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Principles of Whole Organ Transplantation

THE EVOLUTION of whole organ transplantation has been one of the most remarkable chapters in the history of medicine and one of the least expected. In 1961, the Nobel Laureate Burnet wrote in the *New England Journal of Medicine* that "... much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success. . . ."⁶ This pessimistic view was published scarcely more than a year before the avalanche of successful clinical renal transplantations in 1962 and 1963 that extended such procedures beyond the seemingly exotic identical and fraternal twin cases of the mid and late 1950s.

The principles of whole organ transplantation were developed with the simple kidney model. However, it was natural that transplantation technology would be applied to the grafting of other organs, including the liver, heart, lung, heart plus lung, pancreas, spleen, and intestines. In this chapter, we will examine the ingredients of these astonishing developments during the last two decades, speculate about how the momentum of this progress can be sustained and accelerated, and point out how transplantation technology is apt to influence pediatric surgery in the years ahead. In so doing, we will consider immunosuppression, tissue matching, and organ procurement (and preservation) in that order. The surgical technique for specific organ transplantations is discussed in other chapters.

Immunosuppression

Immunosuppression is the unique feature of whole organ transplantation. In describing the first successful case of identical twin transplantation in 1956, Merrill et al.³⁰ wrote, "Tissue transplantation including that of a functioning kidney appears to be a feasible procedure in identical twins, but to date successful per-

manently functioning homografts appear to be limited to such individuals." The statement reflected acceptance of Medawar's²⁵ thesis that rejection was an immunologic phenomenon as well as an acknowledgment that there was no known way to prevent this process.

Therapeutic Beginnings

Yet by 1960, the possibility of weakening the recipient immune process with corticosteroids,⁴ total body irradiation,^{14, 25} or the cytotoxic drug 6-mercaptopurine^{7, 46} or its imidazole derivative, azathioprine,⁸ had been established in animals. Sporadic attempts to use these techniques for renal homotransplantation in humans were so unsuccessful^{33, 34, 80} that it was widely thought that the immunosuppression requisite to prevent rejection would inevitably lead to immunologic invalidism and lethal infections.

Double-Drug Therapy

Renal transplantation became a practical reality in 1962 and 1963 with the marriage of corticosteroid therapy (prednisone or prednisolone) to baseline therapy with azathioprine (Table 38-1).^{49, 61} The use of this synergistic drug combination, which quickly found its way into the other principal transplantation centers of the day,¹⁹ permitted fundamental observations to be made, including the fact that rejection was a reversible process.⁶¹ With the passage of time after the operation, a change in the relation between the graft and the host often occurred, permitting eventual reduction of drug doses.^{49, 61} Patients who did not require chronic high-dose corticosteroid therapy to retain their grafts could return to useful social and vocational function and without the fear of immunologic invalidism. The double-drug therapy with azathioprine and prednisone remained the gold standard of transplantation for many years.

TABLE 38-1.—CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION AND USED FOR OTHER ORGANS

AGENTS	YEAR DESCRIBED AND REPORTED	PLACE	DEFICIENCIES	USED FOR EXTRARENAL TRANSPLANTATION
Azathioprine	1962 ^{33, 34}	Boston	Ineffective, dangerous	No
Azathioprine-corticosteroids	1963 ^{49, 61}	Denver	Suboptimal	Yes
Thoracic duct drainage as adjunct	1963 ^{17*}	Stockholm	Nuisance; requires 20-30 days pretreatment	Yes
ALG† as adjunct	1966 ⁵⁹	Denver	Still suboptimal	Yes
Cyclophosphamide substitution for azathioprine	1970 ⁶³	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total lymphoid irradiation	1979 ^{35, 68}	Palo Alto, Calif., Minneapolis	Dangerous; extensive preparation; not quickly reversible	No
Cyclosporine alone	1978-79 ⁹	Cambridge, England	Suboptimal	Yes
Cyclosporine-Corticosteroids	1980 ⁶⁴	Denver	Under evaluation	Yes

*It was not realized until much later that pretreatment for 3-4 weeks before transplantation was a necessary condition.⁶⁵
†Antilymphocyte globulin.

Triple-Drug Therapy

Changes made during the next 16 years (see Table 38-1) consisted of modifications of, or additions to, the original double-drug treatment. Most of the modifications were designed to blunt the attack of the lymphocytes, which had been recognized as the mediators of rejection. The most significant addition was the use of antilymphocyte globulin (ALG) as an adjunct to azathioprine and prednisone.⁵⁹ The ALG consisted of antibodies against human lymphoid tissue, which were raised in horses, rabbits, goats, or other animals by immunizing them to human lymphocytes. When thymic lymphocytes were used for immunization, the product was called antithymocyte globulin (ATG). The antibody-containing globulin was extracted, purified, and made ready for intramuscular or intravenous use.

The use of the ALG or ATG was limited to the first few post-operative weeks or months, because the foreign animal globulin evoked an immune response from the treated patients, manifested as immune elimination of the globulin or, worse, anaphylactic and other dangerous immunologic side effects. Nevertheless, an improved quality of immunosuppression was obtained by adding ALG to azathioprine and prednisone.^{37, 59} In recent years, there has been much interest in using ALG for the specific indication of rejection. It was shown 15 years ago that ALG could rescue rejecting kidney and liver grafts in dogs many days after transplantation as effectively as if ALG treatment had been used from the outset,⁵⁰ and this concept has been the basis of many successful clinical trials.⁶⁷

In spite of its great potential value, ALG has not been universally employed as a part of the antirejection armamentarium because of several limiting features noted in Table 38-2, including the fact that the globulin has been in no sense a standardized agent. The problems with standardization could be eliminated with the new hybridoma technology introduced by Kohler and Milstein.²³ With hybridoma cells injected into the peritoneum of mice, a homogeneous (monoclonal) antihuman-lymphocyte antibody can be produced. Therapy with monoclonal antibodies was introduced into clinical medicine by Cosimi et al.,¹² who administered the so-called OKT3 antibodies, which selectively deplete T-lymphocytes and cause lymphopenia. The objective was to reverse kidney graft rejection that was nonresponsive or poorly responsive to corticosteroid therapy. The features of the OKT3 antibodies are summarized in Table 38-2, including the side reactions.

The possibility that a safer and more specific kind of mono-

clonal antibody can be developed was raised in a recent report by Takahashi et al.⁶⁹ They described a new kind of mouse monoclonal antibody (see Table 38-2) derived from independent hybridomas and directed against lymphoid blast cells of the kind that invade grafts. In animals and in preliminary clinical trials in Japan,⁶⁹ these putative CBL antibodies have consistently reversed established renal homograft rejection without causing lymphopenia or any toxic manifestations. The features of the CBL antibodies are summarized in Table 38-2. The blast cell specificity is explained by the nature of the immunogen. Spleen cells from Balb/C mice immunized three times against human leukemia cell lines are removed and fused with myeloma cells; 10,000,000 hybridoma cells are injected intraperitoneally in mice, and the monoclonal antibody-rich ascites is harvested in 2-3 weeks.

It will be surprising if monoclonal ALG does not play an important role in immunosuppressive practice in the future. Less discriminating techniques of lymphoid depletion have been used clinically in the last two decades (see Table 38-1), including thymectomy,⁴⁹ splenectomy,⁴⁹ total lymphoid irradiation,^{35, 68} and thoracic duct drainage (TDD).^{17, 65} These have been virtually abandoned, largely because of their inconvenience, dangers, unproved value, or various combinations of these factors.

For a number of years, it was considered that azathioprine was the one essential drug upon which effective immunosuppression depended. This dogma was overthrown by the demonstration in 1970 that cyclophosphamide, the commonly used cancer chemotherapeutic agent, could be freely substituted for azathioprine.⁶³ In an academic sense, this was an important observation, because cyclophosphamide had been thought to be an anti B-lymphocyte drug, whereas azathioprine was thought to have considerable T-lymphocyte specificity. From a practical point of view, cyclophosphamide was no better than azathioprine, and because its side effects were substantial, its use has been restricted to substitution for azathioprine for the indication of idiosyncratic reactions to the latter drug.

Years of Consolidation (1963-1980)

The results obtainable with the immunosuppression techniques available by 1963 represented a quantum leap from a zero potential of renal transplantation to a broadly applicable procedure. Almost from the beginning, using the original double-drug therapy, it was possible to obtain a 70% 1-year graft survival after intrafamilial transplantations without good histocompatibility

TABLE 38-2.—KINDS OF ALGs

	CONVENTIONAL ALG* OR ATC† ^{37, 50, 59, 67}	OKT3 MONOCLONAL ¹²	CBL MONOCLONAL ⁶⁹
Standardized	No	Yes	Yes
Target cells	All lymphocytes	T-lymphocytes	Immunoblasts invading grafts
Amount heterologous protein injected in adult/day	500-1,000 mg	5 mg	5 mg
Irrelevant antibodies	99%	50%	< 50%
Lymphopenia	Usual	Invariable	Never
Chills, fever	Common	Invariable	Never
Antiforeign protein antibodies evoked in patient	Yes	Yes	Expected
Rejection reversal incidence	65%	88%	89%

*Antilymphocyte globulin.
†Antithymocyte globulin.
‡The conclusions about CBL antibodies have not yet been confirmed.

matching.^{49, 61, 66} With the use of triple-drug regimens (which had in common the lymphoid depleting procedures), the 1-year related graft survival could be pushed up to 85% or higher.^{37, 59, 66}

The limitations of all of the aforementioned kinds of immunosuppression were most clearly exposed when nonrelated donors (for the most part cadavers) were used.⁶⁶ The United States' national expectations of cadaver renal graft survival were shown by Opelz et al.³⁸ and by others²⁷ to be in the 50% range, even in recent times. The main achievement until 1980 was the reduction in patient mortality, which in part resulted from return of many patients to dialysis in the event of a graft rejection. Very low patient mortality was reported by centers that followed the philosophy of giving up kidneys early if complications ensued, but 1-year cadaver kidney graft survivals were reported as low as 40%.⁷⁵ Others with cadaver graft survival as high as 60% or 65% reported an exceptionally high patient mortality.³⁷ What was being done was to delineate the biologic limitations of the so-called conventional techniques of immunosuppression available at those times. These limitations were so extreme that transplantation of other cadaver organs such as the liver, heart, lung, and pancreas remained unpredictable and experimental.

It has been shown by Opelz et al.³⁹ and Terasaki and his associates⁷³ that graft survival after cadaver kidney transplantation can be improved by preparing the recipient with whole blood transfusion. It is possible that some kind of accidental enhancement is thereby achieved. However, part of the explanation of this effect is that patients with a high capacity of immunologic response are sensitized by multiple transfusions and develop wide reacting antibodies that preclude consideration for renal transplantation, because donors who have a negative cross-match with such recipients can no longer be found. The result is to exclude selectively such unfavorable candidates from the recipient pool. As many as a third of multiple transfused recipients can follow this tragic pathway. For this reason, many renal transplant surgeons have been opposed to the transfusion preparation, but its wide use has contributed to the growing numbers of non-transplantable patients who have become a burden in all active renal dialysis programs. For potential recipients of extrarenal organs, such deliberate preparation by transfusion is even less acceptable. An example would be a potential cardiac recipient for whom the option of artificial organ support analogous to dialysis does not exist. Accidental sensitization by blood transfusions with consequent antibody formation and the inability to find a donor would eliminate consideration of transplant candidacy. Thus, recipient preparation with transfusions is not a satisfactory means to improve graft survival.

The watershed year for improved organ transplantation was 1978. In that year, there were at least three possible ways in which it was envisioned that immunosuppression could be improved. One was with TDD as an adjunct.⁶⁵ A second possible new technique was with total lymphoid irradiation,^{35, 68} a procedure upon which we will spend little time, because it has been largely abandoned (see Table 38-1). The third possibility of improving the prospects of transplantation was with an interesting drug then called cyclosporin-A (now cyclosporine). Many great expectations of transplantation for the future rest with cyclosporine.

The Cyclosporine Era

Cyclosporine is a fungus extract that was discovered and characterized to an unusually complete degree by scientists of the Sandoz Corporation in Basel, Switzerland. The basic immunologic studies were performed by Borel et al.,⁵ who proved the impressive immunosuppressive qualities of this agent in a num-

ber of autoimmune models in rodent experiments as well as with skin homografts in mice. The first clinical trials with cyclosporine for solid organ transplantation were undertaken by Calne and his associates⁹ at Cambridge in the middle of 1978. From their efforts came one of the most important publications in the history of transplantation.

Their article contained both good and bad news.⁹ The good news was that transplantation of a number of cadaver kidneys and a few livers and pancreases had been carried out successfully without any corticosteroid therapy. This was an achievement never before consistently attainable with any other single agent. The bad news was that there had been an unacceptably high patient mortality, that three of the 34 recipients whose cases were reported had developed lymphomas, and that none of the kidney recipients had achieved normal renal function. Thus, the report was tantalizing, but its publication just before the first clinical trials in the United States were scheduled created great pressure to abort the American trials. Two trials were nevertheless undertaken. One restricted cyclosporine to the first 2 post-operative months, after which it was replaced by azathioprine.¹⁰ The results were not satisfactory.

At the University of Colorado, a full-scale trial proceeded.⁶⁴ In the Colorado trial (since transferred to Pittsburgh), it was realized at once that cyclosporine could not prevent rejection systematically when used alone, and that the optimal exploitation of the drug would require ancillary treatment with corticosteroids.⁶⁴ Although the treatment schedules were not fully standardized at that time, the 1-year primary cadaver graft survival in the pilot trials at Colorado was nearly 80%.⁵⁷ In the following year, a randomized trial comparing cyclosporine-corticosteroid therapy with therapy by azathioprine and prednisone was carried out. A 1-year graft survival in the experimental group was 90% vs. the expected 50% in the "controls."⁴⁵

The patterns of convalescence that could be expected after cadaver renal transplantation under cyclosporine-corticosteroid therapy were clearly delineated, and algorithms were developed to guide therapy.⁵¹ The kinds of convalescence that could be expected were divided into Class 1 (good graft function and no secondary deterioration), Class 2 (initial graft function with later deterioration), and Class 3 (anuria from the outset). Each of these kinds of recovery required a different approach to immunosuppression, in which the main maneuverability was by adjustments of the corticosteroid doses. The details of the treatment plan are beyond the scope of this chapter. Suffice it to say, with the appropriate attention to details of cyclosporine-corticosteroid management, cadaver renal transplantation became overnight a spectacularly successful way of treating end-stage renal disease.

An extremely important additional observation with cyclosporine-corticosteroid therapy has been that cadaver kidney retransplantation has been two or three times more successful than in the past with conventional immunosuppression, and with a patient mortality that has been less than 5%. With this latter observation, the temptation has been removed to overtreat recipients of primary kidney grafts who are having difficulties with unusually severe or persistent rejection. In such cases, the graft should be written off and removed, realizing that the patient has essentially as good a chance after retransplantation as on the original occasion.

The major improvements in renal transplantation made possible with cyclosporine-corticosteroid therapy will necessitate a revision of the strategies and policies of renal transplantation that have slowly evolved over the years. First, the widespread use of living related donors, which has been justified in the past on the basis of results better than those with cadaver transplantation, will become obsolete. There have been a number of donor deaths throughout the world after living related transplantation,

probably about 20 in total. This is a very small fraction of the total number of living related donors, but any mortality represents a penalty, however small, that is no longer justified if equivalent results can be obtained using cadaver kidneys.

Second, tissue typing, which in nonrelated cases has never been a major factor in donor selection (at least with matching at the A and B loci), will be even less important. In the trials of cadaver transplantation under cyclosporine-corticosteroid therapy, the donor-recipient matching was random or nearly so and, consequently, the matches at the A, B, and D_r loci were uniformly bad. This indicated the ability of cyclosporine-corticosteroid therapy to override histoincompatibility and other potentially adverse immunologic factors to an extraordinary degree (see later section).

However, cyclosporine-corticosteroid therapy cannot prevent the hyperacute rejection of kidneys that is mediated by preformed cytotoxic recipient antibodies (see later). This means that antibody analysis of recipient sera and donor-recipient cross-matching will be as important as ever, and perhaps more so. Poor-risk patients, including diabetics, will become increasingly more attractive candidates, because they can be treated without the penalties of chronic high-dose corticosteroid therapy.

The interface between dialysis and transplantation will become altered in future years, a point of particular importance in countries like the United States in which both of these alternative kinds of therapy are so well developed.

Extrarenal Whole Organ Transplantation

To fully exploit the advances in immunosuppression, even for kidney transplantation, will require an increased supply of organs, which each region will have to generate on behalf of its own citizens. The importance of a supply of cadaver donors extends far beyond the field of nephrology. The application of what has been learned about immunosuppression to the transplantation of cadaver organs other than the kidney has been a natural event,⁵⁵ as will be emphasized in subsequent chapters, and one that is certain to change the character of pediatric surgery.

Special Considerations in Children

When clinical renal transplantation was made feasible in 1962 and 1963 by the combined use of azathioprine and prednisone,^{49, 61} there were expressions of concern about subjecting children to such drastic therapy.⁴⁴ However, the first report of consistent success in treating infants and children^{49, 58} was promptly confirmed,^{16, 18, 36, 79} although acceptable results were obtained only with consanguineous donors. A number of special pediatric transplantation centers were established^{24, 26, 43} at which there usually has been a major effort to find genetically related donors. Failure to do so, and consequent transplantation of cadaver kidneys, has been associated with a higher incidence of graft loss, death, and unacceptable morbidity from chronic high-dose corticosteroid therapy. With organs such as the liver and heart, there has been no option but the cadaver donor. Major progress in cadaver transplantation was stalled for almost two decades, despite efforts at tissue typing, better understanding of rejection, and the modest improvements in immunosuppression summarized in Table 38-1 up to the cyclosporine era. The inhibition of normal growth in infants and children, whose maintenance corticosteroid requirements were high, was a special source of concern.

When cyclosporine was first tested, it was not available for evaluation in patients under 18 years of age because of the unknown risks from side effects. The initial fear that there might be an exorbitant incidence of *de novo* lymphomas⁹ has proved unfounded. Other side effects, including nephrotoxicity, hepa-

totoxicity, hirsutism, motor dyskinesias, and gum hyperplasia, have been manageable by dose adjustments.^{45, 51, 57, 64} Furthermore, it has become obvious in children that normal growth and development can be expected in cadaver organ recipients under cyclosporine-corticosteroid therapy, because the maintenance corticosteroid doses have been low.⁵⁴ Most of the infants and children who have received cadaver kidneys, livers, and hearts appear normal.

These results and observations have made us believe that transplantation of a variety of cadaver organs increasingly will become a practical and attractive reality in more pediatric health care centers.^{21, 54} In fact, it is hard to envision a tertiary pediatric hospital without such a capability.

Tissue Typing

Antigen Matching

At the beginning of this chapter, the earlier opinions of Burnet⁶ and Merrill et al.³⁰ were cited about the impossibility or implausibility of organ transplantation without genetic identity. In the first identical twin cases of renal transplantation, the efforts that were made to be sure of genetic identity were extraordinary and ultimately included skin grafting.³⁰ It is no distortion of concept to say that the current tissue matching between donors and recipients is an attempt to come as close as possible to the ideal circumstances of the original Boston identical twin cases.

The possibility of tissue typing by serologic methods was raised by Dausset¹³ in 1958 in his description of antiwhite cell antibodies in certain human sera. The assumption was that the patients had been accidentally sensitized to white cell antigens. Payne and Rolfs⁴¹ expanded the serum donor pool by showing that multiparous women had a higher-than-average incidence of such antibodies, and, later, sensitization was deliberately caused by whole blood transfusion or the infusion of white blood cells. van Rood and van Leeuwen⁷⁸ introduced computer technology to make sense of and to categorize the bewildering array of polyvalent antibodies found in the sera of such patients who had been accidentally or deliberately sensitized.

A critical step in the painful process of antibody detection, collation, and classification was the development of a microcytotoxicity assay by Terasaki and McClelland⁷² in 1964. The cytotoxicity of test lymphocytes by such antisera indicated the presence of the same or similar antigens as those that originally sensitized the serum donor. Failure of such a reaction implied the absence of the antigen. It was appreciated from the beginning that many of the antisera reacted against the same or similar lymphocyte antigens. Between 1963 and 1968, these antisera were classified by direct testing and by computer techniques according to the specificity of action. Eventually, it became possible to define human lymphocyte histocompatibility antigens (HLA) against which groups of antisera reacted. By 1970, it was appreciated that there were probably two principal histocompatibility (HLA A and B) loci on the same chromosome and that the transmission of these loci, each containing two antigens, followed classic Mendelian law. In subsequent years, an additional locus, the so-called D_r locus, which may be the single most important determinant of cellular immunity, has been described.^{32, 42, 77}

Although the story of the histocompatibility chromosome required nearly two decades to be fully played out, it was appreciated by 1964 that the antigens being detected by the above-described antibodies were probably part of the human histocompatibility system. Thus, it was natural to look for a correlation between the outcome after renal transplantation and the match of antigens between the donors and recipients. The first investi-

gation of this possibility was carried out by Dr. Paul Terasaki of Los Angeles on patients treated by us at the University of Colorado. Because almost all of the kidneys were from living volunteers (70% related, 30% unrelated), most of the donors were also available for postoperative typing studies. The results did not show a strong influence of matching⁶⁰ and defined a need for a prospective trial of tissue matching, which was the first such effort in the world.⁷⁴

A powerful correlation could not be demonstrated between the quality of matching and the outcome. With Dr. Charles Holgrimson of the University of Colorado and Terasaki and his associates, we updated the interpretation of the cytotoxic specificity of various sera, incorporating the new information acquired in the 1964–1969 study period.

The revised donor and recipient HLA types were made as accurate as could be achieved at that time for almost 200 cases with a minimum follow-up of at least 1 year. Study of the University of Colorado cases of renal transplantation with 2-year biopsies on all surviving patients included histologic examination of all tissues by Professor K. A. Porter of St. Mary's Hospital and Medical School, London. The resulting histopathologic grades, plus tests of graft function, and the clinical success or failure of the transplantation provided objective criteria by which matching could be judged.

The fact that the results were better in related than nonrelated transplantation was compatible with the conclusion from earlier studies about the relevance of HLA antigens to histocompatibility, but mainly because the supreme advantage in all the parameters studied was evident with *perfectly* matched sibling transplantations. Within all other related donor transplantations, the quality of matching of the four antigens of the A and B loci seemed not to make a major difference in the outcome. In patients who had received nonrelated kidneys, there was the same lack of correlation between typing and the outcome.

The results precipitated a shudder throughout the typing world when they were presented at the American Society of Nephrology meeting, because the prospect of using HLA typing as an important instrument of donor-recipient matching (especially in cadaver cases) was seriously questioned for the first time. This information was annotated and represented at the American Surgical Association on April 28, 1970.⁶²

Terasaki was not yet convinced of the validity of the conclusions. Beginning in early 1970, he and his associates gathered data on some 1,000 cadaver kidney cases from several centers for an analysis to be presented in September at the International Transplantation Society meeting in The Hague. The additional data did not change the message. The quality of matching as measured by the serologic techniques was not a reliable method to select a cadaver donor for any given recipient.³¹ In very large series reported up to recent times, the percentage gain in 1-year cadaver graft survival per antigen matched at the A and B loci has ranged from insignificant to 2 or 3 percentage points.^{27,38}

Increasing the graft survival while at the same time reducing the risk in cadaver cases has become one of the great challenges of applied immunology. In more recent years, the discovery of the new D_r locus has reawakened hope that typing can be instrumental in improving the outlook of nonrelated recipients.^{32,42,77} However, it is probable that improvements in immunosuppression will be more important, as suggested in the first section of this chapter. The complexity of the histocompatibility system has proved to be so great that donor-recipient matching for many patients is not a realistic possibility.

Detection of Preformed Antibody States

In 1965, Terasaki et al.⁷¹ described the first example of "hyperacute rejection." The authors explained the loss of a kidney

on the operating table by the action of cytotoxins in the recipient's serum, which were shown in retrospect to kill the lymphocytes of the kidney donor. The observation was confirmed by Kissmeyer-Nielsen et al.²² of Denmark during the following year and by Terasaki's own team.⁴⁰ Since then, a vital role of tissue typers has been to prevent such immunologic calamities by insisting upon a negative crossmatch when donor lymphocytes and other cells are crossmatched against recipient sera.

Workers in Terasaki's laboratory have subsequently shown that of the variety of antibodies that could be detected in recipient sera, not all are harmful.^{15,20,70} The lymphocytotoxins that are associated with hyperacute rejection are of the IgG class and directed against T-lymphocytes. Because they are detected at 37 C, they have been termed the T-warm antibodies.⁷⁰ In contrast, warm antibodies of the IgG class directed against B-lymphocytes do not cause hyperacute rejection, and "cold" IgM antibodies may actually increase the chance of graft survival.^{15,20,70,76}

Although a positive cytotoxic crossmatch is to be greatly feared in planning a renal transplantation, Ting⁷⁶ has recently reviewed the circumstances in which a positive crossmatch may not lead to hyperacute rejection. It is important to emphasize that the full significance of a positive crossmatch and the conditions under which such a crossmatch can and cannot be accepted have not yet been thoroughly worked out. There is a great need for further information about the significance and nature of antibodies that either do or do not cause hyperacute rejection. Every major renal transplantation center in the world that has been in operation for more than a few months has a list of prospective cadaver kidney recipients who have become "untransplantable" by virtue of their preformed antibody status. Many of the tests that have condemned such recipients to a life on dialysis may eventually prove to be wrong. Even with those antibodies that cause hyperacute rejection, all hope may not be lost. Efforts have been made to prevent hyperacute rejection in patients with widely reacting T-warm antibodies by reducing the immunoglobulin concentration with thoracic duct drainage for a month or longer. A number of pharmacologic techniques have been used to prevent the abrupt destruction of homografts in these unfavored recipients, but to date none has been found satisfactory.

Organ Procurement and Preservation

A great increase can be expected in the demand for cadaver kidneys and other vital organs. Throughout the years, a uniform procedure has been developed that is flexible enough to allow the excision of various organ combinations without jeopardy to any of the individual grafts.⁵²

In so-called heart-beating cadavers, studies can be obtained of the function of individual organs. Cardiovascular-respiratory instability may be reflected in the necessity for vasopressor support, poor blood gas values, or other adverse findings common in patients in intensive care units. Most brain-dead donors can be maintained and improved with conventional intensive therapy, and an attempt can then be made to coordinate the needs of transplant surgeons in different parts of the country.

The Principle of Core Cooling

The intraoperative infusion of cold fluids is the essential first step. With all organs, the guiding principle is avoidance of warm ischemia. This is achieved by carefully timed and controlled infusion of cold solutions into anatomical regions, the limits of which are defined by preliminary dissection.

Cooling of an organ graft by intravascular infusion of chilled lactated Ringer's solution at the time of circulatory arrest expands by many times the duration of organ viability and allows the unhurried application, if desired, of other more sophisticated

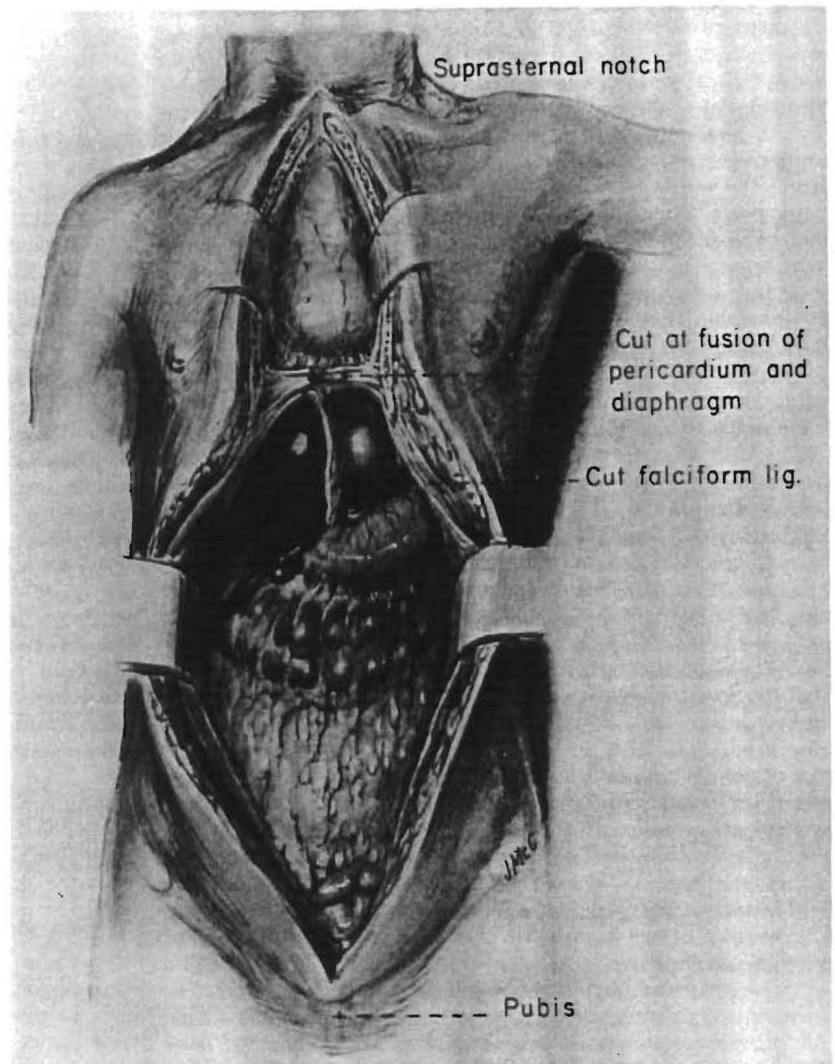


Fig 38-1.—Total midline incision used for multiple organ procurement. (Used by permission.⁵²)

preservation measures. The concept of core cooling was introduced in the laboratory for liver transplantation 25 years ago⁵⁶ and promptly applied clinically for the preservation of the kidney⁴⁹ and other organs. Lactated Ringer's solution has a low potassium content and is nearly isotonic.

Chilled special solutions with an electrolyte composition similar to that in cells were shown in 1969 by Collins and coworkers¹¹ to extend the permissible limit of cold renal ischemia beyond that achievable with isotonic solutions. The same effect has been shown with livers.³ Cardiac surgeons have cooled the heart with various cardioplegic solutions having potassium concentrations of about 20 mEq/L. The simplest way to cool any organ internally is by preliminary *in situ* infusion of lactated Ringer's solution and then infusing the individual organ with specified amounts of a special solution after its removal.

Graft Nephrectomy

A complete midline incision is made from the suprasternal notch to just above the symphysis pubis (Fig 38-1). The long incision provides good exposure for removal of the heart, both kidneys, the liver, and other thoracoabdominal viscera. All of the multiple organ removals can be envisioned as modifications of the evisceration techniques for cadaver kidney removal that were described by Ackermann and Snell¹ and by Merkel et al.²⁹

The extraperitoneal space is entered by incising the peritoneal reflection and sweeping up the ascending colon, cecum, and distal small bowel (Fig 38-2). After freeing the ureters, distal aorta, and inferior vena cava, the kidneys can be infused *in situ* with a cold solution through an aortic cannula (Fig 38-3). Almost all of the infusate will pass into the kidneys if the superior mesenteric artery and celiac axis are occluded (see Fig 38-3).

The washed-out kidneys are now removed from below (Fig 38-4). All tissues passing posteriorly are cut, staying close to the ligaments and muscles covering the vertebral bodies (see Fig 38-4) and continuing superiorly.

After the kidneys and/or other organs have been cooled and excised, segments of the iliac arteries and veins are routinely removed and placed in a cold tissue culture solution for refrigeration. Such grafts can be lifesaving in the event of unexpected technical problems in the recipient.⁵³

Total Hepatectomy

Removal of the liver requires only minor modifications of the foregoing basic technique. If the anatomy is normal, the splenic and left gastric arteries are dissected, ligated, and divided (Fig 38-5), and the celiac axis is dissected as far back toward the aorta as is convenient. The aorta is clamped above the celiac axis (Fig 38-6). After ligating and dividing the gastroduodenal artery and

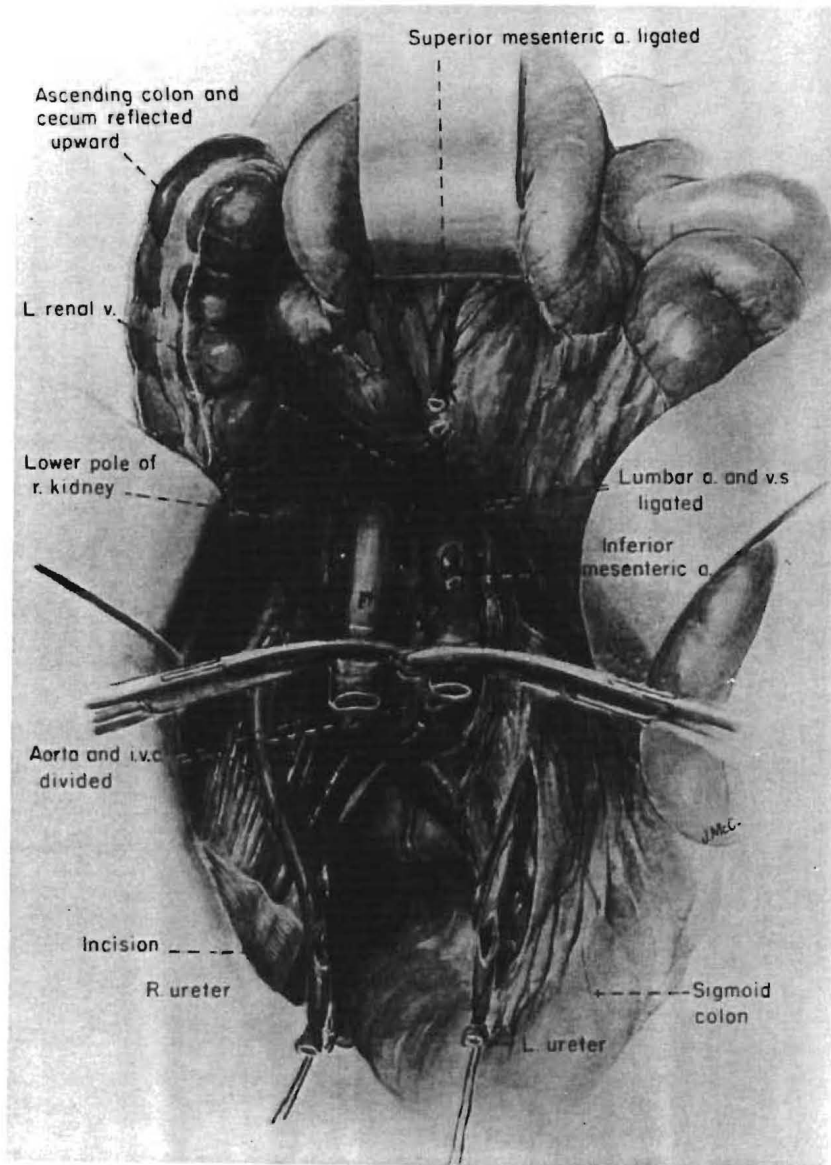


Fig 38-2.—Nephrectomy: preliminary steps for in situ infusion of kidneys in a cadaveric donor (pronounced dead by neurologic criteria) with an effective circulation. (Used by permission.⁵²)

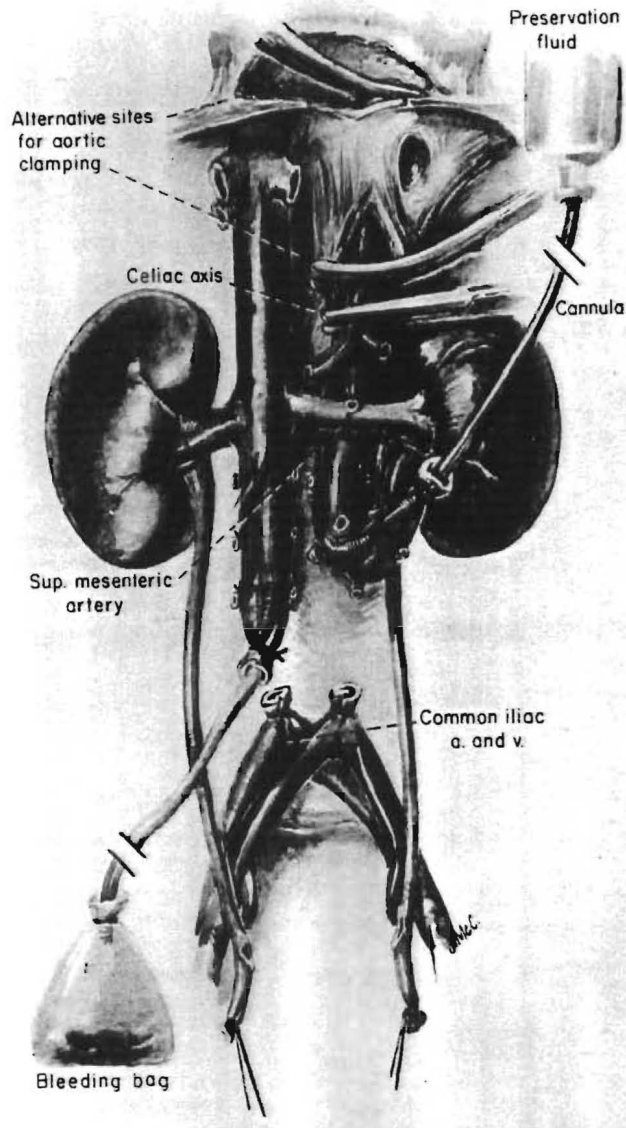


Fig 38-3.—Nephrectomy: in situ infusion of kidneys with cold preservation fluid through the distal aorta, with a venous bleed-off from the distal inferior vena cava. The aorta is clamped proximally at one of the sites shown in Figure 38-3. (Used by permission.⁵²)

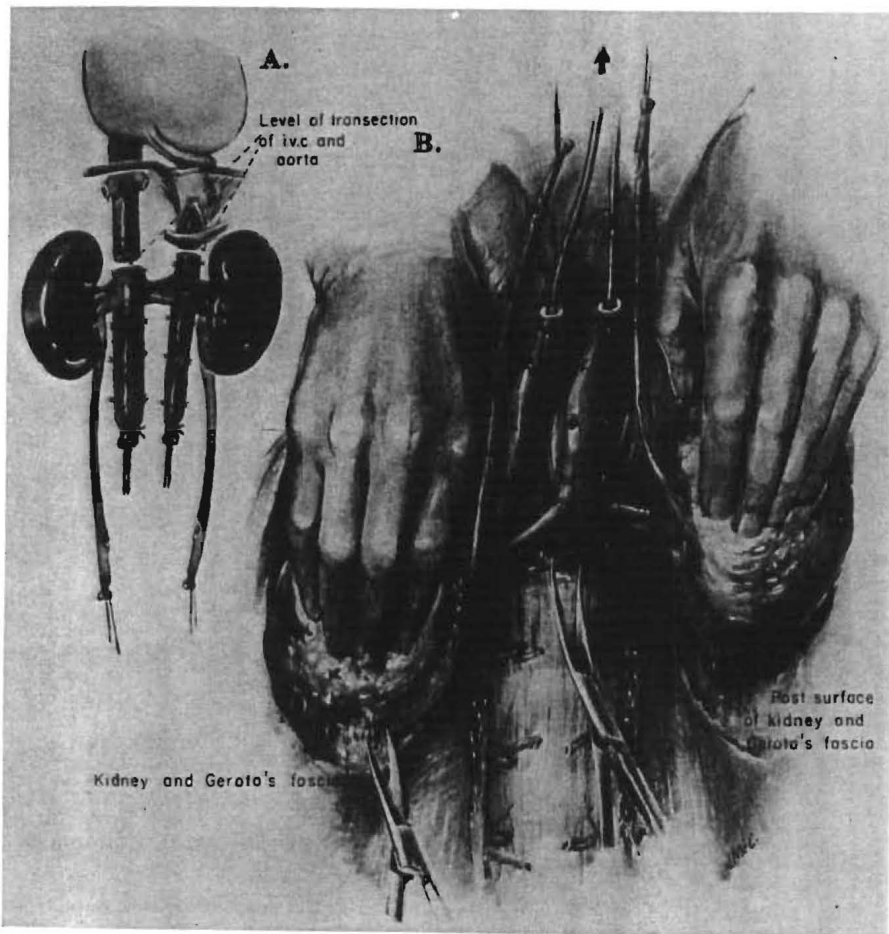


Fig 38-4.—Nephrectomy: removal of perfused kidneys en bloc. The kidneys and great vessels are held anterior to the plane of scissor dissection. (Used by permission.⁵²)

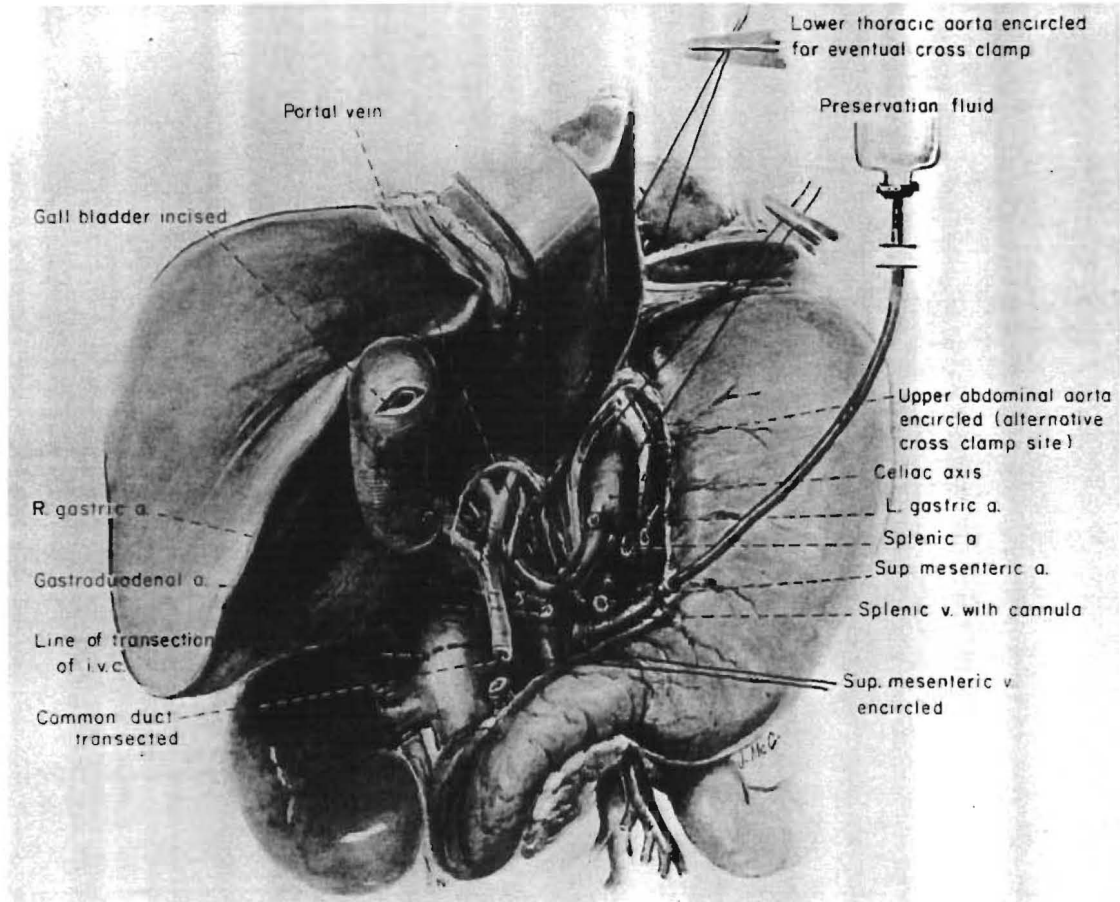


Fig 38-5.—Hepatectomy: hilar dissection and transection of the common duct as an initial step in multiple organ harvesting. Note that the splenic vein (or alter-

natively the superior mesenteric vein) is cannulated for eventual delivery of preservation fluid. (Used by permission.⁵²)

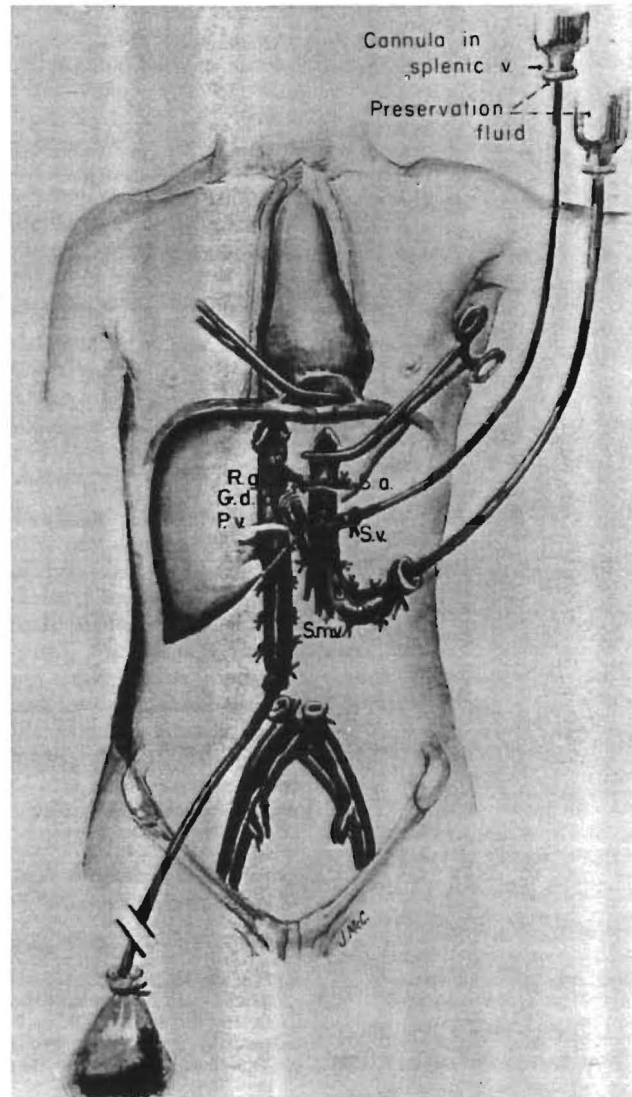


Fig 38-6.—In situ infusion technique used when the kidneys and liver are removed from the same donor. (Rga, right gastric artery; Gda, gastroduodenal

artery; PV, portal vein; SA, splenic artery; SV, splenic vein; SMV, superior mesenteric vein.) (Used by permission.⁵²)

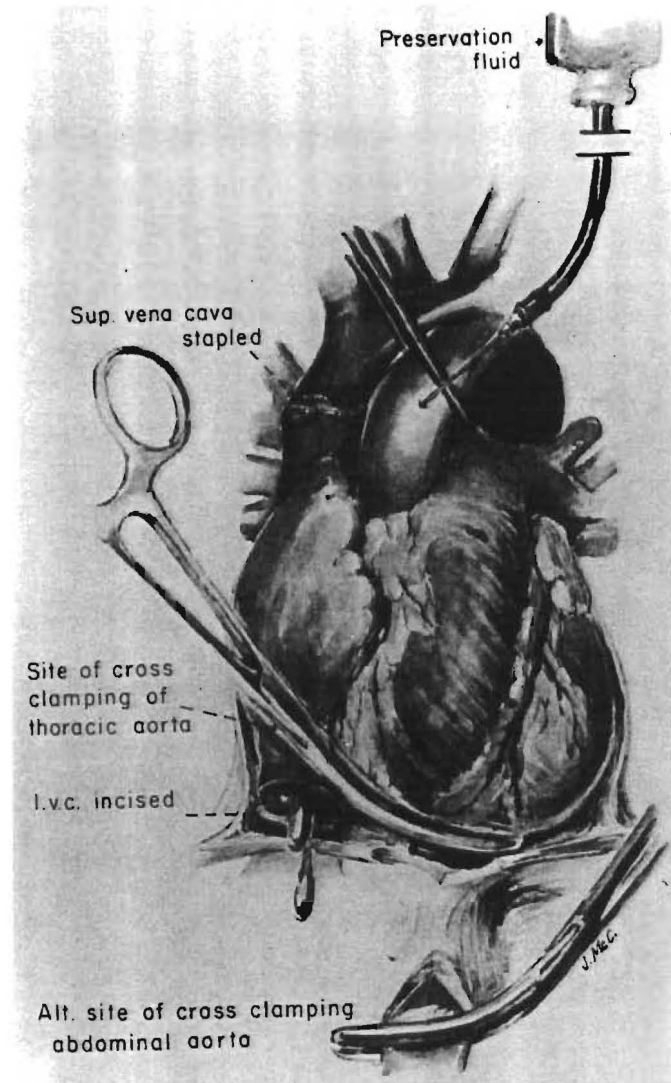


Fig 38-7.—Final steps if the heart is to be removed in combination with nephrectomies and/or hepatectomy. See text for details. (Used by permission.⁵²)

the right gastric artery, the portal vein is cleaned inferiorly to the junction of the splenic vein and the superior mesenteric vein. The liver is infused through the splenic vein as well as through the aorta (see Fig 38-6).

The cooled liver is quickly excised and refrigerated. The 10 or 15 minutes required to remove the liver are not harmful to the kidneys, which are not subjected to any warm ischemia whatsoever, because they have been cooled in situ. With the liver out, removal of the kidneys en bloc is carried out as described under graft nephrectomy. The renal excision is greatly facilitated by the absence of the liver. Vascular grafts are removed as described previously.

Removal of the Heart

The simple preparatory steps described under graft nephrectomy or hepatectomy are completed. The cardiac team now assumes command. The principle that is followed is to disconnect the thoracic and abdominal aortic circulation by aortic cross-clamping at one of the encirclement levels just above or below the diaphragm (Fig 38-7) at the precise moment of cessation of

heartbeat, with immediate graft cooling of both abdominal and thoracic viscera.

The way in which the organs are removed with multiple graft procurement defines an explicit priority list of heart, liver, and kidneys in that order. The heart must function immediately upon transplantation, and the liver must function within a few hours, whereas immediate function of renal grafts is not a prerequisite for survival of the recipient.

Hearts and livers from multiple harvests have been of uniformly good quality. The rate of acute tubular necrosis requiring hemodialysis in patients whose kidneys were obtained at multiple organ harvests has been only one fifth of the lowest incidence reported after the harvest of kidneys alone.^{47,48} The exceedingly low rate of renal injury could reflect the acceptance of only very good donors for hearts and livers, or the fact that there is a high intensity of skilled surgical and anesthesiologic input in such cases. However, the most important factor probably is the systematic use of a superior method of nephrectomy that totally precludes any period of warm ischemia for all organs and that eliminates the manipulation that can unknowingly damage the organs if vascular skeletonization techniques are used.

Other Organ Combinations

The general principles herein described can be applied to graft pancreatectomy or intestinal graft removal. If the whole pancreas is transplanted, as we recommend, the combination of liver and pancreas removal is incompatible.

Preservation by Continuous Perfusion

The organs harvested with this technique are usually kept in "slush" at near 0 C until their transplantation within time limits of 6, 8, and 48 hours for the heart, liver, and kidneys, respectively. Sophisticated techniques for continuous perfusion of all these organs have been developed, but have been widely used only for kidney grafts. The perfusion technique for kidneys was described by Belzer et al.,² using an asanguinous and oncologically controlled fluid. The method is a good one, but the quality of preservation in the first 2 days has not been markedly better than with the simpler infusion and slush method. Better continuous perfusion techniques should permit the extension of preservation times of all organs.

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39 JOHN S. NAJARIAN / NANCY L. ASCHER / S. MICHAEL MAUER

Kidney Transplantation

Selection and Evaluation of Patients for Renal Transplantation

PEDIATRIC RENAL TRANSPLANTATION is increasingly accepted treatment for end-stage renal disease in the child. In 1968, Merrill⁴⁵ listed several factors believed to be important in recipient selection, including (1) age, (2) failure to respond to good medical management, (3) absence of reversible factors, (4) normal lower urinary outflow tract, (5) absence of major extrarenal complications, (6) absence of malnutrition, (7) absence of pancytopenia, and (8) ABO compatibility. Many of these limitations are arbitrary and unnecessarily restrictive. At the University of Minnesota, there is one primary indication for renal transplantation: renal failure that cannot be corrected. Absolute contraindications to transplantation are (1) ABO incompatibility, (2) cytotoxic antibodies against donor lymphoid cells, (3) active infection, and (4) malignancy not under control. Specific problems in the pediatric transplant population are addressed as clinical experience grows. This philosophy has led to transplantation in younger and smaller children than previously seemed possible. It is now common for us to accept infants under 6 months of age and 6 kg in body weight as recipients of adult kidneys. These advances in surgical technology and medical management, which do not compromise patient or graft survival (see below), have profound implications for patient selection. In the past, the dialysis support of the neonate or very young infant, with the aim of achieving 1 year of age and 6-8 kg in body weight before transplantation, was so formidable as to discourage all but the most aggressive and persistent physicians from undertaking this commitment. With recent progress in infant peritoneal and hemodialysis, improved understanding of nutrition problems and renal osteodystrophy in small uremic children, and with the availability of earlier transplantation, this undertaking is no longer unreasonable. However, because infants in renal failure or with congenital nephrotic syndrome often manifest delay in psychomotor development, the task of applying exclusion criteria based upon estimated intellectual potential has become substantially more difficult in that such prognostication in young infants is even less dependable than in older infants and young children.

Because the limits of recoverability of psychomotor potential currently are undefined, children with psychomotor retardation of undefined cause are accepted by us as transplant candidates. On the other hand, children with marked retardation from a specific cause, such as birth asphyxia, structural abnormalities, and metabolic disorders, have been excluded. In any case, children with these disorders rarely present as candidates for transplantation. Using liberal acceptance criteria, approximately 97% of the patients evaluated are deemed suitable candidates for transplantation. Experience since 1968 with over 200 patients less than 18 years old has demonstrated the advances and improved results of transplantation in infants^{12, 15, 37} and children.

Although it is desirable to postpone transplantation until the patient requires dialysis, some children require transplantation earlier. In children with the congenital nephrotic syndrome, there may be failure to thrive despite aggressive attempts at medical management with diuretics, nutritional supplementation, and control of frequent infections. Failure of such therapy for 2-3 months has led to transplantation in these patients with serum creatinine levels as low as 1 mg/dl.³⁸ Further, it is our impression that patients with primary hyperoxaluria should undergo transplantation early, avoiding protracted periods of renal insufficiency or dialysis that may contribute to increased extrarenal accumulations of oxalate in stones, which can provide sources of oxalate that can compromise the transplanted kidney.⁶⁰ Finally, there is evidence accumulating that uremia in infancy in a substantial proportion of patients may be associated with progressive deterioration in CNS structure and function.^{2, 23, 59} Although this may eventually constitute a compelling argument for earlier transplantation, considerable further study is required before clear therapeutic guidelines emerge.

In general, transplantation is not recommended in uremic children with growth failure. Aggressive nutrition, including gavage feeding of infants and children with low caloric intake, leads to slow but steady growth, even in children with advanced uremia. We and others have carried out successful transplantation into ileal loops in children with abnormal lower urinary tracts because of congenital anomalies or neuropathic bladders. Children with previous malignancies (e.g., bilateral Wilms tumors)