DUKE-ELDER LECTURE: NEW CONCEPTS ON THE ROLE OF AUTOIMMUNITY IN THE PATHOGENESIS OF UVEITIS

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I am deeply honoured to be invited to give the 6th Duke-Elder lecture. Duke-Elder is renowned for his many contributions to ophthalmology, but first and foremost he was one of those rare ophthalmologists who saw the importance of applying the scientific method to fundamental clinical problems and it was for his work as a scientist that he was elected Fellow of the Royal Society.

His major scientific interest was in the physiology of the ocular fluids but among his many other works he found time to make observations on uveitis. In the William McKenzie Memorial Lecture of 1930, he wrote that the 'pathology of vitreous inflammatory deposits was well understood'.[1] I'm not sure we would agree with that today. In a further paper in the Lancet concerning the prognosis of iritis and iridocyclitis, he stated, on the causation of uveitis, 'That most cases of . . . uveitis are due to infective foci . . . must be accepted as a fact'.[2] However, he further observed that uveitis caused by an infectious agent was 'not necessarily due to enlodgement of toxin in the eye but mostly (represented) an allergic sensitisation response'. I think many of us would lean towards this view and I hope to show you here today that there are very sound scientific reasons why this concept probably still holds true.

Inflammation of the eye and endogenous uveitis were included in an early English language textbook of ophthalmology by William McKenzie and several varieties of uveitis were described including sympathetic ophthalmia. However, even this paradigm of an autoimmune disease was not recognised as such since concepts of immunological responses were poorly developed. McKenzie considered that the disease was transmitted by interocular neural transfer,[3] and indeed there is evidence for such mechanisms in experimental models.[4] However the temporal delay in second eye involvement could not be explained by such mechanisms.

Advances in the discipline of immunology led Paul Ehrlich[5] to develop the concept of autoimmunity and to the notion that autoimmune responses were self-destructive (horror autotoxicus). However, he considered that autoantibodies were a normal occurrence and that somehow they were inactivated by anti-autoantibodies, pre-empting current network theory[6] by some eighty-three years. Studies by Ulenhueth[7] on autoantibodies to lens proteins supported Ehrlich's views of regulatory controls of autoantibody responses. Somewhat later, sympathetic ophthalmia was recognised as an autoimmune disease and the putative antigen identified as melanin.[8,9] This view held for many years and melanin is still implicitly regarded as the putative autoantigen for certain forms of posterior uveitis.[10] However, the importance of the retina in autoimmune intraocular inflammatory disease had already been highlighted in some early experimental studies by Hess and Romer in 1906 (for review see Faure[11]).

These initial studies in the field of autoimmunity fell into relative obscurity as the emphasis of immunological research was placed on immunochemistry and the structure of immunoglobulins, rather than on the functional role of the cells which produce these and many other molecules. It was not until the late 1950s that cellular aspects of immunology returned to the fore and that concepts of autoimmunity became established. Even today there is continuing controversy concerning the notion that uveitis may represent one form of autoimmune disease.

IS ENDOGENOUS UVEITIS AN AUTOIMMUNE DISEASE?

Uveitis is generally categorised by its dominant site of activity, i.e. anterior uveitis or posterior uveitis, each of which is pathogenetically and clinically a discrete entity. Anterior uveitis is usually an acute self-limiting disease and is closely linked with Major Histocompatibility (MHC) Class I- antigens, particularly HLA B27, while posterior uveitis is more frequently associated with MHC Class II antigens and is often chronic in nature. Although infective causes of uveitis are well documented, the search for causative organisms in individual cases is commonly

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unrewarding, and despite associations with other systemic diseases, most cases of endogenous uveitis are considered idiopathic.

Posterior uveitis presents as a heterogeneous group of syndromes with no obvious relationship (Table I), but they often have features in common. For instance, focal choroido-retinal infiltrates are a feature of several disorders including sympathetic ophthalmia,[12] sarcoidosis,[13] and the resolving phase of Vogt-Koyanagi-Harada's disease.[14] Most of these syndromes also have some degree of retinal vessel inflammation (retinal vasculitis), even if it is merely a capillaritis causing vascular leakage at the macula as in pars planitis or intermediate uveitis; and a *sine qua non* for endogenous posterior uveitis is vitreous cellular infiltration.

Pathological studies have been relatively infrequent for obvious reasons and generally have been performed on end-stage severely injured eyes associated with sympathetic ophthalmia, or on eyes which have otherwise been removed because they are blind and painful. Immunohistological studies have identified CD4+ T(helper) cells, CD8+ T(cytotoxic/suppressor) cells, and macrophages in varying proportions in inflammatory exudates in the choroid and in the perivascular infiltrates in the retina.[15] Dalen-Fuchs nodules appear to contain a high proportion of macrophages in addition to CD4+ T cells[16] (Fig. 1a, b and c).

However, these studies do not help us to understand the cellular mechanisms of tissue damage in posterior uveitis. Accordingly, on the premise that these diseases are autoimmune in nature, many attempts have been made to identify the autoantigen. Initially, these studies focused on possible uveal antigens and melanin was considered to be a candidate autoantigen. However, many attempts to induce ocular inflammation in experimental animals with repeated systemic injections of uveal tissue extracts were singularly unsuccessful in inducing disease. In 1965, Wacker and Lipton immunised guinea pigs intradermally with extracts of retinal tissue and produced a severe, reproducible, dose-dependent panuveitis with a single injection of antigen.[17] Subsequent studies identified a soluble retinal antigen in the photoreceptor outer segment, retinal S-antigen,[18] which was also under study by other groups as a regulatory protein for phototransduction (otherwise known as arrestin).[19] Several retinal antigens have now been described including interphotoreceptor retinol binding protein (IRBP)[20] (rhod)opsin[21] and phosducin,[22] all with the ability to induce posterior uveoretinitis, and a retinal pigment epithelial cell protein which produces a predominantly anterior uveitis. The best characterised of these antigens are S-antigen and IRBP; furthermore, the inflammatory response they induce in the eye has many similarities to human posterior uveitis.[23] Indeed, the response can be titrated by dose to produce a low-grade, subacute or chronic inflammation with predominantly Dalen-Fuchs type lesions (Fig. 1d), a moderately severe inflammation with retinal vasculitis and extensive retinal damage (Fig. 1e), or a hyperacute type of response with massive exudative retinal detachment or retinal necrosis (Fig. 1f) (for a detailed review of the pathology see Forrester *et al.*[23]).

Table I. Clinical forms of posterior uveitis. The table includes only a small sample of the many syndromes which present as posterior uveitis

Pars planitis
Intermediate uveitis
Sympathetic ophthalmia
Sarcoidosis
Birdshot retinochoroidopathy
Retinal vasculitis (peripheral periphlebitis)
Central retinal vasculitis
Behçet's disease
Vogt-Koyanagi-Harada's disease
Acute retinal necrosis

Inflammation induced in this model is assumed to be autoimmune in nature since the inflammation is inducible with heterologous, homologous or autologous antigen and most of these proteins have been highly conserved during evolution, thus showing considerable sequence homology between species. The disease which they induce is termed experimental autoimmune uveoretinitis (EAU) and the target cell has been identified as the photoreceptor cell partly on the basis that the cells appear to home in on this layer of cells from the earliest stages of the disease[24] and partly because most of these antigens derive from the photoreceptor/RPE interface. EAU has many similarities in its method of induction to other autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE), experimental autoimmune thyroiditis (EAT), and collagen-induced arthritis, all of which are deemed to be organ-specific although less is known about the precise cellular target in these diseases.

A major advantage of these models for human studies is that the earliest stages of the disease can be investigated. Thus it has been shown that at the onset of the disease CD4+ T cells and macrophages predominate in the lesions, while CD8+ T cells appear later in the disease.[25] B cells increase in number during the healing phase of the disease while MHC Class II expression occurs on several cells from the earliest stages of the disease.

However there are many questions raised by these models of autoimmunity. Firstly, the evidence that they are autoimmune is circumstantial and dependent on a number of assumptions. Indeed, what do we mean by the term autoimmune disease? Secondly, if these models do represent autoaggressive immune responses, how do they produce their effects?

CURRENT CONCEPTS OF AUTOIMMUNITY

The concept of autoimmunity is fundamental to the immune system. Langman[26] described the first law of the immune system as follows: 'Any mechanism of host defence against infectious agents which has the capacity to destroy macromolecules, requires a recognitive component which can distinguish self from non-self.' Such a law holds true even for simple organisms, like amoeba. Thus in the microcosm of a pool of rain water, an amoeba

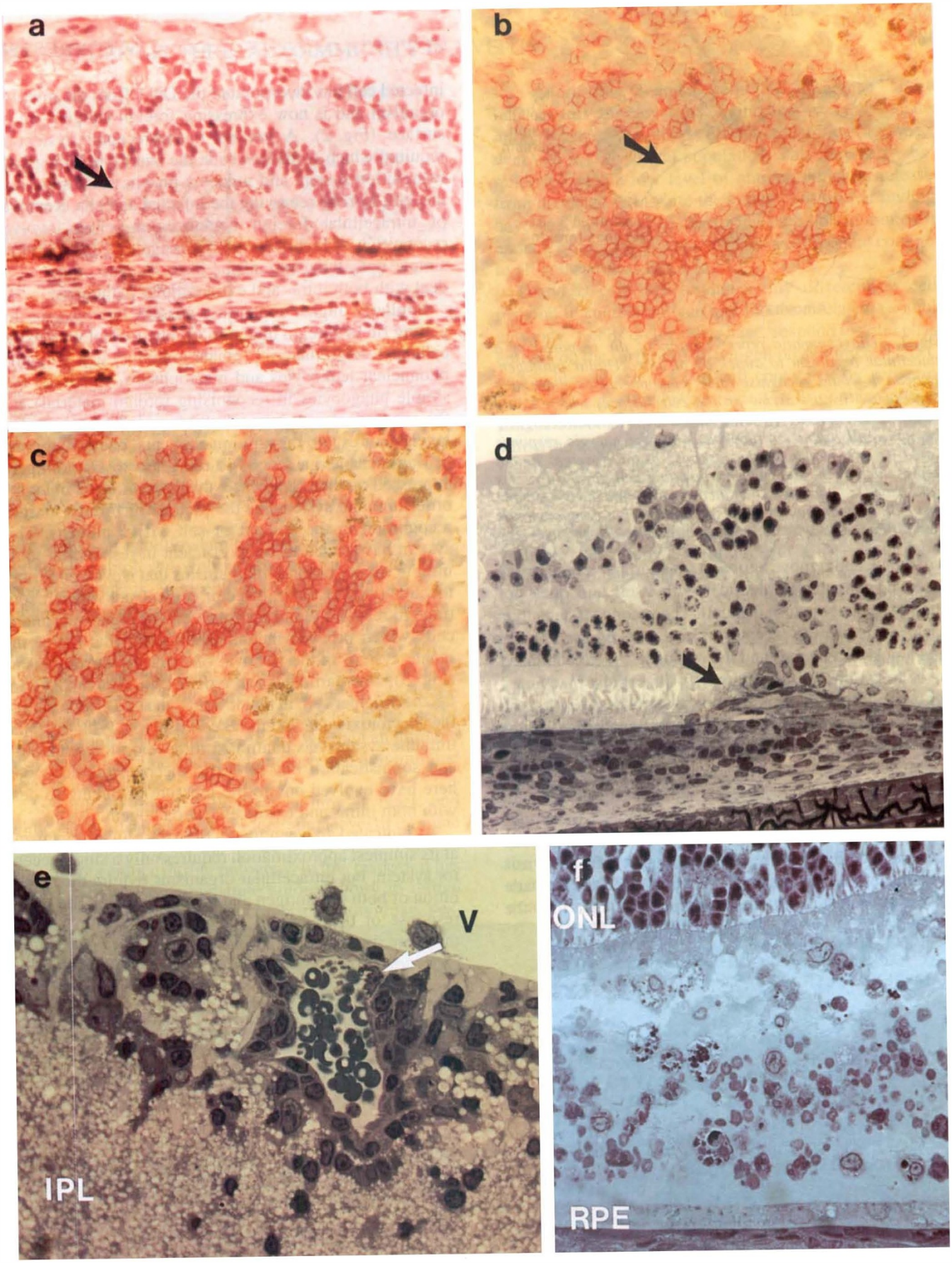

Fig. 1. *(a) Dalen-Fuchs nodule at the chorioretinal interface (arrow) in a case of sympathetic ophthalmia. (b) CD4+ T cells (stained red with anti-CD4 antibody in the APAAP technique) in a choroidal granuloma in a case of sympathetic ophthalmia. The centre of the granuloma is located around a vessel (arrow). (c) CD8+ T cells (APAAP technique using anti-CD8 antibody) in the same case as (b). (d) Microgranuloma at the chorioretinal interface (arrow) in guinea pig EAU. Note the greater involvement of the inner retinal layers and the choroidal mononuclear cell infiltrate. (e) Retinal (peri)vasculitis in the rat model of EAU. Note that the infiltrating cells in the perivascular site are predominantly mononuclear. Note also the changes to the endothelial cells with signs of 'activation' (HEV like changes, see later in the text). V, vitreous; IPL, inner plexiform layer. (f) Extensive exudative retinal detachment in rat EAU with marked subretinal inflammatory cell infiltrate. RPE, retinal pigment epithelium; ONL, outer nuclear layer.*

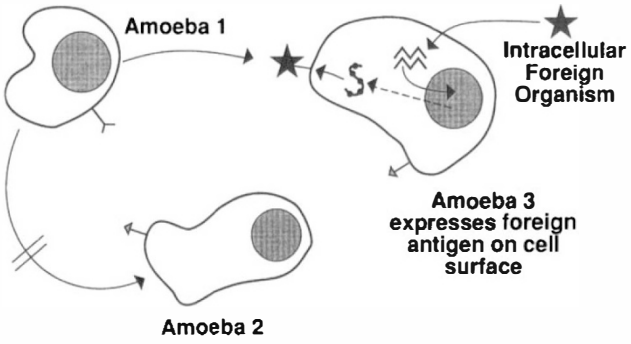

Fig. 2. *Diagrammatic representation of the response of a unicellular organism to attack by an intracellular pathogen. Amoeba 1 would recognise 'self' components on amoeba 2 (represented by the arrow on the cell surface) which would induce a state of anergy in amoeba 1. Amoeba 1 would recognise the same self ligand on amoeba 3 but the anergic response would be over-ridden by the response to the 'foreign' ligand (represented by the star) which constitutes cell surface proteins transcribed from foreign DNA incorporated into the DNA of the host cell. Recognition of both self and foreign components is therefore necessary for removal of intracellular organisms.*

will attack and remove a foreign invader, but it recognises a second amoeba as identical with itself and does not attempt to phagocytose that cell. The second amoeba thus has a mechanism (a receptor) which is recognised by the first amoeba (a ligand) and the response which is induced in the first amoeba is to 'switch off' its cellular machinery for phagocytosis. This is an important concept i.e. that the first interaction between receptor and ligand is to induce non-responsiveness or anergy in the cell.

A mechanism such as this enables the cell to deal with extracellular foreign organisms without destroying itself. However, this system does not allow the cell to remove intracellular foreign organisms. An amoeba which has been infected by an intracellular pathogen such as a virus or parasite, still has its 'self' receptor and would evade attack by a healthy amoeba, despite the fact that the infected cell has incorporated the DNA from the invasive organism and is now expressing foreign antigens on its surface (Fig. 2). A second ligand-receptor system is required which would override the anergy-inducing self-recognition system and induce a phagocytic response in the cell, thereby removing the infected amoeba. Removal of intracellular foreign organisms therefore involves recognition of both self and foreign antigen. In this way simple unicellular organisms have become equipped to deal with both intra- and extra-cellular pathogens.

Similarly, higher organisms possess two systems for getting rid of foreign material: (a) one to deal with extracellular foreign material (innate immunity e.g. polymorphonuclear leukocytes and macrophages, which act like simple phagocytes in recognising foreign material) and (b) one to deal with intracellular foreign organisms. The latter requires two recognition elements, one to recognise self antigens and a second to recognise foreign antigens expressed on the cell surface: this is manifested in higher order immune systems as the process of foreign antigen recognition in the context of self MHC antigens. This system has proved to be so efficient in responding to an infinite variety of foreign organisms that it evolved further towards two classes of effector cells: T cells which continue to respond to intracellular foreign organisms and B cells which produce factors (antibodies) that 'help' the innate system in the removal of extracellular organisms (Fig. 3). One particular cell type is central to this system i.e. the T helper cell, in that it 'arms' the two effector cells, the T cytotoxic cell and the B cell (Fig. 3). With time, the immune system has continued to develop in complexity and sophistication but the basic mechanisms described here have evolved due to the pressure of having to deal with both intra- and extra-cellular pathogens.

As indicated above, removal of extracellular organisms at its simplest approximation requires only a single receptor system, but intracellular organisms require the recognition of both self antigen and foreign antigen. The initial response of the immune cell on contact with antigen, therefore, is the induction of a non-responsive or anergic state induced by the 'self' component of the antigen on the

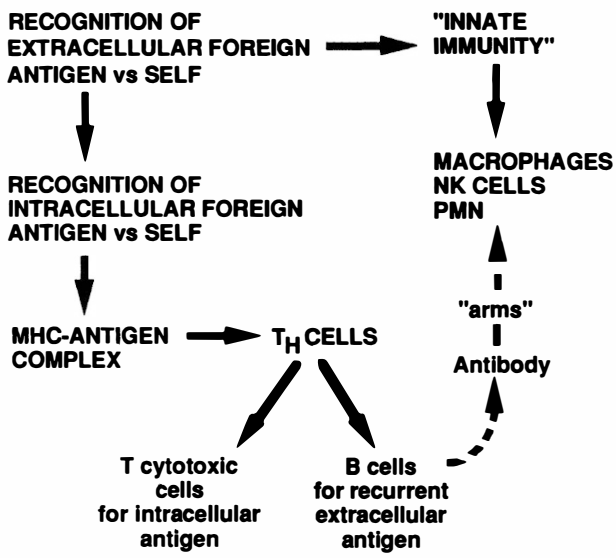

Fig. 3. *Flow diagram of the evolutionary development of different types of immune cells.*

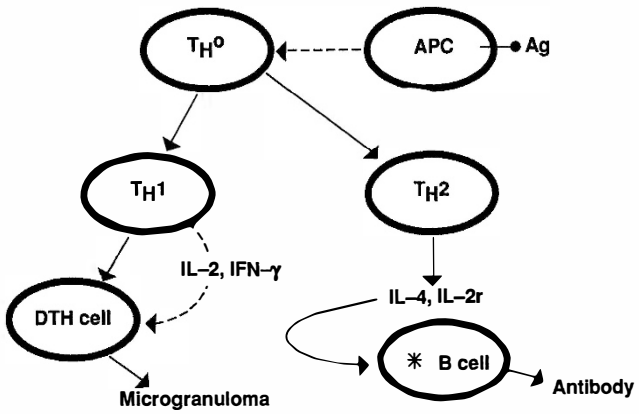

Fig. 4. *Classification of types of T cell on the basis of their cytokine production and the immune response they induce. Th0, resting T cell; Th1, T helper cell (type 1); Th2, T helper cell (type 2); APC, antigen presenting cell; DTH, delayed type hypersensitivity; Ag, antigenic peptide.*

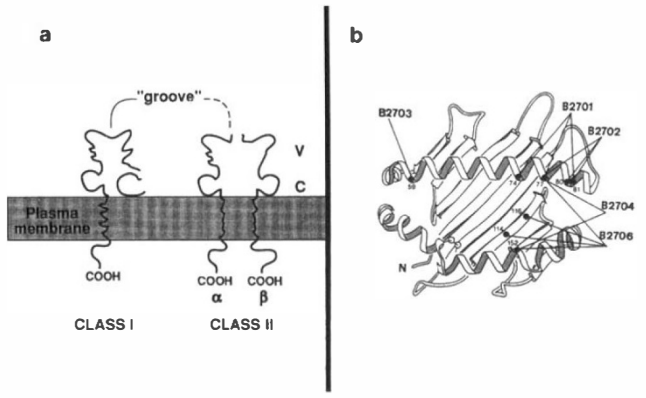

Fig. 5. *Representation of the MHC class molecules at the cell surface, depicting (a) their subunit chain structure and (b) an* en face *view of the 'peptide binding' groove, with sites for amino acid substitutions associated with different allelles of HLA B27. V, variable region of the extracytoplasmic portion of the MHC molecule; C, constant region of the extracytoplasmic portion of the MHC molecule; α, β, chains of the MHC Class II molecule.*

cell surface. It is only when the 'self' component of the antigen is complexed with a 'foreign' component that a second signal is induced and an immune response mounted; in contrast, if the second component of the complex is also a autoantigen, then no second signal occurs and the cell remains in a state of anergy or tolerance. However if an autoantigen is not recognised as self (e.g. if there is cross-homology with foreign antigen to which the organism has recently become exposed as in the mechanism of molecular mimicry, see below), then an immune response is mounted to the autoantigen and autoimmune disease may occur.

As with all things biological, nothing is black and white. Thus all autoantigens induce some level of immune response depending on the nature of the antigen and its time of appearance during ontogeny. In this respect, it has proved difficult to demonstrate autoimmunity to retinal antigens in human uveitis since normal individuals possess autoreactive T and B cells to S antigen[27,28] and to IRBP[29] and the level of antibodies or cell-mediated immune responsiveness is often not significantly greater than that in the general population. This may partly be a reflection of the low level of antigen which is released from damaged retina into the system, but similar findings have been observed in other presumed autoimmune diseases,[30] except where the antigen is a component common to all cells such as DNA in SLE.[31]

T and B cells are fundamentally different. B cells respond to soluble antigen and induce effects via soluble antibody. T cells on the other hand, respond to solid phase antigen on the surface of an antigen presenting cell (APC) and induce effects via cell-cell contact or by activating other cells e.g. effector/cytotoxic T cells or macrophages. Interaction of an APC with a naive or resting T cell leads to autocrine activation of that T cell via the cytokine, interleukin-2 (IL-2), and its receptor on the T cell, the IL-2 receptor (IL-2r). This produces clonal expansion in the T cell.

The central cell for all immune responses is the CD4+ T(helper) cell. Activation of a resting CD4+ T cell by an APC may induce that cell to differentiate in one of two ways: the T helper-1 (Th1) cell secretes IL-2 and interferon-γ, which produces a delayed type hypersensitivity (DTH) response and activated macrophages; the T helper-2 (Th2) response leads to IL-4 production and activation of B cells with secretion of antibody (Fig. 4).

Presentation of antigen by the APC occurs via recognition of the antigen bound to cell-surface major histocompatibility complex (MHC) antigen by a receptor on the T cell known as the T cell receptor (TCr) (Fig. 5). CD4+ T cells recognise MHC Class II antigens while CD8+ T cells recognise MHC Class I antigen. Crystallography studies have shown that the antigenic peptide occupies a groove in the Class I molecule formed between α and β chains of the extracellular domain of the molecule (Fig. 5). A similar relationship has been inferred for the Class II molecule.

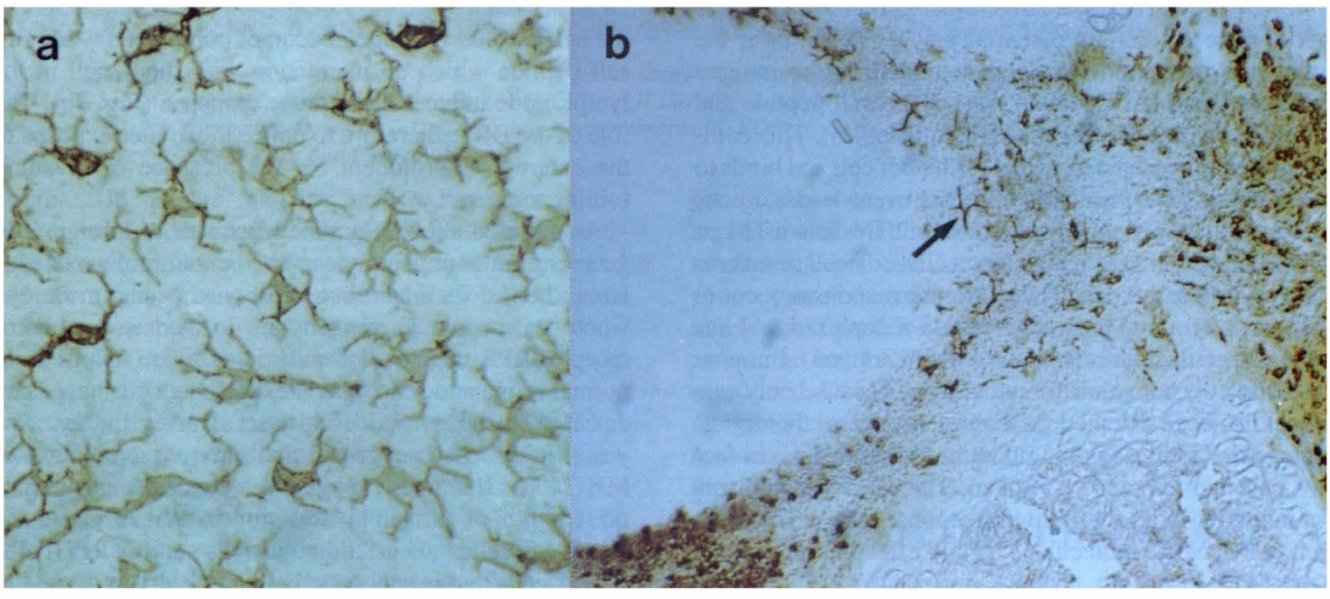

Fig. 6. *Dendritic cell networks in (a) the skin (b) the trachea. Note the prominent appearance of dendritic cells in the upper respiratory epithelium (arrow). Rat tissue.*

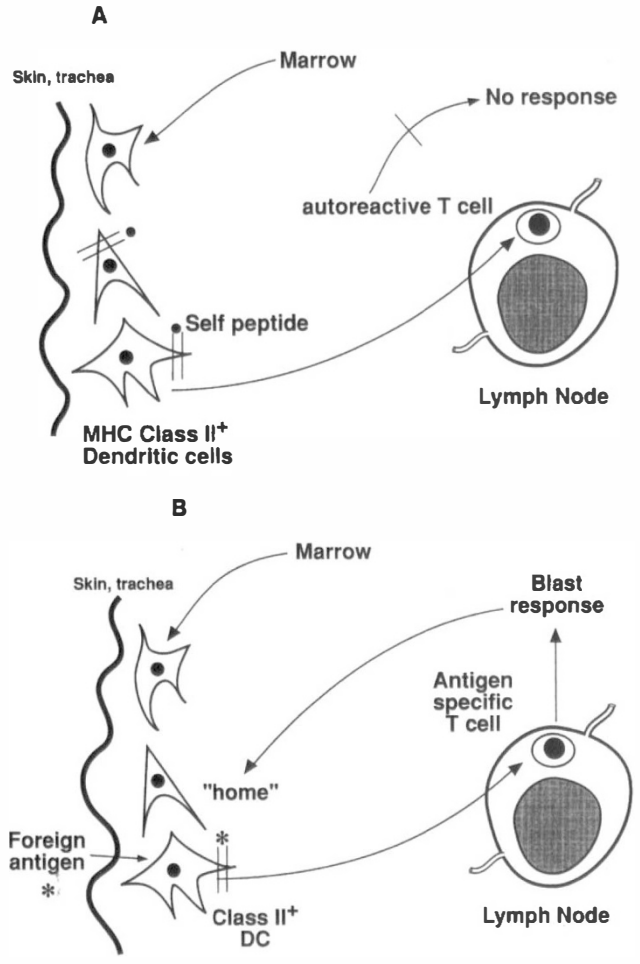

Fig. 7. *Antigen capture by cells lining potential entry sites for pathogens. (a) Dendritic cells which contain autoantigenic peptides in their MHC Class II 'grooves' normally induce a state of anergy in local lymph node T cells. (b) Dendritic cells which sample foreign antigen induce a proliferative response in antigen-specific T cells.*

It will be clear therefore that for an immune response to occur there are certain essential players in the cast: the antigen is processed (partially degraded) by an antigen presenting cell (APC) to the level of a small peptide and combined with self antigen (MHC molecules). This complex is then presented to a CD4+ T helper cell and binds to the receptor (TCr) on that cell. This event leads to activation of the T cell which then differentiates into a Th1 or a Th2 cell which in turn activates a CD8+ T cell or macrophage (Th1) or a B cell (Th2). Immune responses occur in this way to foreign antigens because a duplex signal has been detected (self antigen and foreign antigen). Immune responses do not occur to autoantigen because only one signal has been detected (self antigen), unless the organisms is fooled into thinking that the autoantigen is in fact non-self and tolerance is broken. The same mechanisms for induction of an autoimmune response are used i.e. antigen, APC, MHC molecule, TCr and effector cells.

ANTIGEN PRESENTATION IN THE EYE

Presentation of antigen combined with MHC Class II self-antigen to CD4+ T cells is a function of professional antigen presenting cells (APC) such as macrophages, dendritic cells and B cells. B cells perform their APC function as a secondary response i.e. as part of the memory or recall response in circumstances where the organism has already been exposed to the antigen. In addition the B cell uses its antigen-specific surface IgG molecule to 'capture' antigen prior to endocytosis. The B cell therefore behaves in a rather specialised way in this context and is not relevant to initiation of the immune response.

The macrophage is generally recognised as a major APC and engages in non-antigen specific endocytosis of antigen for processing. It may also endocytose antigen complexed to antibody (an immune complex) by way of its receptor for the Fc portion of the antibody. A memory response would also be required. However, the macrophage is 100 times less effective as an APC than the dendritic cell and unlike the dendritic cell, it cannot present antigen to naive or unprimed T cells. The macrophage, in contrast, is more efficient in endocytic function and may co-operate with dendritic cells by delivering antigen to the dendritic cell in a more presentable form.

The dendritic cell (DC) is therefore seen as the cell most likely to be involved in *de novo* immune responses. DCs are bone-marrow derived cells which are to be found in the lymph nodes and spleen and at sites of entry of antigen into the organism. They form an extensive network of connecting cells in the skin, trachea and intestinal tract (Fig. 6) and constantly 'traffic' between these tissues and the lymphatic system. DCs constitutively express high levels of MHC Class II antigen which in the resting state is thought to be occupied by processed peptide from self-antigen or to exist in the unoccupied state. Thus when the DC has sampled autoantigen in the periphery, it circulates to the lymph node where the self peptide-MHC complex induces a state of anergy in autoreactive T cells, thereby maintaining a state of tolerance (Fig. 7a). However, if the DC has been exposed to foreign antigen at a site of entry, the MHC Class II antigen becomes complexed with non-self peptide which on interaction with the T cell in the lymph node induces an immune response (Fig. 7b). The role of the DC is therefore to police those sites exposed to the external environment for the presence of invading foreign antigen.

As outlined above, immune responses to foreign antigens and autoantigens occur by the same mechanisms. How, then, does an immune response occur in the eye where the presumed antigens are located at the photoreceptor/RPE interface? Dendritic cells are absent from normal retina and few Class II expressing cells have been detected in the normal uveal tract. During the last few years, it has been suggested that aberrant expression of MHC Class II antigen by organ-resident cells may permit presentation of antigen by non-professional APC to autoreactive T cells.[32] Thus, although cells such as RPE cells, Muller cells and retinal endothelial cells do not normally express MHC Class II they can be induced to do so *in vitro* in the presence of cytokine, especially interferon-

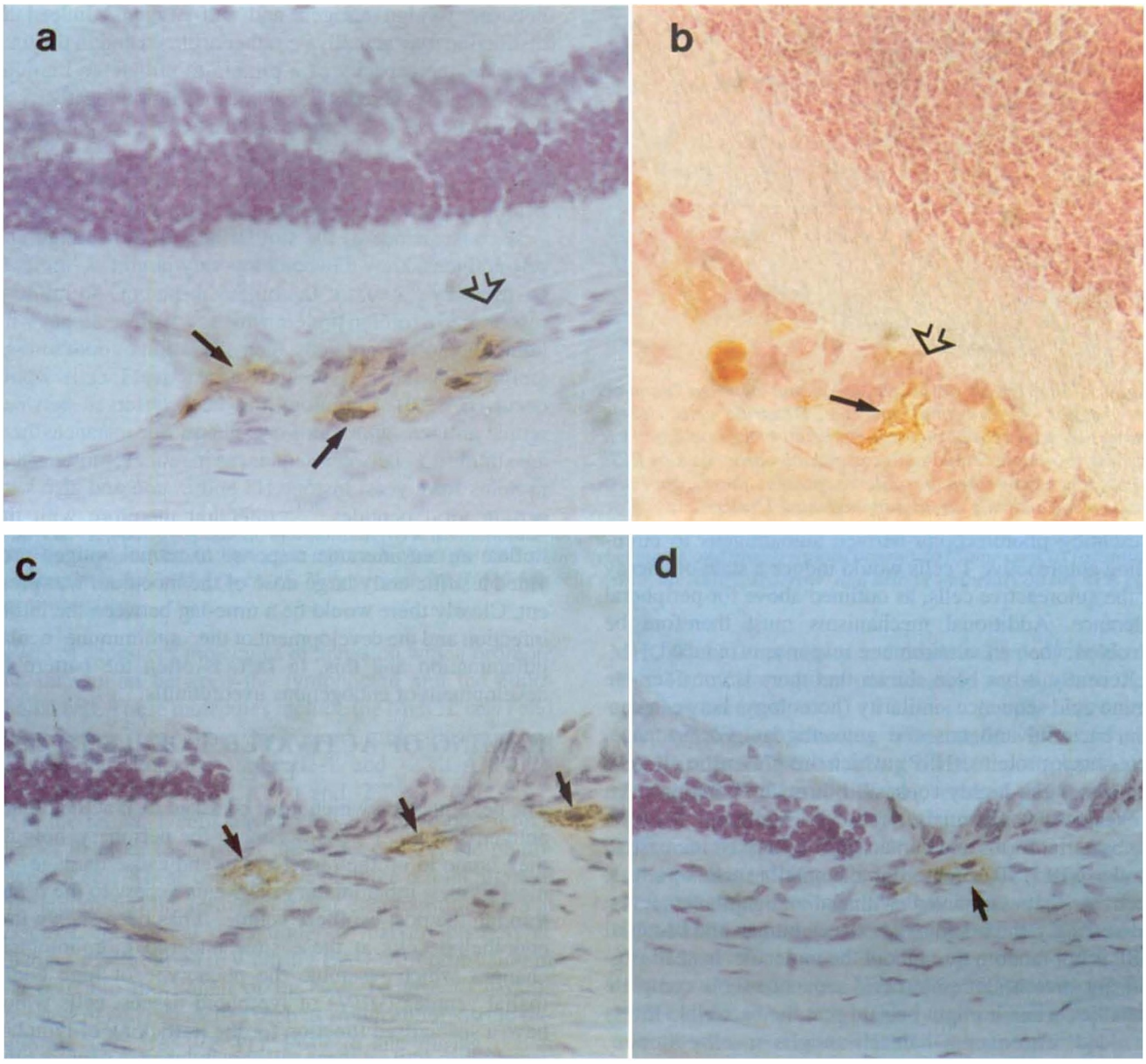

Fig. 8. *Immunohistochemical studies of normal rat eye tissue using frozen sections and a streptavidin-biotin-peroxidase labelling technique. Sections stained with antibodies to (a, b) MHC Class II showing dendritic cells in the choroid (arrows), closely interacting with the RPE cells (arrowhead); and (c, d) macrophage determinants (c, ED2; d, ED3) showing macrophage-like cells in the uveal tissue at the region of the pars plana (arrows).*

gamma.[33] In human[34] and rat[35] eyes with uveoretinitis, RPE cells have been noted to express MHC Class II antigen although this has not always proved to be the case and some controversy exists.[25] In addition, RPE cells are poor presenters of antigen when tested in functional assays,[36] while Muller cells[37] and ciliary body epithelial cells[38] may even down-regulate immune responses.

Recently, a re-examination of the normal uveal tract has revealed the presence of a large network of Class II positive cells which span the thickness of the choroid and send processes into intimate contact with RPE cells (Fig. 8a and b). In addition there is a mixed population of tissue and bone-marrow derived macrophages which closely communicate with the dendritic cells (Fig. 8c and d). There is therefore no need to invoke a mechanism of antigen presentation within the eye which involves aberrant expression of MHC Class II by resident cells. Instead, a mechanism can be envisaged whereby retinal antigens are phagocytosed during the normal process of outer segment renewal and peptides from these antigens are transported across the basal RPE into the cytoplasm of the closely-associated DC. The DC then presents the peptide to randomly circulating autoreactive T cells which are present normally in the circulation and would traffic through the choroid (Fig. 9).

INFECTION AND AUTOIMMUNITY

A mechanism such as this, however, does not explain how autoimmune disease occurs. Rather, it is an explanation of how tolerance to retinal antigens is maintained since DCs

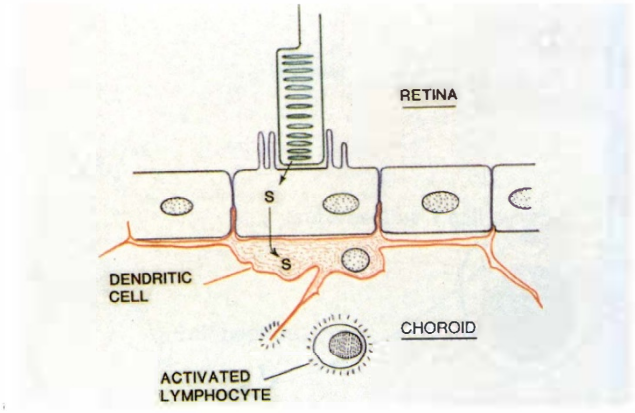

Fig. 9. *Diagram of proposed interaction between 'immune cells' at the chorio-retinal interface. Dendritic cells closely interacting with retinal pigment epithelial cells would be in a position to sample retinal antigens partially processed by RPE cells; they would then be able to present these processed antigens to randomly circulating activated T cells.*

presenting photoreceptor-derived autoantigens to circulating autoreactive T cells would induce a state of anergy in the autoreactive cells, as outlined above for peripheral tolerance. Additional mechanisms must therefore be involved when an autoimmune response is induced.

Recently it has been shown that there is considerable amino acid sequence similarity (homology) between certain bacterial antigens and autoantigens. For instance, heat-shock proteins (HSP), which are present in all cells and have been highly conserved through evolution from prokaryotes to mammals, show 50% homology between the bacterial forms and human HSP. A marked increase in synthesis of HSP is induced in mammalian cells by stress, such as that associated with inflammation or fever. Interestingly, the homology between human and bacterial HSP is not random throughout the molecule. Instead, significant stretches of amino acid sequence show complete identity.[39] Thus it might be said that the bacterial HSP is 'studded' with mammalian self-antigen or self-epitope.

HSP are just one of many examples of similarities

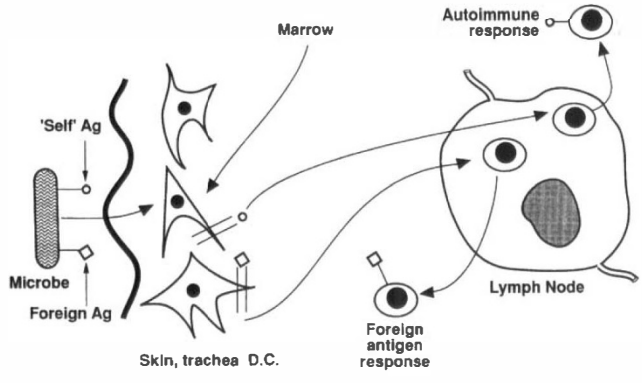

Fig. 10. *Capture of foreign antigen which coincidentally possesses regions of protein sequence (epitopes) identical to regions on human autoantigens (represented as 'self' antigen on the microbe in the diagram) could initiate immune response to both the foreign protein sequences and to the autoantigen, thus breaking tolerance (anergy) to the autoantigen and leading to autoimmune disease.*

between 'foreign' antigens and 'self-antigens'. Indeed the distinction may actually be rather artificial and in the final analysis, the capacity of a protein to initiate an immune response may merely be related to its immunogenicity or pathogenicity. Thus self-antigens belong to the poorly immunogenic group of proteins while certain non-self antigens (but by no means all such 'foreign' antigens) belong to the strongly immunogenic group.

A consequence of the similarity between foreign and self-antigens, known in contemporary jargon as 'molecular mimicry', is that if the organism mounts an immune response to a foreign protein which contains epitopes with homology to self-antigens, then activation of both foreign antigen-reactive T cells and autoreactive T cells would occur (Fig. 10). Homology has been observed between retinal antigens and micro-organisms. For instance, there are similarities between sequences in retinal S antigen and proteins from yeast histone H3 and *E. coli* and also with certain viral peptides.[40–42] Infection therefore with the appropriate pathogenic strain of the organism might initiate an autoimmune response to retinal antigen provided a sufficiently large dose of the inoculum was present. Clearly there would be a time-lag between the initial infection and the development of the 'autoimmune' ocular inflammation and this, in fact, is often the pattern of development of endogenous uveoretinitis.

HOMING OF ACTIVATED T CELLS TO THE EYE

The next question which must be asked is, if activation of antigen-specific T cells occurs in the periphery, how do they home in on the target organ and cause damage? In most tissues, inflammatory cells gain access to the tissue through the post-capillary venule. It has been shown that endothelial cells at these sites undergo morphological changes which resemble the phenotype of high endothalial venules (HEV) of lymphoid tissues, cells which have a specialised function for the trafficking of lymphocytes.[43] In addition, these cells are induced to express high

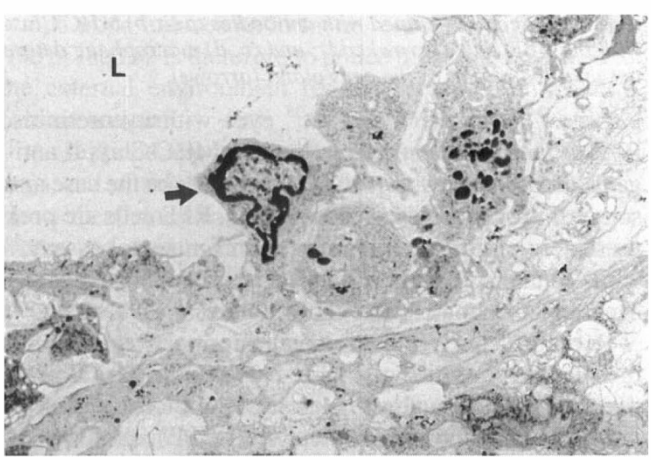

Fig. 11. *Electron micrograph of retinal venular endothelial cells (arrow) showing marked protrusion of the activated endothelium into the lumen (L) of the vessel. Note also the prominence of cytoplasmic organelles in the cell.*

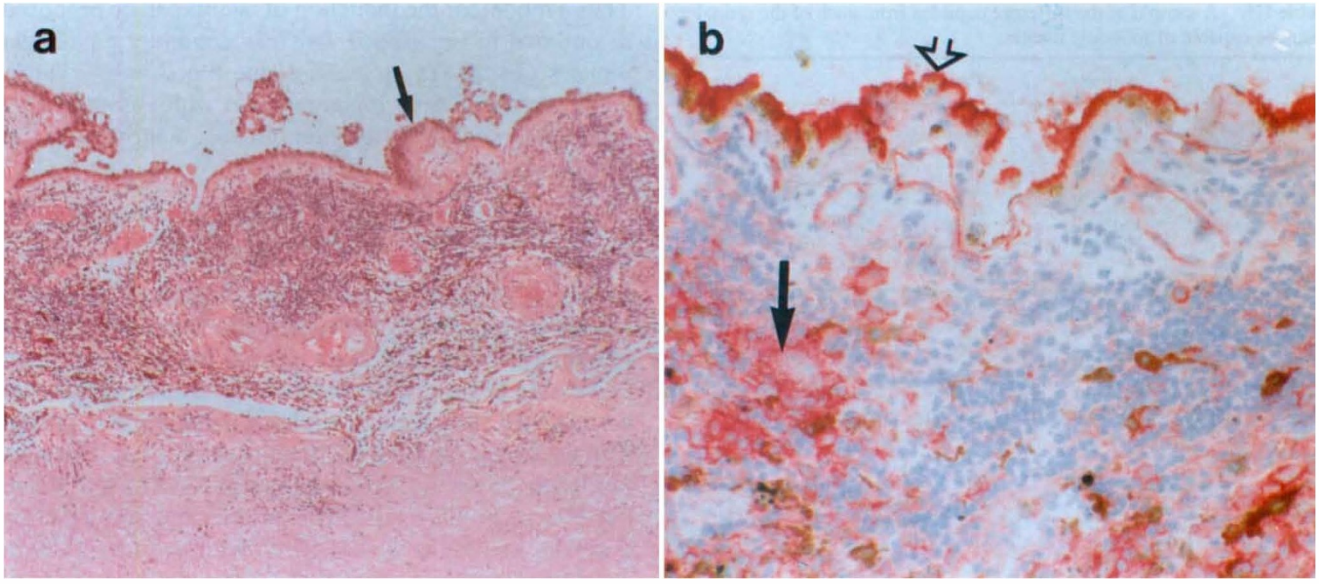

Fig. 12. *Human sympathetic ophthalmia. (a) Extreme thickening of the choroid in the inciting eye, with development of 'lymphoid' follicles or granulomata. The retina is detached and the RPE shows hyperplasia and proliferation (arrow). (b) Same case as (a) stained with antibody to ICAM-1 (see text). Note presence of ICAM-1 in cells within the follicles (arrow) and also prominently on the RPE cells (arrowhead).*

levels of accessory molecules of adhesion which promote the interaction between the lymphocyte and the endothelial cell. These molecules include the MHC Class I and II molecules plus other 'adhesion' molecules such as intercellular adhesion molecule-1 and -2 (ICAM-1,2), V-CAM, P-CAM and ELAM-1 and -2.[44]

In the retina, T cells have to traverse the blood-retinal barrier in order to arrive at the target cell i.e. the photoreceptor cell. These cells include both the retinal pigment epithelium and the retinal vascular endothelium. Retinal vascular endothelial cells undergo marked phenotypic changes resembling HEV during EAU with protrusion of the cell into the lumen of the vessel and considerable increase in cell organelles such as rough endoplasmic reticulum[45] (Fig. 1e; Fig. 11). Prior to and during ocular inflammation endothelial cells express increased levels of MHC Class II molecules and other 'adhesion' molecules (Fig. 12) indicating that considerable activation of these cells has occurred.

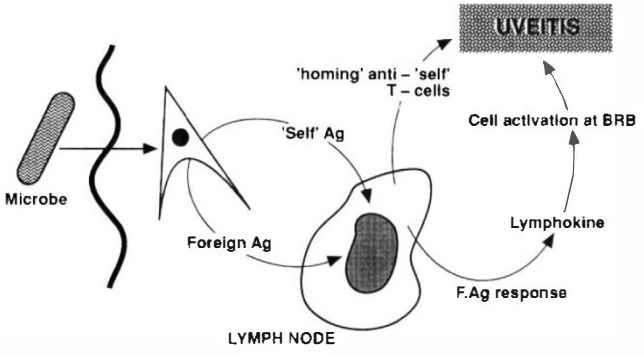

Fig. 13. *Model for the induction of uveitis involving: initiation by a foreign antigen; cross-reacting epitopes with autoantigen causing activation of autoantigen-specific T cells; activation of blood-retinal barrier cells, with expression of adhesion molecules, during the course of the immune response to the foreign antigen; and 'homing' of activated autoantigen-specific T cells to the target organ e.g. the retina. BRB, blood-retinal barrier; F.Ag response, foreign antigen response.*

Morphological changes associated with activation occur in the RPE cells during transcellular migration of lymphocytes.[46] These cells also express high levels of ICAM-1 constitutively and functionally with regard to adhesion of CD4+ T cells.[47]

Furthermore, RPE cells in human eyes with sympathetic ophthalmia have been shown to express high levels of ICAM-1 in addition to other adhesion molecules[48] (Fig. 12).

Many of the functional and morphological changes in these cells are inducible with lymphokine[49] particularly when administered systemically. It is therefore possible that the systemic response to infection with a foreign antigen leads to activation of cells at the blood-retinal barrier rendering them susceptible to lymphocyte-endothelial cell adhesive interaction. At a later stage when the autoreactive cells have become activated by cross-homology between the foreign and self-antigen, these then preferentially bind to and migrate across the barrier towards the target cell.

Table II. Ethnic distribution of HLA antigens in groups at risk of posterior uveitis. (These data were kindly provided by Professor M. Mochizuki.)

	Ethnic Group			
HLA antigen	Japanese	European Caucasians	American Caucasians	American Indians
A29	0.4*	7.4	8.1	4.4
B27	0.8	7.7	7.5	1.5
Bw51	15.9	13.9	9.3	43.5
DR4	41.4	18.3	27.3	47.8

*Per cent of antigen-positive in normal healthy populations of each ethnic group.

Table III. A sample of the different peptides from each of the retinal antigens capable of inducing uveitis

Antigen	Peptide
S antigen	M
	N
	K
	680
IRBP	r14
Rhodopsin	324–348
	331–342

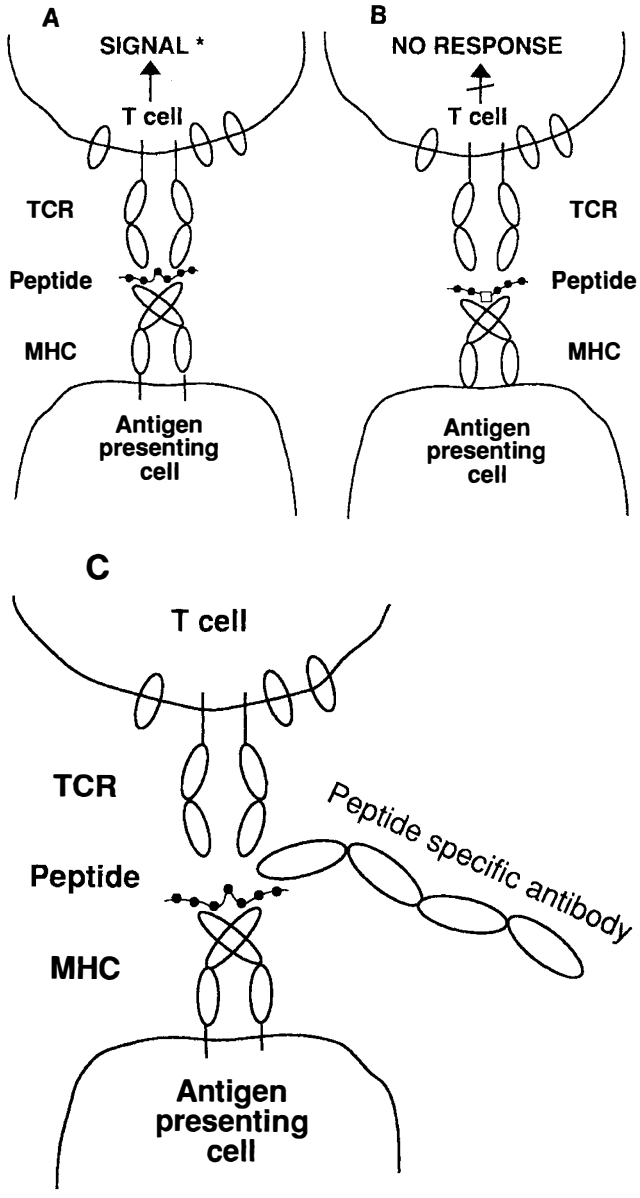

Fig. 14. *Strategies for blockade of the T cell receptor using blocking antibodies or peptides. (a) Presentation of the peptide to the T cell leads to an antigen specific T cell signal and proliferation of the T cell. (b) Presentation of a modified peptide which still has sufficient affinity for the peptide-binding groove on the MHC molecule but is unable to induce a signal in the T cell leads to peptide blockade. (c) Binding of a peptide specific antibody to the peptide while it is in the groove prevents initiation of the T cell signal by steric hindrance.*

Thus a model for the induction of uveitis can be proposed, as outlined in Fig. 13, in which infection by a pathogen induces changes in the cells of the blood retinal barrier which prepares them for interaction with autoreactive T cells activated by cross-homologous epitopes on the foreign antigen.

SUSCEPTIBILITY TO AUTOIMMUNE UVEITIS

Induction of autoimmune uveitis therefore depends on several factors which are required to interact before the immune response can occur. These include appropriate processing of antigen to produce uveitogenic peptides, the correct MHC molecule to bind that peptide and to present it on the surface of the APC, and the correct T cell receptor to interact with the MHC complex. As outlined above, there are many different MHC alleles but only a few of these are known to be associated with uveitis (i.e. to be capable of combining with the appropriate uveitogenic peptide). For MHC Class I alleles, the classic association is with HLA B27, suggesting that this type of uveitis is linked to an intracellular pathogen/autoantigen. Similarly HLA B51 is linked to Behçet's disease and HLA A29 to birdshot retinochoroidopathy.[50] The racial distribution of these MHC alleles closely parallels the incidence of these uveitides, which further suggests a vectoral spread of the disease but with strong linkage to genetic susceptibility (Table II). The MHC Class II antigen, HLA DR4, is the major antigen associated with several autoimmune diseases such as diabetes and rheumatoid arthritis and it too has a link with posterior uveitis.

The nature of the uveitogenic peptide(s) or epitope(s) in retinal autoantigens such as S antigen and IRBP, which interact with the MHC antigens, has also been deduced from analytical studies using synthetic peptides, studies of immunodominance, proteolytic digest studies and other means.[20,42,51–53] These have shown that certain peptides in each of these molecules appear to be responsible for their uveitogenicity (Table III). However, each MHC molecule has the ability to bind several different peptides and in this respect is rather less specific in its interactions than the antigen-antibody response. This property has been used to interfere with the induction of the immune response; for instance, by replacing one or more amino acids in the peptide sequence, an immunogenic peptide can be rendered non-immunogenic but still retain the capacity to bind with the MHC molecule. Thus it can be used to block the induction of the disease by 'peptide vaccination'.[54]

A different strategy, but one still aimed at interfering with the peptide interaction with the T cell receptor, is to block induction of the disease with specific monoclonal antibodies that bind to sites on the molecule close to the active uveitogenic epitope. Several such antibodies have been identified by the technique of epitope mapping,[55] and some of these have also been shown to inhibit induction of uveitis[56,57] (Fig. 14).

Susceptibility to autoimmune disease also depends on having the 'right' T cell receptor. Thus it has been shown

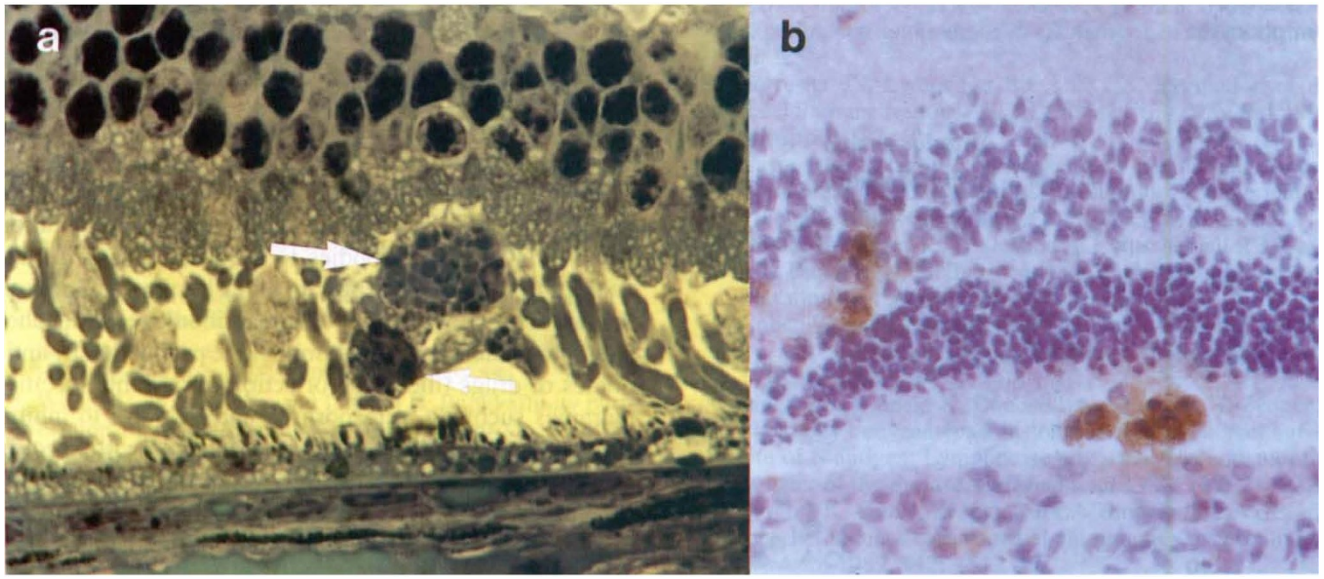

Fig. 15. *(a) EAU in the guinea pig. Two large macrophages in the photoreceptor outer segment layer (arrows) in the early stages of the disease. (b) EAU in the rat. ED3 staining macrophage in the photoreceptor and outer plexiform layers. ED3 is a monoclonal antibody against a specific subset of macrophages which may have been specifically activated.*

that certain variable chains in the T cell receptor are associated with a greater frequency of disease, such as the Vβ8 chain and multiple sclerosis although this association does not appear to be as strong as was originally suspected.[58,59] Despite these contradictory findings, similar associations between TCr variable gene sequences and susceptibility to disease have also been reported with EAU.[60] These studies hold out the promise of inhibiting the disease by using monoclonal antibodies which bind to the T cell receptor or, one stage further, by using T cell vaccines i.e. clones of T cells aimed at suppressing the antigen specific T cell.

Susceptibility to disease is not only dependent on having the appropriate genetic make-up but also on having the correct machinery in place to cause damage to the tissue. The nature of the effector cell in EAU and still less in human uveoretinitis, is at present unknown. While most of these organ-specific diseases, including EAU, are CD4+ T cell mediated diseases much of the damage appears to be mediated by macrophages. Indeed, the first cell to appear at the target site is the macrophage (Fig. 15a)[24] and recent studies suggest that these cells may be specifically activated (Fig. 15b).[61]

As indicated above, activation of the CD4+ T cell by the APC may drive the response down either of two pathways to produce a Th1 cell or a Th2 cell. The direction of this response is determined by the type and concentration of cytokine produced by the activated T cell. Cytokines are the critical and final players in this production and the nature of the tissue damage and indeed, the duration of the entire response, is dependent on these short-acting, short-range agents. Thus the response can predominantly be a delayed type hypersensitivity (DTH) i.e. one with a large macrophage component, or there can be a shift towards B cell activation with a marked antibody response and a closing down of the response.

CLINICAL EVIDENCE FOR AN AUTOIMMIUNE RESPONSE TO RETINAL ANTIGENS IN UVEITIS

This subject has been reviewed on several occasions previously and only a brief comment is included here.[62,63] It has been extremely difficult to demonstrate antigen specific responsiveness to retinal antigens in human uveoretinitis, either by studies of specific antibodies or by searching for antigen-specific cellular immune responses.[28,63–65] The most recent studies have shown that certain patients may have cellular immune specificity to retinal antigens or their fragments.[27] However, it remains clear that many normal individuals also respond to retinal autoantigens and that tests like these are not yet of value to the clinical ophthalmologist.

Other studies have sought evidence of lymphocyte activation and there is evidence that patients with active uveoretinitis especially retinal vasculitis, may have higher levels of activated T cells in their circulation, as determined by measurement of their IL2-r expression (Fig. 16).[66,67] However, these cells have not yet been shown to be antigen specific, and indeed it is unlikely that many of them are, since even within experimental lesions, the majority of T cells are non-antigen specific. It would appear that only a very few specific T cells are required to initiate an immune response and that cellular activation of non-specific T cells is induced in a cascade-like manner, probably driven by cytokines. Perhaps therefore we should not expect to find clinical evidence of antigen-specific autoimmunity until we can develop tests that are sensitive at the single cell level.

THERAPEUTIC CONSIDERATIONS

The theme of this lecture was autoimmune mechanisms but it would be incomplete if reference to therapy were not

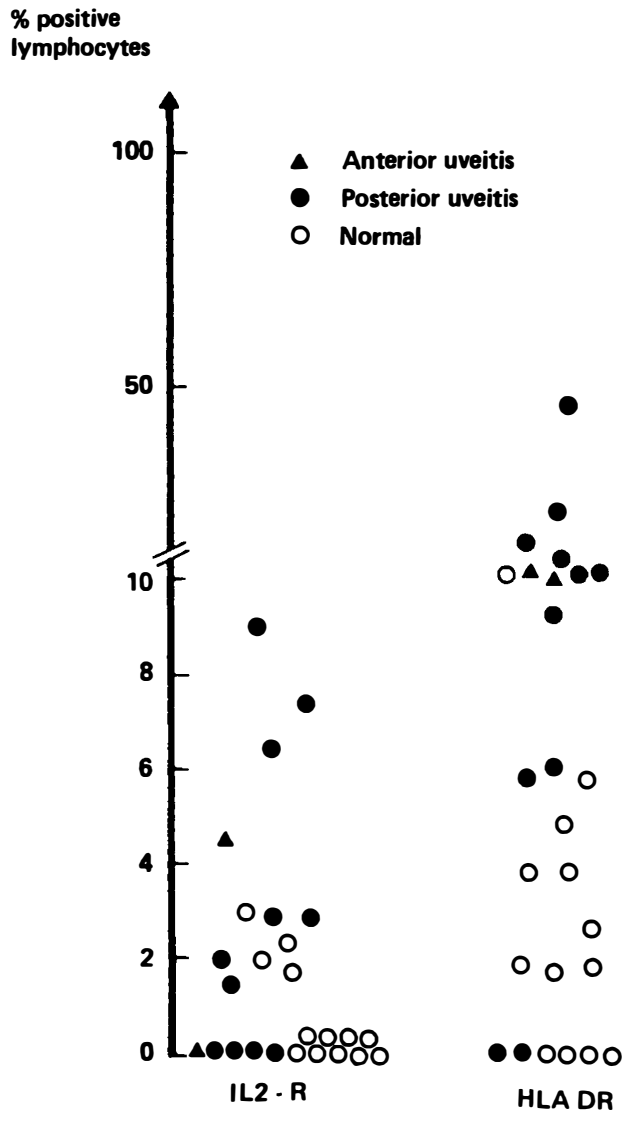

Fig. 16. *Expression of cell activation markers on peripheral blood leukocytes from patients with uveitis vs normal healthy controls. IL2-r, interleukin-2 receptor; HLA DR, one class of human Class II antigen.*

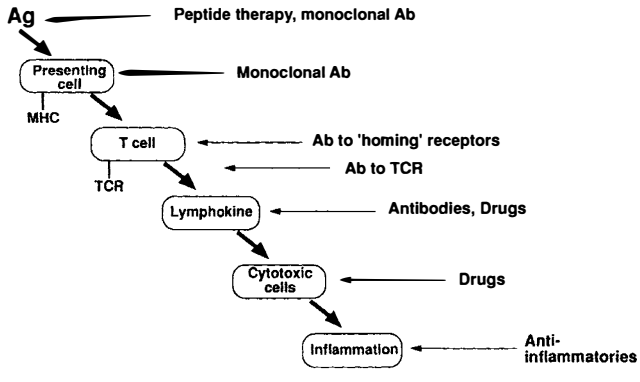

Fig. 17. *Flow chart of possible therapeutic strategies in autoimmune disease.*

made in the light of the new information. I have briefly alluded to possible approaches involving such modalities as T cell vaccines, peptide vaccination and antigen-specific monoclonal antibodies. There are however many potential sites of immunointervention in the sequence of events that leads to an (auto)immune response. Figure 17 summarises some of these. In addition to the above strategies, it might be possible to block antigen presentation using monoclonal antibodies to the MHC Class II molecule or to the T cell receptor; to block homing of T cells to the target organ with monoclonal antibodies to the 'adhesion' molecules; to inhibit lymphokine production by antibodies or drugs (the mode of action of current 'specific' therapies such as Cyclosporin A and FK506); to inhibit cytotoxic cells and activated macrophages with specific agents; and as a last resort to develop the range of anti-inflammatories which can interfere with the action of the many non-specific cells at the site of tissue damage.

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Key words: Autoimmunity, Uveitis, Retina, Antigen processing, Molecular mimicry.

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