Deliberate Donor-specific Blood Transfusions Prior to Living Related Renal Transplantation

A New Approach

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In order to select MLC incompatible one-haplotype related donor-recipient pairs that would achieve better graft survival and in an effort to alter the recipient immune response, 45 patients received three fresh blood transfusions from their prospective kidney donors. Recipient sensitization was evaluated by cross-match testing weekly sera obtained during and after the blood transfusions against donor T- and B-lymphocytes at 5 C (cold) and 37 C (warm). Thirteen (29%) of the 45 potential related recipients developed a positive warm T-cell cross-match or a persistent warm B-cell cross-match to their blood donor and related transplantation was not performed. Thirty-two (71%) patients had an appropriate negative cross-match to their blood donor. Thirty of these patients subsequently received kidneys from their blood donor. Ninety-seven per cent of the kidneys are functioning from one to 25 months with a single graft failure due to a patient discontinuing immunosuppressive medication. In addition to the excellent graft survival there was an unusually low incidence of rejection episodes in the recipients of kidneys from their blood donor so that the posttransplant course paralleled that of HLA-identical siblings. This approach may have future application with two-haplotype mismatched donor-recipient pairs, both related and unrelated.

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OUR CENTER[18] AND OTHERS[1,22] have previously demonstrated that graft survival in one-haplotype matched related recipients with a high mixed lymphocyte culture (MLC) index is similar to that obtained with cadaver transplants. Improved future results in disparate living-related donor-recipient pairs will probably depend on some new approach, rather than on greater nonspecific immunosuppression with its attendant risk of increased patient morbidity and mortality. In order to select potentially successful transplants from among immunologically disparate related recipients, a pretreatment protocol with deliberate donor-specific blood transfusions was initiated at the University of California, San Francisco (UCSF) two years ago.

Since donor blood transfusions given to recipients before renal allografting might result in sensitization to the donor and subsequent hyperacute rejection, clinicians previously were hesitant to employ this technique in human renal transplantation. Recent reports stated that deliberate transfusions with donor-specific blood was never used[24] and could not be justified.[20] Rationale for our trial was based on multiple factors, both experimental and clinical. Past animal studies have shown that prolonged renal allograft survival could be obtained by actively conditioning the host with fresh donor blood at varying intervals prior to organ grafting.[4,6,9] In addition, there was remarkable clinical success reported with intermittent pretransplant injections of donor lymphocytes in four recipients,[12] and in a patient with long-term graft function following retrospective discovery of two pretransplant blood transfusions from the parent donor.[14] Our findings of a salutary effect of random pretransplant blood transfusions in immunologically disparate living-related recipients[18] encouraged us to pursue a trial of donor blood pretreatment in human living-related transplantation.

This report represents the results of a deliberate donor-specific blood transfusion protocol instituted at UCSF, 14 years after the initial report by Halasz[6] showing the effectiveness of donor blood as a conditioning agent in laboratory animals.

Presented at the Annual Meeting of the American Surgical Association, Atlanta, Georgia, April 23–25, 1980.

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0003-4932/80/1000/0543 $01.00

Patients and Methods

Forty-five one-haplotype matched related donor-recipient pairs (sibling or parent–child) were prospectively selected for the donor-specific blood transfusion (DST) protocol on the basis of an MLC with a high stimulation index (SI $\geq$ 7), Rh compatibility, negative direct cross-match, and an acceptance of the potential risks of sensitization and transfusion reaction. All donor-recipient pairs selected were highly motivated and well-informed. The two-way MLC technique has been the same procedure prospectively used at this center for all potential living related donor-recipient pairs since 1972 and has been previously reported.[3]

The DST procedure involves administration of approximately 200cc of fresh (within 24 hours) whole blood or packed cell equivalent on three separate occasions at approximately two-week intervals. Immunosuppression was not given during and after the transfusion period, but was initiated two days prior to transplantation. Slight variation in the amount of blood administered and in the interval of administration were dependent upon regional blood bank preferences in obtaining subunit amounts of blood and on logistics in obtaining satisfactory transfer or mailing of blood from geographically distant potential donors.

Potential recipient sensitization against a donor was closely monitored by cross-match testing of weekly recipient sera obtained during and after the blood transfusion period until the time transplantation was performed. In general, the sera collected until two to three weeks after the last transfusion were tested at one time against freshly-obtained donor cells. On the basis of these results a determination was made whether to proceed with medical donor evaluation and scheduling of the prospective renal transplant. All subsequent weekly sera, including sera obtained immediately prior to transplantation, were tested again against fresh donor cells on the day prior to transplantation. The cross-match testing was performed against isolated donor T- and B-lymphocytes at 5 C (cold) and 37 C (warm). Weekly sera were also screened by the UCLA Tissue Typing Laboratory in double blind fashion against a random panel of 30 unrelated donors for cold B-, warm B-, and warm T-cell cytotoxic antibodies.

Transplantation was performed only if the cross-match at 37 C was negative to isolated T- and B-cells. Time of transplantation varied from two weeks to six months after the last transfusion, with most patients transplanted approximately three to six weeks after the last transfusion.

The course of the grafted kidney was closely monitored by serial serum creatinine testing and 1-131 hippurate scintiphotographic studies. The renal scans were performed at 24 hours after transplantation and on any suspicion of possible rejection crisis.

Immunosuppression was the same uniform therapy used for all living-related recipients since September, 1972, and consisted of azathioprine and prednisone, as previously described.[17] Azathioprine and prednisone were initiated two days before the scheduled renal transplant. Therapy for rejection consisted of increased oral daily prednisone to a maximum dosage of 3 mg/kg, unless the clinical situation warranted a lower dosage.

Graft loss was dated as of the time of loss of renal function requiring return to chronic dialysis or transplant nephrectomy. Patient death from any cause was included as a graft loss. Percentage graft survival was calculated by actuarial methods[10] and is expressed as percentage survival $\pm$ standard error (SE). When comparisons were made between groups, the chi square test was used to evaluate statistical significance.[8] When evaluating bivariate correlations, Pearson's r was computed. Means are expressed as $\pm$SE.

Results

The mean MLC stimulation index for the 45 donor-recipient pairs who completed DST was 18.8 $\pm$ 2. Thirty-two (71%) DST patients were accepted as potential recipients for a kidney from their blood donor on the basis of a negative warm T-cell cross-match on the multiple serial specimens and in absence of a persistent warm B-cell cross-match. Three of these patients demonstrated transient positive warm B-cell cross-match activity, but this was not present on the several weekly samples immediately prior to transplantation. In addition, six patients showed a transient positive cold B-cell cross-match, which did not contraindicate subsequent transplantation.

Thirty of the 32 patients have received kidneys from their blood donor. Two of the 32 patients were not transplanted from their blood donor because findings on the medical evaluation of the potential donor contraindicated renal donation. These included asymptomatic bilateral renal artery fibromuscular dysplasia in one patient and an unsatisfactory creatinine clearance in another. These two patients subsequently received and have normally functioning cadaver kidneys.

Outcome of Transplantation from the Blood Donor

The 30 DST patients receiving kidneys from their blood donor range in age from 7–54 years and include 11 (37%) insulin-dependent juvenile diabetics. The mean follow-up is 7.1 $\pm$ 1.1 months.

Hyperacute rejection has not occurred, and 1-131 hippurate scintiphotographic studies 24 hours after

TABLE 1. *Clinical Characteristics of Living Related Recipients*

	Mean Age (Years)	Per Cent Male	Per Cent Diabetic Patients	HLA-A & B Locus Antigens Matched	Donor HLA-A2 Mismatch (No. Patients)	MLC SI	Dialysis Time (Months)	Per Cent Patients With Non-DST Pretransplant Blood Transfusions
With DST (n = 23)	27 ± 3	52	35	2.3 ± 0.1	4	18.9 ± 2.0	12 ± 2	65
Without DST								
1-haplotype match								
high MLC* (n = 34)	27 ± 2	59	27	2.1 ± 0.1	0	11.4 ± 0.7	10 ± 2	68
low MLC† (n = 74)	30 ± 2	58	7	2.6 ± 0.1	1	2.2 ± 0.3	11 ± 1	46
HLA-identical (n = 69)	32 ± 1	49	9	4.0 ± 0.0	0	1.3 ± 0.1	12 ± 2	33

* S.I. ≥ 7. † S.I. < 7.

transplantation have all shown good renal uptake of the isotope with satisfactory excretory function. There were no technical complications. Twenty-nine of the 30 kidneys (97%) are presently functioning from one to 25 months after transplantation. The single graft loss was a diabetic patient who discontinued immunosuppressive medication at two and one-half months following transplantation. Graft function, however, did not rapidly deteriorate, and dialysis was not required until three and one-half months after transplantation.

Comparison was made of the 23 consecutive DST recipients followed at least three months with the other consecutive related recipients transplanted since September, 1972, when a uniform immunosuppressive protocol was adopted. No patients were excluded. The living-related recipient categories were well defined on the basis of prospective family tissue typing and MLC. Table 1 assesses comparability of patient groups and shows an apparent higher risk in the DST recipients because of the higher incidence of insulin-dependent juvenile diabetics, HLA-A2 mismatches, and the higher MLC SI. The DST recipient received a mean of 631 ± 34cc of donor blood with a mean period of 1.7 ± 0.2 months from the time of last transfusion until transplantation.

Table 2 shows three-month and one-year graft survival rates for these same living-related groups. The graft survival results in the DST group are similar to those achieved with HLA-identical siblings. The mean serum creatinine of those patients with functioning grafts at three months are 1.3 ± 0.1 mg/dl for all recipients in the DST group, and 1.6 ± 0.2 mg/dl, 1.3 ± 0.1 mg/dl, and 1.5 ± 0.2 mg/dl, respectively, for the one-haplotype high MLC, one-haplotype low MLC, and HLA-identical groups.

TABLE 2. *Per Cent Graft Survival*

	3-Month	1-Year
With DST (n = 23)	100	94 ± 5*
Without DST		
1-haplotype match		
high MLC (n = 34)	65 ± 8	56 ± 9*†
low MLC (n = 74)	90 ± 3	89 ± 4†
HLA-identical (n = 69)	99 ± 1	96 ± 2

* $p < 0.005$.
† $p < 0.0006$.

Rejection Episodes

Only 11 (37%) of the 30 patients receiving kidneys from their blood donor have thus far experienced a rejection episode. The incidence of rejection episodes occurring during the first three months following transplantation was evaluated and comparison made between the 23 DST recipients followed a minimum of three months and the other living-related patient groups (Table 3). There was an unexpected early appearance of an acute rejection episode in the ten DST recipients who experienced such an episode within the first three months after transplantation. Rejection was first evident at 6.9 ± 1.7 days (range: 1–20 days) following transplantation in the DST recipients experiencing such an episode (Fig. 1), compared to 11.4 ± 2.1 days in the one-haplotype high MLC recipients, 15.7 ± 1.7 days in the one-haplotype low MLC recipients, and 25.4 ± 2.3 days in the HLA-identical recipients. Two DST patients required dialysis during rejection therapy, but in both patients the creatinine returned to prerejection levels and there was always good isotope uptake by the

TABLE 3. *Recipients with Rejection Episodes at Three Months*

With DST (n = 23)	44%*
Without DST	
1-haplotype match	
high MLC (n = 34)	82%*
low MLC (n = 74)	62%
HLA-identical (n = 69)	49%

* $p < 0.006$.

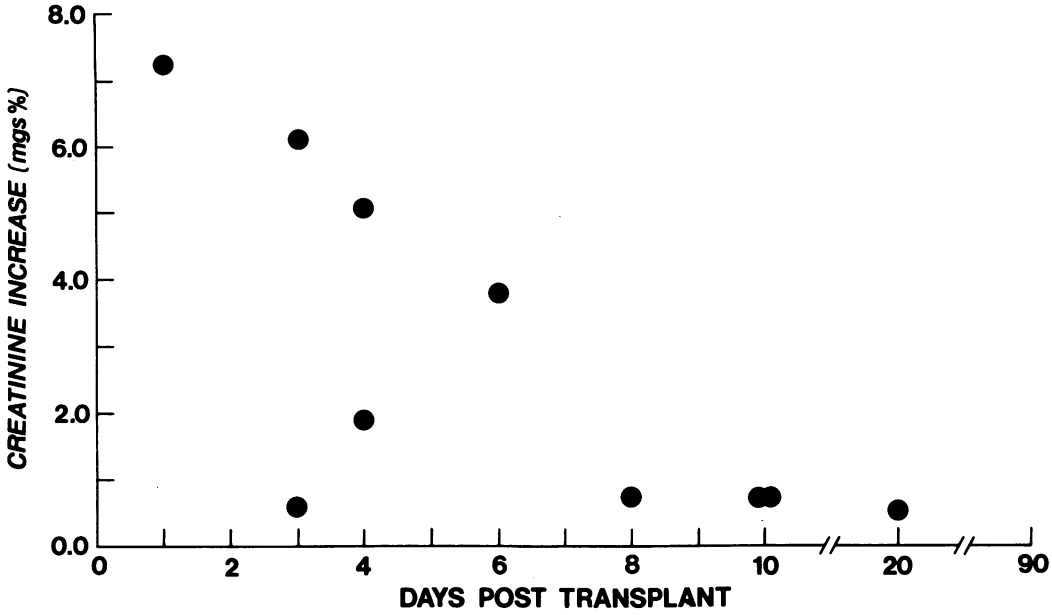

FIG. 1. Time of onset vs. severity of first rejection episode in the ten DST patients experiencing a rejection episode during the first three months posttransplant. Creatinine increase is measured from the lowest creatinine obtained immediately prior to diagnosis and treatment of rejection. $r = -0.62$, $p < 0.03$.

kidney on 1-131 hippurate renal scintiphotography. In the other eight patients, the rejection episode was mild and easily reversed, with an increase in creatinine from 0.6 mg/dl to 5.1 mg/dl (mean: 1.8 ± 6 mg/dl) from pre-rejection levels. In fact, creatinine elevation was equal to or less than 0.7 mg/dl in five patients. No patient required dialysis in the absence of rejection.

Administered donor-specific blood was either whole blood or packed cells. Neither form appeared to be more favorable in avoiding rejection episodes, which occurred in six of 13 patients receiving whole blood, three of seven receiving packed cells, and in one of three patients receiving a combination of whole blood and packed cells.

Four patients have experienced a second rejection episode. One is the patient with the highest current creatinine in the series (2.6 mg/dl), and Figures 2 and 3 represent the biopsy taken from this diabetic recipient two and one-half months after transplantation.

Sensitization to the Blood Donor

Thirteen (29%) of the 45 DST potential related recipients developed a positive warm T-cell cross-match or persistent warm B-cell cross-match to their blood donor, and related transplantation was not performed.

Only ten patients (22%) had a positive warm T-cell cross-match, which developed after the first transfusion in five patients, after the second transfusion in three patients, and after the third transfusion in two patients.

Three patients (7%) had a persistent warm B-cell cross-match, but without a concomitant positive warm T-cell cross-match. Donor-specific warm B-cell antibodies developed after the first transfusion in two patients, and after the third transfusion in one patient. Repeated sampling continued to show a positive warm B-cell cross-match in these patients, and it was our judgment that without a better appreciation of the risks after DST, that related transplantation with a persistent warm B-cell cross-match positive donor could not be carried out.

Four of the ten positive warm T-cell cross-match patients have subsequently received cadaver transplants. Two of the grafts have failed, while the other two grafts are now functioning more than eight months after transplantation with creatinines of 0.8 mg/dl and 1.3 mg/dl.

Cytotoxic Antibody Screening

The same weekly sera that were evaluated for specific humoral response to the blood donor were also screened in double-blind fashion against a random panel of 30 potential unrelated donors. Table 4 summarizes increases of 10% or more for cold B, warm B and warm T-cell antibody levels from the baseline determination at the start of the DST process. Only nine of the 45 DST patients exhibited such an increase in warm T-cell cytotoxins, and eight of these patients had developed a positive cross-match to their blood donor. All nine patients with increased warm T-cell cytotoxins received third party transfusions in addition to the DST.

Panel reactivity was also separately analyzed according to patient groups receiving and not receiving other third party transfusions with the DST. There were 15 patients who had no past history and did not receive third party transfusions during the DST process. None of these developed increased warm T-cell panel sensitization. In contrast, increased warm T-cell sensitization was observed in nine of 30 patients with other third

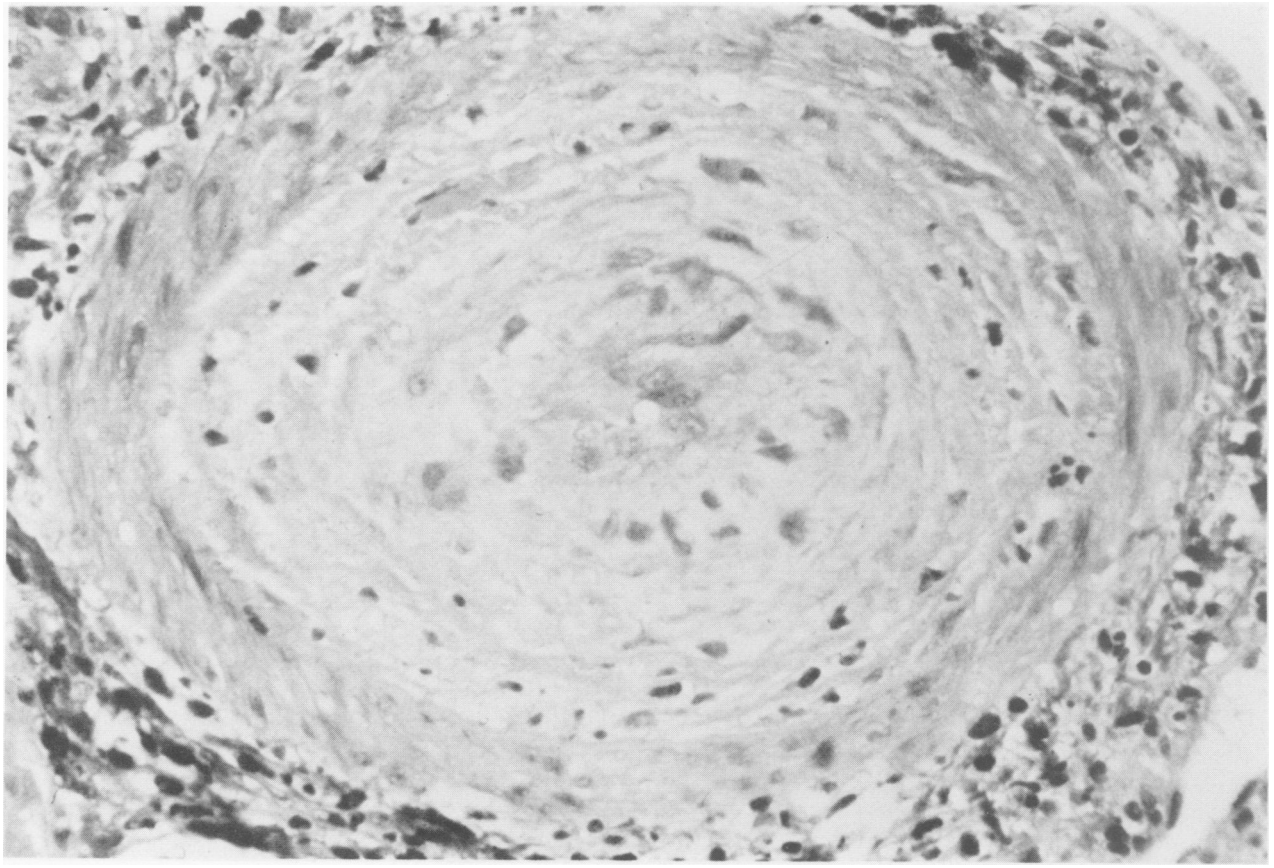

FIG. 2. Medium size artery with occlusion of its lumen secondary to intimal cell proliferation, edema and fibrosis. There are several neutrophils present at the intimal-medial border (hematoxylin-eosin ×600). The glomeruli appeared normal, and there were only a few mononuclear cells in the interstitium.

party transfusions ($p < 0.05$). Three of the 15 patients without other transfusions and without increased panel sensitization developed a positive cross-match to their blood donor. One of these latter patients had a persistently positive warm B-cell cross-match to the blood donor but no panel warm T-cell sensitization until after the administration of two random transfusions more than two months after the completion of the DST process. Administration of the random transfusions resulted in a 0–76% increase in warm T-cell antibodies.

Of the 30 patients receiving a transplant from their blood donor, only three had any warm T-cell panel activity, with the highest levels being 26, 73 and 93%. These three patients had respectively received 30, seven and two random blood transfusions. In only one of these sensitized patients was there an increase from the baseline level at the start of the DST process, and this patient received seven units of blood immediately before, during and after the DST process.

Thirteen (43%) of the 30 patients receiving a transplant from the blood donor had cold B-cell antibody levels of 10% or greater. In ten of these an actual increase of 10% or greater was noted during the DST process. Eighteen (60%) of the patients receiving a transplant from their blood donor actually had cold B-cell antibody levels of greater than 5%, but a minimum level of 10% was thought to absolutely assure the presence of the cold B-cell cytotoxins.

Donor HLA-A2 Mismatch

We have previously been reluctant to proceed with transplantation when the recipient was mismatched against the donor A2 antigen, because of impaired graft survival compared to those patients in whom the mismatch was not present.[16] Six of the 45 patients with DST were mismatched against their blood donor's A2 antigen. Despite the repetitive challenge with the A2 blood donor, sensitization was surprisingly not detected and all six patients have now received grafts from their A2 blood donor. All kidneys (four followed from four to 18 months) have normal renal function and only two patients have experienced mild rejection episodes.

Discussion

Results of renal transplantation have shown no real improvement in graft survival during the past five years. Emphasis on improving graft survival by more effective

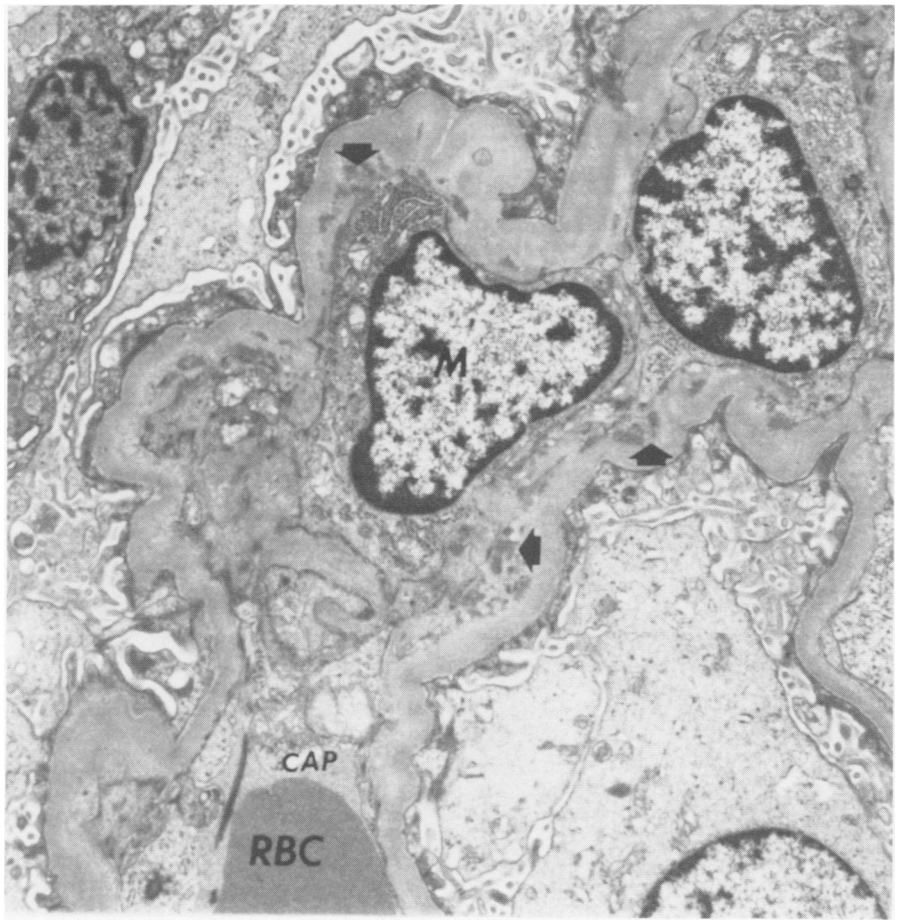

FIG. 3. The electron micrograph shows multiple small electron dense deposits (arrows) in the mesangial matrix (×9000). Immunofluorescence studies showed IgG, IgM and C_3 corresponding to the same distribution of the deposits demonstrated by electron microscopy. M = Mesangial cell. CAP = Capillary lumen. RBC = Red blood cell.

immunosuppression will only result in increased mortality and prohibitive morbidity compromising the patient's quality of life following transplantation. Currently, the patient without a compatible related donor to permit good graft survival is either relegated to cadaver transplantation or not referred at all. In addition, those patients awaiting cadaver kidneys are oftentimes forced to wait prolonged periods because of the limited availability of cadaver organs.

The DST protocol described appears to optimize the possibility of immunologically disparate related recipients receiving transplants with excellent graft survival. In addition, the low incidence of generally mild rejection episodes and their ease of reversibility allows those

TABLE 4. *Patients with 10% or Greater Increase in Panel Antibodies During DST Monitoring*

Antibody Categories			Number of Patients			
				Negative Donor-Specific Cross-match		
Cold-B	Warm-B	Warm-T	Total (n = 45)	Transplant Performed (n = 30)	Transplant Not Performed (n = 2)	Positive Donor-specific Cross-match (n = 13)
			20	17	2	1
↑			3	3	0	0
↑	↑		7	6	0	1
↑	↑	↑	5	1	0	4
	↑		6	3	0	3
↑		↑	1	0	0	1
	↑	↑	3	0	0	3

↑ = 10% or greater antibody increase. Blank = no increase.

patients receiving kidneys from their blood donors an outcome and posttransplant course similar to that achieved with HLA-identical sibling matches. Since only a minority of motivated, medically-suitable, related donors prove to be immunologically compatible (low MLC) with their respective recipients, the impact of a successful DST protocol would be to allow an increased number of patients the opportunity of successful living-related transplantation. In addition, this favorable result would be achieved without the morbidity and mortality risk of excessive immunosuppression.

The mechanisms operative in the DST protocol are probably two, neither of which is mutually exclusive. The first and more readily demonstrable is the process of selection. The DST segregates "responders" from "nonresponders" by monitoring the specific humoral response to the specific blood donor. The precision with which unfavorable sensitization can be detected relates to recent developments in transplantation serology that can discriminate various T- and B-cell antibodies.[21] The reliability and accuracy of this testing has been confirmed by the absence of hyperacute and accelerated rejection in DST recipients subsequently receiving kidneys from their blood donor. Among these patients were two with selective nonresponse to their blood donor, despite the presence of greater than 70% levels of warm T-cell cytotoxic antibodies to the random panel.

The DST protocol was also beneficial to the "responders," since their responsiveness was tested and confirmed through the blood transfusions. The DST protocol exposes the approximately 30% of immunologically disparate donor-recipient pairs in whom a strong immune response to the blood donor develops. Quite possibly a similar immune response would occur if the kidney were transplanted without the DST. The kidney would represent a continued rather than an intermittently transient presence of the same immunogens, which would lead to irreversible rejection. For these potential donors the process of blood donation is harmless compared to donating a kidney that would probably be rejected. An added advantage is the reduced risk of transmitting hepatitis, since the blood transfusions are from a relative with known medical history.

The second mechanism that could be responsible for the excellent graft survival in the DST patient not developing donor-specific warm T-cell or persistent warm B-cell antibodies is the modification of the host immune response with the blood transfusions. Because the immunogenic exposure involves repetitive transfusion of donor-specific antigens in a modest dose, tolerance is a possibility. An attractive hypothesis relates to the induction of suppressor cells, which may mediate inhibition of donor-specific cell-mediated-lympholysis cells.[23] Enhancing antibodies are also a real consideration in that the recipient has encountered, by means of the DST, the same antigens present on the subsequently transplanted kidney. As has been suggested, enhancing antibodies are primarily directed against IgM on B-lymphocytes.[2] The detection of $\geq 10\%$ levels of cold B-cell antibodies (IgM anti-IgM antibody[2]) to the random panel in 43% of the DST recipients makes it theoretically plausible that these antibodies may mediate enhanced graft survival at body temperature. This incidence of cold B-cell cytotoxins was much greater than encountered in randomized recipients.[7] Certainly, the existence of cold B-cell antibodies has not proved harmful.

Evidence for immune host alterations induced by DST is still lacking. However, analysis of the immunologically desirable HLA-identical sibling transplants, where recipients with third party pretransplant blood transfusions did significantly better than nontransfused recipients, suggests that selection did not mediate the beneficial effect of blood transfusions in this group.[13]

The protocol for the number of transfusions, the amount of blood transfused, the timing, and also the period from the last transfusion until transplantation are only partially clear. The need for no fewer than three transfusions is suggested by the fact that donor-specific warm T- and persistent warm B-cell antibodies developed after the third transfusion in two and one patients, respectively. A lesser number of transfusions may not have elicited this humoral response. Donor-specific warm T-cell antibodies obviously are deleterious. It is controversial, however, whether transplantation against a positive warm B-cell cross-match is harmful in cadaveric transplantation, but since this antibody represents a donor-specific response in the DST patients, we have been reluctant to proceed with transplantation against this potential real barrier. Donor specific B-cell antibodies were shown to develop posttransplantation in a group of 18 recipients with treatment resistant allograft rejection.[19]

The administration of approximately 200cc of donor blood on three separate occasions at two-week intervals has proved effective and is the maximum amount of blood that could be easily accepted from an individual who will likely undergo major surgery as a renal donor. We have minimized the effect of donating 600cc by placing the blood donors on iron supplementation. The interval between the last transfusion and transplantation was less than two months in all but two patients, in whom extenuating circumstances forced postponement of the transplant until three and six months. This was necessitated because of recipient illness in the first, and an imposed waiting period for

full donor recovery from an emergency cholecystectomy in the second patient. Evidently, the beneficial transfusion effect was still present, as neither patient has had a rejection episode and each has normal graft function at nine and 19 months following transplantation.

No immunosuppression is given during the transfusion process which allows full expression of the recipient immune response to the repetitive transfusion challenge. An attenuated humoral response brought about by concomitant use of immunosuppression could theoretically escape detection by cross-match testing and result in hyperacute rejection. Newton and Anderson[12] did use azathioprine from the time of first intravenous injection of lymphocytes in their four patients, and there was no early kidney loss. However, hyperacute rejection did occur after donor cell infusion in another patient with concomitant azathioprine and steroid administration.[11] Since the incidence of sensitization after DST is approximately 30%, Newton and Anderson's success may have been attributable to a favorable genetically predetermined donor-specific response in these patients and not to the azathioprine. It was the eighth patient in our series who was first noted to be sensitized to his blood donor.

Donor-specific transfusions appear to be a practical approach for an immunologically disparate related match, in that they do not jeopardize eventual cadaveric transplantation for the patient sensitized to his blood donor. Only one of the 15 patients receiving only DST and no third party transfusions developed any warm T-cell sensitization to the random panel on serial antibody screening of the same weekly serial serum samples. This solitary patient developed only a 6% level of warm T-cell cytotoxins on the screen. In fact, of the total 45 DST patients, only nine developed 10% or more increased broad warm T-cell sensitization to the panel from the initial baseline determination and all had received additional third party transfusions with exposure to multiple other transplantation antigens. The DST protocol, in contrast, results in repetitive exposure of the same limited antigens because of the use of a single one-haplotype matched blood donor. The eventual outcome of cadaveric transplantation in the DST sensitized patient remains to be determined, but these patients are prepared for optimum graft survival with cadaver transplantation by the antecedent transfusions.[5] Among the multiple factors influencing cadaver graft survival, antecedent blood transfusions override all other considerations.[15,25]

The center initiating the DST protocol must be alert to the possibility of early acute rejection episodes, as was evidenced in five patients with rejection crises at one to four days. These events were all successfully treated with increased steroid dosage, but the nature of these and other immunologic responses in this patient population must be further elucidated by immunologic monitoring and renal biopsies. The two biopsies thus far obtained at the time of acute rejection have shown a remarkable paucity of interstitial mononuclear cellular infiltrates.

The early results of the DST protocol in insulin dependent juvenile diabetics encourages this approach rather than cadaveric transplantation when the potential related donor is a one-haplotype match and MLC incompatible. The results with cadaveric transplantation in the diabetic are generally recognized as suboptimal when compared with the nondiabetic.

The question arises whether random third party blood transfusions might be as beneficial as DST in improving transplantation results with immunologically disparate living related donor-recipient pairs. We have previously reported that third party pretransplant blood transfusions do modify the course of the high MLC donor-recipient pairs, resulting in improved graft survival.[18] Of the 34 one-haplotype, high MLC recipients, there was a 73 ± 9% one year graft survival in those 23 patients with pretransplant blood transfusions, compared with 18 ± 12% in those with no transfusions. Of those patients with pretransplant blood transfusions, 78% did have a rejection episode during the first three months after transplantation. The rejection episodes were more severe and the posttransplant course more difficult in these patients, compared to the essentially benign course in the DST patients. Third party transfusions in HLA nonidentical recipients with high MLC is a consideration where there is Rh incompatibility and a motivated, willing donor. Fortunately, the incidence of Rh incompatibility is low, and during the time period of the 45 DST patients we encountered, only one patient required use of random third party transfusions because of Rh incompatibility. There is the future consideration with Rh incompatibility that red cells could be separated out and the platelets and leukocytes be administered primarily.

In summary, the early results with donor-specific transfusions have provided highly encouraging results in the absence of hyperacute rejection. One can be optimistic about this approach if long-term follow-up fails to reveal delayed dissipation of the observed salutary transfusion effect. Additionally, the described DST protocol offers a relatively simple and easily monitored design without apparent harm to either the potential donor or recipient. In fact, a potentially unsuccessful living related transplant can be avoided while the transplants actually performed have reasonable prospects of success. This approach in the future may possibly involve two-haplotype mismatched donor-recipient pairs, both related and unrelated.

Acknowledgments

The authors gratefully acknowledge the following: Susan Hopper, R.N. for coordination of transfusions with dialysis units; Mark Hermes, Larry Cardman, Marianne Gumbert, Roswitha Heintz, Richard Karp, Victor Lim, Margaret Rheinschmidt, and Frances Sturtevant for technical assistance, and Beverly Hill for editorial assistance. The authors also wish to express appreciation to the many nephrologists and dialysis units in California and Nevada for their cooperation with this new approach to transplantation.

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Discussion

Professor Lars-Erik Gelin (Gothenburg, Sweden): The transplant program in San Francisco has contributed a great deal to clinical transplantation. Today we have learned about donor-specific blood transfusions prior to HLA-nonidentical and to MLC-reactive related renal transplants, stressing improved and excellent graft function after three months and after 12 months. The price to pay, however, was a sensitization of about one-third of the intended transplant pairs.

Since 1977, we have required at least three blood transfusions to be given to the recipient six weeks before transplantation, without observing a sensitization in more than one patient, who underwent acute transfusions because of an intercurrent operation.

We have, however, given leukocyte pooled blood. That might be one explanation for the lack of sensitization. My first question to Dr. Salvatierra is: What kind of blood did you transfuse?

With the protocol, we have obtained (slide) a 95% graft survival among our HLA-nonidentical related renal transplants in contrast to the 70% graft survival rate at 12 months we had prior to this protocol.

(slide) The striking improvement in graft survival and function became evident in our retrospective study of primary cadaveric grafts before we introduced the compulsory pretransplantation program. The recipient who did not receive any blood transfusions before the grafting had a 30% lower graft survival rate at 12 months than the previously transfused recipients.

(slide) In our series, we have been able to identify two important factors which when combined result in a poor outcome of cadaveric grafting. These are two incompatibilities in the HLA B-locus in nontransfused recipients, as seen from this slide. When, however, only one incompatibility existed for HLA B-antigens in the previously transfused recipients, the graft survival was the same as for grafts without foreign antigens.

For these reasons, I do not believe the donor specificity in the transfusions is the important factor, and again I stress Dr. Salvatierra's hypothesis that induction of suppressor cells might well result from nonspecific blood transfusions.

I would like to hear Dr. Salvatierra's comments on the different kinds of blood used for pretreatment, and the time schedule before transplantation.

Dr. Nicholas A. Halasz (San Diego, California): It is fascinating for those of us who started out in transplantation ten or 12 years ago and initially used buffy-coat-poor blood and then switched to frozen blood when it became available in order to avoid all those evil antigens present in leukocytes, platelets and plasma to see ourselves turning around and using blood intentionally in recipients, initially nonspecifically. Now Dr. Salvatierra tells us that blood of