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TRANSPLANTATION
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RENAL TRANSPLANTATION AT THE UNIVERSITY OF COLORADO[1]

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SUMMARY

From March 1962 to April 1966, 118 patients were treated with renal transplantation, 3 with kidneys from identical twins, 9 with cadaveric homografts, and 106 with homografts from volunteer donors. Sixty-two of the patients are still alive after nine months to almost five years. The only completely satisfactory group was that of the identical twin recipients.

The results after homotransplantation have not materially improved during this time despite the acquisition of increased experience, adjustments of timing and dosage of azathioprine and prednisone, and attempts to identify biologically suitable donors in advance of operation by tissue typing. It is suggested that an *impasse* has been reached, beyond which further reduction in mortality and morbidity will depend primarily upon the effective application of new immunosuppressive techniques.

In spite of the increasing acceptance during the last five years of renal homotransplantation as a legitimate clinical undertaking, those responsible for the care of such patients have been keenly aware of the imperfections of the therapeutic techniques employed during this time. Investigators in several centers including our own have tried to vary systematically the timing and dosage of the two most important immunosuppressive agents, azathioprine and prednisone. Furthermore, efforts have been made to apply antigen-matching techniques for donor selection with the hope of thereby reducing the need for these drugs.

In this report, we will suggest that an *impasse* has been reached, imposed by the inherent limitations of the agents used to control rejection. A survey of our own experience has shown that the acquisition of increased experience, the institution of variations in therapy, and even the application of antigen typing methods for donor selection have not eliminated or even significantly reduced the morbidity and mortality after transplantation. The cases can be divided into four groups.

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IDENTICAL TWINS TRANSPLANTS

All three patients had glomerulonephritis. They were 27, 20, and 54 yea old when their operations were performed 58, 42, and 9 months ago. Each no has normal renal function although the patient with the longest follow-u has had persistent microscopic hematuria for almost five years. A biopsy i the second case after two years was normal.

FIRST LIVING DONOR SERIES

These 64 patients were operated upon from 34 to 50 months ago. Forty-si received kidneys from family members (20 parents, 23 siblings, and 3 aunts uncles, or cousins); the other 18 donors were nonrelated. No other effor was made to match donor-recipient pairs than, with a few exceptions, to ensure against ABO blood group incompatibilities. The first 45 patients were treated solely with azathioprine until rejection developed, at which time prednisone was added. The last 19 received both drugs from the beginning. Actinomycin C and local homograft irradiation were used irregularly.

Thirty-two of the patients are still alive. The survival of the recipients of related kidneys is 29 of 46 (63%). In contrast, only three of the 18 patients in the nonrelated group (16.7%) remain alive (Fig. 1), one by virtue of a second graft after 2½ years.

The change in the timing of prednisone administration in the second part of the series did not result in an increase in the total amount of this drug which was given. By using large quantities of steroids from the beginning, the incidence of severe early rejections was reduced, making it possible to attenuate dosage at a more rapid rate. The consequent balancing effect is shown in Figure 2 in which the average dose per day for the first 105 days was found to be almost identical for the recipients of related homografts in both the earlier and later groups who lived this long; analysis of the nonrelated cases revealed the same thing.

During the acquisition of the series, there was a trend to conservatism in

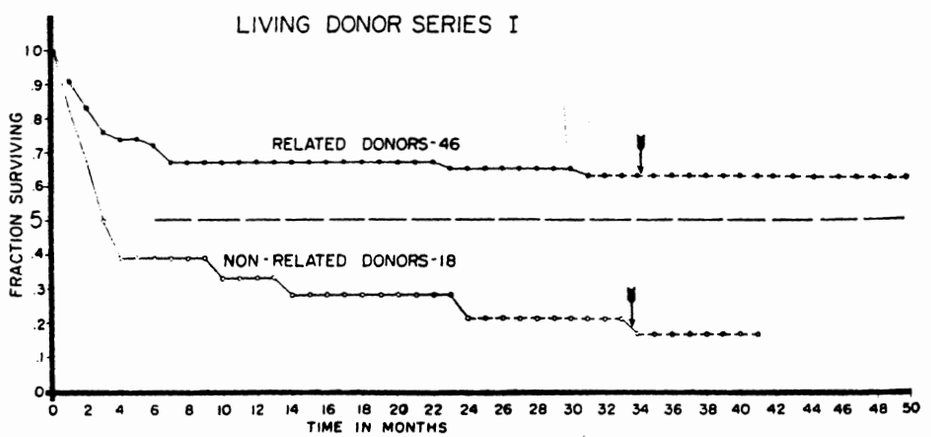

FIGURE 1. Survival in the first series of 64 patients treated with homografts from living donors. All patients are alive beyond the points indicated by the vertical arrows. Follow-up is thus 34 to 50 months.

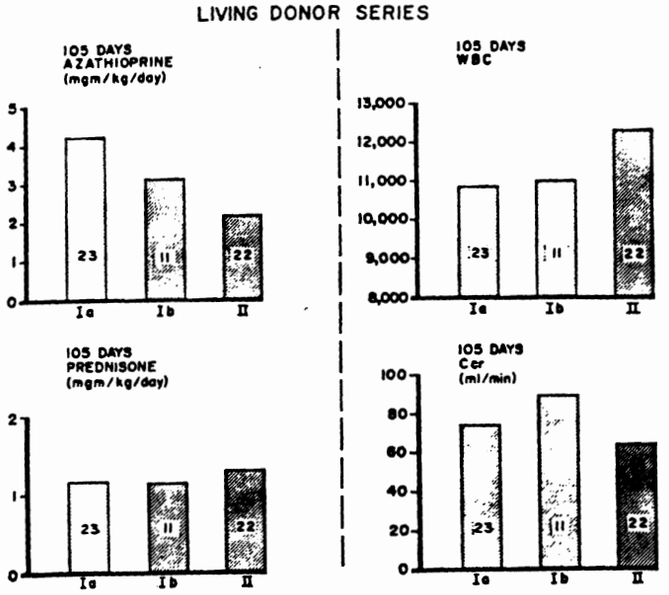

FIGURE 2. Analysis of doses of immunosuppression in the two fractions of the first and in the second series of homotransplantations from living related donors. The division of the first group was on the basis of differences in the administration of steroids; the first patients (a) received Prednisone for the specific indication of rejection and the later patients (b) received this drug prophylactically from the time of operation. The data are from the first 105 postoperative days; patients who failed to live this long were excluded. The influence of these changes on the white cell counts and creatinine clearance is shown.

the use of azathioprine (Fig. 2) which reflected growing apprehension about the acute bone marrow depression which was then a common complication. An expected corollary change was an increase in the white cell counts (Fig. 2).

Average renal function, illustrated in terms of creatinine clearance was slightly better in the second group of patients who were treated from the beginning with prednisone (Fig. 2) but the difference was not statistically significant.

Studies of these original cases provided hope that future results could be improved using white cell antigen matching in donor selection. Thirty-seven of the original 64 patients who survived for at least one year were typed by Terasaki along with their respective donors. It was found that the best clinical results tended to be in those cases with a high degree of donor-recipient compatibility of lymphocyte antigens. Furthermore, there was a very firm correlation between the completeness of this matching and the quality of preservation in the homograft biopsies studied at about two years (2).

SECOND LIVING DONOR SERIES

These 42 patients received homografts 9 to 27 months ago from volunteers who were chosen insofar as possible on the basis of the best available

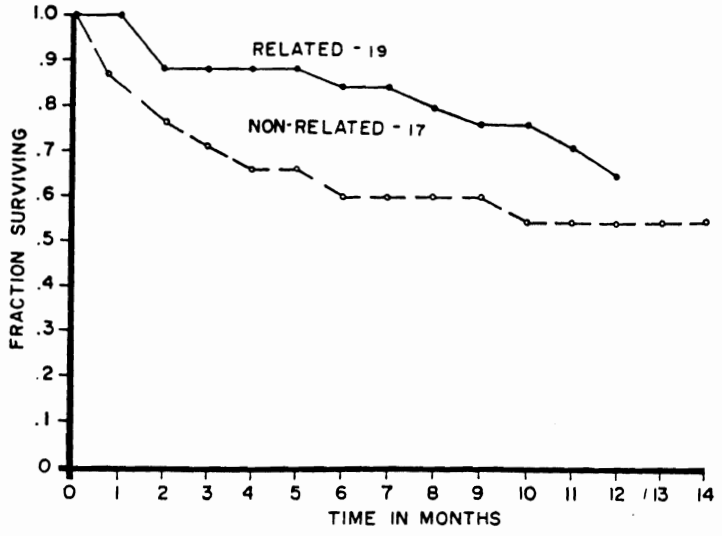

FIGURE 3. Survival in the first year following homotransplantation in the second living donor series. The patients included have been followed from 12 to 27 months. One of the nonrelated group subsequently died after 17 months.

antigen match. In 25 cases, there were related donors (15 parents, 9 siblings, 1 uncle). Because the selectivity within most families was limited, the quality of matching was only slightly (and not significantly) better than could have been achieved with random intrafamilial pairing; the donor pool for the 17 nonrelated cases was a large one allowing much greater discrimination (*3*). Immunosuppression was similar to that in the previous series except that prednisone was usually started in relatively small doses on the day of operation and later increased if required for control of rejection.

Twenty-five of the patients are still alive, 17 of 25 (68%) in the related and 8 of 17 (47%) in the unrelated groups. The statistics for the first 36 cases, all operated upon 12 months or longer ago are shown for the first year in Figure 3. The survival after one year was slightly worse in the related cases (63.1%) than in the original series, but it was better (53%) in the nonrelated cases; one of the latter patients subsequently died of hepatitis after 17 months. With the delay in mortality which distinguished the second from the first series, an almost universal lethal factor in unsuccessfully treated cases was found to be infection with uncommon fungal, protozoan, and viral organisms. The resultant change in the character of the autopsy findings has been discussed in detail by Hill (1).

The previously described tendency to use smaller doses of azathioprine, which had already been noted during the treatment of the original series of patients, continued (Fig. 2) into the last group. Now, however, the penalty became the need to use higher maintenance doses of prednisone; the data shown are from the related cases, but analysis of the nonrelated transplantations revealed exactly the same thing. In spite of this adjustment the

creatinine clearances during the first 105 days was distinctly poorer ($p < 0.05$) than in the first series (Fig. 2). The incidence of acute failure from drug toxicity had thus been greatly reduced but at the expense of less adequate homograft protection, a delayed mortality which is apt to be at least as great as in the original series since several of the patients still living are not doing well, and an unquestionably increased long-term morbidity.

Biopsies of seven of these homografts were obtained at approximately two years. None were normal and only two were free of more or less serious structural abnormalities.

CADAVERIC SERIES

Three recipients, provided with cadaveric homografts in 1963, died within 4 to 39 days with unrelieved uremia. In the last 10 to 14 months, six more similar attempts were made; all of the kidneys functioned following delays of 10 minutes to 23 days after revascularization. Four of these recipients died after 3, 8, 10, and 12½ months with failing grafts and with septic complications of the kind described in the preceding section. An additional patient who had normal function for the first seven months had a late uncontrolled rejection and is awaiting homograft removal and retransplantation. The final patient is one year postoperative with normal renal function.

DISCUSSION

The foregoing observations make it clear that, if renal homotransplantation has become a standard form of therapy for terminal renal disease, it has achieved this status prematurely. Every active transplantation center has its brilliant results, but the incidence of failure is high and, what is worse, it seems to have reached an irreducible minimum employing the "standard" immunosuppressive agents. In our own institutions, the progressively more timid use of azathioprine, combined with altered programs of prednisone administration, has virtually eliminated the early postoperative deaths from acute bone marrow depression, but at the expense of later diminished function and a higher ultimate steroid need in many cases. The eventual mortality has remained relatively fixed with each such adjustment in management.

It is equally discouraging to note that the use of prospective antigen matching for donor selection did not have more influence upon prognosis. This was not surprising in the consanguineous transplantations since selectivity could not be significantly improved due to the problem of supply. This was not the situation, however, in the nonrelated cases where the one-year survival was upgraded by only 20%, reaching the still unsatisfactory figure of 53%. The latter finding emphasizes the futility, with the presently available therapeutic protocols, of envisioning effective and large scale application of tissue typing techniques in cadaver programs.

This does not imply either that the tissue typing methods now being developed are not a direct or indirect measure of histocompatibility factors, or that the use of these techniques will play an insignificant role in transplantation practices of the future. Indeed, evidence has been cited earlier

from many of these same cases (*2*) that the ultimate damage imposed upon the homografts of patients who achieve long-term survival is directly related to the degree of antigen nonconformity between donors and recipients.

Instead, it suggests that antigen matching techniques cannot receive a fair trial with the treatment programs now widely being used unless transplantation is performed only between almost perfectly matched pairs or, alternatively, that they require for exploitation a setting of far more adequate immunosuppression. The former approach would limit consideration to all but a very small number of patients who need this kind of therapy. The latter development would allow extension rather than restriction of the indications for acceptance into a transplantation program. Investigations of new methods of immunosuppression, reported elsewhere in this symposium, provide hope this objective can be realized.

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