6. RENAL TRANSPLANTATION

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It has now been more than 30 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, three patients are still living from this pioneer era, the longest follow-ups being on two young men treated almost six years ago by Murray and Merrill and by Hamburger with homografts from their fraternal twins. Today, American centres do not generally use total body irradiation although it remains an important element in the overall therapy employed by Hamburger and some of the other European authorities; with increased experience, Hamburger's later results with irradiation are not dissimilar to those obtained by other groups with drug 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 September 15, 1964, almost 500 such potentially therapeutic operations were known to have been performed throughout the world by virtue of their entry into the National Academy of Science Registry.

Candidates for Homotransplantation

The requirements for candidacy are simple. The patient should have irreversible renal disease from which life expectancy is limited to a few weeks or months. There should be a normal lower urinary tract. Other serious disease processes must be ruled out. Transplantation is ordinarily a procedure which should be reserved for the relatively young. In patients older than 45 years, the failure rate has been high in most centres, the patient often dying of complications originating in other organ systems.

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 almost nil. 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. 16).

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.

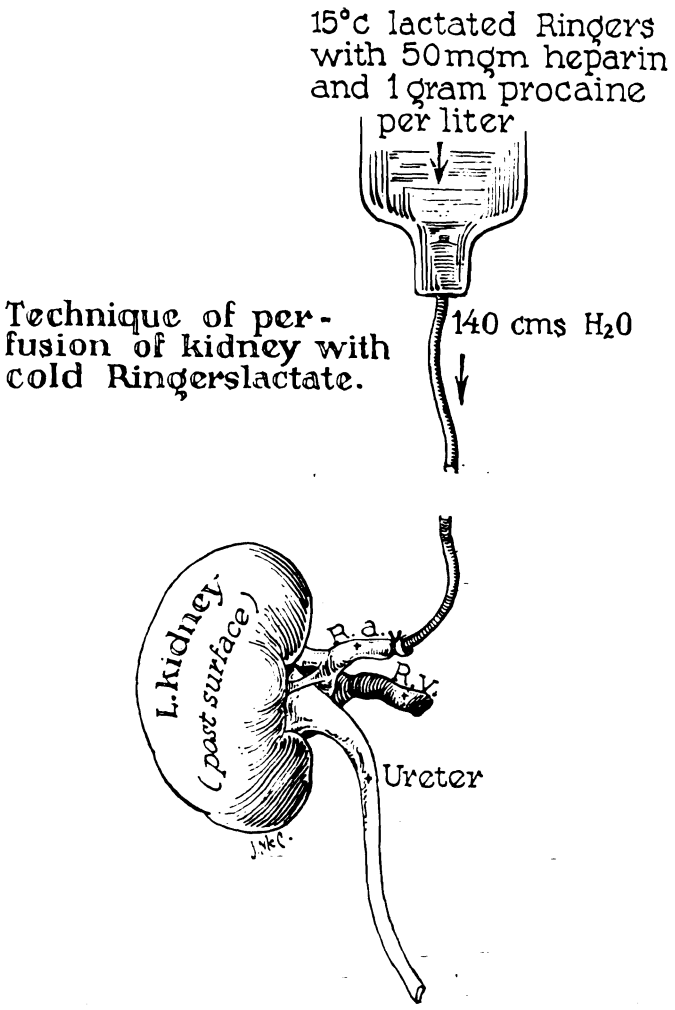

FIG. 16. Method of cold perfusion of renal homograft. Various other solutions have been evaluated including low molecular weight Dextran, either alone or in combination with blood, plasma, or saline. All work relatively well, the principal beneficial effect being the rapidly induced hypothermia.

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 2). It is noteworthy that

TABLE 2

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 2½ years after B to A homotransplantation. Nevertheless, a number of immediate failures have occurred after similar mismatches.

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, 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. 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 often 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 done through a short upper midline incision.

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 agent for the prevention of rejection has been azathioprine. Important additive benefits have been ascribed to prednisone, actinomycin-C and local homograft irradiation. 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 Figure 17. 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 and actinomycin C to pre-existing therapy with azathioprine was followed by a reversal of all of these adverse findings.

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. 17), the large doses of prednisone which

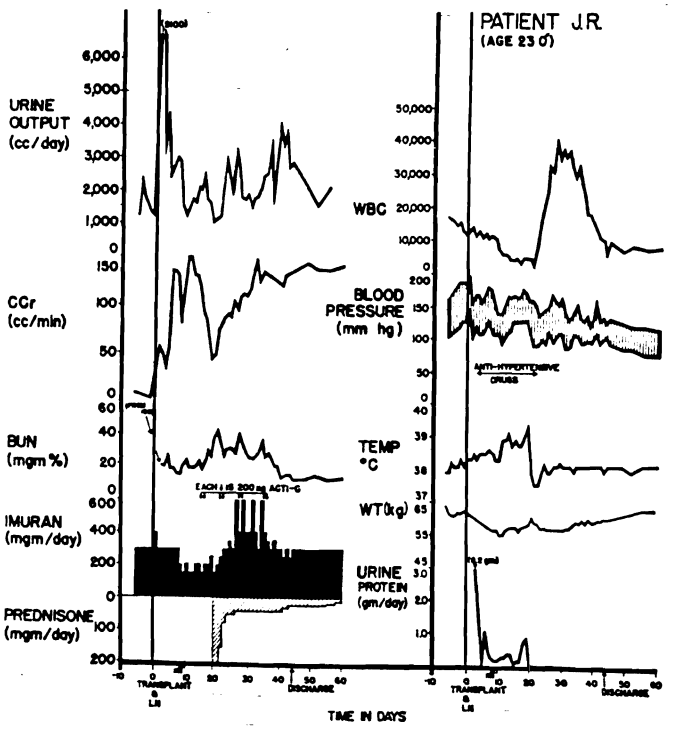

FIG. 17. Classical rejection crisis in a patient being treated with immunosuppressive drugs. Deterioration of renal function began 17 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. The transplantation was on April 17, 1963. Renal function was completely normal in August, 1965. Biopsy of the homograft after two years was normal. Acti-C—actinomycin C; LN—left nephrectomy at the time of transplantation; RN—right nephrectomy. Imuran is synonymous with azathioprine.

were temporarily necessary could be quickly reduced, and in this case they were discontinued altogether within 5 months. 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, as suggested by Woodruff, or in the host, or both, is not known.

The combination of azathioprine and prednisone provides the cornerstone of immunosuppressive therapy in most centres but Calne and Hume have also demonstrated the value of actinomycin-C and local homograft irradiation. Figure 18 illustrates the course of a patient who received all four forms of therapy in December of 1963. In this case the graft repudiation was unusually violent, leading to temporary anuria. The rejection episode was reversed and the patient is still alive with good function after more than one and a half years.

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 although they are of unknown worth. In several patients thymectomy was performed prior to transplantation, primarily because of the evidence in rodent experiments by Miller that the thymus

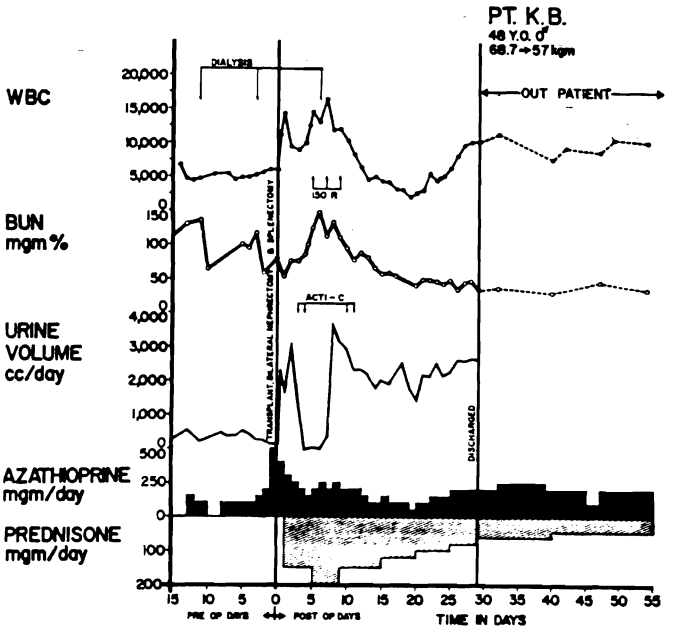

FIG. 18. Use of intravenous actinomycin-C and local irradiation to the homograft during a severe rejection crisis. Note the development of anuria by the fourth post-operative day. Homotransplantation was done December 4, 1963. The patient is still alive with good renal function in August, 1965.

gland is important in the adult in re-establishing reactivity to foreign antigens after a period of immunological depression. The first four patients to receive this procedure in Colorado have had extraordinarily benign late courses. All have had steroid therapy discontinued for at least $1\frac{1}{2}$ years and in none has there been evidence of late deterioration of homograft function. Since other factors such as chance histocompatibility could account for these superior results, the contribution of thymectomy is unknown. Many more recipient patients have had splenectomy in an attempt to reduce the host immunological reactivity. Much more research will be necessary to define whether or not either splenectomy or thymectomy play any significant role in potentiation of homograft survival in the human.

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 19. The young man concerned received a kidney from his brother. After 10 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*. The margin between therapy and toxicity was nonexistent in this case.

In all centres, *bone marrow depression* has been the outstanding toxic feature encountered in the use of azathioprine. More subtle undesirable effects have been observed at a later time. Many patients with homotransplantation have developed *jaundice* late in their course (Fig. 20). Since azathioprine is a known hepatotoxic agent, this may be nothing more than a direct pharmacologic injury to the liver. Alternatively, it may be viral hepatitis in patients whose capacity to resist infection has been generally weakened.

Prednisone therapy contributes, of course, to the increased susceptibility to infection both early and late. In addition, the facial and other changes are an annoyance to most patients whose late renal function is dependent

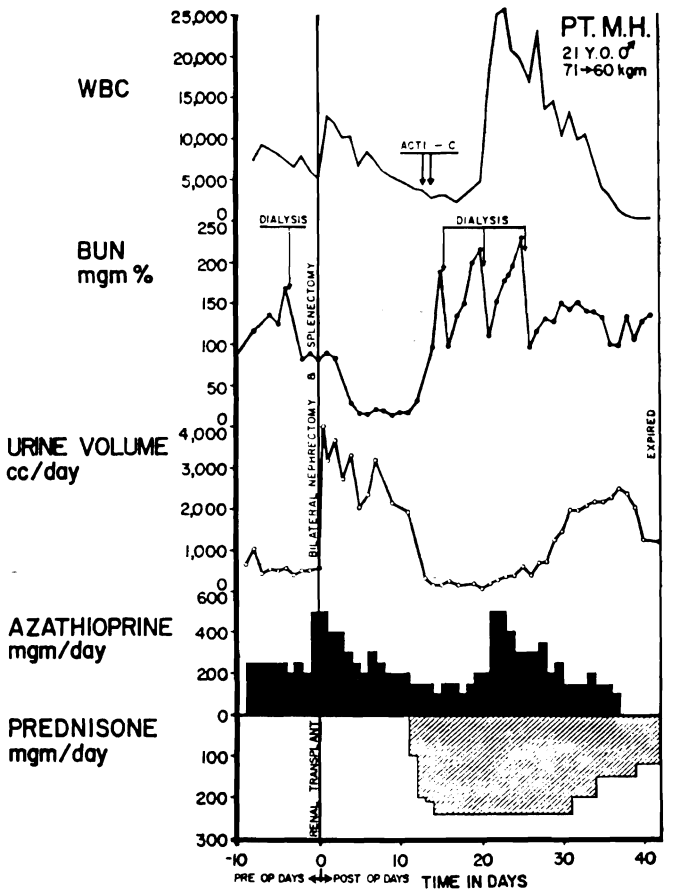

FIG. 19. Typical unsuccessfully treated case, The donor and recipient were brothers, both of A blood type. A violent rejection crisis followed good early function, and anuria developed which lasted two weeks. Although the rejection was reversed and a secondary diuresis began, the patient died from drug toxicity, leukopenia, and septicæmia. Anti-C—Each arrow is 200 μg intravenous actinomycin C.

upon continuing steroid therapy. Pathological fractures have been described in such cases as well as the development of lens cataracts; these complications also are probably due to the steroids.

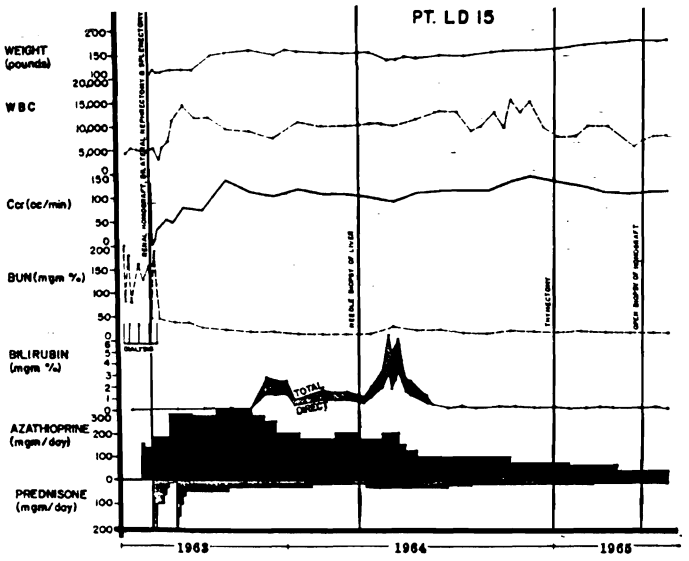

FIG. 20. Drastic reduction of immunosuppression in a patient who became jaundiced after transplantation. Note the development of hyperbilirubinæmia while the patient was receiving large quantities of azathioprine, and its remission as the dose was reduced. His weight has steadily increased as both steroids and azathioprine have been withdrawn. Detailed function studies after 21 months were normal despite a few abnormalities in the renal biopsy performed at this time. The homograft was provided by the patient's brother. The recipient was A blood type; the donor was O. Late thymectomy was performed because of the necessity for attenuation of immunosuppression; the value of this adjuvant procedure is unproven.

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. The fate of these well-functioning, but morphologically damaged, homografts can be determined only by continued observation.

Results and Future Prospects

Imperfect though the currently employed therapeutic methods are, greatly improved early survival after renal homotransplantation has been reported from several centres and it has already become possible to state with relative certainty that homotransplantation will have an increasing role in the general medical armamentarium of the future. Recent clinical results have exceeded any hopes of even a few years ago. Of the first 64 patients treated at the University of Colorado Medical Center with kidneys from volunteer living donors, 37 homograft recipients lived for at least 1 year after operation (Fig. 21) and 36 are still alive from 16 to 32 months (mean 22 months). Within this time limit, the results approach acceptability if homografts from genetically related donors were used; two-thirds of all those patients who received kidneys from blood relatives are still living. With unrelated donors the results are poor since only one-third lived for as long as 1 year (Fig. 21). In our experience the

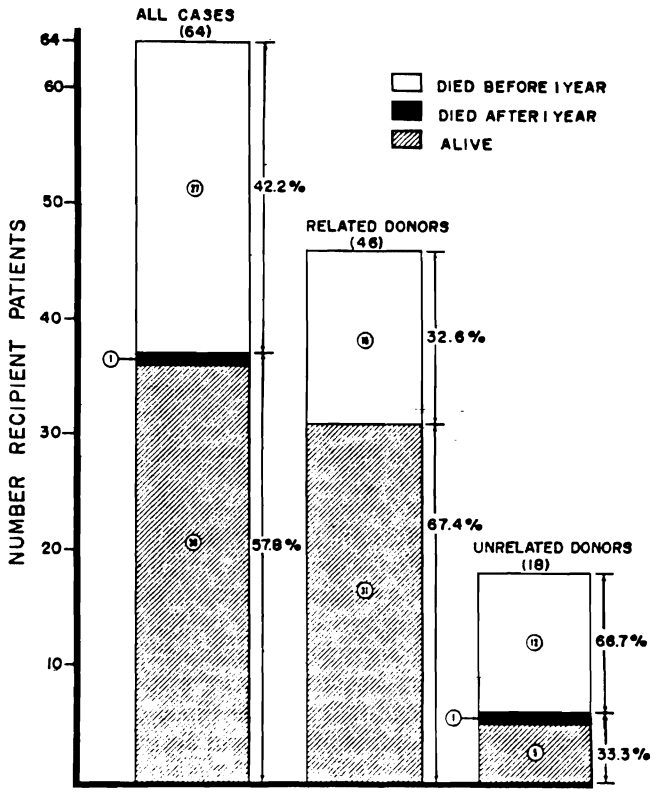

FIG. 21. Results after 16 months or longer in 64 consecutive patients treated at the University of Colorado Medical Center with renal homografts obtained from living donors. Identical twin cases are not included. Only 1 death has occurred after 1 year. Note that more than two-thirds of patients who received kidneys from blood relatives are alive from 16 to 32 months after transplantation. Only a third of those whose donors were unrelated lived as long as a year.

best survival within the related group was with parent-to-offspring transplants, 70 per cent of the recipients still being alive (Fig. 22). In the world experience, sibling to sibling transfers have had the highest success rate.

These results as well as similar pooled statistics from the National Science Foundation Transplant Registry indicate that many uræmic patients, perhaps even the majority, can be materially benefited by renal homotransplantation with relatively complete social and vocational rehabilitation over considerable periods of time. Nevertheless,

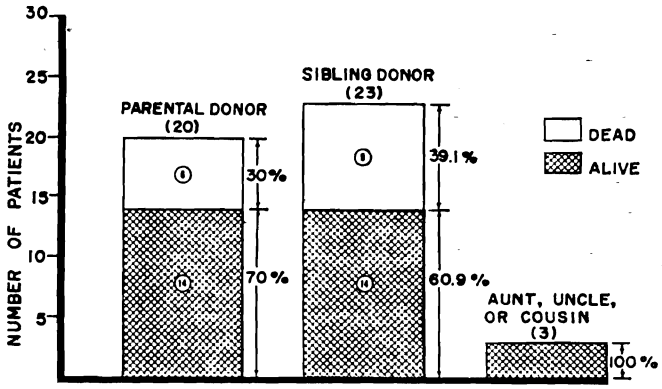

FIG. 22. Breakdown of results at the University of Colorado Medical Center in patients who received kidneys from blood relatives other than indentical twins from 16 to 32 months ago. The best results were with parental donations; in the world experience, however, sibling to sibling transplants have fared somewhat better.

workers in the field who have repeatedly warned that this treatment is experimental are not yet willing to abandon this position. The most important reason for a conservative attitude is that the ultimate life expectancy of the present crop of late survivors is still unknown. Barnes has attempted to answer this question in a statistical analysis of the death rate of those patients already treated and has predicted that further losses from the group of patients still living will occur at an extremely gradual rate.

Whether this is true or not can be determined only by actual observation. In the meanwhile there is legitimate reason for avoiding overoptimism. Not all patients who have reached a late stage of convalescence are well. As mentioned above, there is evidence of continued host-against-graft immunological activity in many of these long surviving patients. It is possible that most of the apparently well patients are living by virtue of renal homografts which are losing a small fraction of functioning parenchyma each day. For the moment, therefore, it would seem most reasonable to regard renal homotransplantation as an effective, but incompletely characterized, form of palliative therapy. Ultimately it may be proven that it is a curative procedure, but that time has not yet arrived.

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