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Thoracic Duct Fistula and Renal Transplantation

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Thoracic duct drainage (TDD) was established for 21–115 days in 40 kidney recipients with an average removal per patient day of 4.7 l lymph and 1.88 billion cells. Cellular and humoral immunity were depressed. TDD and immunosuppressive drugs were started at transplantation in 35 recipients of cross-match negative grafts. Although the results were better than in precedent non-TDD controls, eight patients rejected their grafts before a full TDD effect, and three of the eight developed predominantly anti-B lymphocyte cytotoxic antibodies which were probably responsible for positive cross-matches with their next donors. With continuing TDD, all eight patients had good initial function after early retransplantation. In five more “nontransplantable” patients with performed cytotoxic antibodies, TDD was started 30–56 days before transplantation. In these five pretreated patients, antibodies persisted with positive antidonor cross-matches. Hyperacute rejection occurred repeatedly in two patients with high anti-T (and anti-B) titers, but was surmounted in three patients with lower titers. From the clinical and immunologic data, we have concluded that TDD should be used for pretreatment of all cases with or without prior antibodies, and have suggested an adjustable management plan that takes into account new developments in antibody monitoring.

THE IMPERFECTIONS of immunosuppression for renal transplantation are well known, particularly when cadaveric donors are used.⁴⁶ Treatment often does not control rejection on the one hand, or is excessively dangerous on the other. The consequence is that renal transplantation has not lived up fully to the optimistic expectations of a decade or longer ago, a fact that increasingly has clouded the proper relationship between transplantation and its alternative, dialysis.

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We report here a clinical trial of renal homotransplantation using thoracic duct drainage (TDD) as an adjunct to standard immunosuppressive therapy. The rationale for such an approach was provided by the classical investigations by Gowans and his associates in rats.^{12,24,25} TDD apparently was first tried clinically in 1963 in Saint Louis by Newton and later in Stockholm by Franksson. However, Newton's attempt was not described until 1965,³⁰ nearly a year after Franksson's first report.⁹

The present report will document an apparent improvement of early results in patients who had TDD begun contemporaneously with transplantation or in some cases before. The clinical and immunologic studies of these patients have suggested that adjustments in the timing of TDD could make this procedure even more valuable, and can permit some transplantations to proceed in the face of the kind of anti-donor cytotoxic antibodies that ordinarily cause hyperacute kidney rejection.

Methods

Case Material

TDD was used in 40 patients as an adjunct to classical immunosuppression. Daily azathioprine doses were started on the day of transplantation and kept as high as possible without causing leukopenia. The eventual amount given usually was 1–2 mg/kg/day. Prednisone was started at the time of operation at a dose of 3–5 mg/kg and subsequently reduced by 10–20 mg/day until a level of about 1 mg/kg was reached. Further reduc-

tions were variable and were determined in part by evidence for or against rejection. Antithymocyte globulin (ATG) was given intravenously to 26 patients who had no prior sensitization to equine protein. The ATG doses were approximately 10 mg/kg/day for 14 days, and 10 mg/kg every other day for an additional 2 weeks. Some of the ATG courses had to be shortened because of sensitivity reactions to equine protein.

The use or omission of ATG was not thought to be an important factor in either the TDD cases or the retrospective controls with which they were compared. When producing our own antilymphocyte globulin (ALG), our cadaveric graft survival was improved.^{43,46} However, during the last several years while using a commercial ATG in a clinical trial, there has been no difference in results with or without this agent.

Approximately half of the recipients had splenectomy prior to transplantation. A few more had splenectomy after transplantation because of persistent leukopenia which precluded effective treatment with azathioprine.

The 40 patients who had TDD were consecutive; follow-ups of 5–12½ months are available. They were divided into the categories described below.

Group I: living related transplantation. Primary renal transplantation was performed in five patients who were 16–30 years old (average 25). One recipient had a fully matched sibling donor. The other 4 had maternal (3 examples) or paternal (1 example) donors of whom each had two HLA antigen mismatches with the recipients.

Group II: primary cadaveric transplantation. The 25 patients were 11–55 years old, average 35. They had few HLA matches with their donors, averaging only 0.96 out of the possible 4. Five of the recipients were diabetic, and all five were considered to be poor risk.

Group III: cadaveric retransplantation. These five patients averaged 40 years of age (range 20 to 54), and had previously rejected one (2 examples), two (2 examples), and four (one example) homografts from 15 months to 6 years previously. One patient's donor had 3 HLA matches, one had 2 matches, and 3 had one match only.

Group IV: cadaveric transplantation against preformed antibodies. Five patients, aged 15–38 years, had high titers of cytotoxic antibodies against lymphocyte panels. Furthermore, the recipients' sera had provided positive cytotoxic cross-matches against all organ donors obtained at our center during periods ranging from two months to three years. Consequently, these five patients were considered nontransplantable by conventional criteria. They were pretreated with TDD and given kidneys from cytotoxic cross-match positive donors. In all ten transplantations performed

in these five patients, the recipients' sera killed more than 90% of the donor lymphocytes.

Three more patients, one from Group II and two from Group III, rejected cadaveric grafts and developed antibodies while on TDD which had been started on the day of transplantation. TDD was continued and retransplantation was carried out despite the persistence of anti-donor antibodies.

Thoracic Duct Drainage

Technique and management. The thoracic duct was cannulated in the left neck, except for two patients whose thoracic duct was approached intrathoracically at the T5 level by a right thoracotomy through the fifth intercostal space. Into the duct was placed a Number 4–7 Swan-Ganz double-lumen catheter after cutting off the balloon. For the cervical insertion, the important step of passing the catheter into the upper mediastinum was aided by dilating narrowed segments (usually at valve sites) with metal probes. Postoperatively, heparinized saline (1000 units heparin in 500 ml saline) was infused at about 20 ml/hour through one lumen, and lymph was collected from the other lumen into a dry plastic transfer pack.* The small amount of heparin prevented clotting during subsequent centrifugation, transfer of the cell-free fluid to the appendage bag, and intravenous reinfusion. A day's collection of processed lymph was reinfused continuously throughout the following day. A narrow spectrum anti-staphylococcal antibiotic was given systemically after several of the early patients developed staphylococcal bacteremia.

The daily volumes of lymph were recorded as well as the lymph cell counts. The differential composition was determined after Wright staining and in some samples after nonspecific esterase staining.⁵⁵ From this information, the daily and total numbers of lymphocytes removed could be computed.

It was found that the costs of TDD could be reduced drastically. Initially, the volume differences between collected and processed lymph were made up with plasma. This was found to be unnecessary. In fact, we have recently found that the lymph sometimes could be discarded for weeks or months on end without adverse effects providing adequate volumes of electrolyte solution were given intravenously. Under these circumstances, even the collection bags became unnecessary. The containers for the intravenous solutions were transferred when they were empty to the floor and reused as receptacles for the discarded lymph.

* Special transfer packs for TDD are available from the Fenwall Corporation, Deerfield, Illinois. These have a collection capacity of 600–700 ml.

A few of the lymph fistulas failed spontaneously but usually active efforts were required for discontinuance. The collection bags were gradually raised to slow the lymph flow. After lymph output finally stopped, the cannula was pulled out. A pressure dressing was applied to the supraclavicular triangle.

Timing. In Groups I–III, TDD was started at the time of transplantation and continued for at least 40 days if possible. If the first homograft was rejected, the period of initial failure was considered pretreatment for a second try for which drainage was continued (Fig. 1). The shortest period of drainage in Groups I–III was 21 days, and the longest was 115 days.

The five patients of Group IV with preformed cytotoxic antibodies had TDD started from 30 to 55 days before transplantation. The lymph was discarded and

replaced with plasma or electrolyte solution in the first two patients. Cell free lymph was reinfused in the other three for the first 30–40 days and discarded subsequently.

The three additional patients from Groups II and III who developed posttransplant antibodies while on TDD had their retransplants 28, 90, and 106 days after institution of the lymph fistulas. TDD was still in effect in the first and third of these patients. The catheter had clotted a few days before retransplantation of the second patient.

Immunologic Studies

Cells removed. Cells from the thoracic duct lymph and from peripheral blood were separated by density gradient centrifugation on Ficoll-Hypaque.⁴ T-cells were identified by the direct E-rosette technique using

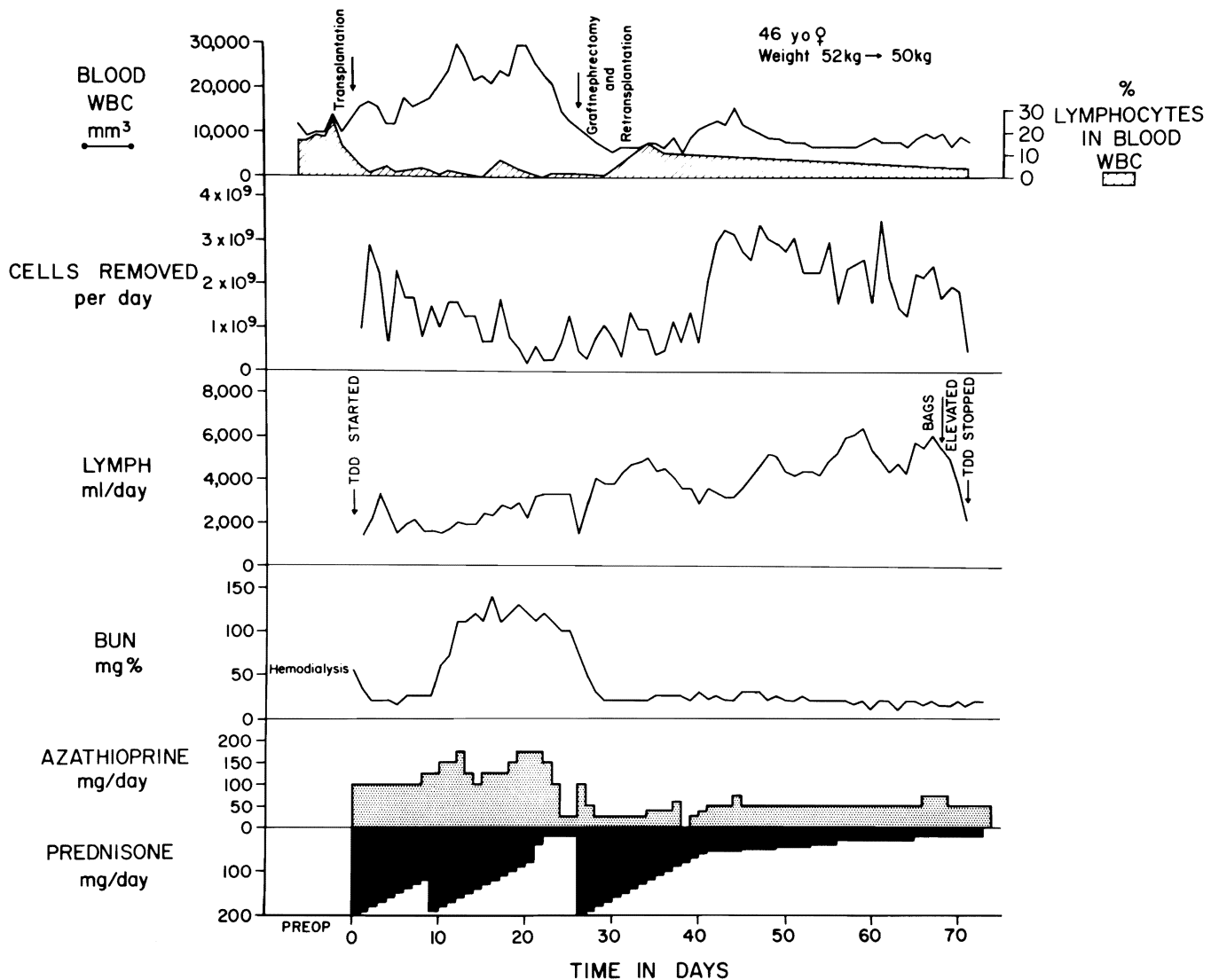


FIG. 1. Prompt retransplantation under TDD. The first kidney was rejected in two weeks, but the second organ transplanted after 26 days of TDD functioned perfectly. Note the slow increase in lymph drainage per day and the variable numbers of cells removed per day. The lymphocyte differential percentage was somewhat reduced during TDD, but because of the variable total white blood count the absolute number of circulating lymphocytes was not much changed.

sheep erythrocytes.³ B-cells were identified by their surface immunoglobulin, as demonstrated with fluoresceinated antipolyvalent immunoglobulin.³⁶ Data was reported as percent T- and B-cells per total lymphocytes.

Cellular immunity. Before TDD or other immunosuppression, skin test reactivity in 25 patients was tested with PPD, tetanus, streptokinase-streptodornase (SKSD), trichophyton, and candida. Nonspecific reactivity was determined with croton oil applications. The tests were repeated after 21 days of TDD, and again two weeks after TDD was discontinued in those cases in which the initial tests had been positive. The lymphocytes from four patients who were SKSD positive were studied *in vitro* for blast transformation after exposure to the antigen.³⁵ The nonspecific mitogenic responses to phytohemagglutinin and concanavalin A were determined *in vitro* of the lymphocytes of 11 of the 25 patients.³⁵ The 11 included four who had at least one positive skin test and seven more whose skin tests were all negative.

Humoral immunity. Twenty-four of the same 25 patients were screened by a hemagglutinin inhibition test⁵ for serum antibodies to A/Victoria and B/Hong Kong influenza. Twenty-two (92%) had preexisting antibodies to A/Victoria and 11 (46%) had anti-B/Hong Kong antibodies. All 25 patients were then given intramuscular bivalent vaccine* five days after institution of TDD. Antibody response to the vaccination was determined 21 days later.

Serum immunoglobulins. Serum and lymph IgG, IgM, and IgA concentrations were measured with radial immunodiffusion† before, during and after TDD.

Serologic studies. HLA typing, direct cross-match testing, and panel cross-matches were with standard techniques.⁴⁷ The panels of 37–42 donors were selected to provide a representative cross section of HLA types.

B- and T-lymphocytes were isolated by nylon wool column.⁴⁷ Five to eight serial 1:2 dilutions of the sera were tested simultaneously against a panel of 22–35 normal individuals. The incubation temperature with antibody was either at 5° or at 37°. Incubation with complement was at 25°. Incubation times were one hour with the serum and two hours with complement.

Results

Reliability and Safety of TDD

During accumulation of the series of 40, attempts at TDD failed in two other patients. Thus, the success rate in establishing TDD for at least 21 days was 95%. In both of the failures, the cervical thoracic duct could not be located despite extensive dissection. In two of the 40 successful cases, the thoracic duct eventually

was cannulated in the right thorax through a fifth intercostal space incision. This approach was used for one patient after the cervical attempt had failed. The other patient's cervical TDD stopped draining after 98 days and the thoracic reoperation was an attempt at continuation.

There was no mortality from TDD *per se*. The most significant complication was in the patient with preformed antibodies whose cervical TDD failed after 98 days. The thoracic duct was recannulated in the right thorax, but satisfactory drainage could not be obtained. She developed an empyema which eventually required thoracotomy and decortication.

Minor complications included local lymph accumulations in the neck, transient edema of the face or left arm, temporary Horner's syndrome in two patients, one example of transient right chylothorax following removal of the cannula, and one retained subcutaneous catheter which was removed later. Four of the first patients developed staphylococcal bacteremia, a complication which was prevented in almost all subsequent cases by the prophylactic administration of narrow spectrum antistaphylococcal antibiotics.

TDD Volumes and Cells

Quantities drained. The 40 TDDs were in place for 58.4 ± 3.5 (S.E.) days (range 21–115). Pooling all 40 patients and all days of drainage, the lymph obtained per patient per day was 4690 ± 240 (S.E.) ml/day. There was considerable variation from patient to patient in the lymph collected, and even in some individual patients from day-to-day (Figs. 1 and 2). The lowest average daily production was 1710 ± 24 (S.E.) ml/day in a patient whose fistula drained for 30 days. The highest output was 7670 ± 210 (S.E.) ml/day from a patient whose drainage lasted for 84 days.

Cells removed. Pooling all 40 patients and all days of drainage, the numbers of cells removed per patient day was $1.88 \pm 0.19 \times 10^9$ (S.E.). In about two-thirds of the patients, there was a progressive decline of the cells removed (Fig. 2), but in the others the source of lymphocytes seemed inexhaustible (Fig. 1). More than 98% of the cells were classified as small lymphocytes by Wright staining and morphologic criteria. However, with nonspecific esterase staining some of the cell collections had as many as 25% monocytes. The percentage of T and B-lymphocytes in the total cell collection was variable, but in most cases the selective T-cell depletion described by Machleder and Paulus²² was not seen. These observations were similar in patients with TDD alone and in those in patients studied during multiple agent immunosuppression including TDD.

Nor was there a uniform effect on peripheral blood lymphocyte total counts and differential percentages

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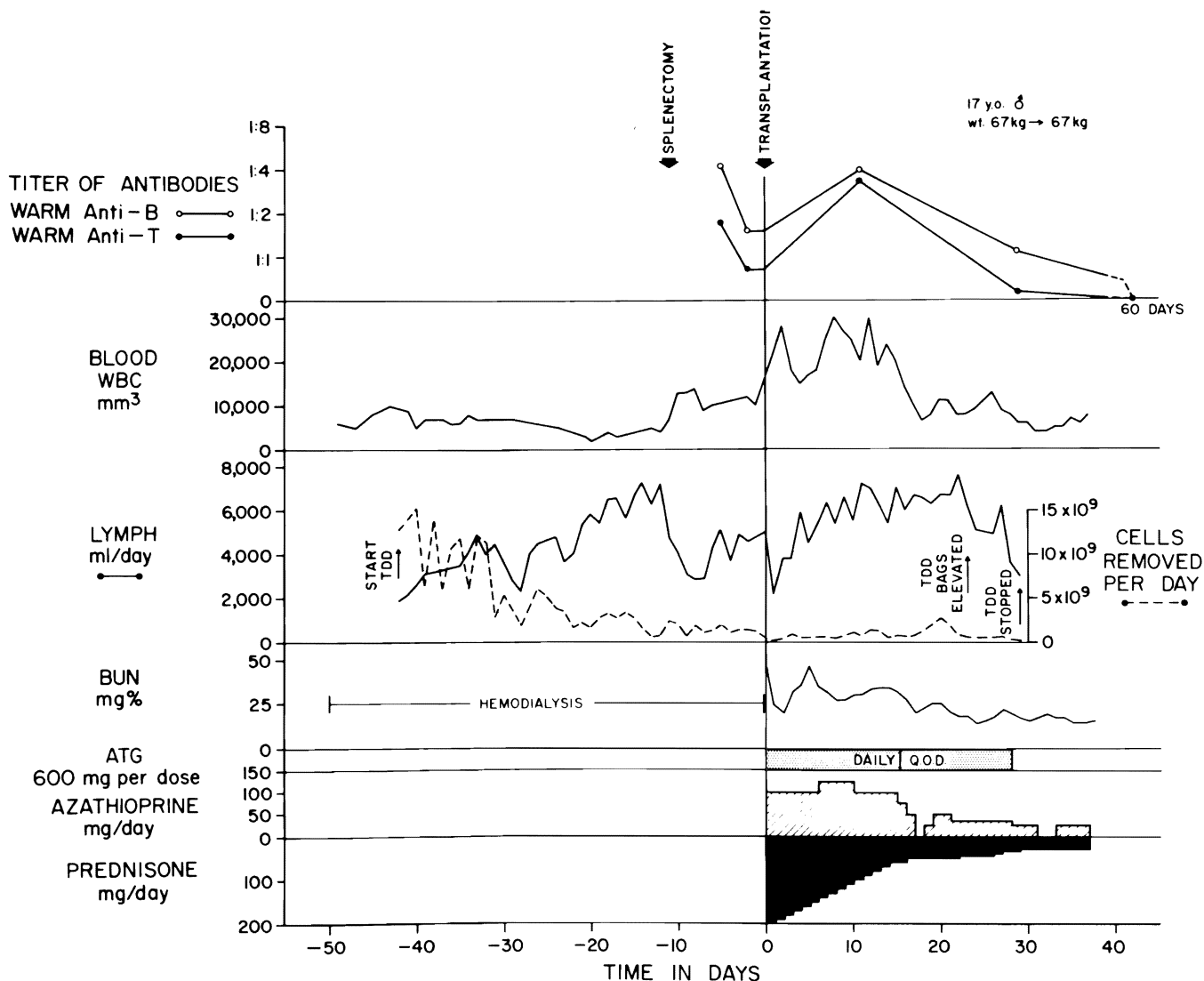


FIG. 2. Pretreatment by TDD in a patient with preformed cytotoxic antibodies. Warm anti-T lymphocyte and anti-B lymphocyte antibodies were still present in the recipient serum at the time of transplantation but these were of low titer. Nevertheless, there was a completely killing positive cytotoxic crossmatch against the donor. Hyperacute rejection did not occur.

although the lymphocyte fractions were often reduced (Fig. 1).

Immunologic Studies

Serologic studies in 8 patients who were given kidneys despite positive cross-matches with their donors are given later with the Group IV clinical results. A number of patients had less specific immunologic assessment.

Cellular Immunity. There were only nine positive skin tests in 6 patients among 25 examined preoperatively. These included one positive reaction for PPD, two for tetanus, four for streptokinase-streptodornase (SKSD), two for candida and none for trichophyton. At the same time, nonspecific reactivity was demonstrable

with croton oil in 24 of the 25 patients. Three weeks after starting TDD, all except one of the nine positive skin tests had become negative; the 24 positive croton oil tests remained positive. The specific skin tests converted to negative both in patients treated solely with TDD and in patients who were concomitantly started on double- or triple-agent immunosuppression. Two weeks after discontinuance of TDD, none of the eight negative skin test conversions had returned to positive. Four patients whose SKSD skin tests disappeared also lost *in vitro* SKSD induced blast transformation of their lymphocytes.

As TDD and other immunosuppression proceeded, responsiveness to phytohemagglutinin and concanavalin A was retained by the lymphocytes of all 11 patients among the foregoing 25 who were tested.

Humoral immunity. Only six (25%) of the 24 patients tested responded to immunization with a significant increase, and in only one of these was the response to both flu strains. Three of the patients (12%) lost pre-existing antifu antibodies during the first three weeks of TDD.

Serum immunoglobulins. As reported before,⁴² immunoglobulins invariably fell during TDD combined with multiple agent immunosuppression. However, this could have been due in part to azathioprine, prednisone and ATG.

The objection did not apply for the five patients pre-treated solely with TDD for cytotoxic antibodies. TDD alone caused drastic reductions in IgG, and less extreme reductions in IgM and IgA (Table 1). The changes were the same without (cases 1 and 2) and with (cases 3–5) lymph reinfusion. After discontinuance of TDD, the immunoglobulins rebounded to or above previous levels even though azathioprine and prednisone were in effect by this time (Table 1).

Mortality From Transplantation

Two (5%) of the 40 recipients died. One patient perforated his ileum eight weeks after transplantation and died 1½ months later with uncontrolled intra-abdominal infection. The second patient developed pancreatitis, pneumonitis (due to *Pneumocystis carinii*) and a cerebrovascular accident. She died five months posttransplantation.

Outcome in Subgroups

Group I: Living related transplantation. Starting on the day of transplantation, TDD was used for 34–78 days. All five of the recipients have life-supporting homografts after six, seven, nine, 11 and 12 months. Renal function is normal in four cases. The fifth patient has a serum BUN of 60 mg/dl and a serum creatinine of 2.5 mg/dl, 11 months after transplantation. This patient had TDD for only 34 days.

We have obtained satisfactory results in similar past cases without TDD.⁴⁶ Of the comparable consanguineous nonmatched recipients treated just prior to the TDD series, four still have good function of their original grafts with follow-ups of 12–22 months. The fifth

retrospective control patient rejected his perfectly matched sibling graft in two weeks.

Group II: Primary cadaveric transplantation. The 25 patients had TDD for 21–92 days, starting on the day of transplantation. One recipient died after 5½ months for a mortality of 4%. By five months, two additional recipients had been returned to dialysis. One declined a second try at transplantation under continuing TDD. A second homograft was placed in the second patient, but had to be removed because of an arterial suture line infection and acute hemorrhage while it was still functioning normally.

Six other patients rejected their first cadaveric kidneys in ten days to two months. Second homografts were placed within a few days or weeks under continuing TDD (Fig. 1). All of the second grafts functioned promptly.

By five months, 16 (64%) of the 25 recipients retained their original grafts and had good to normal renal function. The six patients (24%) who had prompt retransplantation when the first organs were rejected were also free of dialysis. Thus, 22 (88%) of the 25 cadaveric recipients reached five months with graft function. The results were better than in our reported past experience⁴⁶ and superior to that with an immediately precedent series of 25 similar cadaveric cases (Fig. 3). In the retrospective control group, the mortality by five months was 20%. Thirty-two per cent of the patients were back on dialysis. The incidence of patients with a successful first graft was 44%. Including one additional patient who had early retransplantation, the number of patients with adequate renal function was 48%. The improved overall five month success rate (88 versus 48%) was significant ($p < 0.01$). The improved record (64 versus 44%) with first grafts did not reach statistical significance.

Rejection after five months was troublesome both in patients of the TDD and control series. In the TDD group, 24 patients are alive after five to 12½ months but one primary homograft has stable chronic rejection at 10½ months. Two of the retransplants are presently being lost in the sixth month. In the control series, late losses occurred after six and eight months, the latter due to death.

Group III: cadaveric retransplantation. These five

TABLE 1. Immunoglobulins (mg/dl) Before, During and After TDD in Group IV Patients

Patient	S.B.			D.F.			G.F.			S.A.			R.G.		
	G	M	A	G	M	A	G	M	A	G	M	A	G	M	A
Before TDD	1050	81	66	540	120	198	900	48	360	1450	255	235	1240	250	200
Lowest During TDD	163	24	36	141	29	38	190	18	37	360	78	42	350	80	38
1–4 Months Post-TDD*	850	76	54	680	100	120	645	198	200	925	145	245	1450	98	65

* Azathioprine and prednisone being given. Values before and during TDD were without other immunosuppression.

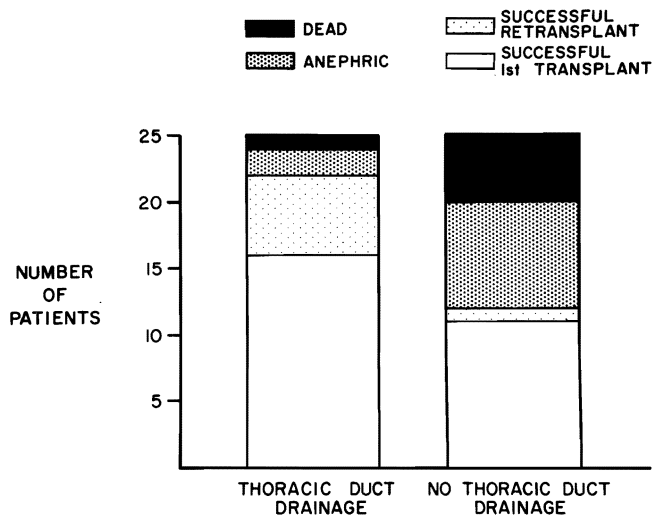


FIG. 3. Results after five months in 50 consecutive recipients of first cadaveric transplants. Twenty-five had TDD and 25 did not. In the TDD group, lymph drainage was continued if the primary kidney was rejected. A second attempt at transplantation was made promptly (Fig. 1).

patients had TDD for 25–105 days, starting at the time of transplantation. By five months, one patient had died of bowel perforations, and one was back on dialysis. The three other (60%) had life-supporting renal function, in one case after retransplantation following rejection of the first organ. Two of the three patients still have life-supporting function after seven and ten months, but one of these grafts has had several late rejections. The third patient rejected his kidney after nine months and returned to dialysis.

Our reported past experience was poor with cadaveric retransplantation in previously failed cases.¹⁶ In five cases immediately preceding the TDD trial, there was one death and two returns to dialysis within five months. Thus, in this small group, there was no significant difference with or without TDD.

Group IV: cadaveric transplantation against preformed antibodies. Two of the five patients with preformed cytotoxic antibodies escaped hyperacute rejection (Fig. 2). Their kidneys are still functioning well after 5½ and eight months. The first kidney of a third patient was placed after 30 days of TDD. It did not function well and had to be removed 19 days later because of its severe platelet sequestration which resulted in a thrombocyte count of 5000 mm³. A second homograft was placed in this patient after 15 more days of TDD (total 45 days). Despite a positive cytotoxic cross-match, it functioned normally for six months, but then underwent a subacute rejection that has been difficult to control with increased steroid doses. The fourth and fifth patients hyperacutely rejected four and two grafts, respectively. They were returned to dialysis.

The serologic findings in the five patients who had preformed antibodies before TDD are summarized in Table 2. The lymphocytes of all ten donors for the five recipients were completely killed by the serum of the recipient in question. However, with panel analysis, the anti-T-cell antibodies in the three patients who had successful transplantation (cases 1–3) started at low titers and tended to drift down during pretreatment with TDD (Figs. 2, 4 and 5). One kidney which was transplanted when the anti-T antibody titer was only 1:1 underwent delayed hyperacute rejection. At the same titer (Fig. 5), a subsequent transplantation succeeded. All kidneys transplanted when anti-T cell titers were greater than 1:4 were hyperacutely rejected (Fig. 6). All five patients also had warm anti-B lymphocyte antibodies during TDD or at the time of transplantation. After transplantation, the warm anti-T and anti-B antibodies remained detectable in two of the successfully treated patients, but eventually at a reduced level (Figs. 2, 4 and 5; Table 2). In the unsuccessfully treated patients 4 and 5, warm anti-T and anti-B antibodies remained high or rose even higher after the hyperacute rejections (Figure 6, Table 2). Cold anti-B antibodies were not present before transplantation in any of the five cases and appeared postoperatively in only one patient (Fig. 2).

Three additional patients from Groups II and III had rejected kidneys and developed antibodies while on TDD. On direct cross-match their sera incompletely killed the lymphocytes of their second donors. With panel analysis at that time, two of the three patients had low anti-T titers of 1:1. All three patients had warm anti-B antibodies (1:1 to 1:16). The changing serum antibody conditions in one of these patients before, during and after TDD and two transplantations is shown in Figure 7.

Discussion

Standard immunosuppression worldwide has been with azathioprine and prednisone^{15,27,40,44,54} to which heterologous antilymphocyte globulin (ALG) may be added.^{29,41,43} Cyclophosphamide can be substituted for azathioprine.⁴⁵ Prednisone is the only highly adjustable component of these so-called double and triple drug programs, but despite massive steroid therapy, failure to control early rejection has been distressingly common. With related but imperfectly matched donors, the one year kidney survival in large cooperative series has hovered at about 70%.³⁴ In a survey of 4474 recipients of first cadaver grafts treated in 195 American transplantation centers between 1971 and 1976, Opelz, Sasaki, and Terasaki³⁴ recorded a 45% kidney loss rate at six months and a 55% loss rate at one year. Isolated centers including our own here reported somewhat

TABLE 2. Group IV Patients with Positive Antidonor Cross-Matches

Patient Transplant No.	S.B.		D.F.	G.F.	S.A.				R.G.	
	1st	2nd	1st	1st	1st	2nd	3rd	4th	2nd	3rd
Per cent of kidney donor lymphocytes killed by patient serum (direct crossmatch)	>90%	>90%	>90%	>90%	>90%	>90%	>90%	>90%	>90%	>90%
Per cent Anti-T Abs (panel crossmatch) just pre-transplant	48%	NA	92%	35%	75%	75%	NA	NA	92%	100%
Duration TDD before transplantation (days)	30	45	49	43	55	58	61	88	55	72
Titer Anti-T Abs										
Highest pre-TDD	1:4	1:4	1:5	1:1	1:16	1:16	1:16	1:16	NA	NA
Just pre-XP	1:1	1:1	1:3	1:1	1:4	NA	1:8	1:8	1:16	1:64
Mean post-XP	NA	1:1	neg	1:1	NA	1:2	1:8	1:8	1:64	NA
Titer Warm Anti-B Abs										
Highest pre-TDD	1:32	1:4	1:12	1:0.5	1:32	1:32	1:32	1:32	NA	NA
Just pre-XP	1:32	1:32	1:8	1:2	1:8	NA	1:32	1:16	1:32	1:128
Mean post-XP	NA	1:16	neg	1:1	NA	1:4	1:16	1:16	1:128	NA
Per cent Cold Anti-B Abs										
Highest pre-TDD	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Highest post-XP	0%	0%	23%	0%	0%	0%	0%	0%	0%	0%
Outcome	Delayed hyperacute rejection	Functioning 8 mos	Functioning 8 mos	Functioning 5 mos	Hyperacute Rejections (4)				Hyperacute Rejections (2)	

NA = not available. Abs = antibodies. XP = Transplantation.

better results particularly with the use of high potency ALG,^{29,48} careful case selection,³⁸ or scrupulous tissue typing,³² but the specter of a 50% unfavorable outcome has been faced by recipients of first cadaver kidneys in most centers. Early or delayed retransplantation in such cases has been even less satisfactory.^{2,16}

TDD was added to our treatment protocol in an effort to improve this situation. After its introduction clinically by Franksson in 1964,⁹ TDD as an adjunct to azathioprine, prednisone and, in some cases, ALG, was given clinical trials in Stockholm,^{10,11} Boston,^{28,49} Galveston,^{8,37} and Lyon.^{1,50} Since all of these reports

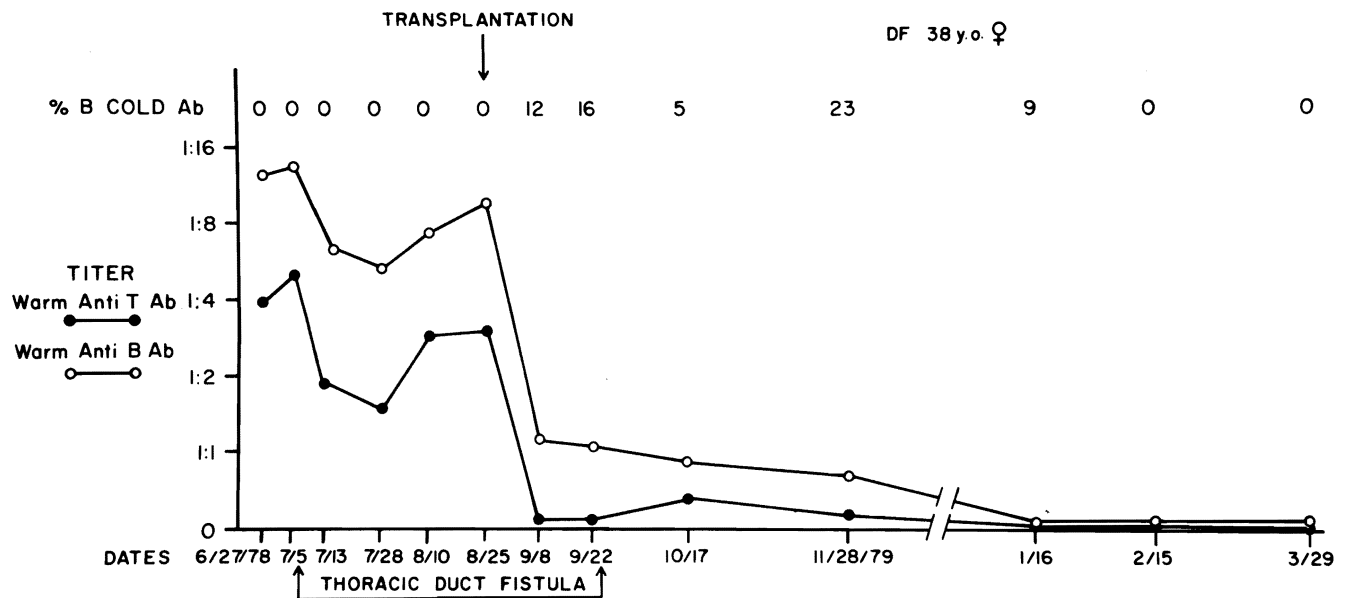


FIG. 4. Antilymphocyte antibodies in a patient pretreated with TDD for 49 days. Note that the anti-T antibody titer was relatively low at the time of successful transplantation.

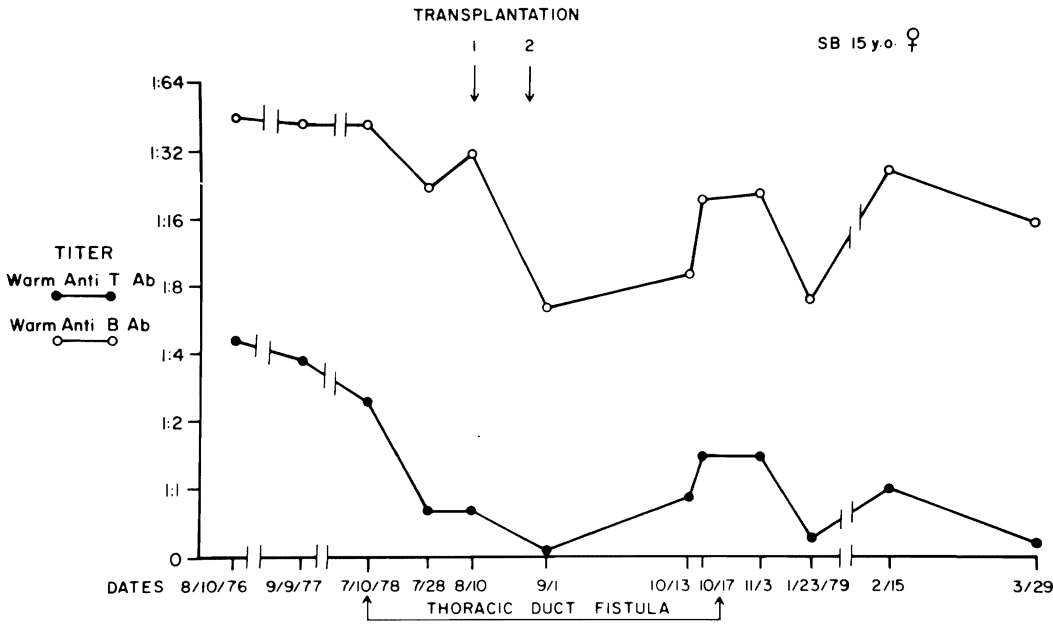


FIG. 5. Antilymphocyte antibodies in a patient pre-treated with TDD. The first homograft underwent a delayed hyperacute rejection. The second one escaped this fate. Note the persistence of antibodies after transplantation. The patient who is now eight months postoperative is slowly losing her kidney after an initial period of normal function.

claimed a benefit from TDD, especially in cadaveric cases, it was surprising that the efforts were abandoned. The most important reason apparently was the inability to consistently obtain effective lymph drainage, an objection that was almost completely eliminated in our trial. Annoyance to the patients and expense were other factors. In addition, clinical reports from Italy,²³ Brazil,¹⁷ and Japan³⁹ were considered discouraging even though the quality and duration of lymph drainage were suboptimal.

Only Walker and Johnson and their associates at Vanderbilt persisted.^{20,31,52} In 1977, they described the

use of TDD for about one month to prepare 50 poor risk patients for cadaveric kidneys. The graft survival two to five years later was almost 75%, nearly twice as good as in a control group. The propriety of pre-treatment has been supported by the observations of Machleder and Paulus²² who used TDD as the sole immunosuppressive treatment of autoimmune diseases such as rheumatoid arthritis and scleroderma. Machleder and Paulus²² recently delineated in humans the time curves for suppression of humoral and cell-mediated immunity, greatly extending the observations of a number of earlier investigators.^{1,6,8,13,37,51} The demon-

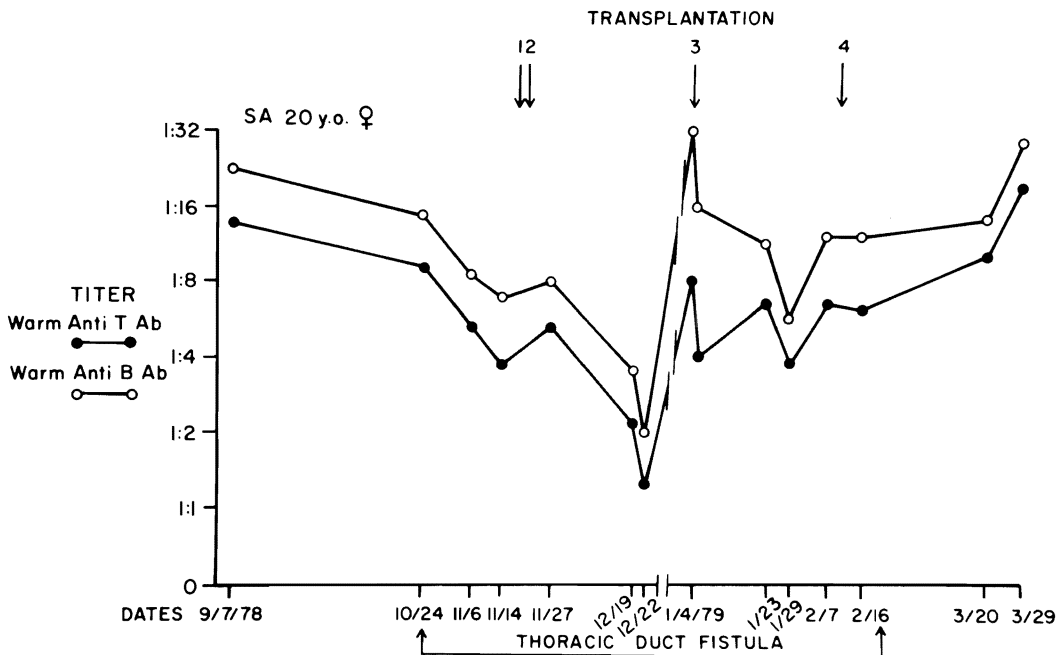


FIG. 6. Antilymphocyte antibodies in a patient who hyperacutely rejected four kidneys in spite of pre-treatment with TDD. Both warm anti-T and anti-B antibodies remained high throughout. The presence of high titer anti-T-lymphocyte antibodies would dissuade us from making future transplantation attempts until these could be lowered.

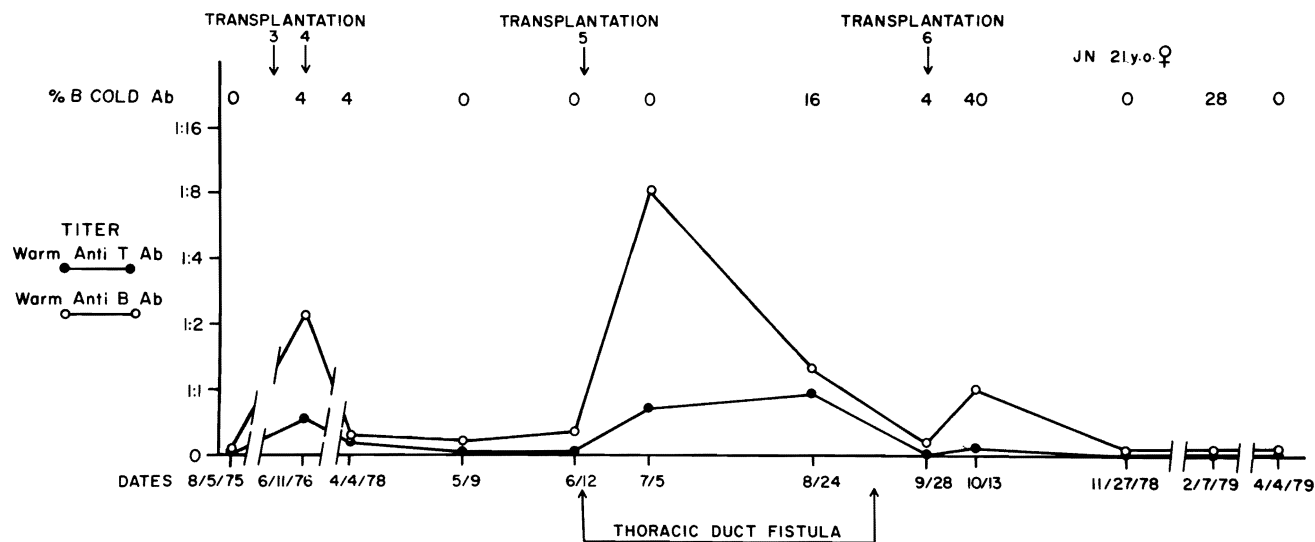


FIG. 7. Antibodies in a patient who had rejected four kidneys prior to TDD. TDD and transplantation were performed at the same operation. Note the brisk antibody response to this homograft which was promptly rejected. The second and successful transplant was carried out after 106 days TDD.

stration of humoral antibody suppression with TDD was particularly important since it confirmed earlier claims by Tunner et al.⁵¹ and Graber et al.¹³ that had been denied by others^{1,8,37,50} in spite of the incisive animal work by McGregor and Gowans.²⁴ In humans, substantial immunosuppression required three weeks and the full effect of thoracic duct drainage as the only immunosuppressive device was not established until 30 days. Although less extensive, our own immunologic data herein reported were compatible with those of Machleder and Paulus.

TDD in our trial was used differently in that TDD usually was instituted at the time of transplantation instead of preoperatively. Pretreatment in patients without antibodies was omitted because of the unpredictable availability of cadaveric organs and because of our subsequently allayed fear that TDD could not be maintained throughout long waiting periods. However, the foreseeable penalty was the irreversible rejection of several kidneys during the "uncovered" first three or four weeks. The corollary policies which we accepted were to consider these periods of graft loss as pretreatment for a subsequent organ, and to maintain thoracic duct drainage until retransplantation. Eight retransplantations were performed with these conditions and none of the grafts was rejected acutely; only one kidney was lost early and that because of delayed hemorrhage from an infected renal arterial suture line. Under ordinary circumstances, such early retransplantation in past experience has often been futile and sometimes dangerous.^{2,14,16}

A probable beneficial influence of thoracic duct drainage used in this way was evident in the 30 patients without preformed antibodies who were submitted to

transplantation for the first time and who have been followed for 5–13 months. These included five recipients of consanguineous grafts, of whom all have stable renal function. After five months 22 (88%) of 25 primary cadaveric recipients have life-sustaining renal function either with their first (64%) or promptly inserted back-up (24%) graft. At five months the results in the 25 cadaveric cases were almost twice as good as in 25 immediately precedent and similar controls not treated with TDD.

In spite of these findings, we now recommend TDD pretreatment. The need for so many back-up grafts has been unnecessarily wasteful of organs, to say nothing of the emotional trauma and extra risks imposed on the recipients. One discouraged patient withdrew from consideration for a replacement graft. In another case, the infection which necessitated removal of a perfectly functioning second transplant probably originated from the rejected primary graft.

Moreover, the immune reaction during the uncovered first several weeks was vigorous enough not only to cause several graft rejections but to permit, as well, a potentially harmful antibody response which was thought in retrospect to be anamnestic in some patients with prior but undiagnosed sensitization. The ability to perform retransplantation in such cases in spite of an antibody storm probably reflected the deepening suppressive effect of TDD upon humoral as well as cellular immunity. Undetected presensitization has been suspected to be a particularly common problem in patients undergoing retransplantation and this may have contributed to the inferior results in this small subgroup of our series. But even in those having transplantation for the first time, high

immunologic responsiveness with or without a component of presensitization has long been known to be an adverse feature^{33,53} and one which would be mitigated with TDD pretreatment.

Knowledge of the humoral antibody suppression caused by TDD prompted an effort to pretreat five patients whose sera contained such broadly ranging preformed cytotoxic antibodies that there was little or no hope of finding a suitable cadaveric donor. Before thoracic duct drainage, all five patients possessed the anti-T lymphocytotoxins of the IgG class which are associated with hyperacute rejection^{7,18,47} as well as the less malevolent^{7,21,26,47} but still harmful^{18,19} warm anti-B antibodies of the IgG class. Cold anti-B IgM antibodies which have been associated with active enhancement^{7,13,47} were not present preoperatively.

Three of the five recipients had successful transplantation, one by virtue of a second homograft after an indolent variation of hyperacute rejection including massive platelet sequestration had destroyed the first organ. The thoracic duct drainage had not eliminated anti-T lymphocytotoxins, and high-kill positive cross-matches were present with the actual donors. However, the anti-T-cell titers at the time of the successful transplantations were at moderate levels at the same time as there was profound immunoglobulin depletion. In the two unsuccessful cases, there was equivalent serum immunoglobulin depletion by TDD, but the anti-T-cell titers remained high.

The 60% eventual success rate in the 5 patients transplanted despite positive cytotoxic antidonor cross-matches was the same as that reported earlier after TDD by Niblack et al.³¹ In future cases, careful monitoring of anti-T-cell cytotoxic antibody titers may give a better signal when to proceed. If high titers are refractory to thoracic duct drainage, additional pretreatment with azathioprine, prednisone, and ALG will have to be considered as well as removal of blood IgG by plasmaphoresis. It is possible that discarding the lymph as was done in cases 1 and 2 expedited antibody depletion. Because replacement of discarded lymph with plasma was so expensive, this practice was stopped. It has since been learned that lymph losses can safely be replaced with intravenous electrolyte solutions for long periods.

The wider use of TDD together with exploitation of recent typing advances cited earlier is apt to change policies and practices in transplantation. Recipients (particularly those needing cadaveric organs) always have been ruled by the donors, with the final decision about candidacy hinging mainly on the conventional negative cytotoxic crossmatch and to a minor extent on HLA matching. In the future, it seems

probable that the recipients wishes can be given greater weight. As in the past, the first step will be to check for antibodies against a lymphocyte panel. If these are found, they should be classified as warm or cold anti-T or anti-B. With such information, a decision can be made about an appropriate duration of TDD pretreatment.

We believe that all recipients should be pretreated with TDD with the possible exception of those who have perfectly matched sibling donors. We suggest TDD pretreatment for about 21 days in recipients who have been antibody free or who have cold anti-B cytotoxins, and who have a negative conventional cytotoxic crossmatch with the donor. Patients possessing warm anti-T and/or anti-B lymphocytotoxins should have TDD pretreatment for 30 or 35 days before transplantation, even if crossmatch negative donors can be found before this time. Patients who have crossmatch positive donors after 35 days of TDD can have transplantation if the responsible antibody is the warm anti-B variety. However, if anti-T antibodies persist and are responsible for positive direct cross-matches, a necessary condition for proceeding would be a low titer (<1:4). If this cannot be achieved with TDD alone, pretreatment with other immunosuppressive agents should be considered.

With successful transplantation, TDD will usually be discontinued after a total preoperative plus post-operative duration of about 60 days. Final upward adjustments of prednisone should then be considered. Machleder and Paulus²² showed a return of immunologic responsiveness over several months after stopping TDD. Several of our cadaveric recipients who were on low maintenance doses of steroids developed late rejection after stopping TDD, and at least two probably will soon lose their homografts.

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DISCUSSION

DR. CHARLES THOMAS FITTS (Charleston, South Carolina): The problem that Dr. Starzl alluded to early in his abstract and at the onset of this talk has been an extra-ordinarily frustrating one to transplant surgeons. As immunologists have been unable to provide us with an effective and safe method of selective immunosuppression, they have turned with prodigious energy and enthusiasm to develop a complex array of time-consuming, expensive and frequently unreliable measurements designed to predetermine when a kidney transplant will be successful and when it will not. The theoretic result of this philosophy is to achieve nearly 100% graft survival. Since this is to be achieved by only transplanting between individuals with no significant immune disparity, however, the practical result will be slowly but surely to decrease the number of patients receiving transplants. That should not be our objective.

What Dr. Starzl has presented here today is a welcome advance in attacking the real problem, which is to control the patient's immune system to his benefit. He has utilized one of the more predictable and reliable tests of the battery that the immunologists have come up with, namely, the complement-dependent cytotoxic rematch, to indicate the need for a particular type of immunosuppression, rather than as a contraindication for transplant.

(slide) I am doubly pleased that the method successfully used is one with which our group had early experience and which our data in retrospect would predict its likely success in this situation; that is, a predetermined, humorally mediated immunity between donor and recipient. In both animal and human studies in the late 1960's, our data showed extremely effective abrogation of the humoral response, both primary and secondary, as shown here with thoracic duct depletion.

It is my opinion that the benefits will not be limited to this area alone but will extend to cellularly mediated problems as well.

The Vanderbilt transplant group has apparently been finding much the same results as reported here today, and I am greatly encouraged that a powerful tool, which has been lying around for some time, is about to be picked up and put to extremely effective use in transplantation.

DR. ALLAN ELIOT DUMONT (New York, New York): Dr. Starzl has shown us clearly, that it is the removal of thoracic duct lymphocytes, rather than lymph-borne globulin, that is critical in the preparation of these patients for transplantation.

It is particularly interesting that serum immunoglobulin levels fell so rapidly, despite the reinfusion of the antibody-rich lymph. These findings are consistent with the idea that thoracic duct lymph includes a functionally distinct pool of immunologically competent cells, presumably B-cells, which synthesize and release antibody molecules into lymph and into blood.

In some earlier studies (slide), we found that a number of human thoracic duct lymphocytes stained with fluorescein-labeled antibody to human gamma globulin. This is a smear of human thoracic duct lymph, showing one such positive staining cell.

Actually, about 4% of thoracic duct lymphocytes contain antibody globulin, and this proportion increases rapidly as thoracic duct lymph continues to be drained.

We also found that when these cells are maintained in culture, they incorporate labeled amino acids into immune globulin. In patients

with high titers of cytotoxic antibodies, the kind of Dr. Starzl has described to us, specific depletion of these cells may, in fact, be the most important effect of thoracic duct drainage.

DR. JOSEPH E. MURRAY (Boston, Massachusetts): I am reassured that Dr. Starzl is focusing his skill and careful study to a re-evaluation of thoracic duct fistula and drainage. This is a blunt tool which deprives the recipient of many of his immune mechanisms, but Dr. Starzl has sharpened this tool by his study of its placement in relation to the exposure to antigen.

Some problems with thoracic duct drainage are worth comment; it is time consuming, expensive and increases bed occupancy. There are additional problems of centrifugation and reinfusion; so it will probably not be used by most transplantation centers until it has proved its effectiveness. Nevertheless, I am thrilled that Dr. Starzl is re-evaluating the technique with his usual care and skill.

DR. THOMAS E. STARZL (Closing discussion): I agree with Dr. Dumont that the removal of the cells, in some way that we do not fully understand, and possibly by the mechanism which he described, cuts off the immunoglobulin production rather than reducing immunoglobulin by its removal from the thoracic duct lymph.

The amount of immunoglobulin or, for that matter, proteins in the thoracic duct lymph is about only half of that in the serum, and so, if mechanical removal were attempted, it might be best done by peripheral plasmapheresis, since the highest concentration of IgG is there.

In response to Dr. Fitts and Dr. Murray together, I have the impression, more like Dr. Fitts and less like Dr. Murray, that thoracic duct fistula is a practical undertaking in terms of cost-effectiveness, and even possibly in terms of time invested. At the same time I understand perfectly Dr. Murray's concerns from the perspective of his trials ten to fifteen years ago.

In their important pioneering work done in Boston in the 1960's, Murray and his associates reported unequivocally improved results with thoracic duct drainage, particularly in their experience with related cases. It has always been surprising to me that that procedure was abandoned at Harvard, Galveston, and some other places.

In reading back over that early work, I did notice that TDD was time-consuming, that it was expensive, and, furthermore, that it was a procedure not fully reliable. In the Boston series, failure to achieve significant thoracic duct drainage was about 50%, and in the Stockholm series of Franksson, the figure was even higher. It created a situation in which one could not know for sure what was being offered the patient.

That problem was rectified for us by a young surgeon named Dr. Larry Koep, who had the bright idea of using a Swann-Ganz catheter for the cannulation. He cut the balloon off the Swann-Ganz catheter and thus created a double lumen, using one lumen for infusion and the other for collection. Exploiting this advance in instrumentation, he learned how to advance the catheters into the mediastinum. He had solved most of the problems that had confounded the pioneer workers with thoracic duct fistula with a technique that had a 95% reliability.

I do want to make my position clear, while at the same time paying tribute to Dr. Murray and those others who worked before. I believe that pretreatment with thoracic duct fistulas should be used for all patients, related and unrelated, with the possible exception of double haplotype identical siblings, and that it will have a broad, and not a narrow, use in clinical transplantation.