Editorial on Recent Advances

Histocompatibility in corneal grafting

The first clear corneal graft was reported by Zirm (1906) and soon afterwards Magitot (1911) suggested that clouding of a graft was due to biologic incompatibility. Since those days, there have been enormous advances in surgical techniques and suture materials. Progress has also been rapid in preservation of donor material and in immunology, including immunosuppressive therapy, and corneal graftings are now made frequently. Yet, even in nonvascular cases the reaction or rejection rate is as high as 12 per cent. Other estimates for nonvascular cases range from 30 to 35 per cent, but immunosuppressive therapy has reduced the failure rate after these rejection episodes to less than one-third. Further, it is well known that a vascularized corneal bed greatly increases the risk of the allograft reaction, as do inflammation and regraftings.

The early stages of corneal homograft reaction were studied experimentally by Polack, who demonstrated the importance of lymphocytes in initiating the rejection of the endothelium. A schematic illustration of the possible afferent and efferent arcs of the immunologic reaction reflex to the corneal graft was presented by Jones.

The role of ABO antigens. More than 60 years ago, Elschig presumed that ABO incompatibility between donor and recipient would lead to late corneal clouding. The presence of ABO antigens in the cornea was later demonstrated by Nelken and co-workers. This team showed that the graft often became cloudy if the recipient was presensitized by red blood cells from the same donor. They found that clouding was accompanied by a high serum isoagglutination titer, which they regarded as further evidence possibly implicating the ABO antigen system. Clinical experience in this respect has been conflicting. The discrepancies may be due to the many complex causes leading to corneal allograft rejection.

The role of HL-A histocompatibility antigens. HL-A typing procedures have identified cell-surface antigens determined by two closely linked autosomal cistrons. Typing is generally done with leukocytes. However, the HL-A histocompatibility antigens can also be detected on human corneal epithelial cells, keratocytes, and endothelial cells, and corneal cells and lymphocytes from the same donor are concordant in HL-A typing. The two pairs of genes determine the expression of two allelic series of antigens, designated as the “first” and “second” segregant series. Depending upon homozygosity at these loci different antigens may be found on the cells, their number ranging from zero to four, with a maximum of two from each series.

The production of humoral antibodies against HL-A antigens in patients with vascularized corneal beds and immunologic rejection of allografts was demonstrated by Stark, Opelz, and Newsome.

Animal experiments. The evidence for involvement of HL-A histoincompatibility in the corneal allograft reaction is, so far, sparse. Interestingly enough, it has recently been the subject of two experimental studies. In 1975, Bennett and co-workers found a probably significant difference between a group of rabbits with corneal donors completely histocompatible for the RL-A locus (success rate 9 in 10) and another group mismatched with corneal donors histoincompatible at the RL-A locus.
(success rate 1 in 9). Both groups had a 7 mm. penetrating graft to a corneal bed heavily vascularized in response to standardized alkali burns. These results support those obtained in 1971 by Ehlers and Ahrons,8 who used a 6 mm. interlamellar allograft to pre-immunized rabbits.

In contrast, Lang, Riekhof, and Steinmüller12 also writing in 1975, question the importance of histocompatibility in corneal allograft reactions. These authors worked with rats instead of rabbits, and some of their animals happened to have ghost vessels of unknown origin in the cornea. They concluded that in the nonvascular cornea there is no significant difference between isografts and “weak” or “strong” allografts. The technique of interlamellar keratoplasty sounds easy, but to divide a 2 mm. button exactly in two “with epithelium and endothelium intact” is difficult. The cell-rich epithelium and endothelium are easily torn and swept away when the button is transferred to the pocket. Consequently, these grafts may have varied considerably in antigenicity.

In the classic series of Muller and Malemene,13 the allograft reaction developed without sensitization only in one rabbit of sixty that received a 6 mm. penetrating nonselected transplant. Further, the danger of rejection is known to be diminished in lamellar grafts and apparently is even less when the graft is put into an interlamellar pocket. Thus, in my opinion, the evidence of Lang, Riekhof, and Steinmüller12 is inconclusive. There is also evidence that in similar experimental situations rejection is not to be expected even in the group of “strong” allografts. When the animals were sensitized against lymph cells or skin nine weeks after grafting, no difference could be expected between the “weak” and “strong” allografts, as the authors themselves point out. This is consistent with the observation by Kornblueth and Nelken14 that lamellar allografts in rabbits are refractory to added host sensitization. It seems to me that even in the vascularized or presensitized recipients of “weak” or “strong” allografts the evaluation is inconclusive, because of the possible variation of antigenic stimuli, the original unknown pathology, and the activation of these ghost vessels postoperatively.

Clinical studies. Clinically, HL-A incompatibility was first recognized and avoided in skin grafts. Organ transplantsations were then made possible by combining HL-A matching with immunosuppressive therapy. Recently, the importance of presensitization to HL-A antigens and antibody production to HL-A has been confirmed.13 Thus, cross-matching and antibody screening policies may influence conclusions about HL-A matching.

In corneal transplantation, possibly because the nonvascular recipient cornea gives a relatively good prognosis and a tissue-typed donor cornea is not available, it has not been customary to use HL-A-compatible material. Gibbs, Batchelor, and Casey16 of the Queen Victoria Hospital, London, used fresh donor material in a random series of 100 HL-A tissue-typed corneal graftings. The donor-recipient pairs shared none, one, or two HL-A antigens, and not a single pair shared three or four HL-A antigens. The authors found that cases with vascularization rejected less often if they shared two antigens. In the less compatible combinations the risk of rejection was higher. Ehlers and Kissmeyer-Nielsen17 of the Arhus Kommunal-hospital, University of Arhus, Denmark, used fresh donor material, too. Their series comprised 50 transplantations, five of which were excluded for various reasons. In the group which shared three HL-A antigens (C match) grafting was successful both in the six patients who were ABO-compatible and in the other three, who were ABO-incompatible, although one of these had late clouding. The authors concluded that for corneal grafting C and even D matches are good (one or two donor antigens not present in recipient). Clear grafts were significantly more frequent among the more HL-A compatible than among the less compatible graftings.
Allansmith, Fine, and Payne from San Francisco, had a series of 43 nonselected corneal donor-recipient pairs, all of them mismatched for two to four antigens. The degree of mismatch did not seem to correlate with the fate of the graft. These authors regarded further HL-A typing of nonselected corneal donor-recipient pairs as not fruitful, but suggested a study of the role of anti-HL-A antibody.

Our material from the Eye Clinic of the University of Helsinki includes 80 corneal graftings, 34 of them being untyped controls. Both fresh and cryopreserved donor corneas were used. Our aim was to find good matches for both HL-A and ABO antigens. Cross-matching tests were performed between the recipient sera and donor cells. Corticosteroids (and Imuran in desperate cases) were used for immunosuppressive therapy.

Before the introduction of cryopreservation in 1973, it was difficult to obtain histocompatible donor corneas. Our series comprises three groups. In the first group there were 27 well-matched donor-recipient pairs with 0-1 mismatches to HL-A histocompatibility antigens (A, B, and C matches). The allograft was rejected in only one case (4 per cent). In this failure, the recipient cornea was heavily vascularized and the case was also complicated in other ways. In the second group, 19 pairs were mismatched for two to four histocompatibility antigens and rejection occurred in 21 per cent. In the third group of 34 untyped graftings, rejection occurred in 26 per cent. When cases with a vascular recipient bed in the first group (with fully or nearly compatible donor cornea) are considered separately, rejection occurred in 8 per cent, and in the untyped third group in 39 per cent. Interestingly, one well-matched donor cornea has remained clear for three years, although it was the fifth transplant after four allograft reactions, two in each eye. This suggests that well-matched grafts may be useful even in presensitized cases.

Our study is continuing. The results so far indicate that, with immunsuppressive therapy, the HL-A-compatible donor cornea is successful even when the prognosis is otherwise poor. In addition, there seems to be evidence that, even in avascular cases, incompatible grafts may run a risk of rejection, e.g., owing to cross-reactions between HL-A histocompatibility antigens and some bacterial antigens.

Thanks to recent advances in corneal preservation, surgeons can now use compatible donor corneas. Continued efforts are still necessary for the final evaluation of the importance of the histocompatible donor cornea.

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REFERENCES