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Transplantation of the Kidney

Thomas E. Starzl, M.D., Ph.D.

Professor of Surgery, University of Colorado
School of Medicine and Chief of Surgery, Denver
VA Hospital

Thomas L. Marchioro, M.D.

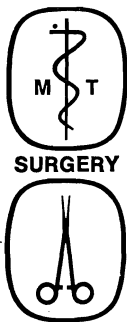
Associate Professor of Surgery, University of
Colorado School of Medicine, Markle Scholar;
and Assistant Chief of Surgery, Denver VA
Hospital

Volker Zühlke, M.D.

Fellow in Surgery, Recipient of Scholarship of
Deutsche Forschungsgemeinschaft, Germany

Lawrence Brettschneider, M.D.

Instructor in Surgery, University of Colorado
Medical Center



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HETEROTRANSPLANTATION of sub-human primate kidneys to patients suffering from uremia was initially attempted in the late 19th Century. The first effort at homotransplantation was made by Voronoy in Russia in 1936. In the succeeding 16 years there were additional sporadic efforts at clinical renal homotransplantation, first without immunosuppressive therapy and later with total body irradiation of the recipient. The almost universal failure of these attempts provided little reason to hope that transplantation of the kidney would ever be a clinically useful method of therapy.

Despite the tragedies and disappointments, these pioneer efforts established a foundation

Thomas E. Starzl, M.D., Ph.D.

Professor of Surgery, University of Colorado School of Medicine and Chief of Surgery, Denver VA Hospital

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for subsequent trials. Two patients provided in 1958 and 1959 with kidneys from their fraternal twins in Boston and Paris, respectively, are still alive; both received sublethal total body irradiation. Using the same therapy, Hamburger, Dempster, and Küss reported non-twin cases in which chronic survival was achieved. A cousin was the donor for Hamburger's patient, a brother for Dempster's, and a non-related cadaver for Küss's.

In the meantime, important experience was accumulated from study of identical twin cases studied in Boston by Merrill and Murray. Since an immunologic barrier is not present under these circumstances, it was more easily possible to define the technical requisites for success, to obtain valuable information about the response of the recipients to rapid correction of their uremic state, and to define both the risks and the prognosis of the donors.

From the Departments of Surgery, University of Colorado Medical School and the Denver Veterans Administration Hospital, Denver, Colorado.

In 1962 a sudden change took place in the outlook after renal homotransplantation, a change which was brought about by the employment of certain pharmacologic agents for immunosuppression. It seemed at first that these agents had a considerably greater margin of safety than ionizing irradiation, although subsequently Hamburger and his associates have achieved almost equivalent results with total body irradiation. In the ensuing 4 years, a large number of patients have been treated with renal homotransplantation, approximately 1,000 cases in all. Although the techniques currently available are still imperfect, the results have established beyond doubt that transplantation of the kidney and other organs can be expected to occupy a prominent place in the therapeutic armamentarium of the future.

WHAT HAS BEEN ACCOMPLISHED?

During the early part of what might be termed the modern era of renal transplantation, every group was undergoing a learning process. Mistakes in both the surgical and medical therapy were common. In addition, there was at this time no practical way of determining prior to operation whether or not a biologically suitable donor was being employed. The matching of donors and recipients was on an entirely fortuitous basis without any predictability about the magnitude and perseverance of the subsequently expected rejection.

Despite these very severe limitations, substantial chronic survival was attained in a number of centers. At the University of Colorado Medical Center and Denver Veterans Administration Hospital a group of 64 patients were treated with kidneys from living volunteer donors between November of 1962 and March of 1964. Thirty-seven of these patients lived for as long as one year, 34 lived for at least two years, and on June 15, 1966, 33 are still

surviving after 2½ and 3¾ years (Figure 1). All of these patients except one are still living on the function of a single kidney; the exceptional patient has been re-transplanted.

In the original series in which donor-recipient pairing was on a random basis, there was a highly significant difference in the results when blood relatives were used as donors compared to that achieved with non-related donors. Of 46 patients who received kidneys from parents, siblings, aunts, uncles, or cousins (excluding, of course, identical twins), 31 or 67% lived for 1 year, 30 for at least 2 years, and 29 until the present time. In contrast, only 6 of the 18 patients who received non-related kidneys lived for as long as 1 year and only 4 of these passed the 2-year mark (Figure 2).

Experience with this original group of cases supports several general conclusions. First, more than half of the total group of patients achieved extremely worthwhile palliation. The vast majority of these chronically surviving patients are leading useful lives, and have been relatively completely rehabilitated. It has been equally evident that certain penalties are necessary. Disease entities attributable to the immunosuppressive agents have been seen. The expense of caring for these patients has been great, especially in the early months after operation. The need for further improvement of technique is most keenly appreciated by those who actually have had experience in this field.

CANDIDATES FOR RENAL HOMOTRANSPLANTATION

With the present incomplete state of knowledge, it is essential that the patient be truly terminal with a life expectancy limited to a few days or weeks without either renal dialysis or transplantation. To qualify for candidacy it is desirable that the patient be young, preferably

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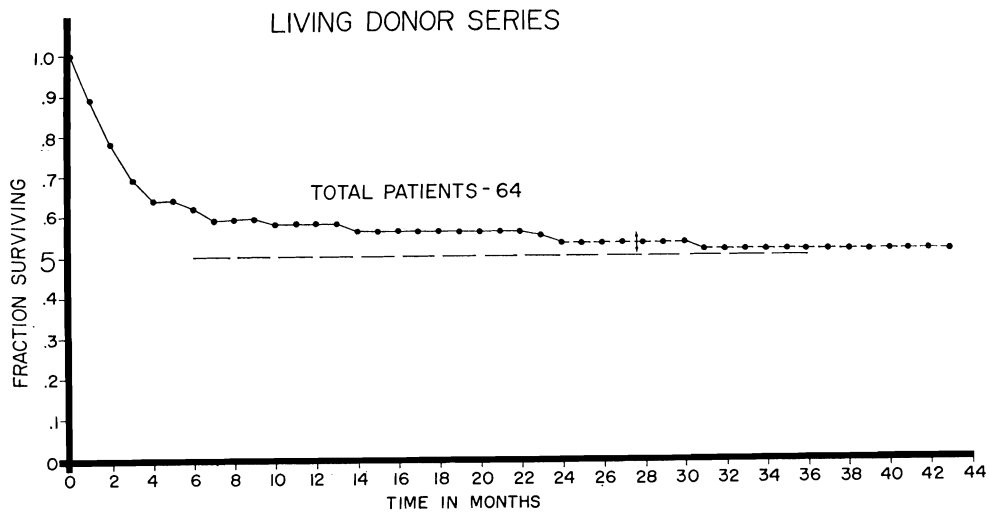


FIGURE 1 Life survival curve of 64 consecutive cases treated at the University of Colorado Medical Center with kidneys obtained from living volunteer donors. The curve is up to date June 15, 1966. All surviving patients are already to the right of the arrow. Note after 2 1/3 years that more than half of the total group are still alive.

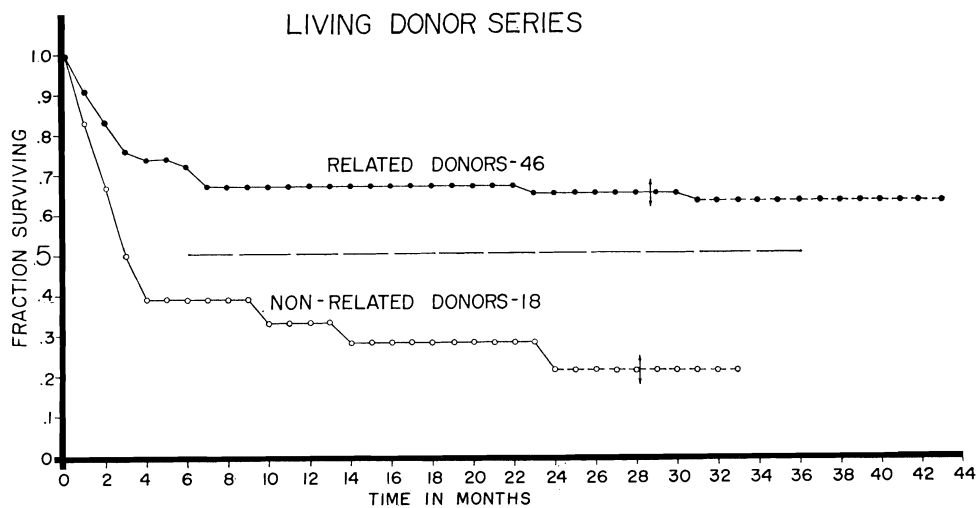


FIGURE 2 Breakdown of the total results shown in Figure 1 according to the source of the homograft. Note that approximately 2/3 of the patients who received kidneys from related donors are still alive, compared to only 22% of those who received non-related kidneys.

less than 40 years of age. He should be free of other disease. In this age group the most important cause of involvement of other organ systems is the renal failure itself since diffuse vascular disease, myocardial injury, brain involvement, or pancreatitis are all complications of uremia.

Because immunosuppressive agents will inevitably reduce the immunologic reactivity of the recipient, it is mandatory that all foci of infection be eliminated in advance of operation. Finally, the presence of a normal lower urinary tract should be proven. As a research undertaking, Kelly and his associates at the University of Minnesota are evaluating the feasibility of employing ileal conduits as receptors for the homograft urine excretion in patients with diseased bladders. As worthwhile as these investigations are, the additional risk under these circumstances would preclude the patient for consideration in most transplantation clinics at the present time.

The final decision for or against transplantation is inevitably influenced by the presence or absence of a suitable donor. During the days when preoperative antigen testing was not possible, the unavailability of a familial donor invariably created grave questions about the advisability of proceeding in view of the very poor results then being obtained with non-related kidneys. As will be discussed below, there is some hope that this situation is changing.

DONOR SELECTION

To be considered as a living donor a volunteer should be less than 50 years of age, in perfect health, and with proven normal renal function. A careful history, physical examination, and electrocardiogram will eliminate a surprisingly large number of candidates. Part of the evaluation of renal function includes de-

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

TABLE 1

termination of creatinine, inulin and para-aminohippurate (PAH) clearances. If these are normal, an intravenous pyleogram and aortogram are obtained as the final steps. It is our general policy not to attempt transplantation of a kidney which has a multiple arterial supply. Although such an organ can be readily revascularized, the necessary ischemic interval is inevitably increased.

Knowledge of the blood type of the recipient and the respective donors is essential information in screening a potential donor pool. Ideally, the donor and recipient should have the same blood type. However, various combinations in which this is not the case are perfectly acceptable. These are summarized in Table 1. It will be noted that the rules for transplantation in the absence of blood group conformity are essentially the same as those which apply to the use of non-matched blood. The O patient who is a universal donor could receive only from another person with O blood type; conversely, an AB patient is a universal recipient but could donate only to another patient of AB type. In the absence of sensitization, the Rh antigen is apparently not an important factor.

It is necessary to provide protection to the

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donor from social pressures which may be brought to bear upon him. This is particularly apt to be a problem within certain families in which a priority of expendability has been ascribed to certain members. The potential donors are examined by psychologists or psychiatrists. If evidence of coercion is uncovered, the patient is pronounced unfit for medical reasons, thereby sparing him from both personal guilt feelings and ostracism from his parents or siblings.

It was not formerly possible to attempt donor screening except by the very crude methods just alluded to. Consequently, the transplantation itself served as a biologic test system in which those patients who had accidentally achieved a good histocompatibility match with their donors were apt to live. Those with a bad match were presumably ruthlessly weeded out. The unacceptability of this approach was particularly well demonstrated by the very poor long-term survival when randomly selected non-related donors were used. During that era there was virtually no available information on the location, nature and number of human histocompatibility antigens.

Subsequently, hope that practical tissue typing schemes are not far off has stemmed from investigations of isoimmune antisera obtained from patients who have accidentally or deliberately been sensitized to white cell antigens. The agglutination, or cytolysis of test cells by such antisera implies the presence of the same or a similar antigen as that which originally sensitized the serum donor; failure of such a reaction implies the absence of the antigen. Using these sera the white cell antigenic differences and similarities between recipients and prospective donors can be compared.

Initially, it was not clear if those antigenic systems being studied had any relation to histocompatibility. Recently, however, evidence has

been forthcoming that this may be the case. The most convincing studies have come from Terasaki of Los Angeles who prospectively typed a group of patients treated in Denver from 13 to 20 months ago. Thirteen of these patients received kidneys from non-related sources, the actual donor being selected from a large pool on the basis of the best possible antigen match with the recipient; because of the large donor panel, a relatively high degree of selectivity was possible. The other 13 were provided with kidneys from familial donors. The limited number of family members did not allow a high degree of selectivity in this latter group, and in fact the quality of donor-recipient antigen match was scarcely better than would have been achieved through chance intrafamilial pairing.

The outcome in this small group of cases is depicted in Figure 3. During the time of available follow-up, the results are exactly the same in both related and non-related cases. Even though the present techniques of antigenic analysis are cumbersome and imprecise, these preliminary results are distinctly encouraging. If and when such techniques can be applied to selection of cadaveric kidneys, many of the ethical and social problems imposed by employment of living donors will be subject to elimination.

WHY IS SUCCESSFUL TRANSPLANTATION POSSIBLE?

The most important drug which has changed the outlook after renal homotransplantation has been 6-mercaptopurine, an agent demonstrated by Schwartz and Dameshek to blunt the immunologic response in animals exposed to various foreign proteins. Subsequently an imidazole derivative of 6-mercaptopurine, termed azathioprine, was developed by Dr. George H. Hitchings of the Burroughs Wel-

come Co. and demonstrated by Calne, Zukowski and others to markedly potentiate homograft survival. Although both 6-mercaptopurine and azathioprine are known to inhibit DNA synthesis, the way in which they prevent or attenuate rejection is incompletely understood. In overdosage, both cause bone marrow suppression but this toxic effect is not necessary for therapeutic efficacy.

With the immunosuppressive protocol now widely employed, azathioprine forms the cornerstone of therapy. Administration is started in advance of operation and continued indefinitely thereafter. In most cases, however,

azathioprine therapy alone is insufficient to prevent homograft repudiation. The employment of prednisone as a second drug is almost always necessary. It can either be used prophylactically from the time of operation or can be instituted at the time of a rejection crisis. Other adjuvant measures such as intravenous actinomycin C or local homograft irradiation may be useful either prophylactically or during a rejection episode but their effect is much more limited.

One way in which azathioprine and prednisone can be employed is demonstrated in Figure 4. The patient received azathioprine

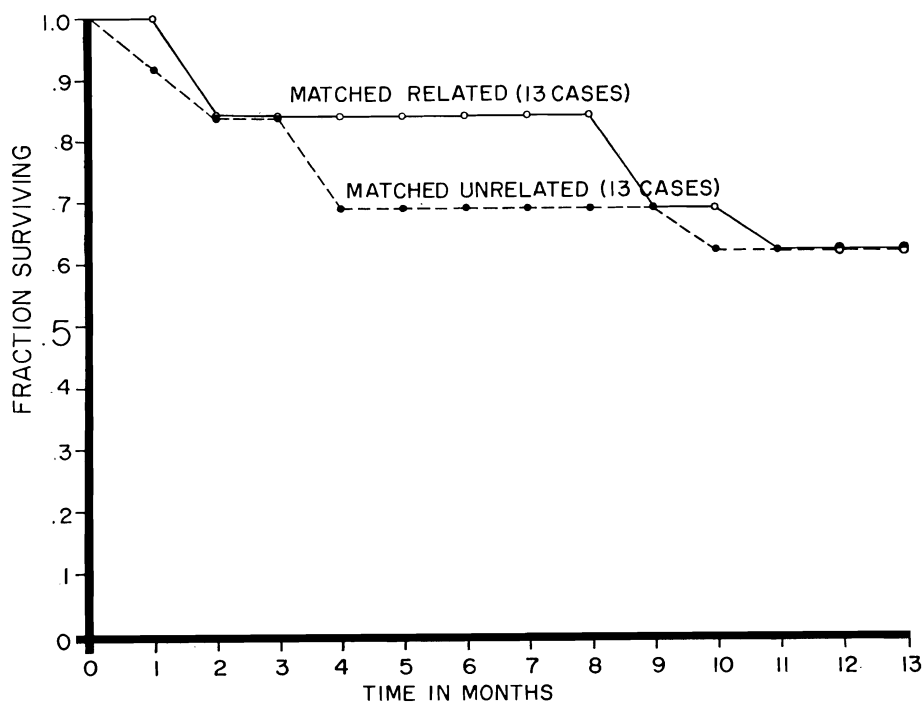


FIGURE 3 Results of renal transplantation in a more recent series of patients, whose donors were selected by Terasaki's antigen matching method. Note that survival after 13 months was exactly the same in both the related and non-related cases; all of these patients are now from 13 to 20 months postoperative. Compare these results with those shown in Figure 2.

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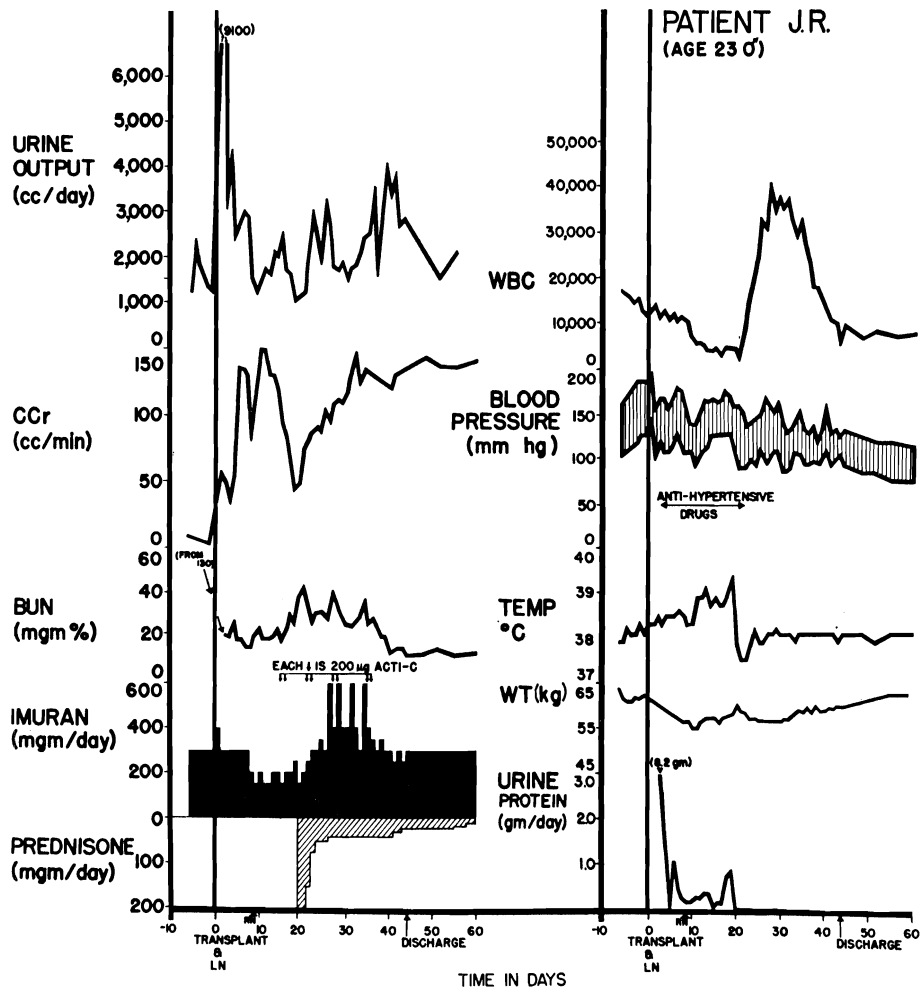


FIGURE 4 Classical rejection crisis in patient treated with drugs alone. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. Note the complete reversal of these adverse events after the institution of steroid therapy. Six months later prednisone was discontinued. The patient who was operated upon in April of 1963 has completely normal renal function more than three years later. A renal biopsy after two years was normal both by light and electron microscopy. Acti-C—Actinomycin C; LN—left nephrectomy at time of transplantation; RN—right nephrectomy. Imuran is synonymous with azathioprine. (By permission of Surg., Gynec. & Obst. 117:385, 1963)

both before and after the time of his transplantation. There was an immediate postoperative diuresis with complete relief of azotemia. The benefit was, however, short lived. Nineteen days later the BUN began to rise secondarily. The creatinine clearance dropped sharply. He developed fever and there was an increase in proteinuria. The addition of large doses of prednisone caused a prompt reversal of all of these adverse events. There was a sharp diuresis, restoration of creatinine clearance, and disappearance of the urine protein. The acute fever was relieved within hours after the first steroid dose.

The course of this patient demonstrates two important principles which have emerged far more clearly from clinical studies than from observations in animal experiments. The first was that rejection is a reversible process, contrary to the deeply entrenched and pessimistic historical view. The second principle concerns the apparent change in host-graft reactivity that evidently occurs rather early after successful renal transplantation. The patient whose course is depicted in Figure 4 illustrates this alteration. In this case, it was initially impossible to maintain good homograft function by means of azathioprine therapy alone. Within 6 months, however, at which time prednisone was stopped, his course was perfectly stable while being treated solely with azathioprine. He is now more than 3 years postoperative and has never had further difficulty.

The reversibility of rejection and the often observed diminishing requirement for immunosuppression are the most important practical events which make it possible to achieve chronic survival. In view of these observations, it is reasonable to wonder if chronically surviving patients require any immunosuppression at all for maintenance of homograft function. In dogs this possibility has been evaluated in a

number of animals by stopping therapy 4 months to 2 years after replacement of either kidney or liver homografts. Approximately 1 out of every 3 such grafts will continue to function without any evidence of further injury. Five animals have been followed in our laboratory from 2 to more than 3 years under these circumstances. Unfortunately, it has been impossible to predict which animals will behave in this way and which will reject their homografts. It is not, therefore, safe to stop therapy in comparable patients.

The explanation for the change in host-graft reactivity is obscure. It is not known if there is an alteration in the host, if alternatively there is some change in the antigenic constitution of the graft, or if both factors contribute. The hypothesis that an enhancement phenomenon was responsible was weakened in the past by the fact that circulating antigraft antibodies which are necessary for tumor enhancement could not be consistently demonstrated in either dogs or man after renal homotransplantation. The possibility that enhancement may be a factor in the development of "host-graft non-reactivity" has recently been strengthened by Iwasaki's demonstration in our laboratories of the presence of highly specific antibodies in the sera of almost all patients after clinical renal transplantation.

IMPERFECTIONS OF THE METHOD

Were it not for the change in host-graft reactivity described above, it would be expected that chronic renal function could be obtained only at the expense of nearly complete immunologic crippling of the recipient. In many cases this has not been necessary particularly when survival beyond the first few months was achieved. Nevertheless, some loss of reactivity to foreign antigens is inevitable in every case. Furthermore, the degree of this

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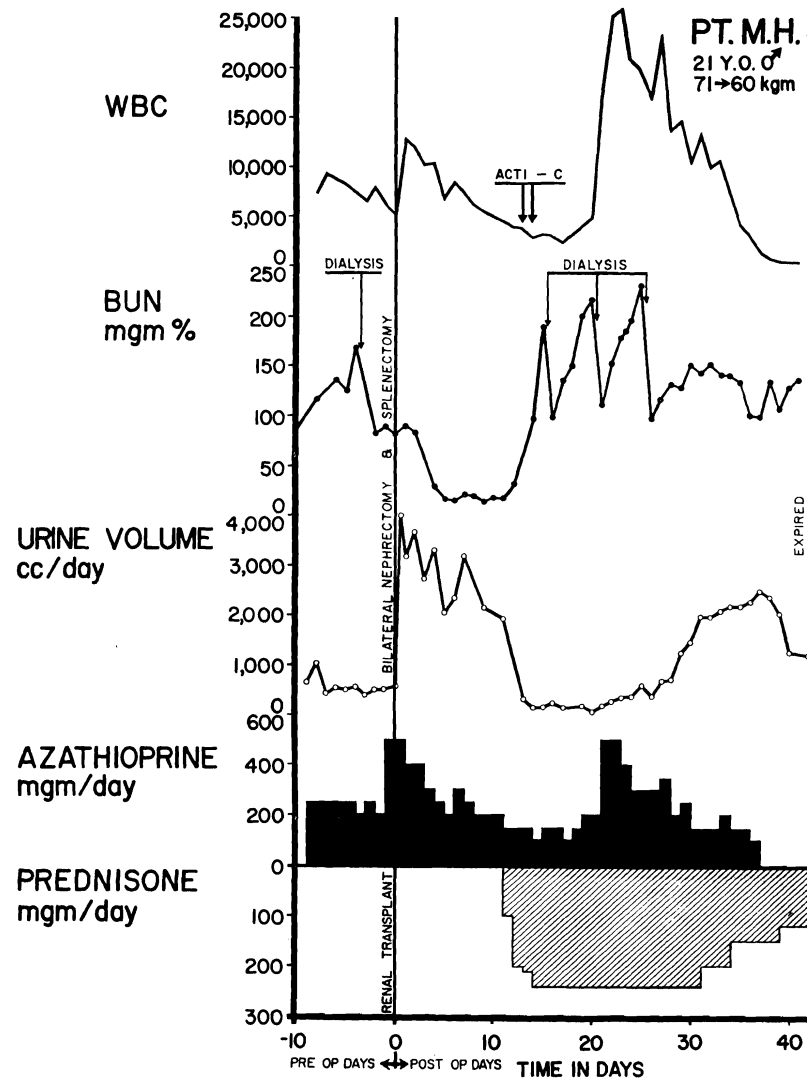


FIGURE 5 Typical unsuccessfully treated case. The donor and recipient were brothers, both of A blood type. A violent rejection crisis followed good early function, and anuria developed which lasted two weeks. Although the rejection was reversed and a secondary diuresis began, the patient died from drug toxicity, leukopenia, and septicemia. Acti C—Each arrow is 200 ug intravenous actinomycin C. (By permission of *Surgery* 56:296, 1964)

loss during the early convalescence when maximum immunosuppression is employed is so great that the margin of safety at this time is extremely slim. It is not surprising therefore that most of the deaths occur early, within the

first few post-transplant weeks or months. Almost invariably these unsuccessfully treated cases follow a typical pattern (Figure 5). After transplantation good homograft function is observed. With a subsequent rejection crisis and

with intensification of immunosuppressive therapy the rejection can be controlled but often at the price of fatal sepsis. The patient illustrated in Figure 5 had a severe but reversible rejection. As renal function was improving, he died of a systemic fungal and bacterial infection.

The use of azathioprine to prevent rejection of kidney homografts presents special problems of toxicity because of the fact that this drug has an important renal pathway of excretion, normally accounting for 25-50% of the ingested dose. During the early postoperative period when renal function is very often unstable, the amount of azathioprine eliminated through the urine may vary from day to day or from hour to hour. As a consequence, dose control is exceedingly difficult. The poor results obtained several years ago with cadaveric homotransplantation may have been partly due to lack of appreciation of this fact. Such patients whose homografts often must pass through a period of acute tubular necrosis before urine excretion commences cannot be treated early with as large a quantity of azathioprine as patients who receive well-functioning kidneys from living donors.

The sepsis which results from miscalculation of dosage has been the subject of considerable study. The majority of infections are caused by common pyogenic organisms but there is also a high incidence of unusual infections with fungi, protozoa (such as *Pneumocystis carinii*), and viruses (such as those of hepatitis, cytomegalic inclusion disease, or herpes zoster).

Although the acute threat of sepsis diminishes after the first few months, a continued morbidity due to the immunosuppressive agents has been observed. Chronic liver disease has been a problem in many patients. In some, this apparently started as a viral hepatitis; one such patient died 157 days after operation from

acute yellow atrophy. In others jaundice has appeared and waxed and waned for as long as 1 year. In still others, hypoproteinemia and decreased bromsulphalein (BSP) excretion have been observed without evident antecedent acute liver disease. In many cases the cause for these hepatic complications has not been clear. In dogs, azathioprine is highly hepatotoxic, but the evidence that the human liver is similarly affected is equivocal. Steroids can cause fatty metamorphosis or even cirrhosis when administered to experimental animals for protracted periods. In any event, the patient with renal homotransplantation must have hepatic function followed with care.

In addition, other late problems have been observed with range from nuisance factors to life-threatening complications. The most consistent complaints are from patients who require long-term steroid therapy. The cosmetic deformity when high doses must be continued chronically is the cause of much concern particularly to female patients. Infants and children whose continued renal function is steroid dependent do not grow. Pathologic fractures of the femoral neck or vertebrae have been seen in 4 patients apparently secondary to steroid-induced osteoporosis.

Mechanical urological problems must be looked for at routine intervals. Late strictures either at the ureteral anastomosis to the recipient ureter or the bladder have been detected in 4 patients and in another one a stricture developed apparently on the basis of scarring at the site of a previous ureteral rejection.

LATE HOMOGRAFT FUNCTION

The most serious late morbidity, however, is due to continued immunologic activity against the graft. More than a dozen patients amongst our group of chronic survivors have had deterioration of homograft function from 4

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months to more than 1½ years postoperatively. When this complication has occurred it had almost invariably followed reduction of the steroid dose. The development of late rejection under these circumstances constitutes a very long-term or even permanent commitment of the patient to steroid therapy. In many cases the development of a late rejection episode is not dissimilar to that classically observed in the first few weeks. Fever, abrupt oliguria, and rapidly developing azotemia may be seen. This kind of late rejection can usually be controlled, the most important step being an adjustment of the steroid dose.

A more insidious form of late rejection may cause a very gradual loss of renal function over a period of many months. This slow functional deterioration is not strikingly influenced by intensification of immunosuppression.

Chronic homograft function in the recipients of kidneys from blood relatives has been much more stable than in non-related cases. In the former group, studies of creatinine, inulin, and PAH clearances have shown a drop in only a few cases between the first and second years. The recipients of randomly selected non-related kidneys in our original series have, in contrast, almost invariably shown a gradual decline in function not only in the first, but also in the second and third postoperative years. Whether function will be more stable in the more recent series of non-related cases in which donor-recipient antigen matching was performed can be answered only by longer follow-up.

LATE PATHOLOGIC CHANGES

Homograft tissue from 36 of the Denver cases has been obtained from 1 to more than 2 years after operation, either as the result of open biopsy or in 3 cases from autopsy tissue. The resulting pathologic studies performed by

Dr. K. A. Porter of St. Mary's Hospital and Medical School, London, have clarified many of the pathologic features of the chronically tolerated and functional homograft. At 2 years approximately 20% of these kidneys were either completely normal or had relatively insignificant changes. The others had an assortment of abnormalities which were often not associated with serious impairment of renal function.

There were vascular lesions which had many forms; fibrous intimal thickening of interlobular arteries often with rupture or duplication of the internal elastic lamina, deposition of a hyaline-like substance in the subintimal layer of afferent arterioles, and deposition of the PAS-positive hyaline material in the glomerular capillaries. The homografts with vascular lesions often had other secondary morphologic changes; fibrosis of the glomerular tuft, periglomerular fibrosis, interstitial fibrosis, or tubular atrophy.

In addition, the majority of the homografts contained focal accumulations of mononuclear cells. Ten to 40% of these cells consisted of the pyronine positive variety which are traditionally found in acutely rejecting homografts. In the chronically functioning homografts, they seemed to be reasonably well tolerated.

WHAT TO ADVISE THE UREMIC PATIENT

The answer to this question has not been made easier by the improved results after renal homotransplantation during the past few years since this type of therapy is still a hazardous undertaking. Furthermore, the life expectancy of those patients still living by virtue of their chronically functioning homografts is not known. On the other hand, more than half of the patient treated in the era when pessimism was most widespread are still alive for more than 2 to almost 4 years later.

Perhaps the best approach would be to present the actual statistics, initially making no effort to editorialize one way or the other. It is important also to paint an accurate picture of the financial sacrifice and the morbidity which may have to be borne by the patient and his family. If a truly honest presentation is made, the uremic individual and his family will often come to a firm decision without further guidance. Very often this decision will be negative and surprisingly frequently it will be the patient himself who declines further consideration of therapy either with renal transplantation or with chronic renal dialysis.

It is only when such an objective approach is not taken that the physician-patient relationship is threatened. Under these circumstances, a bereaved family may later come to feel that a lost one has been cheated of a form of available therapy, or alternatively in the event of a failed transplant, they may conclude that the potential of the method had been oversold.

THE FUTURE OF RENAL TRANSPLANTATION

The methods of organ transplantation employed now will surely seem ridiculously imprecise to future generations of physicians. What has been achieved to date establishes unequivocally that renal homotransplantation can materially prolong useful life for many patients. However, the best results today are dependent upon a procedure which will be unacceptable in the long run, namely the use of living donors. It is mandatory that techniques be perfected to the point that cadaveric organs can be used with consistent success. Salvage could then be offered to the sick patient without the necessity of subjecting well motivated healthy individuals to medical and surgical procedures.

In order to make this possible, developments are necessary in 3 general areas. First, the typ-

ing techniques described earlier, must be refined and applied to the matching of cadaveric organs against potential recipients. Secondly, new, more specific, and safer immunosuppressive regimens must be evolved. The most promising research in immunosuppression in the recent past has been with heterologous anti-lymphocyte sera. This material is prepared by immunizing animals against the lymphoid tissues of another species. The serum of the immunized animal can then be collected, purified, and injected back into members of the donor series with resulting lymphopenia. The anti-lymphocyte antibody is in the gamma globulin, the administration of which has been found experimentally to be well tolerated. Its use has permitted the long term survival of homografts in rats, mice, guinea pigs, and dogs.

Finally, much more effort will be required for effective utilization of cadaveric organs. The present methods of tissue preservation are crude and effective only for short intervals. Improvements in organ preservation could permit the establishment of banks containing organs which could be studied for histocompatibility characteristics and used electively as needed. To make this possible, a program of public education will be required of the same kind as that which has been so successful for the establishment of eye banks.

Since the autumn of 1965, 7 cadaveric transplantations have been performed at the University of Colorado Medical Center, with attention to some but not all of the above details; the general technique of immunosuppression was not altered from that used in the past for living donor cases. Five of these 7 patients are still alive from 3 to 8 months postoperatively. These results contrast sharply with those obtained with 3 comparable cases in 1963 in which all 3 recipients died within 2 months.

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Summary

Progress in homotransplantation of the kidney has been reviewed. This form of therapy for the patient with terminal uremia has resulted in a 2-year survival of more than 50% at the University of Colorado Medical Center, excluding from consideration identical twin cases. The best results were with the use of kidneys obtained from familial donors; when this has been possible the 2-year survival is al-

most 2/3. With randomly selected non-related living donors the 2-year survival was only 22%.

Although these results indicate the great potential value of organ transplantation, the techniques being employed today are imperfect. The need for progress with better immunosuppression, better histocompatibility analysis, and better organ preservation are outlined.

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