Thoracic Duct Drainage in Organ Transplantation: Will It Permit Better Immunosuppression?

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BETTER clinical immunosuppression may well depend on some completely new approach, such as the exploitation of suppressor cells in some as yet undefined way. There is also the straightforward possibility of better drugs, as exemplified by the exciting reports by Calne on the fungus extract, cyclosporin. A third possibility, which is the subject of this article, is more effective use of an older procedure, thoracic-duct drainage.

HISTORICAL NOTES

The profoundly suppressive effect of this procedure on cell-mediated immunity, antibody responses, and homograft rejection were established in rats by Gowans.[1-3] Woodruff soon demonstrated that synergism of thoracic-duct drainage with another lymphoid-depleting modality, antilymphocyte serum.[4] In 1964, Franksson of Stockholm introduced thoracic-duct drainage into clinical transplantation, combining it with azathioprine and steroids.[5] In all this pioneering work, lymphoid depletion was carried out in advance of transplantation, thus conditioning the host by removing small lymphocytes, which Gowans had shown easily and quickly crossed the interface between blood and lymph.[1]

In the 1960s, further important clinical trials were made, the largest being in Sweden under Franksson,[6,7] in Boston by Murray and Tilney,[8-10] and in Galveston by Fish and Sarles.[11,12] Except for Franksson, these early investigators emphasized pretreatment. In contrast, Franksson provided little pretreatment and maintained the fistulas as long as possible *after* arrival of the renal homografts. Although the details varied, all of the foregoing reports concluded that there was benefit from thoracic-duct fistula. Since the claims were unequivocal, it was surprising that the trials were not taken up elsewhere and that they were even abandoned in the originating institutions. Reasons for nonacceptance of the procedure included nonreliability, expense, and annoyance. In half or more of the cases in Sweden and Boston, the fistulas could not be established or else failed within a few days. In some of the trials, failure to reinfuse the lymph after cell removal caused plasma volume problems.

Another reason for discouragement may have been negative clinical reports from France,[13] Italy,[14] Brazil,[15] and Japan.[16] The latter studies implied or openly concluded that there was no justification for further use of thoracic-duct fistula in human transplantation. However, the volumes and duration of lymph drainage in these studies were generally suboptimal.

The only workers to continue were those at Vanderbilt University in Nashville, Tenn. Walker[17] and Johnson[18] and their colleagues published striking reports in 1977 about 50 cadaveric kidney recipients who were considered medically and immunologically high risk and who were given badly matched kidneys. Thoracic-duct drainage was started about a month in advance of transplantation and continued for variable times afterwards. The graft survival 2–5 years later was almost 75%, nearly twice as good as in a control group.

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An influential paper, not concerned with transplantation, was recently published by Machleder and Paulus of Los Angeles, using human thoracic-duct drainage as the sole treatment of autoimmune diseases, such as rheumatoid arthritis and scleroderma.[19] This superb study defined in humans the time curves for suppression of humoral and cell-mediated immunity originally described over a 5-day period in rats by McGregor and Gowans.[2] The full effect in humans was not achieved until after 30 days.

LIVER TRANSPLANTATION

Machleder's article was given orally in Louisville, Ky., at the Society of University Surgeons in early February 1978. Within a few weeks, we faced seemingly insurmountable management problems with one of our liver recipients who had deteriorating liver function despite treatment with azathioprine and high doses of prednisone. At the same time, there was a massive wound infection and breakdown of his thoracoabdominal incision. Thoracic-duct fistula was started 1 month after transplantation and maintained for 71 days (Fig. 1). Prednisone was reduced from a high level to 10 mg/day. Liver function slowly returned to normal. Although the patient required respirator support for several weeks, he recovered fully, requiring only a final upward adjustment of maintenance steroids 2 months after discontinuance of the thoracic-duct fistula. A second liver patient was treated with thoracic-duct fistula, starting 13 days after transplantation, under worse circumstances, including the presence of enteric fistulas. She also recovered and has also returned home.

We have performed thoracic-duct fistula on 9 liver recipients (Table 1), the two described above after a delay of 2–4 weeks, and 7 more at the time of liver transplantation. Seven of the 9 patients are alive with followups of 1½–6½ months. It has been impossible for us to achieve such consistency of results in the past. One of the two deaths was due to massive infection after a bowel

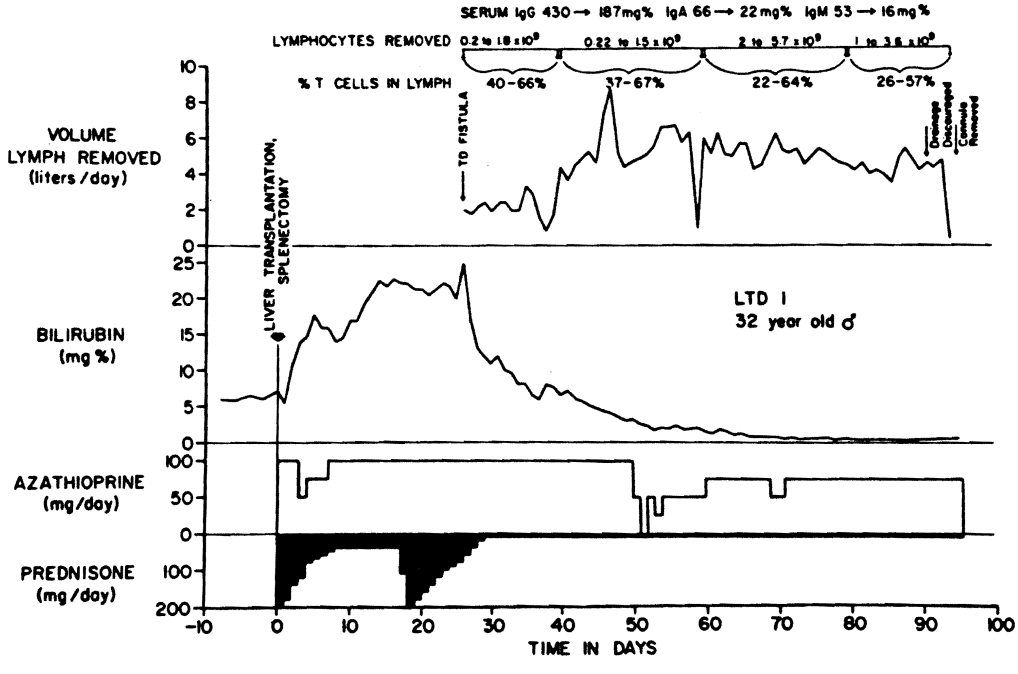

Fig. 1. Use of thoracic-duct fistula 4 weeks after orthotopic liver transplantation for chronic aggressive hepatitis. The

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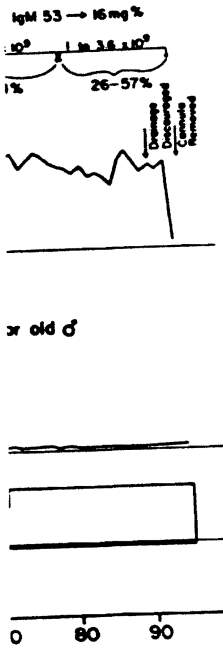

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Table 1. Liver Recipients Treated With Thoracic Duct Fistula

	Alive	Dead	Follow-Up (Months)
7 At transplantation	5	2 (After 16 and 42 days)	1½, 1½, 2, 2½, 4½
2 Delayed	2	0	6 and 6½

perforation. Liver function was always normal. The other patient's homograft did not function well and developed multiple areas of necrosis after transplantation from a B donor to an A recipient. There may have been an element of hyperacute rejection because of the blood group violation.[20]

When thoracic-duct fistula was performed at the time of liver transplantation, the lymph drainage tended to be sluggish at first, reaching, in individual adults, a relatively stable level within a few days. These volumes varied from 3 (Fig. 2) to 7 or 8 liters (Fig. 1). It was interesting in these cases that the number of

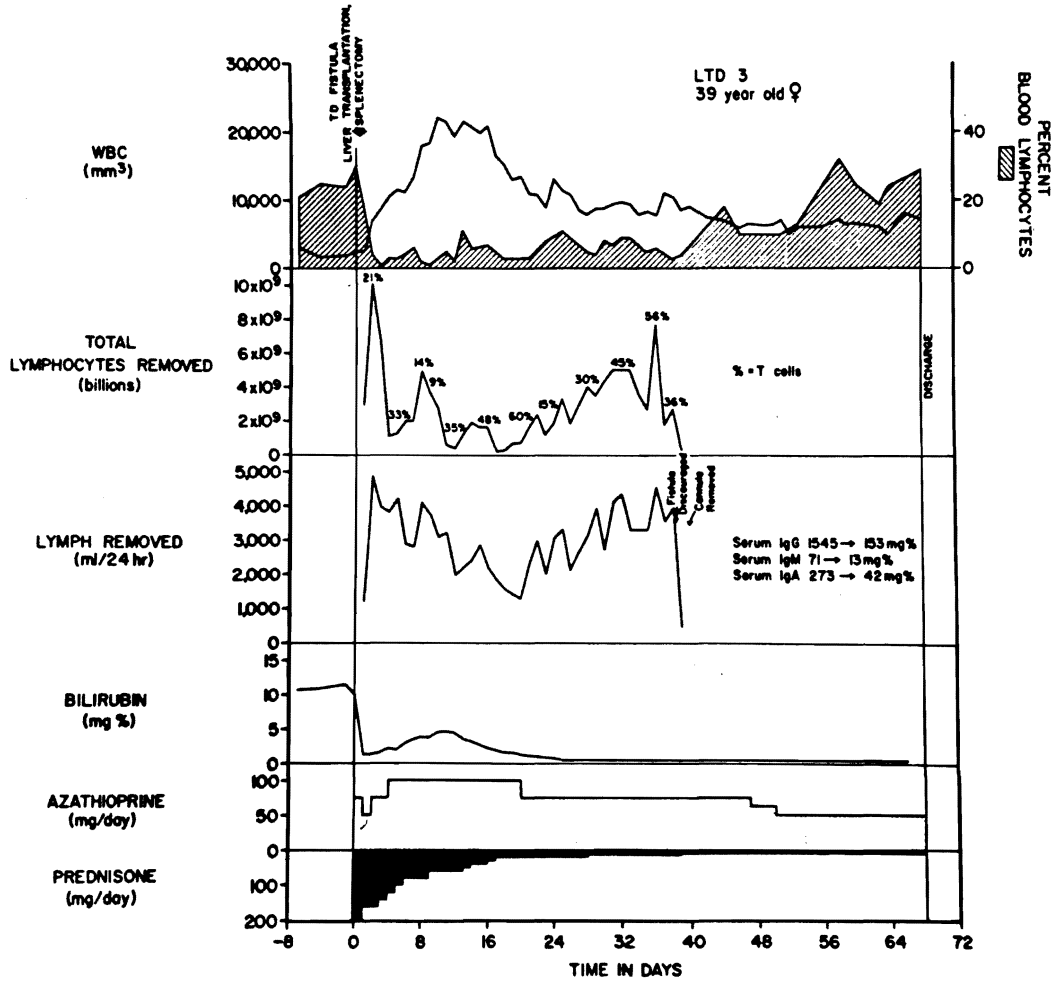

Fig. 2. Course after orthotopic liver transplantation for chronic aggressive hepatitis. Thoracic-duct drainage was started on the day of operation, and the cell-free lymph was reinfused intravenously thereafter. Note: (1) reduction of lymphocyte percent in peripheral blood during thoracic-duct fistula (however, the total lymphocyte count was not much affected because of the concomitant increases in total white count); (2) persistence and late resurgence of total thoracic-duct lymphocytes removed and of the T-cell component of these lymphocytes; (3) profound reduction of serum immunoglobulins while on thoracic-duct drainage.

lymphocytes removed declined at first but returned later in large numbers (Figs. 1 and 2) as if there were a lymphocyte-proliferative response to the homograft antigens. The percentage of T lymphocytes collected in the thoracic-duct lymph tended to remain high throughout the treatment period (Figs. 3 and 4). In all hepatic recipients (Figs. 1 and 2) as well as in renal recipients (Figs. 3 and 4) with thoracic-duct drainage, a remarkable reduction occurred in the serum concentration of the different immunoglobulin classes. This finding has important implications, to be discussed later, in carrying out renal transplantation in the face of antidonor cytotoxic antibodies.

In all but 1 of the 7 liver recipients still surviving, it was possible to reduce the prednisone doses to relatively low levels, below 5 mg/kg (Figs. 1 and 2). The fistulas were then discontinued after 1–2½ months. The azathioprine and steroid management (with or without antithymocyte globulin—ATG) were used as we have practiced in the past, with emphasis on reducing prednisone doses as rapidly as possible.

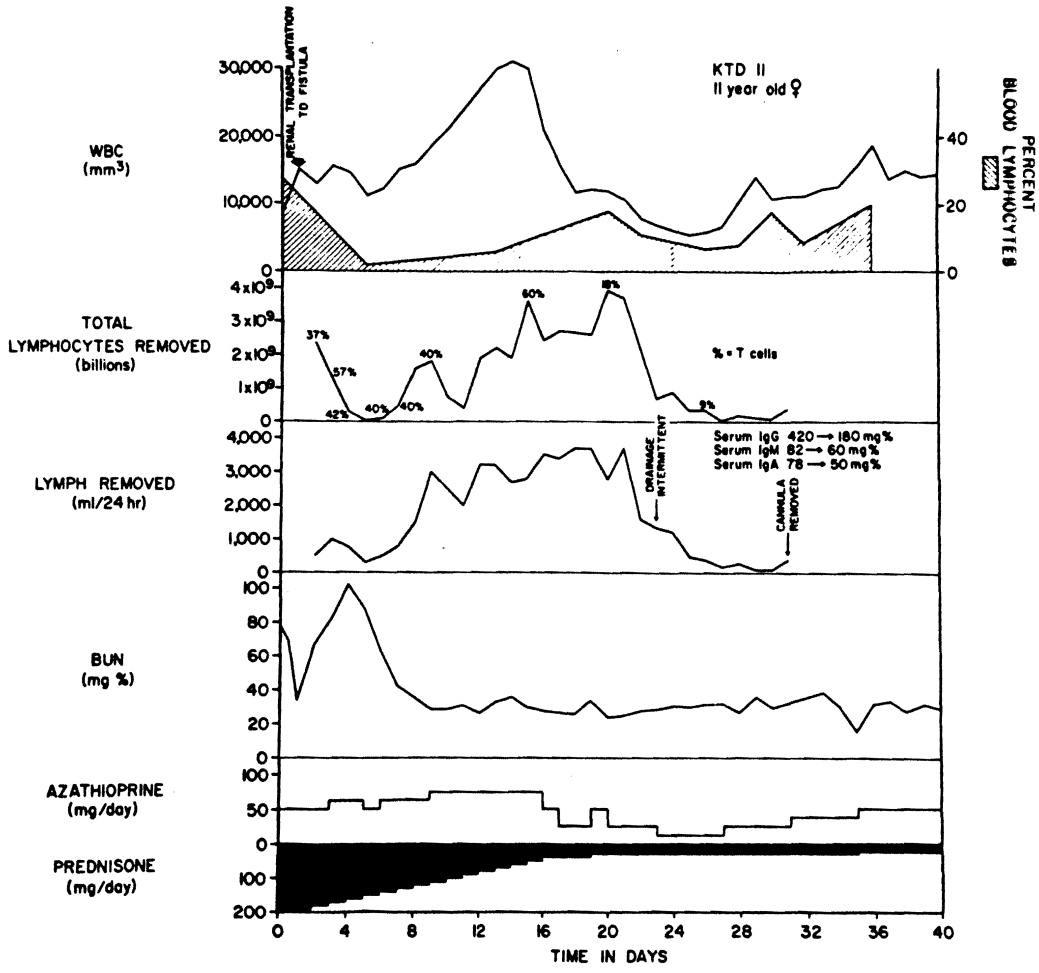

Fig. 3. Cadaveric renal transplantation without a definite rejection. The thoracic duct fistula was maintained for almost a month. Note that the number of lymphocytes removed from thoracic-duct lymph was actually greater at the end than at the beginning of thoracic-duct drainage. The depression of serum immunoglobulin is typical of thoracic-duct drainage, even though the cell-free lymph is reinfused.

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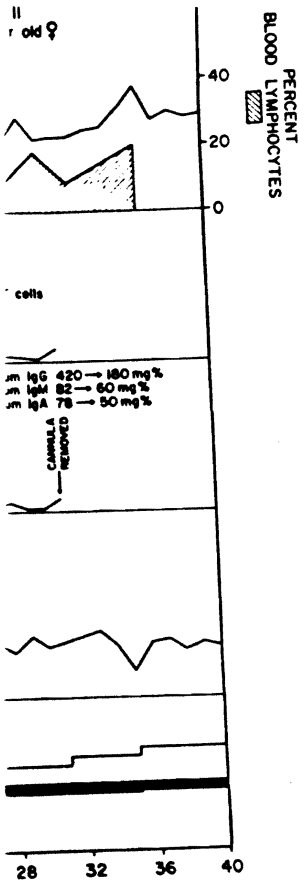

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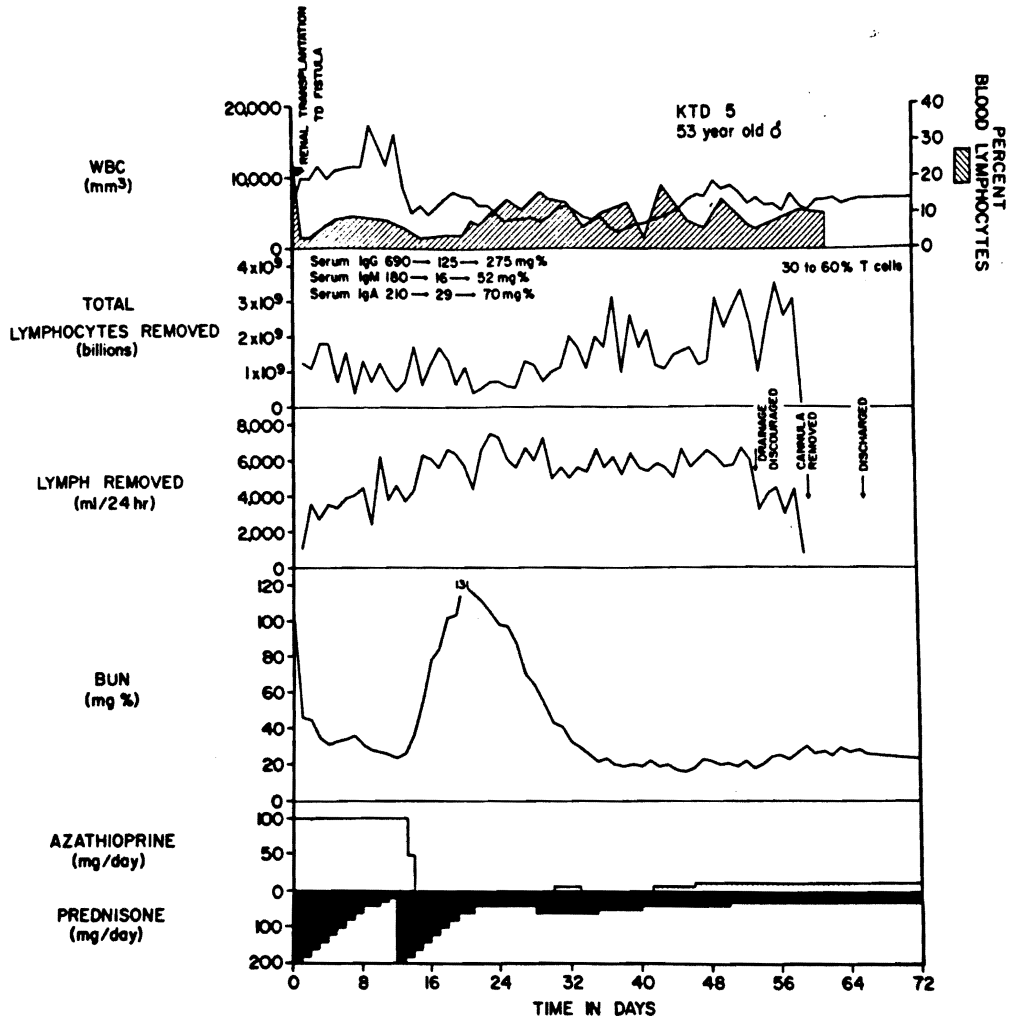

Fig. 4. Moderately severe renal homograft rejection that occurred in spite of thoracic-duct drainage and depended on intensification of prednisone therapy for reversal. Note that the total lymphocytes removed per day was greater at the end of thoracic-duct drainage than at the beginning.

MANAGEMENT OF THORACIC-DUCT FISTULAS

Since thoracic-duct drainage has had a high failure rate, some important details are worth mentioning. In our center, the incidence of successful thoracic-duct drainage has been 94%. The thoracic duct is cannulated in the left neck. Into the duct is inserted a Swan-Ganz catheter, after cutting off the balloon. Valves in the duct are passed by the judicious use of metal probes, and the catheter is placed into the superior mediastinum. Heparinized saline (1000 U heparin in 500 ml saline) is infused at about 20 ml/hr. Providing the infusion is continuous, this small amount of heparin is enough to prevent clotting of the lymph at the catheter tip. Furthermore, additional anticoagulant has not been necessary in the transfer packs.* After centrifugation, the cell-free supernatant in the

*Transfer packs of 400-ml capacity were kindly donated by the Fenwall Corporation, Deerfield, Ill., for these pilot studies. Special transfer packs have been designed for thoracic-duct drainage and will be commercially available by about November 1, 1978 for approximately $4.50 per pack.

collecting bag is passed by a closed system into a second bag. About 99% of the removed cells are small lymphocytes. A day's collection of cell-free lymph is reinfused intravenously throughout the next day.

In our experience and that of the Vanderbilt surgeons,[18] a narrow spectrum antistaphylococcal antibiotic must be given to prevent staphylococcal bacteremia. When a decision is made to discontinue the thoracic-duct fistula, the collection bags are elevated from their normal position near the floor, to above body level, and the heparin infusion is stopped. When drainage stops, the catheter is gently but firmly pulled out.

RENAL TRANSPLANTATION

The same general approach of thoracic-duct fistula at the time of transplantation was carried out in 20 renal recipients treated from 2 to 5 months ago. Three received poorly matched parental kidneys, and the other 17 received poorly matched cadaveric transplants. Sixteen of the 20 organs are functioning at 2–5 months, including 3 of the 3 related grafts and 13 of the 17 cadaveric kidneys.

In Table 2 are given data on the 17 cadaveric cases, which were compared with the last 50 consecutive cadaveric transplantations performed at our center under standard azathioprine–prednisone or azathioprine–prednisone–ATG therapy. The extent of the histoincompatibility was extreme in both groups, with an average of almost 3 mismatches. The percentage of patients treated with ATG was about 60% in both groups.

The quantities of lymph and the numbers of lymphocytes removed during the first 3 weeks of thoracic duct drainage are summarized in Table 3. The volumes were large, averaging 3.4 liters/day.

At 2 months, 13 of the 17 cadaveric kidneys were (and for that matter still are) functioning (Table 4). There were no deaths within the first 2 months, and the creatinine was below 2 mg/100 ml in 10 of the 13 remaining kidneys. The prednisone doses in the first 2 months were not significantly different than in the retrospective controls (Table 5), nor was the incidence of rejection (Table 6), but the percentage of functioning kidneys was higher (77% versus 60%; Table 4). Perhaps something of the late fate of such patients may be inferred from the small number of late graft losses in the earlier studies from Sweden[6,7] and the recent ones from Vanderbilt.[17,18] As mentioned earlier, the graft survival rate at 2–5 years in the Vanderbilt series was 75%.

In Fig. 3 is shown the course of a cadaveric kidney recipient who had no rejection. Thoracic-duct drainage was discontinued after a month and the patient discharged on 25 mg of prednisone. The drainage volume was about 3000 ml lymph/day. Throughout the drainage, T and other lymphocytes persisted in the lymph. There was striking depression of immunoglobulins.

The renal recipient whose course is shown in Fig. 4 had a severe but reversible rejection Consequently, his high volume fistula (whicl produced about 6 liters/day) was left for months. The quantities of lymphocytes an their T-cell components did not diminish.

What has happened to the four patient who rejected their cadaveric kidneys? Or has been successfully retransplanted; tw others, who still have their thoracic-du fistulas in, are awaiting retransplantatio and the family of a fourth patient request discontinuation of the thoracic-duct fistu and treatment with dialysis. When a fi

Table 2. Cadaveric Kidney Transplantation

	No. Cases	Age (Years)	Antigen Matches	Antigen Mismatches	No. of Retransplantations	No. of Patie Given ATC
Thoracic-duct fistula	17	34.4 ± 13.8 (SD)	1.0 ± 0.7 (SD)	2.7 ± 0.7 (SD)	3 (18%)	10 (61%
Controls*	50	42.1 ± 11.8 (SD)	0.8 ± 1.0 (SD)	2.8 ± 1.0 (SD)	18 (36%)	30 (60%

*Consecutive cases: November 1976—June 1978.

Table 3. Thoracic-Duct Drainage in 17 Cadaveric Kidney Recipients

Duration Days (Range)	Total Volume*		Total Lymphocytes Removed*	
	Range	Mean	Range	Mean
23 Days—>2 months	38–106 Liters	72.4 ± 20 Liters	16.8 ± 55.0 × 10^9	25.9 ± 9.8 × 10^9

*In first 3 weeks.

Table 4. Results in First 2 Months After Cadaveric Renal Transplantation

	Kidneys Functioning at 2 Months	Serum Creatinine in Kidneys Functioning at 2 Months		Patients Dead at 2 Months
		>2 mg/100 ml	<2 mg/100 ml	
17 Thoracic-duct fistula	13 (77%)*	3	10	0
50 Controls	30 (60%)	5	25	5†

*Of the 4 patients who lost their grafts, 1 had a successful cadaver retransplantation 4 weeks after the original transplant with continuing thoracic-duct drainage.

†Two of these five patients died with normal renal function.

kidney fails with this approach of thoracic-duct fistula and simultaneous transplantation, the initial period of thoracic-duct drainage in a failed attempt can be viewed as pretreatment for the second kidney and apparently with little risk as reflected by the zero mortality. With the unpredictability of organ supply, the practicality of this strategy is evident in cadaveric transplantation. The early work of Dumont et al.[21] and Singh et al.[22] have indicated that thoracic-duct drainage at the time of skin or renal homotransplantation is as effective as prior treatment, but this clinically important point of timing must be reexamined in the experimental laboratory.

RENAL TRANSPLANTATION AGAINST CYTOTOXIC ANTIBODIES

Even now, in special cases, pretreatment may be advisable or even obligatory. A signal observation was made by Niblack et al. of Vanderbilt[23] who reported that after a month or longer of thoracic-duct drainage, 3 of 5 kidneys were successfully transplanted across positive cytotoxic crossmatches with function of these 3 kidneys more than 2 years. If this observation were reproduced, the large reservoir of untransplantable renal patients that have come to plague every major center would become accessible to treatment. Because of the very drastic reductions in serum immunoglobulins caused by thoracic-duct drainage, the possibility has seemed logical.

We have carried out transplantation in two patients whose sera killed 100% of cells in our test panel as well as the lymphocytes of their donors. The first recipient was given a kidney after 4 weeks of thoracic-duct drainage. The organ did not undergo hyperacute rejection but functioned poorly and had to be removed 19 days later because it was consuming platelets to an alarming degree. In the meanwhile, after 7 weeks of thoracic-duct fistula, a second kidney was placed and, this time, the

Table 5. Mean Prednisone Dose (Mg/Day) at Weekly Intervals During First 6 Weeks After Renal Transplantation With Passage of Time, Patients With Lost Kidneys Were Dropped From Analysis*

	Time in Weeks			
	1	2	3	6
17 Thoracic-duct fistulas	117 ± 34 (17)	93 ± 55 (17)	74 ± 53 (15)	54 ± 47 (13)
50 Controls	138 ± 21 (47)	89 ± 42 (44)	77 ± 42 (42)	60 ± 44 (33)

*Number of cases at each time is in parentheses.

Table 6. Rejections in First 2 Months After Cadaveric Renal Transplantation

	No Rejection	One Rejection	More Than One Rejection
17 Thoracic-duct fistulas	6 (35%)	7 (41%)	4 (24%)
50 Controls	19 (38%)	24 (48%)	7 (14%)

organ functioned adequately. A second patient was given a kidney across a positive crossmatch, and the organ has functioned perfectly. Although these follow-ups are of short duration, they are highly encouraging, since the predictable disaster of hyperacute rejection under these conditions has been avoided.

PANCREAS TRANSPLANTATION

Finally, a partial pancreas (neck, body, and tail) and kidney transplantation was performed in an adult with thoracic-duct drainage. Both first organs were rejected, as was a second kidney placed 13 days after institution of thoracic-duct drainage. However, a second pancreas transplanted across a strongly positive crossmatch after 17 days of thoracic-duct drainage has functioned perfectly for more than 2 months despite very minimal immunosuppression, consisting now of 10 mg/day of prednisone and little (12.5 mg/day) or no Imuran (Fig. 5). The patient, whose daily insulin requirements were 40–60 U now requires no replacement therapy.

SUMMARY

It is possible that thoracic-duct drainage, a major but neglected immunosuppressive adjunct, can have an important impact on organ transplantation. If thoracic-duct drainage is started at the time of transplantation, the

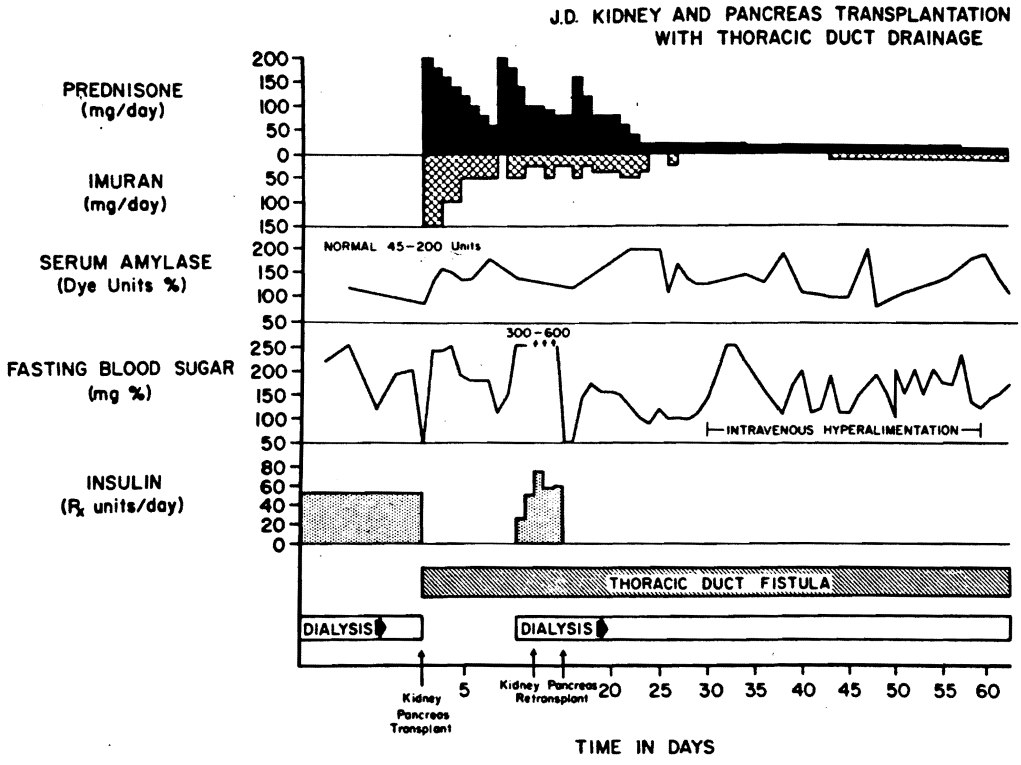

Fig. 5. Course of a patient who received two kidney and two pancreas transplants. The first two kidneys and the first pancreas were rejected. The patient had a strongly positive cytotoxic crossmatch against lymphocytes of the second pancreatic donor, but in spite of this, the organ has functioned perfectly. Note the cessation of insulin requirements from day 18 onward.

practicality of its use in cadaveric cases is greatly enhanced. With kidney transplantation, the penalty of not having pretreatment for the first organ is compensated by the automatic presence of pretreatment if rejection is not controlled and retransplantation becomes necessary. The advantage of adding thoracic-duct drainage to conventional immunosuppression may greatly enhance the expectations for the transplantation of extrarenal organs, such as the liver, pancreas, heart, and lung. There is evidence that pretreatment with thoracic-duct drainage of patients with cytotoxic antibodies may permit successful renal transplantation under these otherwise essentially hopeless conditions. Exploration of the neglected but potentially valuable tool of thoracic-duct drainage seems to us to be highly justified in other centers.

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