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*Editorials*

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## HLA and trachoma

HLA (human leucocyte antigen) molecules, which were initially studied because of their importance in organ transplant rejection, have been found to play a fundamental role in immunity, with the physiological role of presenting peptide antigens to T lymphocytes. HLA class I molecules present peptides to cytotoxic (CD8+) T lymphocytes, which are important in defence against viruses and other intracellular pathogens, whereas HLA class II molecules present peptides to CD4+ T cells, which are important in generating antibody and cellular responses mainly to antigens outside the cell. HLA molecules are thus central to immune defence against infecting micro-organisms and to the development of autoimmunity. High resolution characterisation of HLA alleles by DNA methods has recently become feasible.<sup>1</sup>

Trachoma is the leading infectious cause of blindness. There is evidence that the clinical features both of active inflammatory disease and of the cicatrising sequelae are immunopathologically mediated. In endemic areas, familial clustering of active trachoma cases occurs, and the development of blinding sequelae is found only in a minority of subjects, raising the possibility of genetic susceptibility. In this issue of the *BjO* (p 431), White *et al* report an increased prevalence of DR16 and a decreased prevalence of DR53 class II haplotypes in Omani cases of trachomatous corneal opacity compared with a control population of students, blood and organ donors. In the Gambia, we found an increased prevalence of the class I subtype HLA A\*6802 in subjects with trachomatous scarring compared with age and sex matched controls.<sup>2</sup> Are these results compatible?

Several issues need to be borne in mind when comparing these two studies. The distribution of HLA antigens differs between the Gambia and Oman; DR2 and its DR16 subtype are common in Oman but rare in the Gambia. The two studies did not use the same criteria for cases, or for the selection of controls. Controls should be exposed to the risk of getting the disease, and age and sex are important determinants of trachomatous sequelae. Different approaches were taken in the application of high resolution DNA typing methods to serologically defined antigens so that the subtype association found in the Gambia was not specifically examined in the Omani study. Finally the two studies used different approaches to the problem of multiple comparisons. The HLA antigens are the most variable

human alleles known—for example, there are over 60 known variants of the HLA-B antigens with more being described all the time. Thus, a large number of comparisons between cases and controls is required, and there is a risk that some will appear significant as a result of chance alone. White *et al* elected to use the Bonferroni correction procedure, multiplying the p value by the number of tests carried out, but this increases the converse risk that important associations involving modest increases in risk may be wrongly attributed to chance. In our view, all the associations they report in Table 1 merit examination in other environments.

What mechanisms might underlie HLA trachoma associations? White *et al* discuss the possibilities that molecular mimicry of self antigens may play a role in pathogenesis or that HLA antigens may be receptors for chlamydia. A number of other explanations are also feasible: such associations could represent 'holes' in the T cell repertoire, differences in antigen recognition, signalling, or activation of suppressor T cells. The HLA genes are situated in close proximity to some 200 other genes within the MHC complex on the short arm of chromosome 6, and linkage disequilibrium between HLA haplotype and a true susceptibility allele elsewhere in the MHC might also explain putative associations. We have recently shown that polymorphism in the TNF- $\alpha$  promoter region, which is in the MHC between the class I and class II HLA loci is also associated with trachomatous scarring, but independently of HLA A\*6802 rather than in linkage disequilibrium with it.<sup>3</sup>

Will all this help Omani and Gambian trachoma patients? Recently, single dose azithromycin has been found to be effective treatment for active trachoma,<sup>4</sup> and a community education programme targeted at face washing was found to reduce the prevalence of active trachoma in Kongwa, Tanzania.<sup>5</sup> The high cost of azithromycin and the intense effort required for modest and poorly sustainable gains in the Kongwa study indicate that other interventions are likely to be needed. The identification of susceptibility or resistance genes for human ocular chlamydial infection and its sequelae may help identify those at risk, and might also identify critical mechanisms in the infection, scarring, and blinding processes either as targets for intervention or as considerations in vaccine design. But patients with

trichomatous trichiasis and entropion are likely to need eyelid surgery for a while longer.

ROBIN BAILEY  
DAVID MABEY

Department of Clinical Sciences,  
London School of Hygiene and Tropical Medicine

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## Dry eye

Articles by Kruize *et al* and Tsubota *et al* in this issue of the *BJO* (pp 435 and 439), emphasise two important clinical aspects of dry eye or keratoconjunctivitis sicca (KCS). Not all dry eye symptoms are due to a dry eye and dry symptoms and findings do not necessarily worsen over time, and in fact may improve.

The symptoms are always the same—a sandy, gritty, burning feeling. Unfortunately, the causes of the dry eye are not. There are many different aetiologies of KCS.<sup>1</sup> All too often we associate dry eye symptoms with a disorder of the tear film or tear secretion. In the article by Tsubota *et al* another important cause of dry eye symptoms is reported, Meige's syndrome,<sup>2</sup> characterised by involuntary eye closure (blepharospasm) with middle or lower facial dystonia. In a subgroup of patients with dry eye who failed to respond to topical lubricant therapy, the authors found that more than half of these patients had Meige's syndrome. In patients with blepharospasm, it can be difficult determining whether dry eye causes blepharospasm (secondary) or blepharospasm (primary) causes the dry eye. In general, patients with primary blepharospasm do not show significant improvement in dry eye symptoms with topical lubricants. Therefore, a therapeutic trial of artificial lubricants is a useful diagnostic test to distinguish blepharospasm from other causes of dry eye as the source of symptoms. Meige's syndrome along with dermatochalasis<sup>3</sup> represent conditions which can be characterised by severe eye symptoms with minimal abnormalities of tear secretion, the film, and the ocular surface. In both groups, patient symptoms are ill defined, usually dryness rather than foreign body sensation, grittiness, or burning. Often, there is a complaint of a feeling of watery eyes, but without frank epiphora. The source of the dry eye symptoms in these patients is not known. Patients with Meige's syndrome and essential blepharospasm respond well to botulinum A toxin which may relieve dry eye symptoms as well as blepharospasm.

KCS in primary Sjögren's syndrome (PSS) may not lead to a progressive deterioration in lacrimal gland function.

Those of us who follow patients with PSS find that the onset of symptoms and clinical findings occur over a relatively short period of time, often associated with inflammation of the ocular surface. After several years, symptoms and clinical findings often appear to stabilise without continued progression. The study by Kruize *et al* lends support to this clinical observation. They suggest that PSS patients remain relatively stable after an initial active disease phase.

Patients with secondary Sjögren's syndrome (SSS) were found to have their lacrimal gland function return to normal, perhaps related to remission of the underlying disease process. Non-Sjögren's syndrome patients showed marked improvement in tear function factors after 10–12 years. The authors rightly suggest that the term 'age-related' dry eye be avoided as age-related changes in the lacrimal gland do not necessarily cause a dry eye.

PSS is characterised by an active inflammatory stage followed by a chronic stage. Most of the signs and symptoms are probably due to residual lacrimal gland damage from the initial active disease process. Intervention in the active stage with systemic, or perhaps topical, immunomodulating agents may reduce the severity of the eye disease and improve the long term quality of life of patients with PSS.<sup>4</sup>

J DANIEL NELSON

Department of Ophthalmology, HealthPartners Ramsey Clinic,  
640 Jackson Street, St Paul-Ramsey Medical Center, St Paul,  
MN 55101, and  
Department of Ophthalmology, University of Minnesota,  
Minneapolis, MN, USA

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ROBIN BAILEY and DAVID MABEY

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