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8. RENAL TRANSPLANTATION

T. E. STARZL and C. W. PUTNAM

It has now been more than 35 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 doomed to failure since they preceded an appreciation of the problems to be encountered. Knowledge of homograft rejection was scanty 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 those of 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 upon crippling of 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 are still living from this pioneer era, the longest follow-ups being on two young men treated twelve years ago by Murray of Boston and by Hamburger with homografts from their fraternal twins. Today, there is no major centre in the world using total body irradiation as an important element in the overall 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 donor was available (isograft) 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 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 have proceeded with increasing regularity. By 1971 more than 7,000 such potentially therapeutic operations were known to have been performed throughout the world by virtue of their entry into the American College of Surgeons Registry.

Candidates for Homotransplantation

The standard 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. Recently, indirect indications for renal transplantation have come under evaluation. For example, kidneys have been given to patients with completely normal renal function who were suffering from Fabry's disease. Fabry's disease results from an inborn error of metabolism in which there is a deficiency of the enzyme ceramide trihexosidase with the 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 achieve specific organ function, but rather to provide a source of enzyme.

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 ileal loop. The reasonably good results in these relatively unfavourable situations illustrate the extent to which treatment by transplantation procedures has advanced.

In other respects, the requirements have relaxed for admission to transplantation programmes. 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 40's, 50's and even 60's.

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 to be impossible, the likelihood of subsequent successful transplantation is reduced. A significant improvement is often necessary prior to operation for the patient to have a reasonable chance of tolerating the trauma of surgery and the duress of the post-operative period.

Donor Selection

Renal tissue is available from three general sources. First, there is now ample evidence that cadaveric kidneys can often provide good function. Recently, considerable success with such organs has been achieved by Kolff, Hume, Mowbray, and Hamburger despite the fact that there is a high incidence of immediate functional failure of such kidneys, due primarily to ischæmic injury. 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 latter "dead time" can be considerably minimized by quickly cooling the kidney after its excision (Fig. 1).

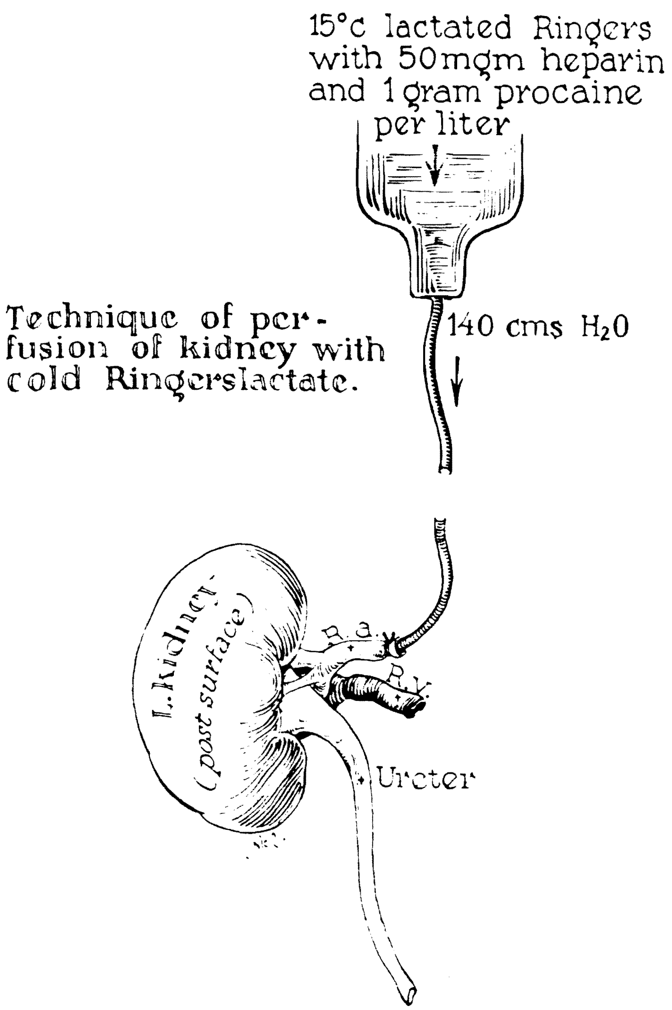

FIG. 1. Method of cold perfusion of renal homograft. Various other solutions have been evaluated including low molecular weight Dextran, either alone or in combination with blood, plasma, or saline. All work relatively well, the principal beneficial effect being the rapidly induced hypothermia.

The improved results obtained by the groups cited above have largely been due to the very carefully controlled circumstances of the undertaking. Most of the recipient patients had been previously maintained in good clinical condition on a chronic dialysis programme. When the cadaveric transplant was carried out it merely represented an incident in a programme of continuing therapy with the artificial kidney. Thus, patients who did not have immediate homograft function could be maintained by an extension of their pre-existing care until recovery from an acute tubular necrosis in the homograft. Ultimately good function has been observed under such circumstances despite initial post-transplant anuria of as long as a month.

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 ischæmic 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 chimpanzee, baboon, and Rhesus 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 the presently available immunosuppressive regimens.

The source of the transplanted tissue has to date been the most important biologic determinant of success or failure. In controlled animal experiments, it has been established that the vigour of rejection is directly related to the degree of genetic dissimilarity between the donor and recipient. It is not surprising, therefore, that the best results have been when blood relatives have provided the homografts, as will be described in a subsequent section. Non-related 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. Until now, 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 an 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 hæmagglutinins 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 hæmagglutinins present in recipients of A, B, or O 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, he could accept a kidney from any donor (universal recipient) since his plasma does not contain anti-A or anti-B hæmagglutinins. 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

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.

long survival has been obtained despite violation of this scheme. One patient at the University of Colorado has normal renal function 9½ years after B to A homotransplantation. Nevertheless, a number of immediate failures have occurred after similar mismatches, apparently by a pathogenesis of antibody-mediated hyperacute rejection analogous (but with a different antibody) to that in the preceding section.

SURGICAL TECHNIQUES

Both the donor and recipient operations involve the use of standard surgical techniques. Donor nephrectomy is more easily accomplished than nephrectomy in renal disease but it must be done with greater care in order to provide undamaged vessels and ureter for anastomosis. It is highly desirable, when living donors are used, or if brain death criteria are accepted for cadaveric donors, to perform pre-operative renal arteriography to determine if there are anomalies of blood supply.

The recipient operation is also quite simple. Ordinarily, the kidney is placed in the iliac fossa contralateral to its donor location, reversing the anteroposterior relationships of the hilar structures (Fig. 2). 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 ureteroureterostomy. Under various circumstances modifications of this technique are necessary either because of the small size of the recipient, or because of disease in the pelvic vessels. It is usually desirable and sometimes obligatory to remove the recipient patient's own diseased kidneys either at the time of transplantation or at a separate operation. This can easily be

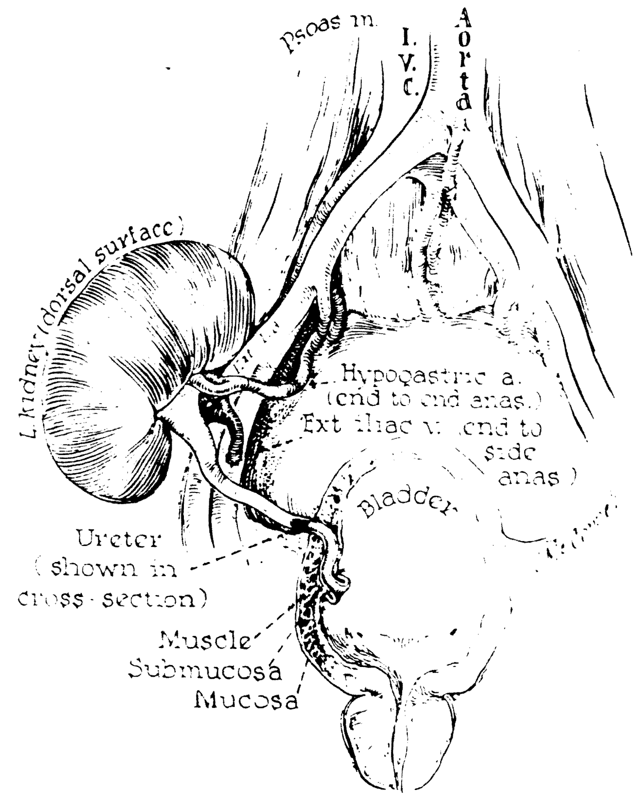

FIG. 2. Usual method of renal homotransplantation. Depicted is the donor left kidney transplanted to the recipient's right iliac fossa.

done through a short upper midline incision. Under these circumstances, splenectomy is always performed at our centre.

If a technically successful homotransplantation is carried out there is massive early post-operative diuresis. In unusual cases this has exceeded 100 ml per hour with the resultant need for meticulous management of fluid and electrolyte replacement. With this restoration of renal function there is a dramatic improvement in the patient's general condition, which persists until the time of homograft rejection.

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 attenuate the vigour of rejection, they frequently do not altogether prevent its clinical manifestation. A quite typical example of homograft rejection in a patient receiving immunosuppression is illustrated in Fig. 3. 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 abrupt drop in creatinine clearance, relative oliguria, a secondary rise in blood-urea, fever, and proteinuria. The addition of prednisone to pre-existing therapy with azathioprine was followed by a reversal of all these adverse findings.

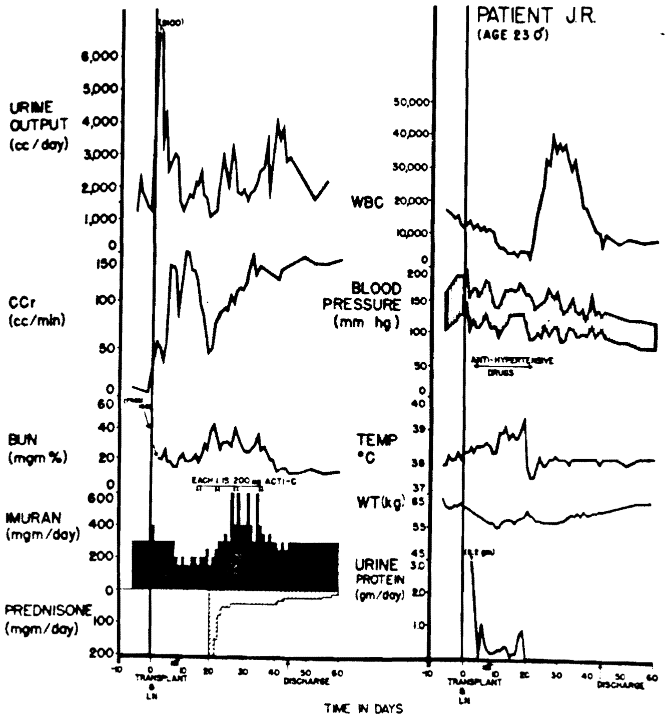

FIG. 3. Classical rejection crisis in a patient being treated with the double drug combination of azathioprine (Imuran) and prednisone. Deterioration of renal function began 17 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. The patient, whose transplantation was on 17 April, 1963, still has excellent function of the same homograft almost 10 years later. Biopsy of the homograft after two years was normal. Acti-C—actinomycin C; LN—left nephrectomy at the time of transplantation; RN—right nephrectomy.

The demonstration that most rejection episodes can be reversed is one of the fundamental disclosures which has made clinical homotransplantation a practical possibility. Moreover, it is now clear that the drastic immunosuppressive measures frequently required for reversal of rejection are not needed permanently. Thus, in the patient described (Fig. 3), 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 10 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 known.

Clinical Immunosuppression

Drug Combinations

A decade ago, in what has been termed the beginning of the modern era of transplantation, the double drug combination of azathioprine and prednisone was introduced as the cornerstone of immunosuppressive therapy. In 1966, heterologous ALG raised in the horse against human lymphoid tissue was added in the formulation of a triple drug programme. The concept was (and is) 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. 4).

Within the last year, a new kind of triple drug therapy has been extensively evaluated in which the alkylating agent, cyclophosphamide, has been substituted for the purine analogue, azathioprine (Fig. 5). 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. It remains to be determined, in view of the different metabolism of these two agents if they can be advantageously combined (possibly serially) in some way which might permit a synergism which has not hitherto been exploited.

Thymectomy and splenectomy. Although the therapeutic methods alluded to above are of more or less unquestioned value, two other biological manipulations have been carried out in many 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. Potential follow-ups of more than 5 years are now available for all these recipients and in each instance samples of the renal homografts have become available either by autopsy or biopsy. The extent of histopathologic abnormalities in these kidneys has been significantly less than in comparable patients whose thymus glands were not disturbed. In spite of this finding, which is the first evidence for potential function of the adult human thymus, the patient survival has not so far been beneficially influenced by thymectomy. Since complete thymic excision can be a formidable undertaking in uræmic humans, this ancillary procedure is not currently being performed in our patients pending further study of the remaining patients in the original series.

As mentioned earlier, splenectomy is performed in all our patients who are submitted to laparotomy for nephrectomies. The rationale is that the spleen participates in an easily demonstrable way in the immunologic response to intravenous 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 most of our patients.

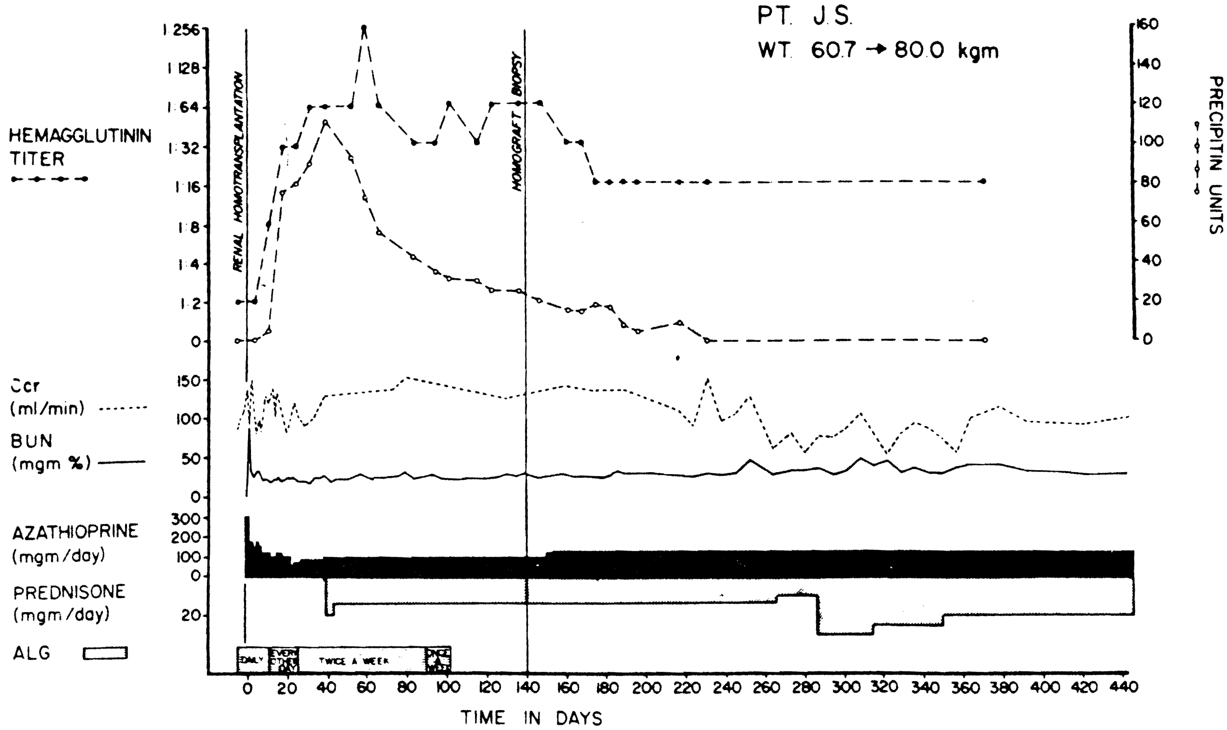

FIG. 4. The course of a patient who received antilymphocyte globulin (ALG) before and for the first four months after renal homotransplantation. The donor was an older brother. There was no early rejection. Prednisone therapy was started 40 days post-operatively because of the high rises in the serologic 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.]

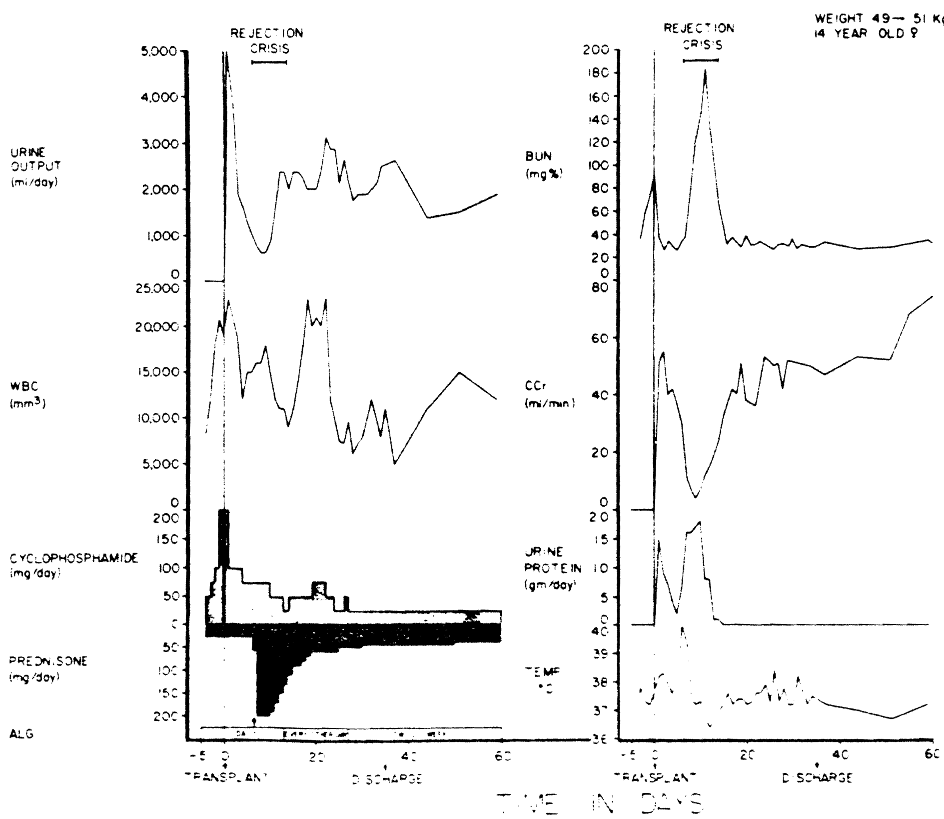

FIG. 5. The first 60 days after the transplantation of a kidney from a mother to her daughter. Although the rejection crisis after a week was a severe one, it was easily and completely reversed. Note that leukopenia was never produced by the daily doses of cyclophosphamide that were usually between 0·5 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. methyl prednisolone intravenously. [By permission of *Surg. Gynec. Obstet.* **133**: 981, 1971.]

Toxicity of Immunosuppressive Agents

Essential though they are 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 failures after homotransplantation are due to complications of the agents used. A typical lethal change of events is shown in Figure 6. The young man concerned received a kidney from his brother. After 10

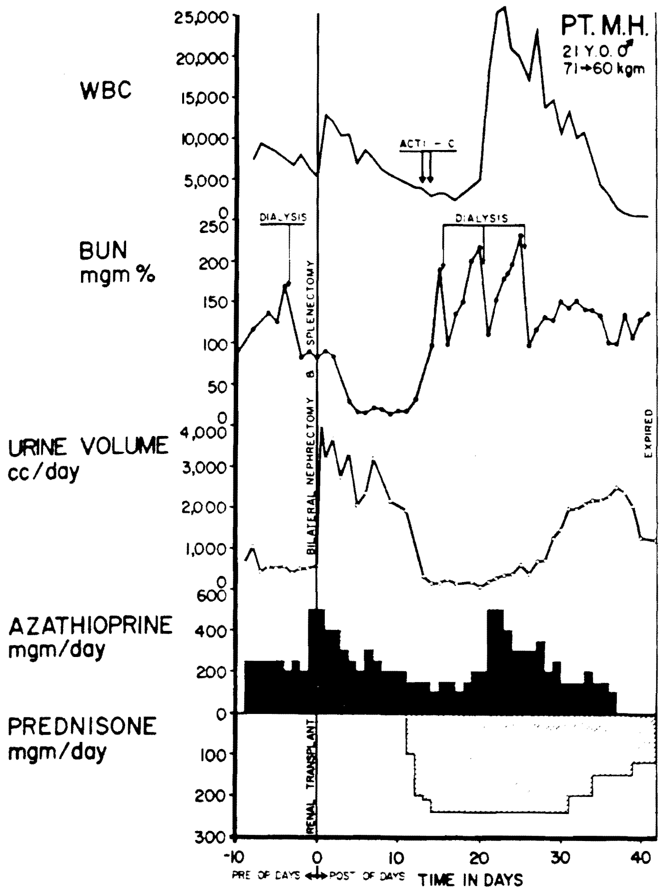

FIG. 6. Typical unsuccessfully treated case. The donor and recipient were brothers, both of A blood type. A violent rejection crisis followed good early function, and anuria developed which lasted two weeks. Although the rejection was reversed and a secondary diuresis began, the patient died from drug toxicity, leukopenia, and septicæmia. Anti-C—Each arrow is 200 μg intravenous actinomycin C.

days of good homograft function a severe rejection crisis supervened, with anuria. The rejection was reversed but after renal function had returned, the patient became leukopenic and died of a fungus and bacterial *blood stream infection*. This complication is due to overdosage with azathioprine; the same kind of bone marrow depression could be caused with 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 micro-organisms for which highly specific antibiotic therapy is 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 per cent 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. In the last five years, numerous *de novo* malignancies have been reported in chronically surviving recipients of renal homografts. In our own centre, almost 10 per cent of the patients who were treated from 1962 to 1968 and who are still alive have developed a carcinoma (13 examples) or a lymphoreticular neoplasm (3 examples). In a world collection maintained in an informal basis in Denver, more than 70 cases of *de novo* malignancy have been compiled. The development of this striking complication provides 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.

It should be emphasized that the increased risk from infection and malignancy does not vitiate the value of transplantation procedures. The infections can usually be controlled and the same has been true using conventional therapy with all but 2 of our 16 patients with neoplasias.

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. Pathological fractures have been described in such cases as well as the development of lens cataracts.

Late Rejection

As mentioned above, the necessity for intensive immunosuppressive therapy tends to decrease late after operation, and a number of patients have now been living for 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 the "chronic" homografts. Kidneys biopsied or recovered at autopsy 1 to 2 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 quite satisfactory way for many years. However, they clearly do not have a normal life expectancy and such grafts have failed as late as 8 or 9 years after their insertion. Then, return to hæmodialysis and/or retransplantation becomes necessary.

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,

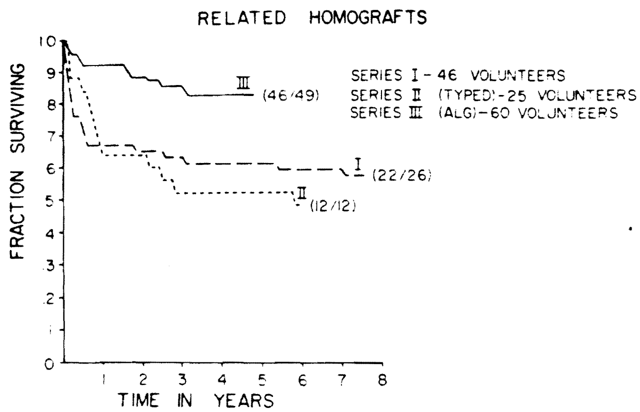

FIG. 7. Life survival curves of 3 groups of recipients of consanguineous kidneys. The patients in series I were treated with the double drug programme of azathioprine and prednisone from 1962 to March 1964 and, consequently have potential follow-ups of 8 to 9½ years. The patients of series II were treated from October 1964 to April 1966 and, consequently, have potential follow-ups of 6 to 7½ years. They received the same drug therapy as in series I and, in addition, an attempt was made at donor selection by HL-A matching. Note that the tissue typing did not influence the survival curve. The recipients of series III were treated with the triple drug programme of azathioprine, prednisone, and ALG between June 1966 and April 1968; they have potential follow-ups of 4 to almost 6 years. In all three series, the denominator indicates the surviving patients whereas the numerator tells the number of originally transplanted kidneys that are still functioning in those survivors.

from which era there are still about two dozen patients living after having had continuous subsequent function of their transplants. Since this time, thousands of patients have benefited from renal homotransplantation and have thereafter 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 per cent (Fig. 7). It is less true of recipients of unrelated (cadaveric) transplants in whom only 60 to 80 per cent of grafts function for as long as a year (Fig. 8). 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. 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.

The research and clinical experience with renal homotransplantation has direct application to the transplantation of other organs. The immunosuppressive tech-

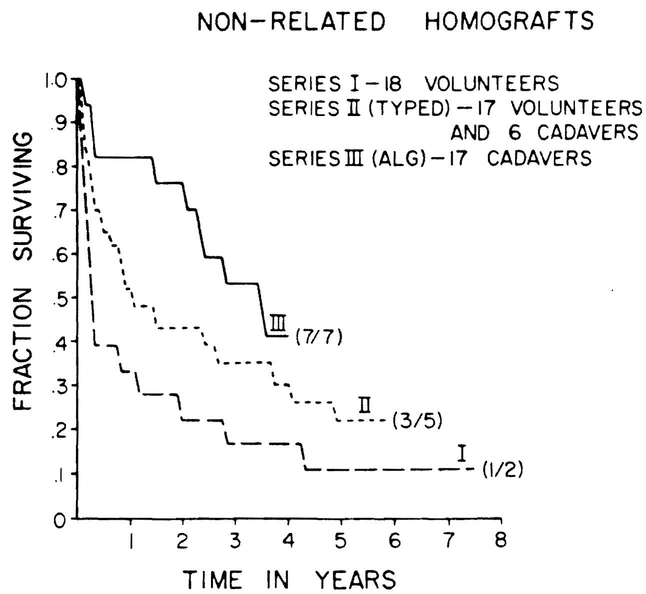

FIG. 8. The results after the transplantation of non-related kidneys. The conditions of treatment, and follow-ups, and the meaning of the figures in parentheses are the same as in Fig. 7. Note that the results with non-related kidneys have been inferior to those with related grafts at all levels of our experience.

niques developed with the kidney model have made possible the limited successes that have been achieved with hepatic, cardiac, and lung transplantation. There are a number of reasons for the high failure rate after transplantation of the 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 even the lack of discriminating techniques to diagnose rejection in its early and most reversible phases.

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