

ver Veterans Administration Hospital with 234 homografts in 216 patients. Ureteroneocystostomy was performed in 178 instances with post-operative difficulties in 16 (9 per cent). Reconstruction by ureteroureterostomy was accomplished in 55 instances with urological complications in 7 (13 per cent). Urological complications were found to be far more life-threatening if they occurred during the first 6 weeks after transplantation. All 5 deaths directly attributable to urological problems occurred in patients who developed difficulties during this period. There was no mortality attributable to urological complications occurring several months to two and a half years after transplantation. The diagnosis and management of all urological complications are described and suggestions made, based on the authors' experience. The wealth of experience described in this article makes it an essential part of the bibliography of any urologist performing renal transplants.

2. Salaman, J. R., Calne, R. Y., Pena, J., Sells, R. A., White, H. J. O., and Yoffa, D.: Surgical aspects of clinical renal transplantation. *Brit. J. Surg.* 56:413, 1969.

The surgical experience, over three years, of 74 kidney transplants from AddenBrooke's Hospital, Cambridge, is reported. This is an excellent review of the surgical procedures that are performed in a transplant unit, their indications, complications, etc. Operations include live and cadaver donor nephrectomies, recipient nephrectomies, and the various methods of transplant employed by this group. Urinary fistulas and leaks are described with some interesting reconstructions.

3. O'Donoghue, E. P. N., Chisholm, G. D., and Shackman, R.: The urological complications of transplantation. *Proceedings of the European Dialysis and Transplant Association* 8:252, 1971.

Reported are 102 transplants, 100 reconstructed by ureteroneocystostomy and 2 by primary ureteroileostomy. There were 13 urinary fistulas. There were no graft nephrectomies or deaths associated with 5 bladder fistulas. Of 5 patients with ureteral fistulas, 2 died and 1 required transplant nephrectomy. Two patients were managed by a unique method—temporary ileo-ureterostomy and subsequent ileoureterocystoplasty with excellent results. Three uncommon pyelocaliceal fistulas likewise responded well to imaginative surgery—in these cases intact omental flap graft. Of 7 patients with ureteric obstruction, only 3 were managed successfully. There were also 2 patients with post-transplant vesicoureteral reflux and persistent infection.

4. Williams, G., Birtch, A. G., Wilson, R. E., Harrison, J. H., and Murray, J. E.: Urological complications of renal transplantation. *Brit. J. Urol.* 42:21, 1970.

The experience at the Peter Bent Brigham Hospital with urinary extravasation in 23 patients out of 158 transplants is reported. The investigators describe the problems associated with diagnosing extravasation, as well as their methods of managing it. In an attempt to decrease the mortality associated with extravasation, they suggest leaving the wound open for drainage as well as proximal nephrostomy. They feel that urinary leaks are only rarely successfully managed with ureteral catheter drainage.

Overview of Renal Homotransplantation: A Ten-Year Retrospective Study

Thomas E. Starzl

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It requires only a few moments of reflection to appreciate how brief is the history of kidney homotransplantation as a practical means of treating people with terminal renal disease. With a few historically important exceptions

recorded by Murray and Merrill, by Hamburger, Küss, and Schackman, and by Dempster (summarized by Goodwin and Martin¹), attempts under total body irradiation to use renal homotransplantation for clinical therapy

This work was supported by research grants from the Veterans Administration, by grants RR-00051 and RR-00069 from the general clinical research centers program of the Division of Research Resources, National Institutes of Health, and by grants AI-10176, AI-AM-08878, and AM-07772 of the United States Public Health Service.

before 1962 were doomed to failure. But in that year and in 1963, three American²⁻⁴ and one European⁵ centers acquired experience with the drug combination of azathioprine and prednisone for the prevention or reversal of rejection. Almost immediately, it became obvious that major progress had been made in the treatment of a failed vital organ system, an achievement that had amplified significance because of collateral advances in renal dialysis technology by which prospective recipients could be resuscitated and maintained in preparation for transplantation. At our center in 1966, a third potent agent, heterologous antilymphocyte globulin (ALG), was added to azathioprine and prednisone in what has been termed "a triple drug" immunosuppressive program.⁶

Groth⁷ has described the steps by which renal hemotransplantation was brought from the state of clinical experimentation to accepted treatment. No attempt will be made in the following discussion to cover that historical ground. Instead, the objective will be only to provide a follow-up on one of the earliest groups of kidney patients in which a substantial number of graft recipients survived beyond the early postoperative period, and therefore became available for observations about the long-term expectations after such therapy. Thus, these comments will be concerned almost exclusively with patients treated by renal homotransplantation from nine to more than ten years ago at the Denver Veterans Administration and Colorado General Hospitals.

CASE MATERIAL

Sixty-four patients underwent renal homotransplantation between November, 1962, and early 1964; they provided the basis for a book⁸ on this subject published in 1964. There were 46 recipients of consanguineous kidneys from 23 siblings, 20 parents, 1 aunt, 1 uncle, and 1 cousin, and 18 recipients of nonrelated kidneys donated by healthy volunteers. Immunosuppression was with azathioprine and prednisone, using two regimens. In 45 cases azathioprine was started alone; prednisone was added in 43 of these 45 patients with the appearance of clinically obvious rejection. In the other 19 recipients both drugs were administered from the outset.

Typing procedures were not available when this series was compiled. Consequently, the donor-recipient matching was not by any kind of immunological guidelines except for the avoidance in all cases after the twenty-third one of the kind of red blood cell type incompatibility that can (but does not necessarily) lead to hyperacute rejection.⁸ Parenthetically, one of our earliest recipients is still alive with perfect graft function more than 10 years after transplantation from a B+ type donor to A+ type recipient, a combination that today would be avoided.

All of the recipients had splenectomy. The first 8 (of whom 4 are still living) had thymectomy prior to transplantation. In the hope of thereby being able to reduce immunosuppression, 9 additional patients had thymectomy from 8½ to 17 months after transplantation. Five of the 9 recipients are still alive, but 3 of them have undergone retransplantation. Although thymectomy may have a subtle but demonstrable effect in humans,⁹ it is no longer performed in our center.

SURVIVAL

THE 46 RELATED CASES

After a heavy mortality (33 per cent) in the first 6 months, subsequent deaths have been uncommon (Fig. 12-1). Thirty-one recipients survived for a half year; of these, 29 and 28 lived for 3 and 5 years respectively, and 24 are still alive after 9 to 10¼ years. Twenty-one of the 24 have function of their original grafts. Two others had retransplantations 5½ and 5¾ years after the first procedure and the secondary kidneys have subsequently functioned for 4¾ and 4½ years. The final patient had function of his first kidney for 7 years, followed by four retransplantations in the next 2½ years. He has a well-functioning kidney at present.

The outcome was not strikingly influenced by the nature of the relationship, whether this be parental, sibling, or other (Table 12-1). The parent-to-offspring results were amazingly stable in terms of recipient survival. At the end of 6 months, 14 of 20 recipients (70 per cent) were alive. By 9 to 10¼ years there were still 13 (65 per cent) alive, although 3 of these were by virtue of retransplantation. Also of interest was the fact that

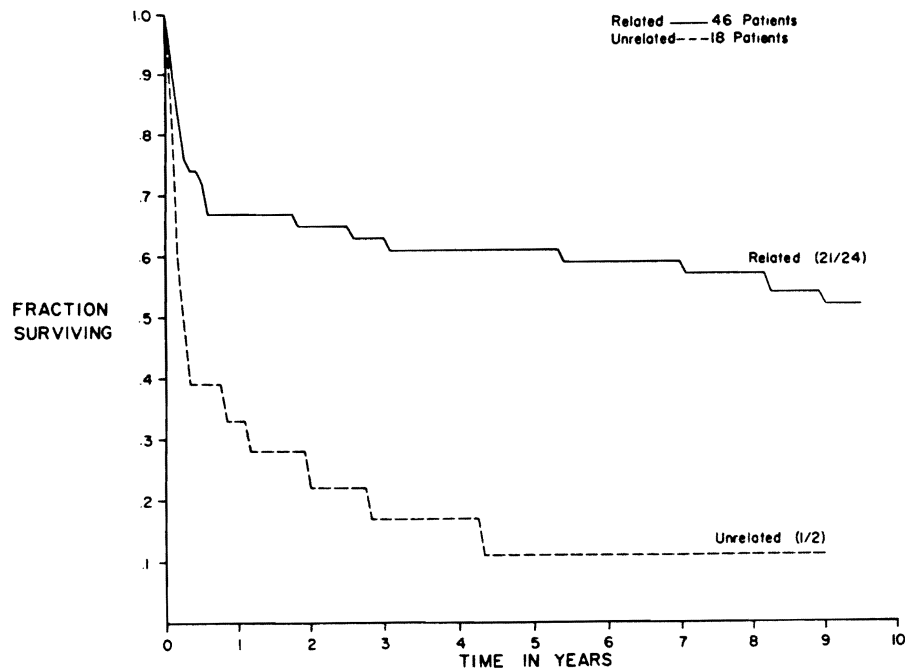


Fig. 12-1. Life survival curves of 64 patients treated from November, 1962, to March, 1964. The denominators in the related and nonrelated curves refer to patient survival and the numerators to survival of the original homograft. Thus, 22 of the 26 living recipients still bear their primary grafts; the other 4 have successful retransplants.

all of the 3 distantly related renal grafts (aunt, uncle, and cousin) were providing superb function nearly a decade after their insertion. (Table 12-1).

The causes of mortality in the first 5 years' follow-up of this series have been exhaustively reported,^{8,9} for which reason only the 4 deaths in the second 5 years will be mentioned. Two patients with adequate renal

function $8\frac{1}{4}$ and 9 years posttransplantation died of chronic aggressive hepatitis of several years duration; one was Australia antigen positive. A third patient had a fatal myocardial infarction after $7\frac{1}{3}$ years. The fourth patient had a technically unsuccessful retransplantation in the sixth year, and committed suicide by refusing to be placed back on hemodialysis.

THE 18 NONRELATED CASES

Two thirds of the recipients died in the first year with a mortality that continued until only 2 patients were left at the 5-year mark (Fig. 12-1). These 2 are still alive after more than

Table 12-1. The Influence of Consanguinity Upon Present Survival in 46 Cases After 9 to 10 $\frac{1}{4}$ Years

Donor	One Year		Three Years		Five Years		Now	
	Patient	Graft	Patient	Graft	Patient	Graft	Patient	Graft
20 Parents	14	14	14	14	14 (70%)	14 (70%)	13 (65%)*	10 (50%)
23 Siblings	14	14	12	12	11 (48%)	11 (48%)	8 (35%)	8 (35%)
3 aunt, uncle or cousin	3	3	3	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)

* Retransplantations were carried out after $5\frac{1}{2}$, $5\frac{3}{4}$, and 7 years. In the last instance there have been four retransplantations in the last $2\frac{1}{2}$ years.

9 years but in the second instance a second homograft from a mother has supported life for the last 6½ years of the total survival.

GRAFT FUNCTION AND IMMUNOSUPPRESSION

In Table 12-2 are shown the average current renal functions of the 26 survivors. These values represent the function of 22 primary kidneys that have been in place for 9 to 10¼ years and 4 retransplants that have been in place for 2 to 6½ years. On the average, the original grafts are performing better than the recently transplanted ones with lower maintenance doses of the immunosuppressive agents.

Arterial hypertension is an almost universal finding in the immediate posttransplantation period and even for several years afterward.^{8,9} This problem has tended to become less with longer follow-up. Only the patient with the most recent retransplantation has severe hypertension. Five other patients receive small daily doses of a combination of antihypertensives. Fourteen of the surviving 26 recipients require no antihypertensive therapy, and 6 are receiving only chlorothiazide. With the generally low steroid doses, there are no examples of steroid-induced diabetes.

THE QUESTION OF CANCER

Six of the 64 recipients (9 per cent), including 4 who are still alive, have developed skin cancers of the face, lip, or arm. Treatment was by standard surgical measures. So far cancer has not been a cause of death in this original group of patients, although we have had 2 deaths from de novo reticulum cell sarcomas in patients treated since 1964.⁹

WAS SURVIVAL WORTH THE PRICE?

There has been a remarkable degree of rehabilitation in this group of surviving recipients. All of those who were adults at the time of transplantation have returned to some kind of full-time work.

Twelve of the present survivors were younger than 18 years (3 to 17) at the time of the original operation. They all returned to school, half graduated from college, 8 now support themselves fully in adult work, and 9 have married. The only one who has spent an excessive amount of time in the hospital is a child originally treated at the age of 3, whose original homograft failed, and who subsequently required multiple retransplantations. He is now 13 years old and is stunted in growth.

Obviously, from the beginning of our program, pediatric recipients have been considered prime candidates for transplantation providing the appropriate variations are made in operative technique,^{8,10} including high vascular anastomoses and the transperitoneal route if necessary (Fig. 12-2). This view^{11,12} was upheld by Williams, Lee, and Hume¹³ and has been confirmed in numerous more recent articles, which are reviewed in Hume's commentary earlier in this chapter. In our experience, the pediatric patient has not been markedly more prone than the adult to recurrent glomerulonephritis, rejection, drug toxicity, or any of the complications of homotransplantation under immunosuppression.

At the time of this original series, potential recipients were screened with great care to rule out those with possible important psychiatric problems. Because of this, it has not been surprising to find exceptional emotional stability amongst those who were accepted and who are still surviving. Excellent adjustments

Table 12-2. Average Current Renal Function and Immunosuppression (Mean ± S.D.) in 26 Recipients of Renal Homografts Surviving 9 to 10¼ Years Posttransplantation (Data Assembled in September, 1972)

	BUN (mg%)	Serum Creatinine (mg%)	Creatinine Clearance (ml/min)	Azathioprine (mg/day)	Prednisone (mg/day)
22 Original grafts	19.8 ± 8.3	1.3 ± 0.5	80.4 ± 22.9	121.0 ± 38.8	8.1 ± 6.3
4 Retransplantation*	39.0 ± 18.5	1.9 ± 0.8	60.0 ± 33.4	82.5 ± 56.8	20.0 ± 7.1
All 26 Patients	22.7 ± 12.2	1.4 ± 0.6	77.3 ± 25.2	115.1 ± 43.1	9.9 ± 7.7

* Patients surviving 2 to 6½ years after retransplantation.

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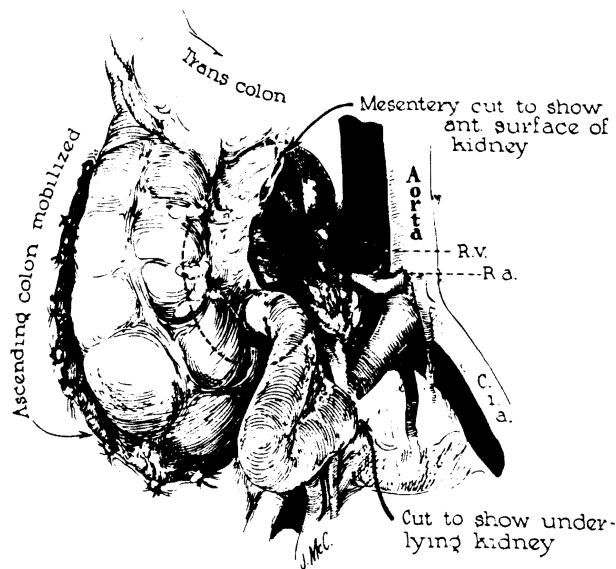


Fig. 12-2. A technique that permits the transplantation of adult homografts to infants or small children. The essential feature is "high" anastomoses of the renal vessels to the vena cava and the aorta or iliac artery. The entire operation can be performed transperitoneally through a midline incision with mobilization of the ascending colon as shown. Alternatively the retroperitoneal route may be selected in children of intermediate size, developing the extraperitoneal space through either a midline or a long oblique lower abdominal incision. (By permission of *Surg. Gynec. Obstet.* 119:106, 1964.)

have been made in spite of such serious early postoperative complications as aseptic necrosis of one or both of the femoral heads in 3 of the adolescents.⁸ These latter patients have learned to walk adequately in spite of their handicaps. Many of the young patients were stunted in growth before and after their transplantations and have had catch-up growth spurts late in their teens. Before concluding that catch-up growth will not occur, a follow-up period of 5 to 10 years may be necessary, as Lilly et al.¹² have emphasized from a study of our cases. Consequently, we have been far less pessimistic about this possibility than both Najarian et al.¹⁴ and Hume (Fig. 12-3). Even so, it is prudent to warn the parents of a pediatric recipient about the possibility of growth retardation.

Nine of the 64 patients of the original series have had children of their own, including 3 by 2 female and 10 by 7 male recipients. One of these offspring had a

meningomyelocele which required surgical correction. It is of interest that all the children issuing from this transplant population came from 26 still surviving. Thus, no orphans have so far been created by the premature death of a transplant patient.

URINARY RECONSTRUCTION

To permit consistent success after renal transplantation, well-known urological procedures were adapted and refined. In our first 64 cases, ureteroneocystostomy of the Paquin-Marshall nipple and tunnel variety¹⁵ was used to reconstitute the urinary tract.^{8,16} The cystotomy through which the ureter implantation was performed was a small one. Pains were taken to ensure watertight anastomoses and cystotomy closures employing fine suture materials and exercising meticulous technique. Because of these precautions, it was found unnecessary to drain the wounds, to place suprapubic cystostomy tubes, or to leave stents. Thus, this important aspect of the technical procedure of transplantation was taken from urology, improved because of the special needs of the immunosuppressed patient, and later brought back as a series of refinements into the standard modern operative urology as applied to nontransplant patients.

With ureteroneocystostomy in these early cases, complications occurred at an incidence of approximately 10 per cent, consisting mostly of anastomotic strictures.¹⁶ If these occurred early in the postoperative course, secondary repair proved to be dangerous. On the other hand, if these reoperations were done after 6 weeks, conversion to ureteroureterostomy or ureteropyelostomy was possible without mortality. The latest complication of ureteroneocystostomy in our experience occurred at 3 years. From then onward to as long as 10 years no further difficulties have been encountered.

In a later series of cases treated from 1964 to 1966, ureteroureterostomy was performed as the primary operation.¹⁶ This practice carried a complication incidence of approximately 10 per cent, consisting mainly of anastomotic urinary fistula from which there were two deaths. There were no strictures.

Although life-threatening complications in our early experience were observed with approximately equal frequency after both pro-

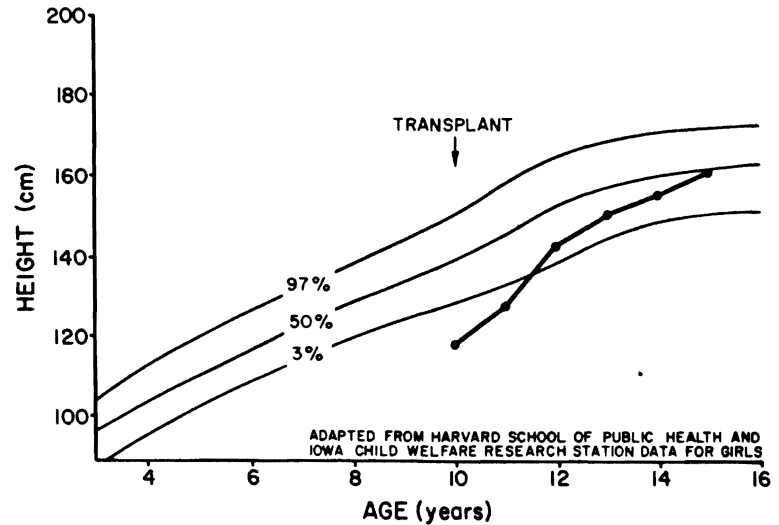


Fig. 12-3. The height percentile growth curve in a 10-year-old girl who was far below the third percentile at the time of renal homotransplantation. After operation, steroids were gradually tapered. She did not reach the 50th height percentile until more than 5 years after surgery. (By permission of *Pediatrics*, 47:548, 1971.)

cedures, it is our opinion, in support of that expressed earlier in this chapter in Hume's commentary, that ureteroneocystostomy should usually be the first choice, particularly since its present-day complication rate is more like 3 per cent than the 10 per cent figure in Prout's original report¹⁷ and in our own.^{8,16} It requires less technical finesse for its performance than ureteroureterostomy or ureteropyelostomy. It has a very low incidence of the dangerous complication of urinary fistula. Finally, the procedure ensures preservation of a long segment of homograft ureter for later anastomosis to the patient's retained ureters should that become necessary either early or late after transplantation.

Whatever the relative merits of these various techniques, it is scarcely debatable that the urologist or surgeon interested in renal transplantation should have the skill to carry out any one of the alternative methods under the appropriate circumstances. For example, if the homograft ureter is too short at the time of the initial operation, the only feasible solution may be with ureteroureterostomy or ureteropyelostomy. Moreover, as mentioned earlier, the latter procedures have been of the utmost importance in treating complications after successful first operations.

PERSPECTIVE FROM EARLY CASES

It is axiomatic that some degree of immunological weakening must be accepted as the price of success after whole organ transplan-

tation under immunosuppression. Because of this, it was once feared that a real margin of safety might not exist which would permit effective graft protection without killing the host. The fallacy of this assumption as it applies to the early postoperative course has long since been proved. Now there is evidence that immunosuppression may be tolerated for intervals that will extend beyond a decade in many instances.

In the early days of transplantation, the feared specter with chronic immunosuppression therapy was infection, particularly with opportunistic organisms for which effective treatment is not available. A second concern has more recently derived from the well-documented increased incidence of de novo malignancy in the transplant population. Both anxieties have a real basis as the observations in this early series have shown. Yet, the incidence and severity of late infection or tumors have by no means cancelled the effectiveness of treatment by transplantation.

Instead, with each passing year the case is strengthened that transplantation represents one of the greatest, although as yet incompletely exploited, therapeutic achievements of modern medicine. It has become clear that about half of our original series of related

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kidney recipients are going to move into the second decade of their convalescence. The poorer results in nonrelated transplantation would have been discouraging if it were not for the great progress made in many centers (see below), including our own with cadaveric transplantation, since the spring of 1964, when the presently reported series was completed.

SUBSEQUENT DEVELOPMENTS

As mentioned in the introduction, heterologous ALG was introduced clinically in 1966 as an adjuvant to azathioprine and prednisone during the critical early posttransplantation period.⁶ Even more recently, we have given the alkylating agent cyclophosphamide an extensive and successful trial in replacement of azathioprine.¹⁸ These clinical investigations have shown that a variety of multidrug immunosuppressive regimens can be used to achieve the desired result after transplantation and have indicated the feasibility and desirability of continuing to search for new therapeutic approaches. Since 1964 and using different treatment programs, the one-year success rate after consanguineous transplantation has risen in many centers to more than

85 per cent. After cadaveric transplantation, a reasonable one-year kidney survival rate is 65 per cent.

It is disappointing to relate that exploitation of HL-A typing in donor-recipient pairing has not had a more prominent role in this improved survival. Strong correlations between the quality of HL-A matching and the clinical outcome have been documented for most transplantation centers only with perfectly matched siblings.⁹ However, tissue typing techniques do permit the identification of states of presensitization by the detection in the recipient serum of cytotoxic antibodies with antigraft specificity. Because there is a high incidence of hyperacute rejection of the homograft under this circumstance, transplantation is usually avoided.¹⁹

From a practical point of view, one of the most revolutionary developments in transplantation in the past 5 years has been Belzer's technique²⁰ of preserving excised kidneys in an extracorporeal perfusion system primed with altered plasma. The reliability of this method has converted cadaveric renal transplantation from an urgent and invariably inconvenient undertaking with inevitable wastage of organs to an elective and highly efficient one.

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