

7. RENAL TRANSPLANTATION

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It has now been more than 40 years since the first attempt was made at human renal homotransplantation. The early efforts to apply this form of therapy to the treatment of terminal renal disease were likely to fail because they preceded an appreciation of the problems to be encountered. Knowledge of homograft rejection was scant and the therapy necessary to prevent this process was not understood at all. Since that time, a rational explanation of rejection has been provided by the studies of Medawar and other investigators. The evidence is overwhelming that rejection is due to immunologic repudiation of the alien tissue by the host. The intensity of this reaction is related to the degree of genetic dissimilarity between the donor and the recipient. Its prevention depends to a greater or lesser extent on crippling the host's capacity for immunologic response to unfamiliar antigens.

The initial attempts at potentiating homograft function by alteration of the host were made with total body irradiation. Such therapy proved to be of value for the prevention of rejection, but the requisite dosage was so high that most of the recipient patients died from bone marrow depression and sepsis. Despite the exorbitant risk imposed, two patients from this pioneer era are still alive twenty years after transplantation by Murray of Boston and Hamburger of Paris with homografts from their fraternal twins. Today there is no major center in the world using total body irradiation as an important element in transplantation therapy.

In spite of the occasional early encouraging experience, the prospect of achieving significant clinical benefit from renal homotransplantation in more than the isolated case seemed remote indeed except when an identical twin (isograft) donor was available, until the discovery by Schwartz and Dameshek of the immunosuppressive properties of 6-mercaptopurine in 1959, and the subsequent testing of this drug and its analogue, azathioprine, by Calne and Zukoski. It then seemed that prevention of homograft rejection could be accomplished with greater regularity and with less risk to the recipient than had been possible with total body irradiation. Long-term homograft viability was achieved in animals without the appearance of concomitant host leukopenia or agranulocytosis. During the ensuing several years, clinical efforts at homotransplantation of the kidney proceeded such that by 1979, more than 40 000 such potentially therapeutic operations had been performed throughout the world.

CANDIDATES FOR HOMOTRANSPLANTATION

The general requirements for candidacy are simple: the patient should have irreversible renal disease from

which life expectancy without dialysis or transplantation is limited to a few weeks or months. More subtle indications for renal transplantation occasionally need to be considered. For example, kidneys have been given to patients with completely normal renal function who were suffering from Fabry's disease, an inborn error of metabolism characterized by a deficiency of the enzyme ceramide trihexosidase and a consequent inability to hydrolyse the terminal galactose of ceramide trihexoside, which therefore accumulates in various tissues. The objective of renal transplantation in such cases is not to replace specific organ function but rather to provide a source of enzyme manufacture.

Just a few years ago, an obligatory condition for renal homotransplantation was a normal lower urinary tract. More recently it has been found possible to successfully implant homograft ureters to seriously diseased bladders, to correct mechanical bladder abnormalities before or simultaneously with transplantation, or in some instances to perform transplantation with urinary drainage into an intestinal conduit.

The requirements have relaxed for admission to transplantation programs in other respects as well. Whereas serious disease in other organ systems used to rule out renal transplantation, this position is no longer supportable. Finally, the age ceiling has been rising steadily. It is still true that transplantation is best tolerated by the relatively young. Nevertheless, increasing numbers of recipients have been treated in their 40s, 50s and even 60s.

Very frequently an interim period of intensive resuscitative therapy is mandatory before a decision for or against transplantation can be made. On many occasions a prospective recipient has entered the hospital in acute heart failure with severe hypertension, anasarca, or with a variety of neurologic complications including profound coma. In most instances these findings can be rapidly reversed by the institution of emergency dialysis. If this proves impossible, the likelihood of subsequent successful transplantation is reduced. A significant improvement is often necessary prior to operation in order for the patient to have a reasonable chance of tolerating the trauma of surgery and the stress of the post-operative period.

DONOR SELECTION

Renal tissue is available from three general sources. First, there is now ample evidence that *cadaveric kidneys* often provide good function. A variable degree of damage is inevitable in the terminal premortem state of the donor, to which is added an additional devascularized period during removal and transfer. The harmful effects

of the ischemic time can be considerably minimized by quickly cooling the kidney after its excision. In recent years legislation supporting the concept of neurologic death has greatly improved the quantity and quality of cadaver kidneys available for transplantation, but the need still far exceeds the supply.

Volunteer living donors provide a second source of renal homografts. Here, the entire procedure for both donor and recipient can be planned in advance and executed with precision. The transplanted kidneys almost invariably work well immediately after operation, since the donors are in good health, the ischemic intervals are short, and in addition the homografts can be further protected, just as with cadaveric kidneys, by perfusion with a cold electrolyte solution immediately after removal.

Finally, it may ultimately become possible to use *renal heterografts obtained from subhuman primate donors*. Efforts have been made to transplant Rhesus, baboon, and chimpanzee kidneys to man, with surprisingly good and unexpectedly persistent function. The Rhesus heterograft transplanted by Reemtsma excreted urine in its human environment for almost a week, and the baboon kidneys used at the University of Colorado functioned for as long as 2 months. One of Reemtsma's patients, who received a pair of chimpanzee kidneys, survived with good to fair renal function for 9 months. Despite these encouraging notes all 20 patients treated with various heterografts are now dead, and it seems unlikely that consistent success can be obtained with currently available immunosuppressive methods.

The source of the transplanted tissue has to date been the most important biologic determinant of success or failure. The best results have been when blood relatives have provided the homografts, as will be described in a subsequent section. Non-relative donors have been less satisfactory, and the poorest results have been with heterografts. In all classes, however, the outcome is still unpredictable in the individual case. Violent and uncontrollable rejection episodes have occurred with familial homografts. Conversely, non-related homografts or even chimpanzee heterografts have on occasion incited little clinically detectable host reaction.

These findings suggest that a wide spectrum of donor-recipient histocompatibility exists with employment of any of these donor pools. Quantitation of histocompatibility factors in the human has not been possible in a precise way, in spite of the efforts of a number of investigators. When such techniques become available, it will be possible to match the prospective recipient with the most appropriate donor, thereby eliminating much of the guesswork in donor selection.

Blood Group Considerations

When possible, donors and recipients are selected of the same ABO blood groups. This is not essential, however. Various mismatch combinations appear not to carry an increased risk providing the transplant is not placed into a recipient whose plasma contains preformed

hemagglutinins directed against red cell antigens which are present in the renal cells of patients who belong to blood groups A, B, and AB. For example, a person of 'O' type can provide a kidney for a recipient of any blood group since the renal tissue of such a donor does not contain A or B isoantigens which could bind with hemagglutinins present in recipients of A, B, or C group. The O patient is thus the universal donor. Because the kidney of an individual with AB blood contains both A and B isoantigens, he could safely donate only to an AB recipient. Conversely, an AB patient could accept a kidney from any donor (universal recipient) since his plasma does not contain anti-A or anti-B hemagglutinins. The rules of tissue transfer across blood group barriers are, therefore, the same as those which apply to the use of non-matched blood in blood banks (Table 1). It is noteworthy that long survival has

TABLE 1
DIRECTION OF ACCEPTABLE MISMATCHED TISSUE TRANSFER*

O to non-O	Safe
Rh ⁻ to Rh ⁺	Safe
Rh ⁺ to Rh ⁻	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*O is universal donor, AB is universal recipient

been obtained despite violation of this scheme. One patient at the University of Colorado has normal renal function 17 years after B to A homotransplantation. Nevertheless, a number of immediate failures have occurred after similar mismatches, probably because of antibody-mediated hyperacute rejection.

SURGICAL TECHNIQUES

Both the donor and recipient operations involve the use of standard surgical techniques. Donor nephrectomy must be done with greater care than nephrectomy for renal disease in order to provide undamaged vessels and ureter for anastomosis. When living donors are used, it is important to perform pre-operative renal arteriography to determine if there are anomalies of blood supply which might preclude donation. Arteriography is less important for cadaver kidney harvesting, where a large incision can readily reveal vascular anomalies and where at least one of the two kidneys is usually anatomically suitable for transplantation.

The recipient operation is usually quite simple. Ordinarily, the kidney is placed in the iliac fossa contralateral to its donor location, reversing the anterioposterior relationships of the hilar structures (Fig. 1). In this way the ureter and pelvis are anterior, the renal artery in an intermediate position, and the renal vein posterior. The host hypogastric artery and external iliac vein are connected to the renal vessels; urinary drainage is provided by performing ureteroneocystostomy or occasionally ureteroureterostomy. Under various circumstances

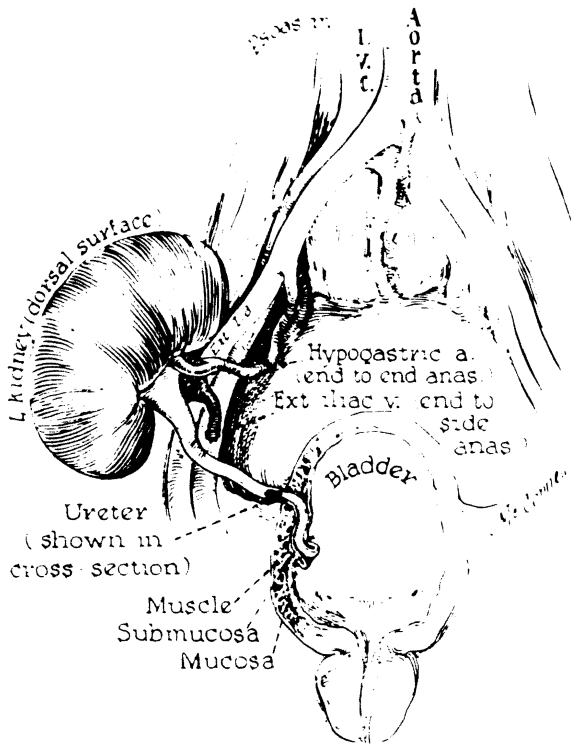


Fig. 1. Usual method of renal homotransplantation. Depicted is the donor left kidney transplanted to the recipient's right iliac fossa.

modifications of this technique are necessary either because of the small size of the recipient, or because of disease in the iliac vessels. It is sometimes necessary to remove the recipient's own diseased kidneys either at the time of transplantation or at a separate operation. This can easily be done through a short upper midline incision. Under these circumstances, splenectomy is usually performed at our center, and splenectomy alone is sometimes done if there is pretransplantation evidence of marked hypersplenism.

If a technically successful homotransplantation is carried out, there is an early postoperative diuresis. In unusual cases this has exceeded 500 ml per hour with the resultant need for meticulous management of fluid and electrolyte replacement. With restoration of renal function there is dramatic improvement in the patient's general condition.

THE EVENTS OF REJECTION

The most useful agents for the prevention of rejection have been azathioprine, cyclophosphamide, prednisone, and heterologous antilymphocyte globulin (ALG). Although these agents diminish the strength of rejection, they frequently do not altogether prevent its occurrence. A typical example of homograft rejection in a patient receiving immunosuppression is illustrated in Fig. 2. There was excellent renal function for more than two weeks after receipt of a homograft from his younger brother. His convalescence was then interrupted by an

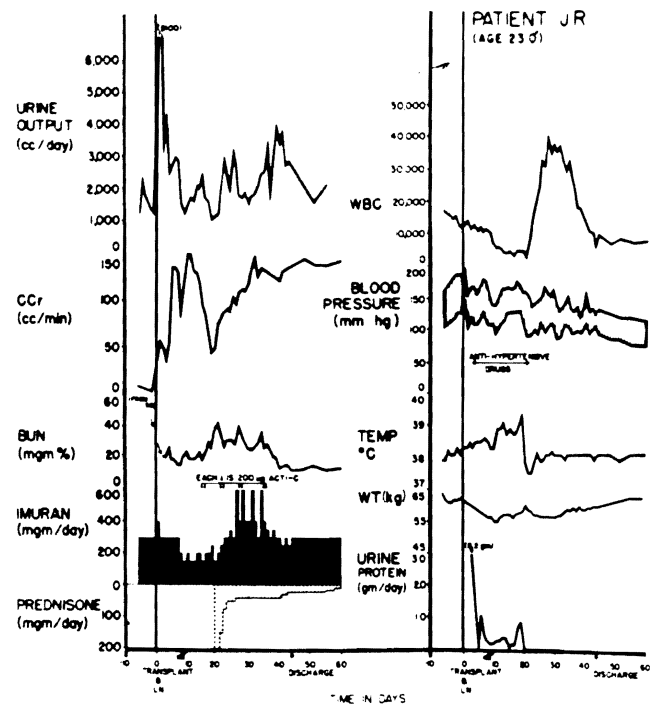


Fig. 2. Classical rejection crisis in a patient treated in 1963 with the double drug combination of azathioprine (Imuran) and prednisone. Deterioration of renal function began 17 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. The patient, whose transplantation was on 17 April, 1963, still has excellent function of the same homograft almost 17 years later. Biopsy of the homograft after two years was normal. Anti-C = actinomycin C; LN = left nephrectomy at the time of transplantation; RN = right nephrectomy.

abrupt drop in creatinine clearance, relative oliguria, a secondary rise in blood-urea nitrogen, fever, and proteinuria. The addition of prednisone to pre-existing therapy with azathioprine was followed by a reversal of all these adverse findings.

The demonstration that most rejection episodes could be reversed was a fundamental disclosure which made clinical homotransplantation a practical possibility. In addition, it is clear that the drastic immunosuppressive measures frequently required for reversal of rejection are not needed permanently. Thus, in the patient described (Fig. 2), the large doses of prednisone which were temporarily necessary could be quickly reduced, and in this case they were discontinued altogether within 5 months. The patient still has perfect renal function almost 17 years post-transplantation. Such observations suggest that some alteration occurs in the relationship between the homograft and the host with the passage of time which diminishes the difficulty of controlling rejection. Whether this change occurs in the homograft or in the host, or both, is not certain.

Clinical Immunosuppression (See also p. 70)

Drug Combinations

In 1962, in what has been termed the beginning of the

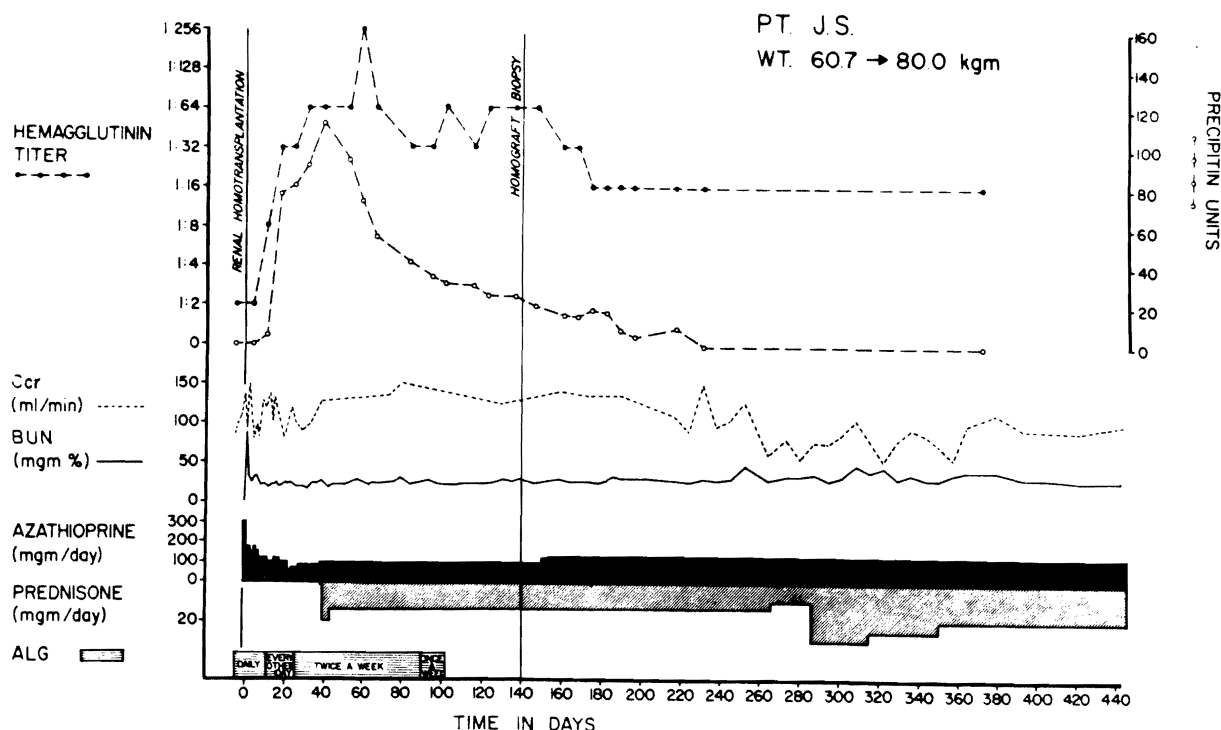


FIG. 3. The course of a patient who received antilymphocyte globulin (ALG) before and for the first four months after renal homotransplantation. The donor was an older brother. There was no early rejection. Prednisone therapy was started 40 days post-operatively because of high rises in the serologic titres which indicated a host response against the injected foreign protein and which warned against a possible anaphylactic reaction. Note the insidious onset of late rejection after cessation of globulin therapy. This was treated by increasing the maintenance dose of steroids. (By permission of *Surg. Gynec. Obstet.* 126: 1023, 1968).

modern era of transplantation, the double drug combination of azathioprine and prednisone was introduced as the cornerstone of immunosuppressive therapy. In 1966, heterologous antilymphocyte globulin (ALG) raised in the horse against human lymphoid tissue was added in the formulation of a triple drug program. The concept was that the ALG should be restricted to the early post-operative course when there was the greatest risk of rejection, and that with the hoped-for 'acceptance' of the transplant the globulin could be safely discontinued within a few weeks or months (Fig. 3). The value of anti-lymphocyte or antithymocyte globulin (ATG) in clinical transplantation, after 13 years of use in human kidney transplantation, is still argued, partly because of the difficulty of consistently manufacturing this biologic product with reliable immunosuppressive potency. Nevertheless, when high potency ALG or ATG can be produced, it is beneficial to the patient.

In the early 1970s a new kind of triple drug therapy was extensively evaluated, in which the alkylating agent, cyclophosphamide, was substituted for the purine analogue, azathioprine (Fig. 4). Even though these drugs are of different chemical classes and act at different phases of the cell cycle, they have proved to be about equally effective and, therefore, essentially interchangeable in triple drug treatment. Since 1972 we have returned to using azathioprine rather than cyclophosphamide for most patients because of our general satisfaction with azathioprine, because cyclophosphamide's

effect on bone marrow is more difficult to predict, and because cyclophosphamide is more likely to cause baldness, azospermia, and hemorrhagic cystitis.

Thymectomy and Splenectomy

Although the above therapeutic methods are of more or less unquestioned value, two other biological manipulations of less certain value have been carried out in some cases.

Between 1962 and 1966, thymectomy was performed prior to transplantation, primarily because of the evidence in rodent experiments by Miller that the thymus gland is important in the adult in re-establishing reactivity to foreign antigens after a period of immunological depression. Follow-ups of more than 5 years for all those recipients, including in each instance samples of the renal homografts obtained either by autopsy or biopsy, showed that the histopathologic abnormalities in these kidneys were significantly less than in comparable patients whose thymus glands were not disturbed. In spite of this finding, which was the first evidence for potential function of the adult human thymus, patient survival was not beneficially influenced by thymectomy. Since complete thymic excision can be a formidable undertaking in uremic humans, this ancillary procedure is not currently being performed in our patients.

The rationale for splenectomy is that the spleen participates in the immunologic response to intravenous

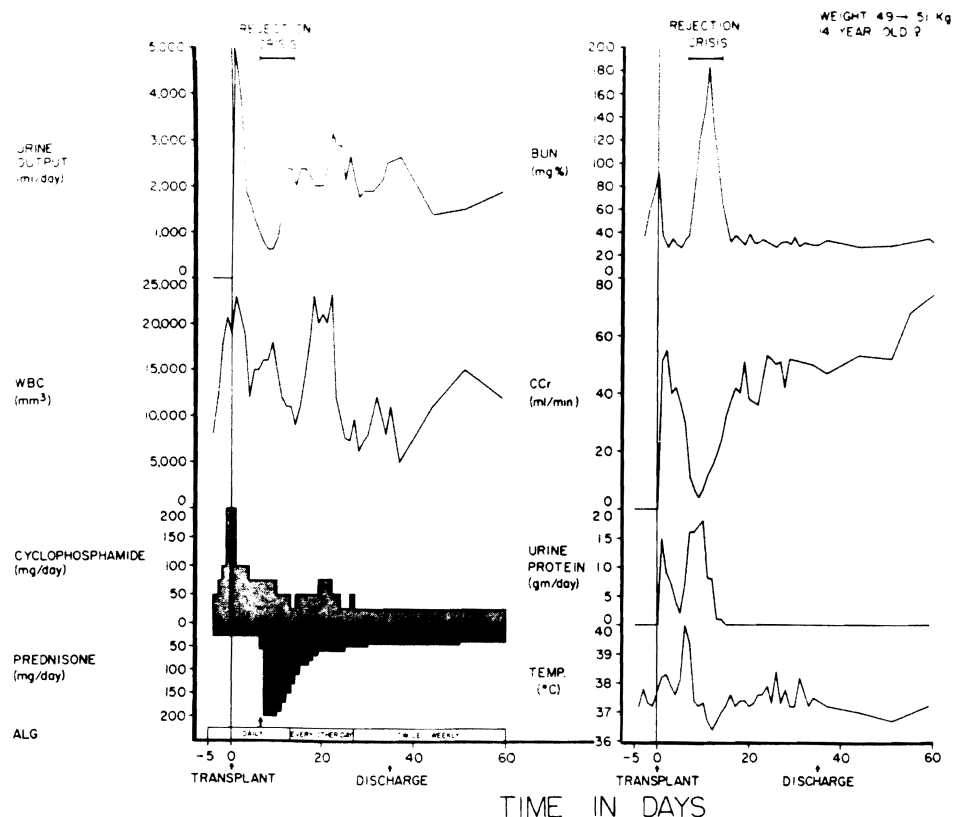


Fig. 4. The first 60 days after the transplantation of a kidney from a mother to her daughter. Although the rejection crisis after a week was a severe one, it was easily and completely reversed. Note that leukopenia was never produced by the daily doses of cyclophosphamide that were usually between 0.5 to 1.0 mg per kg/day. ALG = horse antilymphocyte globulin; BUN = blood urea nitrogen; CCr = creatinine clearance; WBC = white blood cell count; Arrow = 625 mg methylprednisolone intravenously. (By permission of *Surg. Gynec. Obstet.* 133: 981, 1971).

antigen. There is no proof that splenectomy improves survival after renal transplantation, but unlike thymectomy, splenectomy is a simple procedure that does not require a separate operation. Consequently, we continue to perform splenectomy in many of our patients, particularly those whose pretransplantation peripheral white blood counts are consistently below 5000 per cubic millimeter.

Thoracic Duct Drainage

The immunosuppressive effect of thoracic duct drainage has been known for at least fifteen years. Trials with kidney transplant patients in Sweden, Boston, and Texas suggested that the procedure was valuable, but the technical difficulty of keeping the drainage system patent and uninfected probably contributed to the abandonment of this method, except at Vanderbilt University in Tennessee.

Since February, 1978, using a Swan-Ganz double lumen catheter with constant heparin catheter flushing, it has been possible at our center to maintain thoracic duct fistula drainage for several weeks in more than 90% of patients, and for more than three months in selected

patients with chronic high-titers of preformed antibodies. The precise mechanism of immunosuppressive action of this technique is not clear; but it is usually possible to remove at least one billion lymphocytes daily, and serum immunoglobulin G levels fall.

Although the volume of thoracic duct drainage, up to twelve liters per day, imposes logistical problems, it has been a very feasible and safe adjunct to the previous triple drug regimen.

Toxicity of Immunosuppressive Agents

Although they are essential for maintenance of homograft function, the agents used to protect the homograft do so by rendering the patient more susceptible to a variety of inimical antigens. It is not surprising, therefore, that most of the early deaths after homotransplantation are due to complications of the agents used. A characteristic although not common lethal sequence of events is shown in Fig. 5. The young man concerned received a kidney from his brother. After 10 days of good homograft function a severe rejection crisis occurred with anuria. The rejection was reversed but after renal function had returned, the patient became

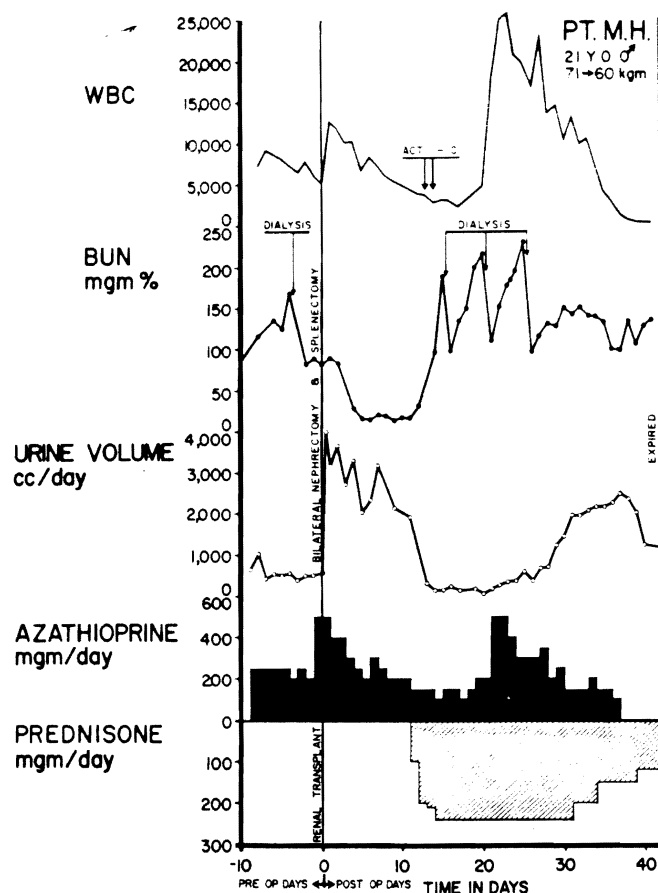


Fig. 5. Typical unsuccessfully treated case. The donor and recipient were brothers, both of A blood type. A violent rejection crisis followed good early function, and anuria developed which lasted two weeks. Although the rejection was reversed and a secondary diuresis began, the patient died from drug toxicity, leukopenia, and septicemia. Anti-C = Each arrow is 200 μ g intravenous actinomycin C.

leukopenic and died of a fungus and bacterial blood stream infection. This complication was due to overdose with azathioprine. The same kind of bone marrow depression could be caused by cyclophosphamide. In recent years, early deaths caused by excessive quantities of these cytotoxic drugs have been virtually eliminated.

At a later time, continuing immunosuppression, particularly if large maintenance doses of prednisone are required, can lead to infection with opportunistic microorganisms for which highly specific antibiotic therapy is often not available. Typically, these infections occur despite adequate peripheral white blood cell counts, and are caused predominantly by fungi, protozoa, and viruses. Bacteria that ordinarily have low pathogenicity such as *Listeria monocytogenes* are also seen with increased frequency. One of the most serious public health hazards resulting from transplantation has been the creation of virus hepatitis reservoirs. Between 10 and 20% of chronically surviving recipients of renal homografts come to have the Australia antigen in their serum which, once identified, tends to be a permanent finding. Even though liver function tests may be normal, these

patients are hepatitis carriers and are capable of infecting other patients or members of the staff.

An increased susceptibility to infection is not the only penalty to chronic immunosuppression. Numerous *de novo* malignancies have been reported in chronically surviving recipients of renal homografts. In our own center, almost 6% of the patients have developed a carcinoma or a lymphoreticular neoplasm. The development of this striking complication may represent an unwelcome clinical confirmation of Burnet's surveillance hypothesis, which holds that the immune system is normally responsible for the identification as 'non-self' and the elimination of mutant cells. Fortunately the commonest malignant neoplasm in kidney transplant patients is highly curable squamous cell carcinoma of the skin.

In addition to its contribution to the foregoing side-effects, prednisone causes facial and other changes which are an annoyance to most patients whose late renal function is dependent upon continuing steroid therapy. Aseptic necrosis of bone and lens cataracts have also been observed.

It should be emphasized that the increased risks of infection and malignancy do not vitiate the value of transplantation procedures. The infections and the neoplasms can usually be controlled.

Late Rejection

As mentioned above, the necessity for intensive immunosuppressive therapy tends to decrease late after transplantation, and a number of patients have now been living for many years with no clinical evidence of immunological activity directed against the homograft. Nevertheless, a significant number of long-term survivors have had manifestations of late rejection, sometimes in a form which resembles that seen early after operation. These late 'crises' have proved to be partially reversible with the resumption of large steroid doses. In such patients, the homograft function can be maintained, but the need for continuous high dose steroid therapy constitutes a threat to a long life expectancy. A more subtle form of late rejection without functional manifestations may be going on in some homografts. Kidneys biopsied or recovered at autopsy one to two years after homotransplantation frequently contain focal aggregates of mononuclear cells, a variety of vascular lesions in both the large and small vessels, lesions of the glomerular basement membrane, and patchy interstitial fibrosis. These morphologically damaged homografts may function in a satisfactory way for many years. However, they clearly do not have an indefinite functional life expectancy, and such grafts have failed as late as 8 or 9 years after their insertion.

Results and Future Prospects

It is not the purpose of this chapter to present clinical data. Nevertheless, a brief statement is in order about what has been achieved so far. The modern era of

whole-organ transplantation began in late 1962 and early 1963, from which era there are still about two dozen living patients who have had continuous function of their original transplants. Since this time, thousands of patients have benefited from renal homotransplantation and have therefore undergone relatively complete social and vocational rehabilitation. This has been particularly true in recipients of consanguineous grafts who now can expect to survive the first post-transplantation year at the rate of approximately 90% (Fig. 6). It is less true of

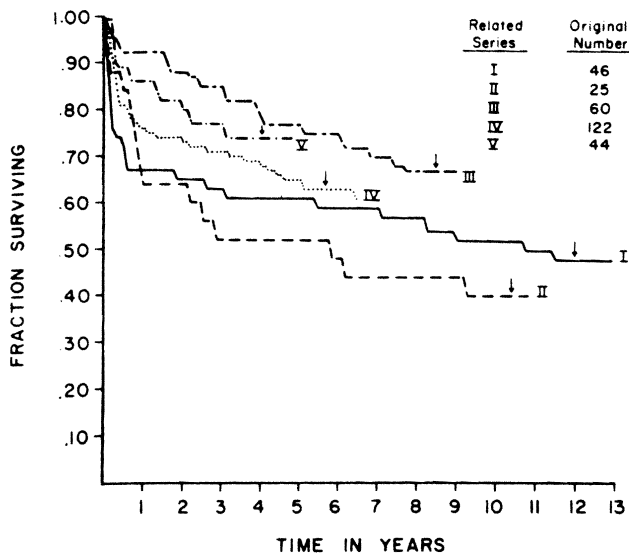


Fig. 6. Life survival curves of patients treated with primary related homografts during five intervals from 1962 to the summer of 1972. Arrows show time of minimum follow-up. (By permission of *Transplantation Proceedings IX*: 1, 1977.)

recipients of unrelated (cadaveric) transplants in whom only approximately 50% of grafts function for as long as a year. After one year the loss rate of grafts and patients has proved to be at a very slow rate in consanguineous cases. With non-related donors the outlook after one year is less optimistic. There is frequently a need for retransplantation especially in cadaveric cases. With both kinds of donors, the experience of the last decade has shown renal homotransplantation to be an exceptionally effective form of palliative treatment for patients with terminal renal disease.

Our recent experience with thoracic duct drainage suggests that this fourth immunosuppressive method, added to corticosteroid, azathioprine, and antilymphocyte globulin, will permit a higher level of patient survival than was previously feasible using only three agents. Our preliminary results using this quadruple

agent approach in recipients of first cadaver kidneys, with short follow-up times of only 3–12 months and with 8 early retransplants, are only 1 death in this group of 27 patients, and 89% (24/27) of these patients currently have functioning transplants. In a small number of cases using pretransplantation thoracic duct drainage, successful kidney transplantation has been possible in spite of high titers of preformed antibodies in the recipient and in spite of strongly positive direct cytotoxic crossmatches between the recipient and the specific donor of the cadaver kidney. The reduction in serum immunoglobulins caused by preoperative thoracic duct drainage for one or two months probably has had some influence on the avoidance of hyperacute rejection, which otherwise would have been expected.

The research and clinical experience with renal homotransplantation has direct application to the transplantation of other organs. The immunosuppressive techniques developed with the kidney model have made possible the successes that have been achieved with hepatic and cardiac transplantation. There are a number of reasons for failure after transplantation of extrarenal organs, but for the most part these reasons are non-immunologic. They include greater technical difficulties; the lack of artificial organs comparable to renal dialysis which could tide the hepatic, cardiac or pulmonary patient over transient periods of poor function; and a lack of discriminating techniques to diagnose rejection in its early and most reversible phases.

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