From: CHRONIC RENAL DISEASE
Edited by Nancy Boucot Cummings, M.D.
AND Saulo Klahr, M.D.
(Plenum Publishing Corporation, 1985)

574

51

The Pretreatment Principle in Renal Transplantation as Illustrated by Thoracic Duct Drainage

Thomas E. Starzl, Richard Weil, III, and Lawrence J. Koep

In spite of all that has been achieved, renal transplantation still provides a flawed and unpredictable service. In the average American center in the decade of the seventies, less than half the recipients of first cadaver kidneys had graft function by the end of the first postoperative year. One reason may be neglect of what has been called the "forgotten pretreatment principle." It is that subject which is addressed here, with particular emphasis on thoracic duct drainage (TDD).

1. Early Clues

In 25 of our first kidney recipients, Wilson and Kirkpatrick[31] used preoperative skin testing and typhoid vaccination to assess cellular and humoral immune reactivity. Immunosuppressive therapy for those patients was with azathioprine to which prednisone was added only if rejection developed.[19,20] After transplantation, the patients previously classified as nonresponders had a mean rejection time of 14.8 days, compared to 4.3

Thomas E. Starzl • Department of Surgery, School of Medicine, University of Pittsburgh Health Sciences Center, Oakland Veterans Administration Medical Center, Pittsburgh, Pennsylvania 15213. ***Richard Weil, III*** • Department of Surgery, School of Medicine, University of Colorado, Denver, Colorado 80262. ***Lawrence J. Koep*** • Phoenix, Arizona 85006. This work was supported by research grants from the Veterans Administration, by Grants AM-17260 and AM-07772 from the National Institutes of Health, and by Grants RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

days in the responders. These findings were not influenced by donor relationship. Wilson and Kirkpatrick concluded that

> These observations support the concept that impaired immunologic responsiveness in uremia is an important factor in successful human kidney transplantation. Furthermore, the difference in rejection times between the responsive and unresponsive groups suggests that the reactive group might benefit from additional immunosuppressive therapy prior to [transplantation]. . . .

Almost a decade later, the prognostic implication of the reactor-versus-nonreactor state of kidney recipients was reemphasized by the antibody studies of Opelz, Mickey, and Terasaki.[16] More recently, Jones *et al.*,[8] Thomas *et al.*,[27] and Opelz and Terasaki[15] came to the same conclusion from the results of *in vitro* phytohemagglutin, concanavalin A, and mixed-lymphocyte culture (MLC) tests all of which are expressions of T-lymphocyte reactivity. The MLC studies[15] were particularly illuminating. The MLC index using third-party lymphocytes was almost as predictive of the outcome after cadaveric kidney transplantation as when the stimulator cells were provided by the actual donor.

Although well known, the foregoing information has had surprisingly little influence on treatment practices. In the early days of our program almost all human kidney recipients were given azathioprine for 8–10 days before transplantation. The practice was based on analogous canine experiments in which average homograft survival was doubled thereby over that obtained when the drug was started on the day of operation.[19] Gradual abandonment of the policy of preoperative treatment of our patients with azathioprine, and often steroids may have been a systematic error inasmuch as other immunosuppressive adjuncts to condition the recipients were not being substituted. As cadaveric transplantation became more common, practical reasons made pretreatment difficult. The waiting period for a cadaver kidney was unpredictable, during which time extra infectious risks were introduced by giving azathioprine with or without prednisone. Furthermore, there were no accepted guidelines about the appropriate duration of such pretreatment. Worldwide, transplantation centers drifted into the practice of starting therapy on the day of grafting.

2. *TDD and the Pretreatment Principle*

The immunosuppressive procedure of TDD has provided an unusually analyzable example of the pretreatment principle and of the loss of much of the value of this procedure if its timing is wrong. TDD was given a trial in several centers 5–15 years ago[1–6,11–13,17,18,28,29] but was never accepted as a major therapeutic tool. This was because the scientific framework for its use in humans had not been worked out.

3. *Contemporaneous TDD*

Eighteen months ago we began a systematic trial with TDD in renal transplantation, starting the lymphoid depletion on the day of grafting along

Table 1. Rejection in First 2 Months of Cadaver Kidneys: Influence of TDD[a]

	Percent rejection		
	Contemporaneous TDD (17)[b]	3 Weeks pretreatment with TDD (13)	≥4 Weeks pretreatment with TDD (14)
Incidence rejection	41%	38%	7%
Irreversible rejection	24%	8%	0%
Deaths	0	1	2

[a] In 50 immediately precedent cadaveric recipients treated with azathioprine, prednisone, and sometimes ALG, the incidence of early rejection was 48%.[22]
[b] Data from ref. 22.

with azathioprine, prednisone, and sometimes antilymphocyte globulin (ALG).[22,23] The protocol was similar to that usually used by Franksson *et al.*[5] The results were somewhat better than in historical controls without TDD, but vigorous rejection was often encountered during the first month (Table 1). The most striking clinical observation was that if the TDD was continued, a second graft could often be performed after failure of the first.[23] It was obvious that TDD was being inappropriately used for the primary transplant. Data in these patients plus precise immunologic studies by Machleder and Paulus[10] in nontransplantation patients established that a pronounced immunodepressive influence of TDD was not established until about 3 weeks and that this effect deepened for another week or so. Kidneys in our early TDD series were being rejected during this uncovered 3 or 4 weeks and, in addition, "antibody storms" in the postoperative period were often seen[23] with a heavy representation of the so-called warm anti-T and anti-B cytotoxic antibodies of the IgG class.[26]

4. *Pretreatment with TDD*

To correct the flaw in therapeutic strategy,[23] a new series was begun using TDD in advance of cadaveric renal transplantation,[24] adding azathioprine and prednisone on the day of operation. This time, the presence of preexisting recipient antibodies was taken into consideration. These antibodies recently were characterized on the basis of their reactivity against homologous T and B lymphocytes at warm (IgG class) and cold (IgM) temperatures.[26] It has been accepted that warm anti-T antibodies cause hyperacute rejection,[26] but the significance of the other antibody varieties has remained controversial. Whatever their meaning, the cytotoxic antibodies could be construed as an index of the patients' immune reactivity, both by their presence before and by their development after transplantation. In the new treatment scheme, patients with no (or only cold) antibodies were scheduled for 3 weeks' preparation with TDD. Those possessing warm antibodies were scheduled for 35 days. If anti-T antibodies persisted and

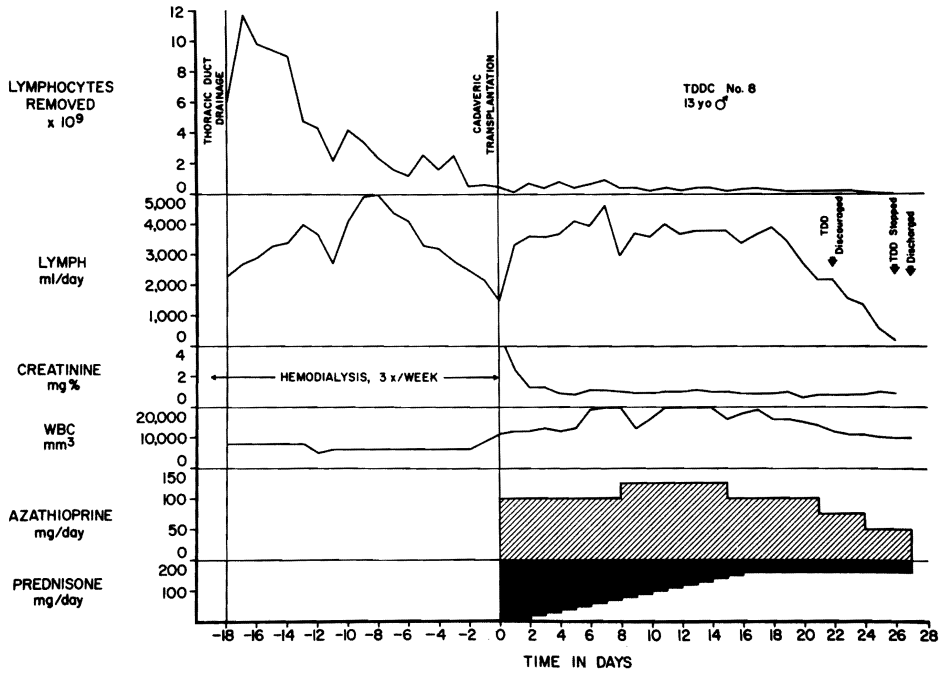

Figure 1. Example of short pretreatment with TDD. Although the patient had a perfect result, it is now known that the conditioning period was too brief. The drop in lymphocytes removed during the pretransplantation period was invariably observed. This finding was in contrast to our experience with TDD started on the day of transplantation in which the number of lymphocytes removed remained high. (The postoperative retention of TDD for about 3 weeks is still our policy.) The patient has had no evidence of late rejection.

reacted against the potential donors, it was shown earlier[23] that a low titer was necessary before proceeding in the face of a positive cross match. After 35 days, acceptance of cadaver donors whose positive cross matches were due to other kinds of antibodies was recommended.

The recipients in this new series represented a modern-day cross section of risk factors. Many of the patients were old with known coronary artery disease, three were diabetics, and three were undergoing retransplantation. Because the donor selection was random except for red-cell-group compatibility, the HLA and DR matches were all poor.[24] The results from the studies permitted precise conclusions about TDD pretreatment.

4.1. Pretreatment of 3 Weeks

Thirteen consecutive cadaver recipients of whom only one had preexisting warm anti-B antibodies had preoperative TDD for 17–28 days. The therapeutic approach is illustrated in Fig. 1. During the pretreatment period, the numbers of collected lymphocytes always fell markedly. After transplantation, the TDD was maintained for at least 3 more weeks.

Table 2. Broadly Reacting[a] Warm Anti-B Lymphocyte Antibodies 2 Weeks after Transplantation

TDD pretreatment for 3 weeks	7/13
TDD pretreatment ≥4 weeks	1/14

[a] Broadly reacting means reactivity against half or more of a 30-donor lymphocyte panel.

During follow-ups of 2–6 months, five of these patients (38%) had rejection, which in four instances was reversible (Table 1). The fifth patient was treated with prompt retransplantation. These patients retained a potent capacity for cytotoxic antibody production. Two weeks after transplantation 11 of the 13 had developed warm anti-B antibodies against a panel of 30 lymphocyte donors, and in seven cases the antibodies reacted against more than half the panel (Table 2). All five of the rejections were in these latter seven antibody-producing recipients. One patient died 1 month after transplantation from acute pancreatitis.

4.2. Pretreatment for 4 Weeks or Longer

Fourteen consecutive cadaveric recipients, of whom four had preexisting warm antibodies, had the longer pretreatment of 26–58 days. After 2–6 months only one (7%) patient had a rejection (Table 1) and that one was so minor as to be equivocal. At the same time, the capacity to generate all categories of cytotoxic antibodies was remarkably reduced. Even though 4 of the 14 recipients already had warm antibodies predating TDD, these tended to diminish during pretreatment, and only 1 of the 14 possessed broad reacting warm antibodies 2 weeks posttransplantation (Table 2).

Two patients died, one from a virus infection after 7 weeks, and the other at 2 months from a massive lidocaine overdosage given inadvertently by her family physician.

5. Long-Term Implications

In these patients, it remains to be seen if a delayed immunologic rebound will cause major kidney losses after discontinuance of TDD. However, Walker,[30] Johnson,[7] and Niblack[14] and their associates have not seen a catch-up deterioration of grafts in patients followed 2–5 years after preoperative and postoperative TDD. Late stability after earlier TDD was also reported recently by Kaplan.[9] It seems likely that the poorly understood change in host–graft relationship that has made clinical transplantation practical will be expedited rather than hindered by properly timed TDD. If so, improvements in early graft survival should be translated into better long-term results.

6. Broader Implications

If the pretreatment principle delineated by the foregoing experience is valid, it will influence other developments and practices in transplantation.

6.1. Other Therapeutic Regimens

It would be surprising if host conditioning, equivalent to that of chronic TDD, could not be achieved with other means over a period of several weeks. An obvious possibility is mechanical removal of lymphocytes from the peripheral blood (lymphapheresis), a procedure for which commercial instrumentation is already available. We have treated two liver recipients and one kidney recipient in this way. The procedures of total lymphoid irradiation[25] and thymectomy are variations on the same theme. So would be pretransplantation conditioning with powerful antilymphocyte sera and globulins, an approach that has been made impractical in patients by immune reactions to the heterologous protein.[21] It is clear that a sufficiently long conditioning period will be required.

Today, for the first time in years, there is the real prospect of better drugs for core immunosuppression, of which cyclosporin A is the most promising, as Calne has reported. (cf. Chapter 50, this volume). The potential value of pretreating with cyclosporin (or other drugs) or alternatively of combining drugs with preoperative lymphoid depletion is obvious. With any such conditioning effort, the use of the battery of *in vitro* immunologic tests now available should permit the curves of preoperative immunodepression to be quantitated for individual patients.

We have in fact treated four patients with cyclosporin for 24–42 days following TDD. The convalescence of these patients has been remarkably uncomplicated. Within 1 or 2 days after transplantation, maneuvers were begun to discontinue the TDD. No steroids or azathioprine were given. It will be interesting to see if cyclosporin itself can be substituted for TDD in the pretreatment period.

6.2. Patient Selection and Histocompatibility

In the past, renal 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 cross match and, in most centers, to a lesser extent on HLA matching. With effective pretreatment by TDD, it has been possible to give weight to the recipient's wishes. Based on the antibody state, a rational decision has been possible about the duration of pretreatment and about the prospects for success without any consideration of tissue match. Once the TDD is instituted, the patient has been assured of transplantation and at a fairly predictable time. The ability to offer transplantation to cadaveric kidney recipients as an elective and planned undertaking has drastically changed our program. The numbers of consanguineous

transplants have dwindled to less than 10% of the total as the prospective recipients have perceived the improved cadaveric situation. The number of cases that can be handled by our fixed-bed unit has substantially increased (60 in the last 7 months), in spite of the time investment for pretreatment which is more than canceled by the ability to discharge patients earlier after a homograft has been placed.

6.3. Other Organs

Improvements in immunosuppression should be applicable for other organs including the liver and heart. The direct application of these findings in liver recipients may pose special problems. Lymph drainage in patients with hepatic disease tends to be voluminous, particularly if ascites is present. Recently, we were forced to perform a liver transplant after only 18 days of TDD because the amount of lymph obtained per day had reached 25 liters, a volume so great that fluid management was becoming difficult. It may be that many of the liver recipients can have safer lymphoid depletion by lymphapheresis or by other kinds of preoperative conditioning discussed earlier. Certainly, pretreatment will be a major factor in patient care as our liver transplant program reopens.

7. Summary

Pretreatment with TDD markedly influences early graft survival and virtually eliminates early rejection, provided that the lymphoid depletion is for at least 4 weeks. Such preoperative recipient conditioning has improved the quality of patient service. It is probable that the pretreatment principle can be applied effectively while using other immunosuppressive measures including drugs.

References

1. Archimbaud, J. P., Banssillan, V. G., Berhardt, J. P., Revillard, J. P., Perrin, J., Traeger, J., Carraz, M., Fries, D., Saubier, E. C., Bonnet, P., Brochier, J., and Zech, P., 1960, Technique, surveillance et interet de drainage du canal theracique, effectue en vue d'une transplantation renale, *J. Chir.* **98**:211.
2. Fish, J. C., Sarles, H. E., Tyson, K. R. T., Remmers, A. R., and Ritzmann, S. E., 1969, The immunologic consequences of lymph lymphocyte depletion, *Surg. Forum* **20**:268.
3. Franksson, C., 1964, Survival of homografts of skin in rats depleted of lymphocytes by chronic drainage from the thoracic duct, *Lancet* **1**:1331 (letter to editor).
4. Franksson, C., and Blomstrand, R., 1967, Drainage of the thoracic lymph duct during homologous kidney transplantation in man, *Scand. J. Urol. Nephrol.* **1**:128.
5. Franksson, C., Lundgren, C., Magnusson, E., and Ringden, O., 1976, Drainage of thoracic duct lymph in renal transplant patients, *Transplantation* **21**:133.
6. Ianhez, L. E., Verginelli, G., Sabbaga, E., and Campos Frere, J. G., 1974, Thoracic duct drainage in human kidney allotransplantation, *Rev. Bras. de Pesquisas Med. Biol.* **7**:265.

7. Johnson, H. K., Niblack, G. D., Tallent, M. B., and Richie, R. E., 1977, Immunologic preparation for cadaver renal transplant by thoracic duct drainage, *Transpl. Proc.* **9:**1499.
8. Jones, A. R., Vaughan, R. W., Bewick, M., and Batchelor, J. R., 1976, Transformation of lymphocytes from patients awaiting cadaver renal transplants, *Lancet* **2:**529.
9. Kaplan, M. P., 1979, Thoracic duct drainage—an overview, *Dial. Transpl.* **8:**781.
10. Machleder, H. I., and Paulus, H., 1978, Clinical and immunological alterations observed in patients undergoing long-term thoracic duct drainage, *Surgery* **84:**157.
11. Martelli, A., and Ronomini, V., 1970, Thoracic duct fistula in human kidney transplantation, in: *Pharmacological Treatment in Organ and Tissue Transplantation* (A. Bertelli and A. P. Monaco, eds.), p. 140, Williams & Wilkins, Baltimore.
12. Murray, J. E., Wilson, R. E., Tilney, N. L., Merrill, J. P., Cooper, W. C., Birtch, A. G., Carpenter, C. B., Hager, E. B., Dammin, G. J., and Harrison, J. H., 1968, Five years' experience in renal transplantation with immunosuppressive drugs: Survival, function, complications, and the role of lymphocyte depletion by thoracic duct fistula, *Ann. Surg.* **168:**416.
13. Newton, W. T., 1955, The biologic basis of tissue transplantation, *Surg. Clin. North Am.* **45:**393.
14. Niblack, G. D., Johnson, H. K., Richie, R. E., Gonzalez, L., Locke, J., and Jackson, D., 1975, Preformed cytotoxic antibody in patients subjected to thoracic duct drainage, *Proc. Dial. Transpl. Forum* **5:**146.
15. Opelz, G., and Terasaki, P. I., 1977, Significance of mixed leukocyte culture testing in cadaver kidney transplantation, *Transplantation* **23:**375.
16. Opelz, G., Mickey, M. R., and Terasaki, P. I., 1972, Identification of unresponsive kidney-transplant recipients, *Lancet* **1:**868.
17. Sarles, H. E., Remmers, A. R., Jr., Fish, J. C., Canales, C. O., Thomas, F. D., Tyson, K. R. T., Beathard, G. A., and Ritzman, S. E., 1970, Depletion of lymphocytes for the protection of renal allografts, *Arch. Intern. Med.* **125:**443.
18. Sonoda, T., Takaha, M., and Kusunoki, T., 1966, Prolonged thoracic duct lymph drainage: Application for human homotransplantation, *Arch. Surg.* **93:**831.
19. Starzl, T. E., 1964, *Experience in Renal Transplantation*, pp. 131–138, Saunders, Philadelphia,
20. Starzl, T. E., Marchioro, T. L., and Waddell, W. R., 1963, The reversal of rejection in human renal homografts with subsequent development of homograft tolerance, *Surg. Gynecol. Obstet.* **117:**335.
21. Starzl, T. E., Porter, K. A., Iwasaki, Y., Marchioro, T. L., and Kashiwagi, N., 1967, The use of antilymphocyte globulin in human renal homotransplantation, in: *Antilymphocytic Serum* (G. E. W. Wolstenholme and M. O'Connor, eds.), pp. 4–34, Churchill, London.
22. Starzl, T. E., Koep, L. J., Weil, R., III, Halgrimson, C. G., and Franks, J. J., 1979a, Thoracic duct drainage in organ transplantation; will it permit better immunosuppression? *Transpl. Proc.* **11:**276.
23. Starzl, T. E., Weil, R., III, Koep, L. J. McCalmon, R. T., Jr., Terasaki, P. I., Iwaki, Y., Schroter, G. P. J., Franks, J. J., Subryan, V., and Halgrimson, C. G., 1979b, Thoracic duct fistula and renal transplantation, *Ann. Surg.* **190:**474.
24. Starzl, T. E., Weil, R., III, Koep, L. J., Iwaki, Y., Terasaki, P. I., and Schroter, G. P. J., 1979c, Thoracic duct drainage before and after cadaveric kidney transplantation, *Surg. Gynecol. Obstet.* **149:**815.
25. Strober, S., Slavin, S., Fuks, Z., Kaplan, H. S., Gottlieb, M., Bieber, C., Hoppe, R. T., and Grumet, F. C., 1979, Transplantation tolerance after total lymphoid irradiation, *Transpl. Proc.* **11:**1032.
26. Terasaki, P. I., Bernoco, D., Park, M. S., Ozturk, G., and Iwaki, Y., 1978, Microdroplet testing for HLA-A, -B, -C and -D antigens, *Am. J. Clin. Pathol.* **69:**108.
27. Thomas, F., Mendez–Picon, G., Thomas, J., and Lee, H. M., 1977, Quantitation of pretransplantation immune responsiveness by *in vitro* T-cell testing, *Transpl. Proc.* **9:**49.
28. Tilney, H. L., Atkinson, J. C., and Murray, J. E., 1970, The immunosuppressive effect of thoracic duct drainage in human kidney transplantation, *Ann. Intern. Med.* **72:**59.

29. Traeger, J., Touraine, J.–L., Archimbaud, J.–P., Malik, M.–C., and Dubernard, J.–M., 1978, Thoracic duct drainage and antilymphocyte globulin for renal transplantation in man, *Kidney Int.* **13**(suppl. 8):103.
30. Walker, W. E., Niblack, G. D., Richie, R. E., Johnson, H. K., and Tallent, M. B., 1977, Use of thoracic duct drainage in human renal transplantation, *Surg. Forum* **28:**316.
31. Wilson, W. E. C., and Kirkpatrick, C. H., 1964, Immunologic aspects of renal homotransplantation, in: *Experience in Renal Transplantation* (T. E. Starzl, ed.), pp. 239–245, Saunders, Philadelphia.