EDITORIAL

TRANSPLANTATION AND THE EYE

It is a pity that so few immunologists have recognised the fascinating conundrums presented by the eye, and that so many ophthalmic surgeons have been reluctant to acquire a theoretical background of modern immunological concepts. Fortunately there are some exceptions, showing that immunologists have not lost their curiosity, nor surgeons, their boldness. The simple truth is that making progress in all biomedical problems demands a multi-disciplinary attack. This truth was reflected in the programme for the Twenty-fourth Cambridge Ophthalmological Symposium (St John's College, Cambridge, 8–9 September 1994), the proceedings of which are published in this issue of *Eye*.

There is a vigorous debate in progress on whether incompatibilities of the major histocompatibility system (in humans, the HLA system) affect the survival of corneal allografts. Experience in human kidney transplantation, summarised by Taylor and Dyer (Cambridge and Manchester, UK), shows that HLA incompatibility does militate against the survival of kidney allografts, and led to the expectation that a similar effect would be observed in corneal allografting. However, there is disagreement on this fundamental point. Taylor and Dyer cite data from centres in the United Kingdom and the Netherlands showing that incompatibilities for HLA class I antigens have a statistically significant detrimental effect on the survival of corneal allografts. In contrast, a careful multi-centre study conducted in the United States yielded the conclusion that HLA matching had no significant influence on corneal allograft survival.

Resolution of this clinically important issue is not simple, partly because the immune response to allografts is still not fully understood. The concept that the response consists of two populations of T lymphocytes was described by Batchelor (London, UK). According to this analysis, one population of T lymphocytes is sensitised by the allogeneic dendritic cells present in an allograft (direct pathway), and the second is sensitised by the indirect pathway in which the recipient's own antigen presenting cells (APC) phagocytose foreign tissue molecules, break them down intracellularly into peptide fragments, and present them to T cells as peptide fragments bound to the recipient's own HLA class II molecules carried on the cell surface of the APC. Normally the direct pathway dominates the early phase of allograft responses against most tissues because 5–10% of peripheral T lymphocytes bear antigen-specific receptors which enable them to be activated by this pathway. In contrast, only 0.1–0.01% of T cells of non-sensitised subjects bear receptors that are activated by the indirect pathway. However, the central 8 mm of a corneal allograft button is almost completely devoid of dendritic cells, the critical cell needed for activation of direct pathway lymphocytes. Accordingly, the fate of a corneal allograft will depend solely upon the destructive potency of lymphocytes stimulated by the indirect pathway in previously non-sensitised individuals. In most non-sensitised individuals, this response is likely to be so weak that rejection does not ensue. However, sensitisation due to previous grafts or other stimuli can cause expansion of T cell clones of both indirect and direct pathways, and may lead to acute graft rejection.

This concept receives considerable support from studies on animal models because it implies that indirect pathway T cells can be the dominant effector population in corneal allograft rejection, the same population of T cells presumed to cause rejection of all allografts differing only by minor system incompatibilities. In discussion, Niederkorn (Dallas, USA) and Streilein (Miami, USA) mentioned their observations on rat and mouse models of orthotopic corneal transplants. These showed that

minor histocompatibility system incompatibilities were, in many strain combinations, stimulators of rejection as potent as those of the major system; also, although skin allografts mismatched only for major system class II antigens are consistently rejected in all recipients, less than 20% of corneal allografts of the same disparity suffer rejection. Katami (Kanagawa, Japan) observed the paucity of dendritic cells in the centre of rat corneas, and showed that rat corneal allografts of 2 mm diameter were permanently accepted across a major system incompatibility, whereas larger grafts, presumably containing significant numbers of dentritic cells, were acutely rejected within 11 days. Clinical ophthalmologists have long been aware of the effect of corneal button size in human corneal grafting.

It seems inescapable that for smaller human corneal allografts placed in previously non-sensitised recipients, the allograft response is largely, if not exclusively, mediated by the indirect pathway, and in that case, HLA and minor system incompatibilities are both likely to have weak immunising potency. However, the larger the graft button, the greater the likelihood that it will contain allogeneic dendritic cells, capable of provoking sensitisation by the direct pathway. Furthermore, in previously sensitised patients (second grafts, etc.) the relative contributions of direct and indirect pathways are likely to be complex. It is particularly in these patients that the effect of HLA matching need further investigation, considering the possibility that sensitisation may proceed by both indirect and direct pathways. Incompatible HLA molecules of the graft may themselves be processed and then presented as peptides bound to the class molecules of the recipient's antigen presenting cells, provided that the peptide fragments have a high binding affinity for the recipient's class II molecules. It is already known that each HLA class II variant possesses its own pattern of high and low binding affinities. Therefore the HLA phenotypes of *both* recipient and donor are predicted to determine whether binding affinities reach the threshold necessary to induce strong activation of the indirect pathway T cells. Our studies on the influence of HLA in corneal allografting will need to be more thoughtful in the future, and it may be productive to see whether we can identify particular donor/recipient combinations that carry an above-average risk of acute rejection.

Certainly corneal grafting is likely to be a rich field for those interested in studying minor histocompatibility systems of man. That these may be of considerable clinical importance was suggested by the work from the group at Bristol (Nicholls *et al.*) who showed in a rat model of corneal grafting that rejection induced by non-MHC antigens was relatively resistant to immunosuppression.

We also need to know more about the numbers and properties of dendritic cells in human corneal allograft buttons, as well as in the recipient. Roake (Oxford, UK) gave a fine review of the differentiation and trafficking of these cells, and Armitage (Bristol, UK) showed that they can be depleted from corneas *in vitro*, although this does not appear to reduce the likelihood of graft rejection – perhaps the dominant role of indirect pathway T cells might be a reason for this.

Immune privilege within the eye was another topic of the symposium that aroused great interest. Streilein (Miami, USA) regarded it as an evolutionary adaptation designed to limit intraocular inflammation induced by immune reactions, blindness being a powerful selective force. He has begun investigating the molecular explanations of this phenomenon, and it is already clear that the spectrum of cytokines and other factors induced following immunisation within ocular tissues differs from the patterns seen in other tissues. This is an intensely exciting area of study, and one that should, in the end, provide us with physiological therapeutic reagents for reducing unwanted sequelae of inflammation.

It is not possible to do justice to many of the other topics of the symposium. These include the exciting fields of xenografting, studies on the transplantability of retinal cells and neural tissue, and many others. Important practical clinical issues were also covered, such as what trends can be recognised from data collected by a national corneal graft registry, and optimal management of immunosuppression after corneal grafting. I can only encourage you to read the individual papers, with the certainty that you will find interest, new ideas, and a wealth of practical experience therein.

J. RICHARD BATCHELOR