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situations makes it essential that all surgeons be familiar with this excellent technique.

McLoughlin MG, Williams GM: J Urol 114:527, 1978, Schweizer RT, Bartus SA, Khan CS: J Urol 117:125, 1977, and Karmi SA, Dager FJ, Ranos E, Young JD Jr: Urology 11:380, 1978

The above three papers are included to make the reader aware of the many and varied causes of late ureteric obstruction. Late perirenal lymphocele, rejection fibrosis, and obstruction caused by the spermatic cord are the factors described.

Castro JE, Mustapha N, Mee AD, Shackman R: Br J Urol 47:603, 1975, and Lenitt SB, Caberwal D, Kogan SJ, Ronas NA, Hardy MA: Urology 13:377, 1979

These two papers stress that in the presence of uncorrectable abnormalities of the lower urinary tract, it is feasible and compatible with long-term graft function to divert the urine into an intestinal conduit or a pre-existing cutaneous ureterostomy.

Lucas BA, McRoberts JW, Curtis JJ, Luke RG: J Urol 121:156, 1979

These authors describe two techniques of ureteroneocystostomy, one of which provides an antireflux mechanism. However, although the importance of reflux in long-term graft failure remains unconfirmed, it is desirable, where possible, to employ a technique or ureteroneocystostomy that will, in the majority of patients, prevent reflux.

OVERVIEW: NEW PROCEDURES IN RENAL TRANSPLANTATION: IMPROVED QUALITY OF LIFE

Richard Weil III and Thomas E. Starzl

The articles in Chapters 12 to 15 were originally published between 1971 and 1979. The most recent of the four (Chapter 12, published in 1979) summarizes the state of the field at that time; the other three articles describe technical aspects of bilateral nephrectomy in transplant recipients, donor nephrectomy in living related kidney donors, donor nephrectomy in cadaver kidney donors, and ureterovesical anastomosis with intravesical and extravesical approaches.

These clinical and technical articles are useful for urologists and for all surgeons who do kidney transplants. The four commentaries, with annotated bibliographies, provide meaningful perspective on the four primary subjects. Although our practices in Denver vary from those of the authors in a number of details (*e.g.*, we do not require pretransplant coronary angiography for all patients of a certain age, we do recipient nephrectomies through an anterior and usually transperitoneal approach, we have usually done pretransplant splenectomy for leukopenia associated with hypersplenism, and we remove cadaver donor kidneys with single vessels individually rather than *en bloc*), we nevertheless regard the principles and the methods described in the preceding articles and commentaries as sound and effective.

During the last 2 years, surgeons performing clinical kidney transplantation, for the first time in more than 10 years have begun to realize the possibility of improving the quality of patient service, which has been long awaited but equally long delayed by lack of improvement in immunosi

Until very recently, the basic tools of immunosuppression have been those defined in the early and middle 1960s, in Denver as well as elsewhere: corticosteroids, azathioprine, and sometimes an antilymphocyte (ALG) or antithymocyte (ATG) globulin.[1] In the United States, for many years the 1-year function of first cadaver kidney grafts has been essentially fixed at approximately the 50% mark in most centers, even with the use of ATG, although a few institutions with especially potent globulins have been able to exceed this unsatisfactory record.[2-5] A quantum improvement in the result of kidney transplantation, particularly cadaver kidney transplantation, has been made to wait for improvements in the immunosuppressive tools, so that better graft survival could be achieved without increased risk of mortality.[6]

Successful kidney transplantation, for most patients, offers a better quality of life than chronic hemodialysis. A minority of patients have a living relative who can donate a kidney for transplantation; therefore, any real upgrading of the service offered by kidney transplantation must have as its centerpiece improved graft and patient survival in cadaver kidney transplantation.

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There are now on the horizon at least five areas of applied immunology that are likely to have strong impact on kidney transplantation and, singly or in combination, to enable cadaver kidney homotransplantation with a high probability of success and a low probability of debilitating side-effects.

HISTOCOMPATIBILITY TESTING

For 15 years, since the introduction of clinical histocompatibility testing, it has been hoped that this tool would make it possible to provide each kidney transplant recipient with a well enough matched graft that only small amounts of immunosuppressive agents would be needed to achieve satisfactory kidney function. However, in the United States the HLA matching system has been disappointing in its ability to predict outcome after cadaver transplantation.

In a recent large survey of more than 100 North American transplant centers with data on 6226 primary cadaver kidney transplants, the 1-year kidney graft function was 51%, with 0–1 mismatched HLA antigens and 43% with 4 mismatched HLA antigens.[7] This small (8%) difference, and only a 51% success rate with well-matched kidneys, illustrates the extremely limited value of HLA matching in a highly outbred population that depends on azathioprine and corticosteroids as the main immunosuppressive agents.

It is possible that a relatively newly defined HLA locus, the HLA–DR locus, may prove to correlate more closely with cadaver graft outcome than the longer established HLA–A and HLA–B loci. The HLA–DR locus is thought to reflect cellular immunity more than humoral immunity, and the HLA–DR matching could therefore is expected to reflect cellular immune differences between kidney recipient and donor. Preliminary data indicate that there is some correlation between matching at least one HLA–DR antigen and cadaver transplant function; however, more experience with this method is necessary before any broad conclusions about its efficacy can be drawn.[8]

Improvements in the characterization of cytotoxic antibodies have made possible more accurate direct crossmatching between recipient and donor with identification of false-positive results. Ayoub and colleagues have demonstrated that recipient anti-B-lymphocyte antibodies will not cause hyperacute rejections and do not contraindicate transplantation even when specifically directed against donor B-lymphocyte antigens.[9] The presence of cold anti-B-lymphocyte antibodies before transplantation has, in fact, been associated with a more favorable prognosis than the absence of cytotoxic antibodies.[10] These cold anti-B-lymphocyte antibodies appear to be enhancing antibodies, and their induction may, in the future, become a method for preconditioning recipients in order to increase the probability of successful transplantation.

BLOOD TRANSFUSIONS

Opelz and Terasaki have demonstrated in a large retrospective study of 1852 patients that increasing numbers of packed red blood cell (RBC) transfusions, given before transplantation, increase first cadaver kidney survival at 1 year; with no transfusions the 1-year graft function was 41%, whereas with more than 20 transfusions, it was 75%.[11] The risk of this method, however, is that elective blood transfusions may, in some patients, produce such high titers of cytotoxic antibodies that transplantation for those individuals may no longer be possible. Salvatierra and associates recently transfused 45 candidates with 1-haplotype-identical related kidney donors; each recipient received 3 infusions of 250 ml of blood from that individual's prospective related donor in preparation for related transplantation. Thirteen (29%) of these 45 patients developed such high titers of cytotoxic antibodies that related transplantation was no longer considered safe and was not carried out. Of the 30 patients who did receive related grafts after the transfusions, 29 had excellent results.[12] Elective blood transfusion is therefore capable of improving the results of transplantation, but this improvement may also decrease the probability of successful transplantation in those individuals who develop cytotoxic antibodies in response to the transfusions.

TOTAL LYMPHOID IRRADIATION

Pretransplantation total lymphoid irradiation (TLI) was shown by Slavin and colleagues to provide effective and specific immunosuppression in rats. This central lymphoid irradiation is delivered through ports that are similar in design to the radiotherapy sometimes given for Hodgkin's disease and is safer than total body irradiation (TBI). In the rats, using pretransplantation TLI combined with infusions of donor bone marrow, Slavin and co-workers induced acceptance of heart and skin homografts from the animal that had donated the bone marrow, without ablating the recipient animal's ability to respond immunologically to grafts from third-party donors.[13] This form of pretreatment is currently being evaluated in patients at the University of Minnesota.*

THORACIC DUCT DRAINAGE

The fourth recent direction in applied immunology for transplantation, thoracic duct drainage, is an approach that was abandoned by most of the centers that had previously employed it until a new technique, with a double lumen catheter and heparin instillation, was described in 1978 by Machleder and Paulus of the University of California at Los Angeles (UCLA).[14] The procedure had previously been technically unreliable in a majority of patients. In 1978, in Denver, Koep and associates developed a modification of the UCLA thoracic duct drainage method,[15] which has permitted effective thoracic duct drainage in more than 90% of patients, including small children. Sixty-five primary cadaver kidney transplant recipients received thoracic duct drainage between April 1978 and December 1979, with follow-up study of 6–26 months to date. Twenty-five patients began their thoracic duct drainage at the time of transplantation, 18 patients had thoracic duct drainage pretreatment for fewer than 28 days before transplantation, and 22 patients had thoracic duct drainage pretreatment for 28 or more days before transplantation. The results in these cases have been reported, and continuing follow-up has confirmed our impression that at least 28 days of thoracic duct drainage

* Najarian JS: Personal communication.

pretreatment are necessary for the procedure to have maximum benefit.[16] The actuarial 1-year patient survival in the group of patients who received at least 28 days of thoracic duct drainage pretreatment is 82%, and the actuarial 1-year cadaver–graft survival is 73%.

Although thoracic duct drainage is safe and effective if carried out for at least 28 days before, as well as for a short time after, transplantation, the procedure requires an additional operation and an additional period of hospitalization. During the last 6 months we in Denver have therefore been working with a new pharmacologic agent in an effort to provide improved patient service without the necessity for additional hospitalization or operation.

CYCLOSPORIN A

Cyclosporin A, a polypeptide, is extracted from a fungus by the Sandoz Company of Basel, Switzerland. The initial clinical trials were carried out by Calne and colleagues at Cambridge, England.[17] In Denver, during the last 6 months, 36 patients received cadaver kidney transplants with Cyclosporin A immunosuppression. All these patients also received corticosteroids, but in smaller amounts than in the past, when azathioprine and prednisone were the immunosuppressive agents. Eleven of the patients received thoracic duct drainage as well as Cyclosporin A and corticosteroids; 25 patients were treated with Cyclosporin A and corticosteroids without thoracic duct drainage. Two of those 36 patients have died: 1 of pneumonia, and one of hemorrhage after coronary artery bypass, 6 weeks after transplantation, with a normal kidney transplant. Two kidneys have been rejected. Not all the kidney transplants are functioning normally, but 32 of the 36 patients (89%) currently have transplants that can sustain life without dialysis. We are optimistic about the long-term effectiveness of Cyclosporin A as an immunosuppressant for transplantation.[18]

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The 17½ years since the first kidney homograft was done in Denver have been characterized by short periods of application of new technologies to improve results, followed by longer periods of consolidation of gains. During the 1970s, the main obstacle to providing patients with better transplantation undoubtedly was unsatisfactory immunosuppression.

In the 1980s, the development of more effective and less toxic immunosuppression appears more probable than at any previous time. This probability carries with it the hope that kidney transplant patients, including those without living–related donors, will be able to look forward to long lives that are not threatened by the morbid side effects of corticosteroids.

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