

Editorial: Progress in uveitis

Until recently uveitis has been a graveyard in ophthalmology. A period of enthusiasm for the subject before the second world war led only to the conclusion that tuberculosis, syphilis, or 'septic foci' did not account for the vast majority of clinical disease. The subject then lay dormant until the 1960s, when toxoplasmosis and toxocara were identified as clinical entities, but in recent years the advances in general immunology, together with the discovery of an animal model for posterior uveitis, have produced a rapidly expanding interest in the field, and it is likely that the elucidation of uveitic disease will be one of the greatest areas of advancement in ophthalmology over the next 10 years.

Initial hope in the understanding of acute anterior uveitis (AAU) came with the discovery of the high prevalence of the HLA B27 tissue type in reactive arthropathies and AAU, indicating a strong genetic susceptibility to the disease. Further progress with AAU has been disappointing, and the inconsistencies in the interpretation of the genetic data have become more apparent and baffling. About 8% of the Caucasian population carry the B27 tissue type, but only a minority will ever develop AAU or a reactive arthropathy. 97% of patients with ankylosing spondylitis are B27-positive, yet only 20% can ever expect to suffer an attack of AAU. In patients presenting with AAU about 50% are positive for B27, yet these patients have identical (though often more severe disease) to those that are negative. Obviously other genetic or environmental factors must be important, but searches for these have so far been unrewarding. α_1 Antitrypsin is a major proteolytic enzyme system and it was suggested that a deficiency of or change in the phenotype of this enzyme might be an important additional factor in predicting susceptibility or severity, as these patients could conceivably have difficulty in removing harmful proteases. Further studies in our department, however, suggest that, though there is a low level of association with the PMz antitrypsin phenotype, this does not seem very clinically significant. Another area of recent interest has been whether or not the bowel flora has a role in the initiation or relapse of AAU. Levels of IgA also tend to be raised, which would support this concept. Initial work concerned klebsiella, but this has widened in scope, and rheumatologists have found that in ankylosing spondylitis there is a cross reactivity between the lymphocytes from B27+ individuals and the enteric bacteria or a supernatant from their culture, which lyses their lymphocytes.¹ Although

localisation of the disease to the spine or eye remains to be explained, this seems to be the most interesting and exciting prospect in this field, and, as before, further developments in the understanding of AAU are likely to ride on the backs of the rheumatologist.

Progress in understanding posterior uveitis (a completely different disease from AAU) has increased owing to the discovery of retinal S antigen and an animal model which can produce a posterior or panuveitis depending on the species used (probably reflecting whether or not the retina has a separate vascular supply), the dose given, and the method and route of administration. Genetic factors are important, as some species of rat are more susceptible than others. It is still not known whether or not retinal S antigen is an important factor in human disease. It was initially thought of as a possible explanation for sympathetic uveitis, but there are in fact some wide disparities. For instance, most cases of sympathetic uveitis involve trauma to the anterior segment where S antigen is not found; attempts have been made to explain this by suggesting that the various cells involved have a common origin from neuroectoderm.² Animal disease varies according to the dosage of antigen given, whereas the clinical severity of sympathetic uveitis does not correlate with the extent of the original injury. Sensitisation to S antigen can be found in a variety of human conditions, such as pars planitis, sarcoid, toxoplasmosis, and birdshot choroiditis, and there does not seem to be any one condition where it can be identified as the single aetiological factor. It remains to be seen whether in a disease such as toxoplasmosis it is released by retinal destruction to be an important factor in producing inflammation or is merely an epiphenomenon. Evidence against its importance is that sensitivity to the antigen does not seem to correlate with disease activity. Polyclonal antibodies to S antigen can be found in healthy people without ocular disease, and it has been suggested that complexes containing anti-S antibodies may indeed have a protective immunomodulatory role in retinal vasculitis by idiotypic mechanisms.³ Some of these contrasts may be explained when careful longitudinal studies of well defined types of uveitis are published.⁴ There now appears to be a family of uveogenic retinal proteins such as rhodopsin and interreceptor binding protein; many of these molecules may have several antigenic sites, and so there is every possibility for complex interactions and modulation.

Another aspect with idiopathic posterior uveitis

has been to look for evidence of systemic abnormalities which might point to the pathogenesis or aid in the diagnosis or monitoring of disease activity and treatment. Not surprisingly immunological abnormalities can be found in patients whose uveitis is associated with systemic disease (sarcoid, Behçet's syndrome, etc.) but these reflect the systemic disease as a whole rather than the ocular events, which are likely to only make a very small contribution to the complete picture.

Previous work on idiopathic posterior uveitis looking for abnormalities in immunoglobulins, immune complexes, or ocular and non-specific autoantibodies has largely been unexciting, and attention has recently been focused on changes in the T and B cell lymphocyte populations obtained from peripheral blood or the eye during surgery. Much of the work has been confused by difficulties in defining diagnostic categories, disease activity, or the effects of treatment and the failure to look at patients in relapse and remission. In the normal person approximately two-thirds of all lymphocytes are T cells, two-thirds of this group are T helper cells (T_H) and the remainder T cytotoxic and suppressor cells (T_S). Studies on AAU have shown no clear changes in T_H and T_S subsets in relapse or remission though many claims have been made. In posterior uveitis, where the inflammation is often more prolonged and severe, changes in T cell subsets have been found. A study from the National Institutes of Health (NIH)⁵ found no difference in the percentages of T_H and T_S cells in a group of patients with posterior uveitis, but when the results were compared as a T_H/T_S ratio patients with active disease were found to have abnormal ratios due to an increase in T_S numbers. Studies of lymphocytes obtained from the eye during surgery are more interesting. They have usually shown that T cells predominate, and the question has been how far these and their subsets reflect active involvement as it would be likely that some cells are present merely as passengers. An interesting paper in this issue of the *BJO* using a sophisticated technique shows that a substantial proportion (20–50%) of the intraocular T cells were activated. Aqueous cell subsets reflected the peripheral blood picture whereas vitreous infiltrates did not. Interestingly, patients with idiopathic uveitis also had increased levels of activated T_H cells in the peripheral blood, suggesting that the ocular inflammation was part of a systemic immunological abnormality, particularly as the activation of T_H lymphocytes reflected disease activity. What the antigenic cause of the activation is remains unknown.

Uveitis is a dynamic process, and animal models are needed to clarify the ocular and systemic events

involving the T cell. In a Japanese study of experimental S antigen induced uveitis in rats⁴ a rise in T_H cells in the peripheral blood was found five days after immunisation. With the onset of disease T_S cells increased, lowering the T_H/T_S ratio. In the uveal tract a T cell infiltrate appeared prior to inflammation and in the early stages more T_H than T_S cells were found. As the disease progressed T_H cells decreased until they could be identified only with difficulty in the late stages. This experiment suggests that T_H cells initiate the inflammatory response and that this is then controlled by T_S cells.

Further evidence of the influence of T cells in a similar animal model comes from an elegant study⁵ from the NIH where T_H lymphocytes specifically sensitised to retinal S antigen were obtained from rats. When these cells were transferred to non-immunised rats they developed uveitis (in the absence of systemic antibody formation to S antigen) with a shorter latent period than that induced by active immunisation. Intravitreal injection produced uveitis in that eye with fewer cells than required for systemic transfer, presumably suggesting that the specific T_H cell must reach the eye to initiate the disease process. In a similar experiment T_S cells were found to downgrade the experimental uveitis, suggesting these cells can modulate the inflammatory process.

In summary a great deal is becoming known about posterior uveitis in rats, but the understanding of human disease is only just beginning.

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