

preventing the continuing growth of a neovascular complex.<sup>9</sup> This might explain the better results in younger patients receiving photocoagulation for neovascular membranes. Equally, disturbance of any pigment epithelial response may be a factor in the recurrent disease seen particularly in elderly patients receiving laser treatment. The effect of radiation on the pigment epithelial response may be critical and the effect of any ensuing atrophy could outweigh short term benefit. This is not, however, seen to apply in this study when patients have been followed for up to 18 months. At that stage, six patients had improved visual acuity while two retained their pretreatment vision and three had suffered further visual loss with exudative changes at the macula.

Our understanding of macular degeneration has come a long way in the past 30 years. Much of this is because of careful attention to detail and the application of new information to future studies. We should not be misled into thinking that this study will provide the final answer and indeed it asks more questions than it answers, but at the same time it adds to our treatment options. Further tissue culture work in respect of the pigment epithelial response to radiation is needed particularly as to how it might affect the older eye. Careful and continued observation of these patients should ensure that other complications and changes do not develop. This study carefully applied the techniques developed in earlier treatment trials, so that a prospective and controlled trial may now be justified with the lower dose

of radiation of 10 Gy, which seems to perform as well as the higher one. Whether such treatment should be used alone or in conjunction with other forms of treatment is an interesting question that will require testing. Membranes in other locations might then be similarly treated, but the radiotherapeutic method employed should be carefully evaluated to be certain that everything is done to exclude unwanted side effects.

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## New entities in uveitis

Uveitis can be associated with many systemic conditions as well as being an organ specific autoimmune disease with inflammation apparently localised to the eye alone. The immunopathology appears to be the same whether the inflammation is part of a systemic disorder – for example, sarcoidosis and Behçet's disease, or localised to the eye as in sympathetic ophthalmia or pars planitis. Effective treatment regimens suppress the immune response whatever the initiating factors, indicating a major role for the immune system in the perpetuation mechanisms of clinically different types of ocular inflammation.

In this issue, Nakao and Ohba describe the clinical features of a uveitis associated with increased frequency of seropositivity for the human T cell lymphoma virus type 1 (HTLV-I). This virus, like human immunodeficiency virus (HIV), is a retrovirus and has already been causally associated with two specific diseases, namely adult T cell leukaemia and tropical spastic paraparesis. However, the association of HTLV-I with uveitis does not necessarily implicate the virus as directly responsible, so other explanations need to be considered.

Could it be a coincidence – a chance association with uveitis occurring in individuals living in an endemic area? The evidence presented in this paper and the other recently by Mochizuki *et al*<sup>1</sup> is against this. Forty one per cent of patients with uveitis (of a type not associated with any known disorder) were found to be seropositive, compared with a local seropositivity rate in southwestern Japan of around

15%, a highly significant difference. Could this be a genetic susceptibility to two simultaneous yet separate agents? Mochizuki states that seroprevalence of the virus in the general population increases with age, whereas the peak age of the uveitis group is lower making this hypothesis less likely.

There are two further possibilities to consider: firstly, that infection with the HTLV-I virus predisposes to infection with another, as yet, unidentified agent which is directly, or indirectly, responsible for the ocular inflammatory disease or, secondly, that HTLV-I stimulation of the immune system generates an exaggerated immunological response which in itself results in ocular damage. If HTLV-I infection resulted in immunosuppression, either directly or as a consequence of T cell leukaemia (through bone marrow involvement or anti-leukaemia therapy), ocular disease could develop as a result of infection with other organisms such as cytomegalovirus, herpes simplex virus, herpes zoster virus, or *Toxoplasma*. The clinical appearances described in HTLV-I associated uveitis, which include marked vitritis and retinal vasculitis, are very much at odds with this hypothesis and are much more suggestive of an overactive rather than underactive immune system. The characteristic clinical ocular features of these infections commonly associated with immunosuppression have not been seen, apart from cytomegalovirus; intraocular malignant cell infiltration has also been reported in a few patients who developed T cell leukaemia.

The most likely explanation, therefore, is that infection with the HTLV-I virus results in increased autoreactivity and autoimmune disease, a situation well described in HIV infected individuals. The increased incidence of Graves' disease, a known autoimmune disease, reported in this paper and by others, supports this view. The favourable clinical response to systemic steroids also suggests involvement of the immune system, though it would be prudent to remember that favourable responses can be seen in some infective forms of uveitis – for example, *Propionibacterium acnes* endophthalmitis following cataract surgery, and with ocular lymphomas. In acute retinal necrosis, now known to be caused by herpes simplex virus or herpes zoster virus in normal individuals, the visual prognosis has not been found to be improved by early intensive administration of high dose acyclovir, and immunosuppression is necessary in some patients indicating that, even in known viral retinal infection, immunological responses play a significant role in the resulting tissue damage.

To date, idiopathic panuveitis has not been a major problem in patients with HIV infection and much of the evidence for increased systemic autoimmunity is based on increased detection of autoantibodies to various tissue antigens in the blood rather than on the development of clinical disease. Dalglish has made the interesting suggestion that if HIV could mimic major histocompatibility antigens on the surface of antigen-presenting cells, autoreactive T lymphocytes may be stimulated which would help explain the marked similarity of some of the clinical features of HIV infection to chronic graft versus host disease.<sup>2</sup> This hypothesis could also apply to infection with other retroviruses such as HTLV-I.

If the immune system does become hyperactive as a result of retroviral infection, does direct sensitisation to ocular antigens occur resulting in the ocular inflammation? Current theories of autoimmunity suggest that T cells respond to specific epitopes on infective agents which in some situations have been found to crossreact with epitopes in specific

tissues. Tissue damage occurs as a consequence of this crossreactivity when these T cells become activated. In addition, CD4<sup>+</sup> T cells infected with HTLV-I are known to express interleukin-2 receptors and to secrete a variety of lymphokines.<sup>3</sup> The uveitis could then be explained by a similarity between epitopes on the HTLV-I virus and ocular tissue antigens – a sort of epiphenomenon or bystander effect occurring as a result of the activation and proliferative responses of the host's T cells to combat the virus.

Mochizuki *et al* studied the inflammatory cells in the anterior chamber using polymerase chain reaction techniques and oligonucleotide primers specific for the proviral DNA of HTLV-I in these patients. These findings were compared with two seropositive patients with other types of uveitis such as toxoplasmosis or Behçet's disease and seronegative patients with uveitis associated with sarcoidosis, Vogt-Koyanagi-Harada syndrome, or Behçet's disease. The viral DNA was only detected in anterior chamber cells of seropositive patients and only in those without features of other specific types of uveitis, although there were only two patients in this group. This is a very interesting finding and further studies with increased numbers of seropositive patients with all types of uveitis are awaited. It is not known whether the cells present in the aqueous in patients with panuveitis are exactly the same in different types of uveitis or whether they also reflect those present in the retina and choroid, both in their type and specificity. These are obviously important facts to be elucidated if the HTLV-I virus is to be implicated in the pathogenesis of this ocular inflammation.

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## Measurement of flare

Tyndall described the light scattering effect of particles in air in 1870, as it happens, in the first volume of *Nature*, and the following year Lord Rayleigh worked out the mathematical principles involved describing what is now known as Rayleigh's law and explaining, for instance, why the sky is blue. Analysis of light scattering has become a routine tool in astrophysics and it is intriguing now that the same physical principles are being used to analyse the intraocular contents.

Damaged ocular blood vessels leak cells and protein whether from trauma, infection, surgery, or inflammation, and the detection of these is a part of any routine ophthalmic examination. Quantification of these signs, however, is difficult. Clinical grading scores of flare and cells are routinely used but these are subjective. Nevertheless they have stood the test of time and are still the technical standard required by the American Food and Drug Administration for the assessment of ocular inflammation. Fluorophotometry has been used to obtain more objective results but this

method has never really been successful because of its invasive nature, poor patient compliance, complex pharmacokinetics, and inability to follow dynamic changes.<sup>1,2</sup>

Laser photometry has been developed over the last 4–5 years by Kowa who has produced a commercially available instrument that measures flare and cells in the anterior chamber by their light scattering effects on a HeNe laser beam. The principle of this technique is that there is a linear relationship between protein concentration and the intensity of scattered light.<sup>3,4</sup> The equipment has considerable advantages in that it is entirely non-invasive and requires minimal patient cooperation; rapid changes in the anterior chamber can be followed over minutes. With this equipment flare measurements are extremely accurate – for example, diurnal fluctuations can be measured in the normal eye.<sup>5</sup> The sampling volume is extremely small (1/120 × 10<sup>6</sup> l) and because of this, cell counts are not particularly accurate unless the numbers are high, owing to the partial volume effect. Although the



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