CLINICAL TRANSPLANTATION

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Edited by

David M. Hume, M.D.

Professor and Chairman, Department of Surgery,
Medical College of Virginia,
Richmond, Virginia

Felix T. Rapaport, M.D.

Professor of Surgery,
New York University Medical Center,
New York, New York

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Contents

KIDNEY TRANSPLANTATION

General Considerations

Procurement of Cadaver Donor Organs

Organ Preservation

LIVER TRANSPLANTATION

HEART TRANSPLANTATION

Introduction

THIS year marks the 21st anniversary of the efforts of a pioneering team of surgeons and internists at the Peter Bent Brigham Hospital in Boston, to apply organ transplantation techniques to the treatment of human disease. Since this historic endeavor, over 5000 kidney, 200 heart, 200 liver, 110 bone marrow suspension, 40 lung, and 35 pancreas and intestine transplants have been performed. Therefore, the time appeared ripe to bring together leading authorities in clinical transplantation in order to provide a forum for the free exchange of views and experiences, and to develop guidelines for the clinical management of the transplant patient.

Now that transplantation has become a commonplace clinical procedure, it is clear that one of the responsibilities of the transplantation community must be to provide standards for the optimal delivery of health care to the transplant patient. It is clear that organ transplantation performed without the appropriate scientific and clinical expertise of a fully committed team of trained professionals no longer meets current standards of medical practice in this specialty. There is no place at this time for sporadic attempts at transplantation by "teams," however surgically skilled, who cannot maintain pace with immunological advances or devote sufficient continuing effort to achieve proficiency in the management of the myriad problems which still beset the immunosuppressed patient.

This volume presents the experience of some of the leading transplantation teams in the United States and abroad. Basic problems in the preoperative and postoperative management of transplant recipients, and surgical techniques of importance in the field are reviewed. Those methods that, in the opinion of the participants, have yielded the best results are described. It is our hope that the material presented will provide useful guidelines for the continued success of transplantation biology and medicine in the treatment of human disease.

David M. Hume
Felix T. Rapaport

Present Role of Histocompatibility Matching in Clinical Transplantation

By D. M. Hume

AN obvious disparity between HLA matching and the ultimate fate of the transplant, particularly in respect to cadaver donors, has led to abandonment of histocompatibility matching in some transplant centers. Although there are many limitations to tissue typing, some very important data can be obtained from its continued use. While the failure of histocompatibility matching to mirror the course of the clinical transplant is in part due to inadequacies of typing techniques themselves,[2] it is also in part due to a failure to interpret the clinical course correctly. For instance, if a well matched transplant develops proteinuria, declining renal function and failure, or if a poorly matched transplant survives for a year, this indicates a priori a, lack of correlation between typing and clinical course. This is not necessarily so, however. Some transplants between identical twins develop proteinuria and fail within a year from recurrent glomerulonephritis even though there is no antigenic disparity. Some transplants that have persisted for 1 yr or more develop declining function as time goes on and ultimately fail, indicating incompatibility despite a favorable early course.

Some of the events which interfere with the evaluation of the clinical course as an accurate indicator of histocompatibility are listed in Table 1. A series of immunological events has to be considered before the clinical course can be used to determine histocompatibility differences between donor and recipient. While it is true that previous sensitization of the recipient to transplant antigens is very unlikely to cause acute humoral rejection of an identically matched donor kidney, it certainly does cause acute humoral (hyperacute) rejection of donor kidneys which share antigens to which the recipient has become immune. Since immunization greatly intensifies the response of the recipient against the donor organ, its presence makes it impossible to interpret the degree of incompatibility that might have existed, had the recipient not become immunized. In the presence of acute humoral rejection, therefore, no judgment should usually be made as to the degree of compatibility of donor and recipient. An incompatibility of HL-A 2, where the donor possesses this antigen but the recipient does not, should be avoided because of the extreme likelihood that this will lead to some degree of acute humoral rejection. HL-A 2 is such a prevalent antigen, occurring in roughly 50% of the population, that there is an excellent chance that a recipient lacking this antigen has already been immunized by blood transfusions that possess it. When the HL-A 2 positive transplant is put in place, therefore acute humoral rejection is likely to follow.

"One hour" biopsies taken 20–60 min after transplantation have revealed surprising findings when studied with immuno-

From the Medical College of Virginia, Division of Virginia Commonwealth University, Richmond, Va.

fluorescence. Even in the absence of acute humoral rejection, an amazingly high percentage of transplants show deposition of immunoglobulins on the endothelium of cortical capillaries and on the glomerular basement membrane immediately after transplantation. Of those kidneys which ultimately did well, 65% to 75% had no immunoglobulin at all, while 25% to 35% had only a 1 to 2+ deposition of IgG and B_1C globulin.[1] Of those kidneys that rejected in less than 120 days, only 10% failed to show B_1C globulin and 45% failed to show IgG. In all instances, this was a 3 to 4+ deposition. A striking disparity between the two groups was also seen with respect to fibrinogen. While only 10% of the kidneys which ultimately did well demonstrated fibrinogen on the early biopsy, 80% of the kidneys that did poorly showed it, and it was always in a greater concentration in the latter group. IgM, on the other hand, was completely unpredictive. An example is shown in Fig. 1. These results indicate that even in those patients not having typical hyperacute rejection, the presence of preformed antibody may play a major role in the fate of the transplant. Unless the presence of preformed antibodies is established by immunofluorescent studies of the 1 hr biopsy, the course of the transplant can be misinterpreted to indicate a greater degree of incompatibility than actually exists.

Table 1. Events Interfering With Evaluation of the Clinical Course as an Indicator of Histocompatibility

Immunological
Previous specific sensitization
Acute humoral rejection
HLA-2 incompatibility
1 hr biopsy
Platelet activators in ALG
Recurrent glomerulonephritis
Recipient or graft survival
Apparent decrease in compatibility
Technical failure
Ineffective immunosuppression
Early death of the recipient
Late death of the recipient from causes unrelated to incompatibility
Apparent increase in compatibility
Highly effective ALG
Tolerance or enhancement
Evaluating transplant function as evidence of compatibility less than 2 yr after transplantation

Many patients now transplanted are given courses of ALG. Some of the ALG contains powerful platelet activators that are capable of producing thrombosis of the renal artery. While this leads to early failure of the kidney, it bears no relationship at all to the presence or absence of histocompatibility. Recurrent glomerulonephritis is perhaps the most difficult immunological event to distinguish from chronic rejection. While it can produce renal failure in a way similar to that seen in chronic rejection, it has no relationship to the presence or absence of histocompatibility. Since the vast majority of patients receiving renal transplants originally suffered from glomerulonephritis, recurrent glomerulonephritis could introduce a significant error into the utilization of the clinical course as a measure of histocompatibility.

Apart from these immunological events, there are other factors unrelated to histocompatibility that can bring about failure of the graft or death of the recipient. Technical failure, the necessity to stop or reduce immunosuppression, the use of ineffective ALG, early death of the recipient from infection or some other cause, or late death of the recipient from hepatitis or cancer, could be misinterpreted to indicate incompatibility where none exists. On the other side of the ledger, a highly effective ALG, or the chance production of tolerance or enhancement might suggest a high degree of compatibility when, in fact, acceptance of the transplant was achieved despite major incompatibili-

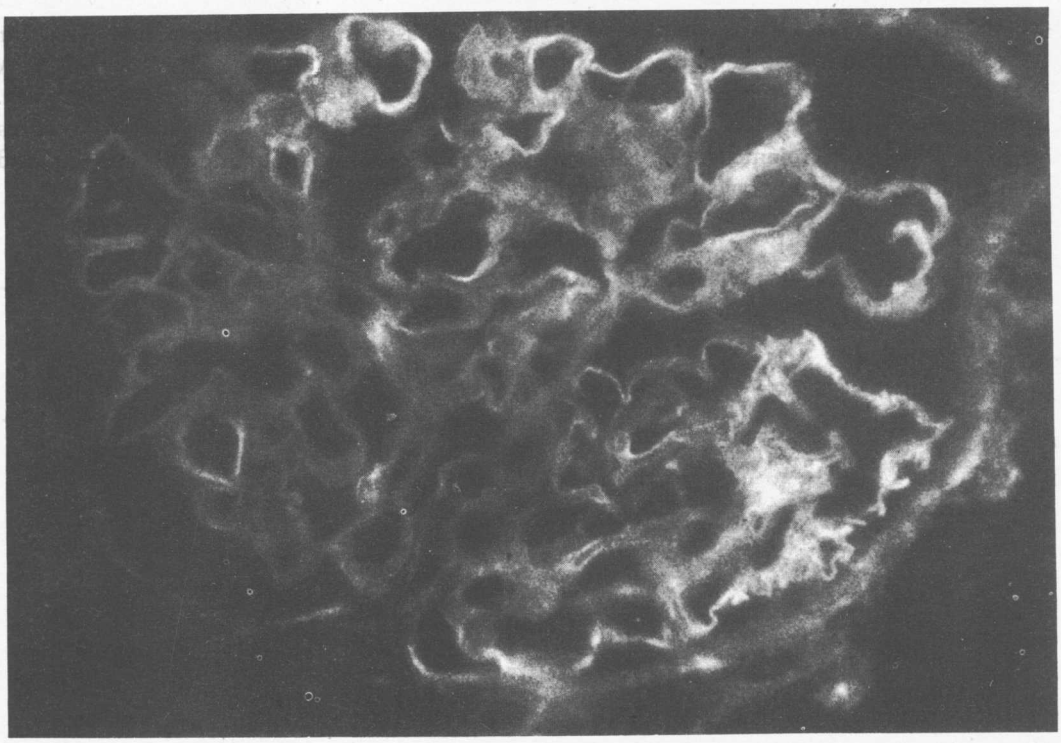

Fig. 1. Patient R. M. (No. 146). A 1 hr biopsy of the kidney transplant showing a 3+ deposition of fibrin on the glomerular capillaries. There was also a 4+ deposition of IgG and B_1C. The patient ultimately went on to reject his kidney despite vigorous immunosuppressive therapy; it was removed on the 55th day.

ties. The same error may be made if function of the transplant is used to judge compatibility before 2 yr after transplantation.[2] Long-term function of the transplant is as important a measure of antigenic differences as early rejection.

There seems little doubt that HL-A identical matched sibling donor–recipient pairs have a much better chance of a benign clinical course than other donor–recipient combinations. There is some evidence that haploidentical pairs, such as seen in some siblings and virtually all parental transplants, are more likely to prove clinically compatible than other nonidentical siblings. All of these groups probably have a somewhat better chance of compatibility than the random cadaver transplant.

CONCLUSION

It seems very important to us to continue to carry out tissue typing and crossmatching in all transplants. At the present time typing is capable of identifying the following factors important to the success or failure of the transplant: (1) Identical matches. (2) Prior sensitization, including testing the recipient's serum against a lymphocyte donor panel, leukocytes of the potential donor, and kidney cells of the donor kidney, and delayed tests, such as immunofluorescence studies of the 1-hr biopsy, and the reaction of host lymphocytes against donor kidney cell monolayers. (3) Haplotypes. Not everyone is convinced that random cadaver haploidentities, such as occur occasionally with HL-A 1–8, 2–7, or 3–7

combinations, have a better chance for success than nonhaplotype combinations; this can only be tested by continued tissue typing. (4) HL-A 2 incompatibility, in the presence of which a recipient lacking this antigen could hyperacutely reject a donor kidney possessing it. (5) Base line data for further studies. (6) The relevance of HLA antigens to disease states of the recipient. (7) Continued efforts to improve techniques of tissue typing, including MLC typing and other methods.

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Histocompatibility Matching Utilizing Responsiveness as a New Dimension

By Gerhard Opelz and Paul I. Terasaki

ALTHOUGH all transplant centers now prospectively type their donors and recipients for HL-A antigens, many of the most experienced centers in the United States are not using HL-A matching as a primary means of selection of cadaver donors and recipients. In siblings, however, unequivocal results demonstrate that HL-A identity results in more than a 90% 1-yr transplant survival rate. The problem of utilizing HL-A typing for clinical transplantation reduces to the question of how to choose between incompatibilities, for 99% of the transplants done today are from HL-A incompatible donors (aside from HL-A-identical siblings). Simple counting of the number of mismatched specificities was proposed by us as a means of classification of incompatibilities.[1] Subsequent large-scale collection of data showed that other factors may influence the recipient's response to the incompatibilities to such an extent that whatever cumulative effect additional specificities of mismatch may have had was largely masked.[2,3] Evidence to the contrary has been brought forth by others that the enumeration of incompatibilities alone can be correlated to significantly different levels of transplant survival.[4] In 1967 we had speculated that "the course of the kidney transplant is influenced more by the level of presensitization than by matching of antigens per se."[5] Most kidney transplant patients are preimmunized by transfusions, and some may be immunized in such a way as to induce tolerance or enhancement. A new matching scheme which considers the reactivity state of the recipient is proposed here. As a measure of responsiveness, the prospective recipient's ability to respond to blood transfusions while on hemodialysis by production of cytotoxic antibodies is used.

From the Department of Surgery, School of Medicine, University of California, Los Angeles, Calif.

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METHODS

Clinical outcome was expressed in terms of graft survival, computed by actuarial methods,[6] and no exclusions were made on the basis of technical error, etc. The transplants were done at over 50 centers in the United States and Canada. Only patients transplanted for the first time from cadaver donors are included. All transplants were performed after January 1, 1969.

In addition to the above restrictions, the plasma of all 870 patients in this study was tested for the presence of lymphocytotoxic antibodies before transplantation. Approximately 190 plasma samples tested in early 1969 were evaluated against lymphocytes from 40 donors, whereas 680 others tested subsequently were reacted against lymphocytes from 90 random donors. Lymphocyte cytotoxicity was measured as described earlier, incubating 0.001 ml of sera with 1000 lymphocytes for 30 min at room temperature, followed by incubation for one hour with 0.005 ml of rabbit complement.

RESULTS

As described earlier, transplant patients classified on the basis of whether they did or did not have cytotoxins before transplantation serves to categorize patients into two distinct populations with a significant difference in survival rates.[7] This difference was confirmed in a new series of 829 patients (Fig. 1). Subdivision of the patients into those with cytotoxins against less than 2% of the population, 3%–4%, 5%–10%,

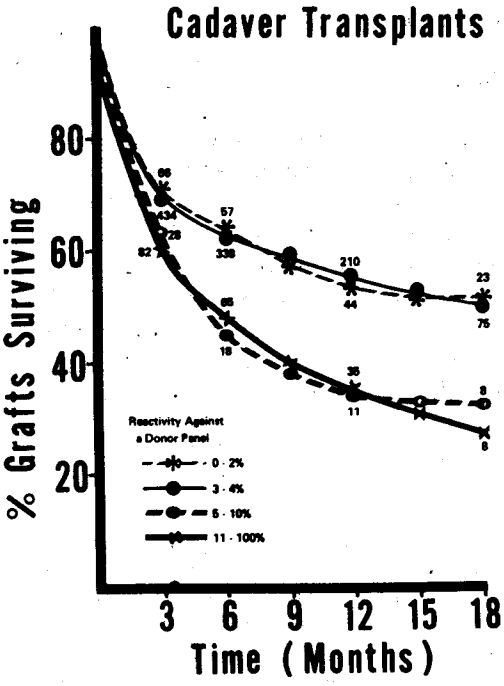

Fig. 1. Survival rates of transplants into patients with cytotoxins. The number of patients in the four categories of reactivity against the random donor panel was 566 in 0%–2% cytotoxins, 98 in 3%–4%, 41 in 5%–10%, and 124 in 11%–100%. The numbers on the lines denote the number of patients at risk.

and 11% to 100% showed a sharp division at 5%, with a clear distinction in transplant results depending on whether or not the patient is sensitized prior to transplantation. Reaction with 5% of the donor panel appears to be the limit of the error within the test system employed. A patient with cytotoxins against 5% of 100 random persons can therefore be considered to be sensitized and to react to a greater degree against kidney transplants from most incompatible donors. An exact parallel in the survival rate and the percentage of reactivity was not seen. The separation, however, of 41 patients with cytotoxins reactive against 51%–100% of the population did show a markedly low survival rate of 22% ± 7% at 1 yr (Fig. 2). In the remaining 124 recipients with cytotoxins against 5%–50% of the panel, a 1-yr survival rate of 40% ± 5% was noted.

Based on the 5% cutoff, the 1-yr graft survival of 664 negative patients vs. 165 positive patients was 55% ± 2% vs. 36% ± 5% (Fig. 3).

As noted earlier[7,8] cytotoxins can often disappear, leaving a patient sensitized but without detectable cytotoxins; 41 such recipients have now been encountered, and their transplant survival is plotted in Fig. 3. The survival rate at one year of 35% ± 7% was almost identical to the survival rate of patients with cytotoxins at the time of transplantation. Thus, once a patient is sensitized, loss of humoral cytotoxins does

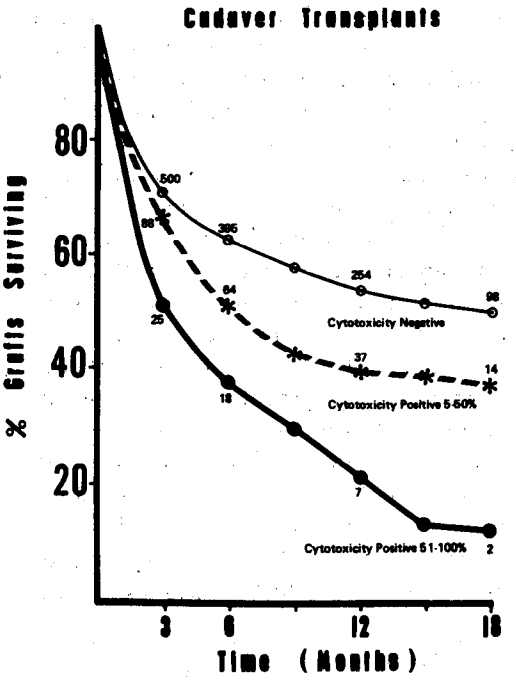

Fig. 2. Separation of hyperimmunized prospective recipients with cytotoxins against lymphocytes of 51%–100% of random donors. The survival rate among such patients can be seen to be markedly lower than among patients with cytotoxins reactive against 5%–50% of the random panel.