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THE PRETREATMENT PRINCIPLE IN RENAL TRANSPLANTATION AS ILLUSTRATED BY THORACIC DUCT DRAINAGE*

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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 70's, less than half of the recipients of first cadaver kidneys were able to boast of graft function by the end of the first postoperative year. One reason may be neglect of what we have been calling the forgotten pretreatment principle. It is that subject which we will discuss today, with particular emphasis on thoracic duct drainage (TDD).

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. After transplantation, the patients previously classified as non-responders had a mean rejection time of 14.8 days, compared to 4.3 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...".

Almost a decade later, the prognostic implication of the reactor versus non-reactor state of kidney recipients was re-emphasized by the antibody studies of Opelz, Mickey and Terasaki (15). More recently, Jones et al. (8), Thomas et al. (27) and Opelz and Terasaki (16) came to the same conclusion from the results of *in vitro* phytohemagglutin, concanavalin A and mixed lymphocyte culture (MLC) tests of which all are expressions of T-lymphocyte reactivity. The MLC

studies (16) 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 to 10 days before transplantation. The practice was based upon analogous canine experiments in which average homograft survival was thereby doubled 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 drifted into the practice of starting therapy on the day of grafting.

THORACIC DUCT DRAINAGE AND THE PRETREATMENT PRINCIPLE

The immunosuppressive procedure of thoracic duct drainage (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. Thoracic duct drainage was given a trial in several centers 5 to 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.

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 with azathioprine, prednisone and sometimes ALG (20, 23). The protocol was similar to that usually used by Franksson (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 non-transplantation patients established that a pronounced immunodepressive influence of TDD was not established until about three weeks and that this effect deepened for another week or so. Kidneys in our early TDD series were being rejected during this uncovered three or four 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).

Pretreatment with Thoracic Duct Drainage (TDD)

Realizing 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 three weeks' preparation with TDD. Those possessing warm antibodies were scheduled for 35 days. If anti-T antibodies persisted and reacted against the potential donors, it was shown earlier (23) that a low titer was necessary before proceeding in the fact of a positive crossmatch. After 35 days, acceptance was recommended of cadaver donors whose positive crossmatches were due to other kinds of antibodies.

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.

Pretreatment of Three Weeks. Thirteen consecutive cadaver recipients of whom only one had pre-existing warm anti-B antibodies had preoperative TDD for 17 to 28 days. The therapeutic approach is illustrated in Figure 1. During the pretreatment period, the numbers of collected lymphocytes always fell markedly. After transplantation, the TDD was maintained for at least three more weeks.

During follow-ups of two to six 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 of the panel (Table 2). All five of the rejections were in these latter seven antibody-producing recipients. One patient died one month after transplantation from acute pancreatitis.

Pretreatment for Four Weeks or Longer. Fourteen consecutive cadaveric recipients, of whom four had pre-existing warm antibodies, had the longer pretreatment of 26 to 58 days. After two to six months only one (7%) patient had a rejection (Table 2) 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 four of the 14 recipients already had warm antibodies predating TDD, these tended to diminish during pretreatment and only one of the 14 possessed broad reacting warm antibodies two weeks post-transplantation (Table 2).

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

Long-Term Implications

In these patients, it remains to be seen if a delayed immunologic rebound will cause major kidney losses after discontinuance of thoracic duct drainage. However, Walker (30), Johnson (7), and Niblack (14) and their associates have not seen a catch-up deterioration of grafts in patients followed two to five years after pre- and postoperative TDD. Late stability after earlier TDD was also reported recnetly 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 thoracic duct drainage. If so, improvements in early graft survival should be translated

into better long-term results.

BROADER IMPLICATIONS

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

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 (lymphaphoresis), 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 (22). 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 is the most promising as Calne will tell us today. 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 following thoracic duct drainage (TDD) for 24 to 42 days. The convalescence of these patients has been remarkably uncomplicated. Within one or two 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.

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 crossmatch 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 upon 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 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 which can be handled by our fixed bed unit has substantially increased (60 in the last seven months), in spite of the time investment for pretreatment which is more than cancelled by the ability to discharge patients earlier after a homograft has been placed.

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 lymphaphoresis or by other kinds of preoperative conditioning discussed earlier. Certainly, pretreatment will be a major factor in patient care as our liver program reopens.

SUMMARY

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

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ILLUSTRATION

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 (see text). The marked drop in lymphocytes removed during the pre-transplantation 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 (20, 23). The postoperative retention of TDD for about three weeks is still our policy. The patient who is now more than seven months after transplantation has had no evidence of late rejection.

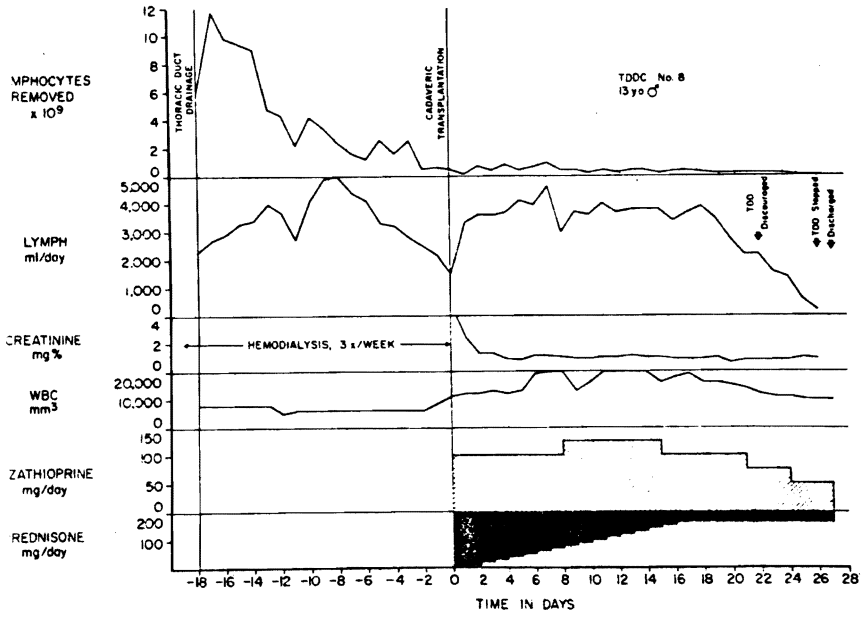

TABLE 1: REJECTION IN FIRST TWO MONTHS OF CADAVER KIDNEYS: INFLUENCE OF THORACIC DUCT DRAINAGE*

	% REJECTION		
	Contemporaneous TDD (17)**	Three Weeks Pretreatment With TDD (13)	≥ Four Weeks Pretreatment With TDD (14)
Incidence Rejection	41%	38%	7%
Irreversible Rejection	24%	8%	0%
Deaths	0	1	2

* In 50 immediately precedent cadaveric recipients treated with azathioprine, prednisone and sometimes ALG, the incidence of early rejection was 48% (20).

** Data from (20).

TABLE 2: BROADLY REACTING* WARM ANTI-B LYMPHOCYTE ANTIBODIES

TWO WEEKS AFTER TRANSPLANTATION

TDD Pretreatment for Three Weeks	7/13
TDD Pretreatment ≥ Four Weeks	1/14

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