

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorials

Treatment of age-related subfoveal neovascular membranes by teletherapy

The changes involved in age-related macular degeneration continue to challenge ophthalmologists and basic scientists. The hopes of laser photocoagulation have faded to some extent but laser remains the mainstay of treatment in selected cases. Estimates vary as to the proportion of patients with neovascular disease who might benefit, but this remains low and treatment, even if successful, may only provide temporary benefit. Although low vision aids provide some help and patients never lose all vision as a result of macular degeneration, its effect on the aging population remains significant. The Royal National Institute for the Blind survey estimates that up to a million people in the United Kingdom are visually handicapped, most of these are affected by aging retinal changes.¹

It is not surprising that, following the initial reports of treatment benefit from laser photocoagulation, other wavelengths of light should have been tried and the application of laser tested in different ways. Treatment of membranes within the avascular zone and indeed under the fovea has been assessed.² Although benefit was shown for small membranes in terms of contrast sensitivity and reading performance, ophthalmologists have not adopted this approach in view of the early loss of central acuity involved in contrast to the slower loss as a result of the natural history.

An understanding of the underlying changes within the choroid, Bruch's membrane, and pigment epithelium is important if we are to progress. Fluorescein angiography has been used to demonstrate that delayed choroidal perfusion is associated with a higher risk of atrophic macular degeneration.³ Indocyanine green angiography extends our ability to study the underlying changes.⁴ The scanning laser ophthalmoscope has been used to study lipofuscin within the pigment epithelium and changes at the level of Bruch's membrane.⁵ Longitudinal studies of drusen have shown that they may provide information about the way an eye is likely to behave. Their behaviour on fluorescein angiography, due to their lipid or water content, seems to act as a predictor to future changes that may occur. Hydrophilic drusen are hyperfluorescent on angiography and tend to associate with neovascular complexes in contrast to hydrophobic drusen which do not fluoresce and tend to associate with pigment epithelial detachments.⁶

Longitudinal studies are obviously important in establishing behavioural patterns and must be undertaken so that those patients most likely to benefit from treatment can be identified. New treatments proposed will need to be tested by pilot studies, but a much larger control trial is needed if statistical benefit is to be proved. Such studies are time consuming, costly and should only be undertaken where

there is a reasonable prospect of benefit. The use of zinc as a dietary supplement to enhance the enzymatic pathways within the pigment epithelium which degrade the phagocytosed photoreceptor debris is one example of a new approach that is yet to be satisfactorily proved. Interferon alfa has been used with some claims of benefit and further multicentre studies are proposed.⁷ Such a study is likely to prove costly and treatment is not without its side effects. The surgical excision of a neovascular membrane is a technical possibility with advanced vitrectomy techniques,⁸ but it is a costly proposal for a condition such as macular degeneration which may be more readily helped by the greater availability of low vision aid services. In approaching any new treatment it is important that *in vitro* studies are undertaken whenever possible as these may provide a relatively quick and cost effective method of determining whether the underlying science is sound and the proposed treatment is likely to be of benefit.

In this issue Chakravarthy *et al* report a pilot study using low dose radiation to the macular region to determine whether this will influence the natural history of subfoveal neovascularisation. In this, they are assessing a less destructive treatment than that involved in subfoveal photocoagulation. This is not an altogether new treatment and *in vitro* work exists to support the validity of their hypothesis. The mature retina is relatively resistant to low dose ionising radiation applied in small treatment fractions. In contrast, the effect of similar energy levels on proliferating vascular cells is more marked which would suggest a selective treatment of benefit that needs testing. The long term effects on the function of the retina, pigment epithelium, and other ocular structures such as the lens and optic nerve have yet to be demonstrated. From the studies quoted, however, it seems that their choice of 10 Gy or 15 Gy is entirely reasonable. They have been careful to identify the beam path to minimise any risk to other structures and not to report this pilot study until patients have been followed for a full year.

This is not a treatment that should be approached lightly and it does need careful monitoring. Criticism could be made of the complex nature of some of the lesions treated but this is a problem that bedevils those treating macular degeneration. However, their reported regression of the membranes treated is encouraging. In such a small study, matched controls are difficult to obtain so that in no way can this be seen as final evidence of benefit, but the results suggest that this is an approach that needs further evaluation. It is the pigment epithelium that absorbs laser energy when this is used, but equally it is that structure which responds to the presence of an experimental membrane and may be instrumental in

preventing the continuing growth of a neovascular complex.⁹ 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*¹ 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.



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Br J Ophthalmol 1993 77: 261-262
doi: 10.1136/bjo.77.5.261

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