to (autoimmune) disease. Perhaps the strongest MHC association with disease in man yet described is that between HLA-A29 and birdshot retinochoroidopathy (>90%),⁹ a discrete clinical entity included within the term endogenous posterior uveoretinitis.¹⁰

It is clear therefore that, although immune mechanisms are currently under intensive investigation in uveoretinal inflammatory disease, they do not necessarily exclude an infectious aetiology, and they must be viewed within the context of genetic and environmental factors. In the final analysis it may not be possible, or even necessary, to unravel all the possible threads in the pathogenesis of uveitis (or indeed of any 'autoimmune' disease). Rather it may be more appropriate to define more clearly the cellular mechanisms involved in the production of tissue damage, so that these

processes can be interrupted by more specific and/or selective immunotherapy.

In this brief review similarities are drawn between various clinical forms of endogenous posterior uveitis and experimental models of autoimmune uveoretinitis (EAU). Certain aspects of the immunopathology are discussed with particular reference to the mechanisms of tissue damage. In addition the role of clinical immunological testing in posterior uveitis is appraised, while possible future directions for immunointervention are indicated.

Clinical presentation of endogenous posterior uveitis

Endogenous posterior uveitis includes several discrete clinical entities (Table 1) which at first sight might seem to be unrelated. Pars planitis (intermediate uveitis), for instance, involves predominantly the peripheral retina and vitreous base, and characteristically is associated with vitreous inflammatory cell infiltrates (snowballs) and extensive sub-retinal chorioretinal infiltrates. Careful examination and fluorescein angiography will, however, show that many of these cases also have signs of peripheral retinal vasculitis, while visual loss is most frequently due to macular oedema, itself usually a manifestation of increased perifoveal capillary leakiness.

Sympathetic ophthalmia is characterised by the focal chorioretinal nodule or microgranuloma – the Dalen-Fuchs nodule. These typically accumulate as healed scars within the fundus after a short self-limiting period of active inflammation. Similar nodules are observed in sarcoid uveoretinitis,¹¹ in Vogt-Koyanagi-Harada's disease during the phase of resolution,¹² and in the less well defined disorder of diffuse choroiditis. They are also frequently the cause of exacerbations of vitritis in cases of 'intermediate' uveitis or pars planitis, where one or two small, round, white foci in the equatorial or pre-equatorial fundus may be sufficient to cause symptoms of floaters. They often escape detection, however, because they are short-lived and self-limiting, and may disappear leaving virtually no trace. When they occur in large numbers, as in sympathetic ophthalmia, less so in sarcoidosis, they have a characteristic appearance of fluorescein angiography during the active phase; hypofluorescent choroidal 'spots' in the early sequence with late hyperfluorescence.¹³ Healed, inactive lesions are overlaid by depigmented retinal pigment epithelium and appear as pigment epithelial defects on fluorescein angiography.

Retinal vasculitis involving the posterior pole may present as an 'idiopathic' disorder or as part of a disease entity such as sarcoidosis, Behçet's disease, multiple sclerosis, systemic lupus erythematosus. The vasculitis may affect small or large

Table 1 Endogenous posterior uveitis – clinical syndromes

Intermediate uveitis	Diffuse uveitis
Pars planitis	Panuveitis
Idiopathic retinal vasculitis	Choroiditis
Sarcoid retinitis/vasculitis	Discrete
Birdshot chorioretinopathy	Serpiginous
Behçet's disease	
Vogt-Koyanagi-Harada disease	
Some pigment epitheliopathies	
Acute retinal necrosis	

vessels and occurs usually as a phlebitis with retinal haemorrhages. Less frequently, an arteritis and phlebitis occur, with widespread retinal infiltrates and ischaemia even to the point of retinal necrosis. Retinal vasculitis rarely occurs in isolation. Careful examination will reveal that chorioretinal infiltrates similar to those in sympathetic ophthalmia are present. In addition, vitreous inflammatory cells are almost a prerequisite for the differentiation of retinal vasculitis from other retinal vascular thrombotic disorders.

Some forms of endogenous posterior uveitis appear to be predominantly choroidal, such as birdshot choroidoretinopathy, in which the hallmark is the widespread distribution of subretinal focal infiltrates and patches of retinal pigment epithelial atrophy. Others appear to be predominantly retinal, such as retinal vasculitis and acute retinal necrosis; while others still produce mainly vitreous cellular infiltration with minimal involvement of the ocular coats.

Some disorders appear to have a clear infectious aetiology such as herpes simplex-induced acute retinal necrosis, cytomegalovirus retinitis, and toxoplasmosis retinochoroiditis, though the evidence for the last has become less compelling in the light of recent data showing no clear serological differences between clinically 'toxoplasma' infected patients and healthy controls.¹⁴ Most uveitis syndromes, however, are of unknown aetiology and much of the reported histopathology has been concerned with endstage disease.¹⁵ Immunohistopathological studies have shown that T cells, particularly T helper (CD4+) cells, and monocytes predominate in many lesions such as the Dalen-Fuchs nodule in sarcoidosis and in sympathetic ophthalmia.¹⁶ Studies of active retinal vasculitis or pars planitis have not been reported in detail but some interesting studies of choroidal changes have been reported in Vogt-Koyanagi-Harada disease.¹⁷ In general, however, the available histological data have supported the concept of an immunologically mediated process in most forms of posterior uveitis.

In addition, despite the differences in clinical presentation, most forms of posterior uveitis have four cardinal features: (1) vitreous inflammatory cells and exudate (vitreous haze); (2) focal choroidoretinal infiltrates; (3) retinal vasculitis; and (4) macular oedema. In some forms there may be a greater emphasis on one or more of these features such as retinal vasculitis or, in birdshot choroidoretinopathy, focal chorioretinal infiltrates. In other forms additional features may be present, such as retinal necrosis, exudative retinal detachment (in Vogt-Koyanagi-Harada disease), or subretinal and preretinal neovascularisation. As will be seen from the discussion below, however, these manifestations represent the spectrum of choroidoretinal responses to an inflammatory stimulus, and this limited clinical set of responses is essentially the same whether the stimulus is immunological, chronic infectious, or a combination of both.

Experimental models of posterior uveoretinitis

Since the pioneering work of Wacker and his colleagues¹⁸ demonstrated unequivocally that proteins within the retina could induce an autoimmune uveoretinitis, several antigens have been described including retinal S (soluble) antigen, interphotoreceptor retinol binding protein (IRBP), opsin, and rhodopsin (for review see Gery *et al.*).¹⁹ Complete amino acid sequence data for these proteins are now available,²⁰⁻²² and considerable information on the immunodominant epitopes of two of them (S-antigen and IRBP)²³⁻²⁵ is known. A single injection of any one of these antigens, when emulsified with Freund's adjuvant and injected into the subcutaneous tissues of an experimental animal, will induce an organ-specific autoimmune inflammation (which includes the pineal gland, the invertebrate third eye). The degree of inflammation varies with the nature of the antigen, the

Table 2 Predominant form of experimental autoimmune uveoretinitis in each animal with different autoantigen

Model	Antigen		
	S	IRBP	Opsin
Rat	Acute	Acute	Moderate
Mouse	Chronic	Chronic	ND
Guinea-pig	Variable	Weak	Weak
Rabbit	Mild	Mild	ND
Monkey	(Retinal) chronic	(Choroidal) chronic	Moderate

IRBP=interphotoreceptor retinol binding protein. ND=not done.

species, and strain (ie, MHC type) of animal, the dose of antigen, the degree of immunosuppression, and the conditions for immunisation^{1,2} (Table 2). In addition, both acute and chronic uveoretinitis models have been developed.²⁶⁻²⁸

Despite the lack of homology between the different antigens, the clinicopathological features of the uveoretinal inflammatory disease in EAU are remarkably similar. An important corollary to this is that each antigen can induce the full range of clinical and pathological features seen in human posterior endogenous uveitis.² For instance, the earliest lesion in both S-antigen and IRBP-induced EAU is a single cell infiltrate in the photoreceptor layer; the site of the target antigen(s).²⁷ A characteristic lesion following this infiltration of cells is the focal chorioretinal nodule, similar to the human Dalen-Fuchs nodule. These develop and subside over a short time span (2-3 weeks), may occur in several places at the same time and sequentially, and progressively increase in number until the outer retina is extensively damaged and replaced by patches of fibrovascular scar tissue. In animals with a retinal vasculature, such as the rat and monkey,^{26,29} vasculitis is frequently observed as an early manifestation. Retinal vasculitis may involve a few small vessels or extend to many vessels and the degree of involvement depends on the dose of antigen. The clinical and fluorescein angiographic features of experimental retinal vasculitis are identical to human retinal vasculitis.

Acute inflammation with massive exudative retinal detachment may be observed with high doses of antigen in susceptible animals and is reminiscent of Vogt-Koyanagi-Harada disease in the acute phase. Acute necrosis of the retina may also occur.² Acute EAU in Lewis rats has been the most extensively investigated model so far, but it represents only one type of uveoretinitis and is probably not the most characteristic of human endogenous uveitis.

In contrast, recent studies have demonstrated that chronic EAU can be induced in certain strains of mouse,²⁸ in guinea-pigs,²⁷ and in rats with antigens prepared in the presence of protease inhibitors.² In these models subretinal neovascularisation may occur in the late stages^{2,28} in precisely the same manner as occurs in human birdshot retinochoroidopathy.

A paradigm for human posterior uveitis has therefore emerged in that a single antigen can elicit the same range of clinical pathological manifestations in the experimental animal as are seen in human disease, and that several different antigens can induce the same limited set of responses. The factors which determine the clinical presentation, therefore, probably relate less to the nature of the antigen than to the dose of antigen, the susceptibility of the host, the genetic predisposition and the prevailing environmental conditions. Furthermore, it is likely that, although the initiating agent may differ, the mechanism of disease production is probably similar in most of these disorders but is modified by one or more of these factors. A relationship to 'infectious' forms of uveoretinitis may be envisaged whereby the initial microorganism-associated retinal inflammation induces breakdown of the blood-retinal barrier and permits

access of polyclonally activated autoreactive T cells to previously sequestered and potent retinal autoantigens, thereby setting up an autoimmune uveoretinitis which becomes self-perpetuating.³⁰

Relevance of experimental uveitis to clinical disease

The initial enthusiasm for detecting autoantibodies to retinal antigens^{31,32} and for demonstrating cell mediated immunity to retinal antigens³³ has become tempered by the observation that antiretinal antibodies occur normally in the general population^{34,35} and also that circulating autoreactive T cells to S-antigen and to IRBP are to be found in healthy individuals.^{35,36} Indeed, it has been suggested that high levels of antiretinal antibodies may be protective against the more severe forms of endogenous uveitis^{34,37} and that, in cases of active sympathetic ophthalmia and Behçet's disease, antiretinal antibodies may in fact be decreased (Forrester, Noble, Chamberlain, *et al*, unpublished observations). These results are not surprising, since only a very small proportion of serum immunoglobulins and circulating T cells are actually autoreactive, and an even smaller proportion will be specific for retinal antigens. Therefore, even if these antibodies and/or cells were proportionally increased, for example, by a factor of 10, they would probably remain below the detectable limit due to the wide range of values which occur in the normal population.

Similarly, other immunological tests of a less specific nature have been unrewarding in studies of endogenous uveitis. These include enumeration of total T and B and T cell subsets, and T/B cell proliferation studies to non-specific antigens.³⁸ For the reasons detailed above it is unlikely that such studies would be informative.

More recently markers of T cell activation have become available, such as the MHC class II surface antigen and the interleukin-2 (IL-2) receptor. These markers have been shown to occur more frequently on circulating T cells in patients with endogenous uveitis,³⁹ and these data would coincide with current concepts of a generalised increase in lymphocytic activation in inflammatory disease. According to this notion 'activated lymphocytes, including activated autoreactive lymphocytes, could gain access to a tissue through defects in the blood-tissue barrier or more probably, through changes in the surface adhesiveness of the local vascular endothelium.^{30,40} If invasive autoreactive lymphocytes come in contact with their respective autoantigen, local clonal T cell expansion would occur with considerable lymphokine production and active recruitment of further T cells and cytotoxic mononuclear cells. A focus of tissue damage with proliferating cells that it, a microgranuloma) would ensue. Since this process, at least initially, occurs at a local microscopic tissue level, it is not surprising that these changes fail to be reflected in the levels of circulating lymphocytes and autoantibodies. The only clue to such a mechanism might be that the overall level of 'activated' lymphocytes in the circulation would in some cases be increased.

Therefore, although endogenous uveitis has been resistant to the label of an 'autoimmune' disease by conventional criteria of autoantibodies and defects in T and/or B cells, there can be little doubt that immunological mechanisms play a major, if not a primary, role in the disease. Firstly, immunohistological studies show considerable involvement of various T cell subsets in many forms of the disease. Secondly, the clinical and pathological features of all types of human uveitis show extensive similarity to the various forms of experimental autoimmune uveoretinitis, induced by recognised retinal autoantigens. And, thirdly, many forms of endogenous uveoretinitis (and experimental autoimmune uveoretinitis) respond preferentially to immunosuppressive

therapy, whether it is relatively broad spectrum as with systemic steroids and azathioprine, or more selective as with the CD4+ T cell inhibitor, cyclosporin A. These observations should direct us in our search for more effective therapy.

Possible immunotherapeutic approaches

The possibilities for intervention in immunologically mediated diseases are several. The aim in immunotherapy is to be as selective as possible in inhibiting the tissue damaging components of the autoimmune response, while sparing the normally functioning cellular immune responses which are required for defence against foreign antigens. Immunomodulation may be achieved by drugs or may be more specifically directed against the autoantigen if this is known. For instance, in experimental allergic encephalomyelitis, which is an autoimmune disease induced by myelin basic protein and has certain similarities to multiple sclerosis, inhibition of the disease can be induced by 'designer' peptides which block the binding site for autoantigens on the MHC molecule of the antigen presenting cell.^{41,42} An alternative approach is to use monoclonal antibodies directed against surface molecules involved in T cell receptor recognition (particularly if they can be 'humanised' by structural manipulation)^{43,44} or against the antigen itself as with EAU.^{45,46} Intervention in this case may be mediated either by direct interaction with the antigen⁴⁵ or via an anti-idiotypic mechanism.⁴⁶ Therapy aimed at inhibiting interaction between the 'activated' lymphocyte and the endothelium – that is, at the site of blood-tissue barrier – is also possible, as has been shown recently in the case of antibodies to intercellular adhesion molecule-1 (ICAM-1) to reduce the severity of the immune response in a primate model of asthma.⁴⁷

At present these potential therapeutic strategies remain essentially experimental in relation to human uveitis. Of more immediate interest, however, are recent advances in drug based immunointervention in which increasingly selective immunosuppression is employed. In this regard, the T cell inhibitor for cyclosporin A (CsA) has been used successfully to control endogenous uveitis both experimentally⁴⁸ and clinically in cases which had become steroid resistant or intolerant.⁴⁹⁻⁵¹ Two major problems arise in relation to CsA therapy for uveitis, namely, nephrotoxicity, and rebound uveitis after sudden withdrawal of the drug. Nephrotoxicity is reduced but is still significant if low dose (<5 mg/kg body weight) CsA therapy is employed. Furthermore, patients at risk of developing nephrotoxicity may be identified by the clear link with hypertension which has recently been shown.⁵¹ That is, if the patient remains normotensive during therapy with CsA, then it is likely that he will escape renal dysfunction.

Some of the newer immunosuppressants may be less nephrotoxic, such as FK506, an inhibitor of T helper cells with an activity similar to CsA but at lower doses. In liver and renal transplant patients, FK506 has been shown to be remarkably free of nephrotoxicity,⁵² but studies in autoimmune disease have not yet been initiated. Other macrolide immunosuppressants such as rapamycin may also have potential in the therapy of autoimmune uveitis.

It can be seen therefore that, although we do not know precisely the nature of the antigens, either foreign or self antigens, involved in the pathogenesis of posterior uveitis, we now have a greater understanding of the mechanisms of immunologically mediated uveoretinal inflammation which has been gained from the study of models of EAU and has led to a more rational and direct therapeutic approach.

J V FORRESTER

Department of Ophthalmology,
University of Aberdeen,
Medical School,
Foresterhill,
Aberdeen AB9 2ZD

- 1 Forrester JV. Chronic intraocular inflammation. *Trans Ophthalmol Soc* 1985; **104**: 250-5.
- 2 Forrester JV, Liversidge J, Dua HS, Towler H, McMenamin PG. Comparison of clinical and experimental uveitis. *Curr Eye Res* 1990; **9** (suppl): 75-84.
- 3 Feltkamp TEW. HLA antigens and uveitis. *Eye* in press.
- 4 Byrom MA, Campbell MA, Hobbs JR, et al. T and B lymphocytes in patients with acute anterior uveitis and ankylosing spondylitis, and in their household contacts. *Lancet* 1979; **ii**: 601-3.
- 5 Wakefield D, Stahlberg TH, Toivanen A, Granfors K, Tennant C. Serologic evidence of yersinia infections in patients with anterior uveitis. *Arch Ophthalmol* 1990; **108**: 219-21.
- 6 BenEzra D, Nussenblatt RB. Ocular manifestations of Behçet's disease. *J Oral Pathol* 1978; **7**: 431-42.
- 7 Faure JP. Autoimmunity and the retina. *Curr Eye Res* 1980; **2**: 215-301.
- 8 Singh VK, Kalra HK, Yamaki K, Abe T, Donoso LA, Shinohara T. Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. *J Immunol* 1990; **144**: 1282-7.
- 9 Priem HA, Kijlstra A, Moes L, Baarsma GS, de Lacy JJ, Oosterhuis JA. HLA typing in birdshot chorioretinopathy. *Am J Ophthalmol* 1988; **105**: 182-5.
- 10 Priem HA, Oosterhuis JA. Birdshot chorioretinopathy: clinical characteristics and evolution. *Br J Ophthalmol* 1988; **72**: 646-59.
- 11 Chan C-C, Metzger R, Palestine A, Kuwabara T, Nussenblatt RB. Immunohistopathology of ocular sarcoidosis. *Arch Ophthalmol* 1987; **105**: 1398-402.
- 12 Inomata H, Sakamoto T. Immunopathological studies of Vogt-Koyanagi-Harada disease with sunset sky fundus. *Curr Eye Res* in press.
- 13 Sharp DC, Bell RA, Patterson E, Pikerton RMH. Sympathetic ophthalmia: histopathologic and fluorescein angiographic correlation. *Arch Ophthalmol* 1984; **102**: 232-5.
- 14 Kijlstra A. Immunological testing in uveitis. *Eye* in press.
- 15 Lightman S, Chan C-C. (1989) Immunopathology of ocular inflammatory disorders. In: Lightman, S, ed. *Immunology of eye diseases*. London; Kluwer Academic, 87-9.
- 16 Jakobiec F, Marboe C, Knowles D, Iwamoto T, Harrison W, Chang S, Coleman D. Human sympathetic ophthalmia. *Ophthalmology* 1983; **90**: 76-95.
- 17 Inomata H. Necrotic changes of choroidal melanocytes in sympathetic ophthalmia. *Arch Ophthalmol* 1988; **106**: 239-42.
- 18 Wacker WB, Donoso LA, Kalsow CM, Yankeeloo JA, Organisciack DT. Experimental allergic uveitis. Isolation, characterisation and localisation of a soluble uveitopathogenic antigen from bovine retina. *J Immunol* 1977; **119**: 1949-58.
- 19 Gery I, Mochizuki M, Nussenblatt R. Retinal specific antigens and the immunopathologic process they provoke. *Prog Retinal Res* 1986; **5**: 75-109.
- 20 Shinohara T, Dietzschold B, Craft CM, et al. Primary and secondary structure of bovine retinal S antigen (48K protein). *Proc Natl Acad Sci USA* 1988; **84**: 6975-9.
- 21 Borst DF, Redmond TM, Elser JE, et al. Interphotoreceptor retinoid-binding protein (IRBP): glue characterisations; protein repeat structures and its evolution. *J Biol Chem* 1989; **264**: 1115-9.
- 22 Kuhn H. Interactions between photoexcited rhodopsin and light-activated enzymes in rods. *Prog Retinal Res* 1984; **3**: 123-56.
- 23 Donoso LA, Merryman CF, Sery TW, et al. S-antigen: characterisation of a pathogenic epitope which mediates experimental autoimmune uveitis and pinealitis in Lewis rats. *Curr Eye Res* 1987; **6**: 1151-9.
- 24 Gregerson DS, Obritsch WF, Fling SP. Identification of a uveitogenic cyanogen bromide peptide of bovine retinal S-antigen and preparation of a uveitogenic, peptide specific T cell line. *Eur J Immunol* 1987; **17**: 405-11.
- 25 Sanui H, Redmond TM, Kotake S, et al. Identification of an immunodominant and highly immunopathogenic determinant in the retinal interphotoreceptor retinoid-binding protein (IRBP). *J Exp Med* 1989; **169**: 1947-60.
- 26 De Zozak Y, Sakai J, Thillaye B, Faure JP. S-antigen-induced experimental autoimmune uveoretinitis in rats. *Curr Eye Res* 1981; **1**: 327-40.
- 27 Forrester JV, Borthwick GM, McMenamin PG. Ultrastructural pathology of S-antigen uveoretinitis. *Invest Ophthalmol Vis Sci* 1985; **26**: 1281-92.
- 28 Caspi RR, Roberge FH, Chan CC, et al. A new model of autoimmune disease. *J Immunol* 1988; **140**: 1490-5.
- 29 Nussenblatt RB, Kuwabara T, de Monasterio FM, Wacker WB. S-antigen uveitis in primates. A new model for human disease. *Arch Ophthalmol* 1981; **99**: 1090-2.
- 30 Liversidge J, Sewell HF, Forrester JV. Interactions between lymphocytes and cells of the blood-retina barrier: mechanisms of T lymphocyte adhesion to human retinal capillary endothelial cells and retinal pigment epithelial cells in vitro. In press.
- 31 Gregerson DS, Abrahams IW, Thirkill CE. Serum antibody levels of uveitis patients to bovine retinal antigens. *Invest Ophthalmol Vis Sci* 1981; **21**: 669-80.
- 32 Uusitalo RJ, Stjenschantz J, Mahlberg K, et al. Serum antibody level to S-antigen in children with chronic uveitis. *Br J Ophthalmol* 1985; **69**: 212-6.
- 33 Nussenblatt RB, Gery I, Ballantine EJ, Wacker WB. Cellular immune responsiveness of uveitis patients to retinal S-antigen. *Am J Ophthalmol* 1980; **89**: 173-9.
- 34 Forrester JV, Stott D, Hercus K. Naturally occurring antibodies to bovine and human retinal S-antigen: a comparison between uveitis patients and healthy volunteers. *Br J Ophthalmol* 1989; **73**: 155-9.
- 35 Doekes G, van der Gaag R, Rothova A van Kooyk Y, et al. Humoral and cellular immune responsiveness to human S antigen in uveitis. *Curr Eye Res* 1987; **6**: 909-19.
- 36 Hirose S, Tanaka T, Nussenblatt RB, et al. Lymphocyte responses to retinal-specific antigens in uveitis patients and healthy subjects. *Curr Eye Res* 1988; **7**: 393-403.
- 37 Dumonde DC, Kasp-Grochowska E, Graham E, et al. Anti-retinal autoimmunity and circulating immune complexes in patients with retinal vasculitis. *Lancet* 1982; **ii**: 787-92.
- 38 Froebel KS, Armstrong SS, Urbaniak SJ, Forrester JV. An investigation of the general immune status and specific immune responsiveness to retinal S-antigen in patients with chronic posterior uveitis. *Eye* 1989; **3**: 263-70.
- 39 Deschenes J, Char DH, Kalita S. Activated T lymphocytes in uveitis. *Br J Ophthalmol* 1988; **72**: 83-7.
- 40 Pab ST, Horst E, Scheper RJ, Meijer GJLM. Mechanisms of lymphocyte migration and their role in the pathogenesis of disease. *Immunol Rev* 1989; **108**: 112-33.
- 41 Urban JL, Horvath SJ, Hood L. Autoimmune T cells: immune recognition of normal and variant peptide epitopes and peptide-based therapy. *Cell* 1989; **59**: 257-71.
- 42 Wraith DC, Similek DE, Mitchell DJ, Steinman L, McDevitt HO. Antigen recognition in autoimmune encephalomyelitis and the potential for peptide-mediated immunotherapy. *Cell* 1989; **59**: 247-55.
- 43 Depper JM, Leonard WJ, Waldmann TA, Greene WC. Blockade of the interleukin-2 receptor by anti-Tac antibody: inhibition of human lymphocyte activation. *J Immunol* 1983; **131**: 690-6.
- 44 Reichmann L, Clark M, Waldmann H, Winter G. Reshaping human antibodies for therapy. *Nature* 1988; **332**: 323-7.
- 45 Dua HS, Sewell HF, Forrester JV. The effect of retinal S-antigen-specific monoclonal antibody therapy on experimental autoimmune uveoretinitis (EAU) and experimental autoimmune pinealitis (EAP). *Clin Exp Immunol* 1989; **75**: 100-5.
- 46 De Kozak Y, Mirshahi M, Boucheix C, Faure JP, Letts LG, Rothlein R. Prevention of experimental autoimmune uveoretinitis by active immunisation with autoantigen-specific monoclonal antibodies. *Eur J Immunol* 1987; **17**: 541-7.
- 47 Wegner CD, Gundel RH, Reilly P, Haynes N. Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. *Science* 1990; **247**: 456-9.
- 48 Nussenblatt RB, Rodrigues MM, Walker WB, et al. Cyclosporin A inhibition of experimental autoimmune uveitis in Lewis rats. *J Clin Invest* 1987; **67**: 1228-31.
- 49 Nussenblatt RB, Palestine AG, Chan CC. Cyclosporin. A therapy in the treatment of intraocular inflammatory disease resistant to system corticosteroids and cytotoxic agents. *Am J Ophthalmol* 1983; **96**: 275-82.
- 50 Towler HM, Cliffe AM, Whiting PH, Forrester JV. Low dose cyclosporin A therapy in chronic posterior uveitis. *Eye* 1989; **3**: 282-7.
- 51 Towler HM, Whiting PH, Forrester JV. Combination low dose cyclosporin A and steroid therapy in chronic intraocular inflammation. *Eye* in press.
- 52 Thomson AW. FK506 enters the clinic. *Immunol Today* 1990; **11**: 35-6.