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A 14-Year Experience with Kidney Transplantation

Richard Weil III, M.D., Gerhard P. J. Schröter, M.D., John C. West, M.D., and Thomas E. Starzl, M.D., Ph.D.

Departments of Surgery, Veterans Administration Hospital and University of Colorado Medical Center, Denver, Colorado, U.S.A.

Abstract

Between November, 1962 and August, 1975, 668 kidney transplants were done in 556 consecutive patients at Denver, Colorado. The Denver experience has been divided into 7 periods of time, according to the conditions of care during each period. The results in related transplantation have changed little during the decade beginning in 1966. The results in unrelated transplantation have not materially changed since 1968. The long-term patient survival after related transplantation has been better than after cadaver transplantation. The results of transplantation in 57 children ages 3 to 18 years have been slightly better than the results of adult transplantation.

The outcome of kidney transplantation and the feasibility of improving this therapy with present techniques are limited by our inability to accurately match each patient with the immunologically best donor and by our inability to precisely control the immune system of the recipient. Rejection is still the main reason for graft loss, and sepsis remains the main cause of patient mortality. More specific and less toxic means of achieving graft acceptance are needed before a higher level of patient service can be realized. However, even with the tools now available, thousands of recipients throughout the world have been returned to useful lives.

Approximately 25,000 kidney transplants were carried out and reported to the ACS/NIH kidney transplant registry prior to the dissolution of this organization in the summer of 1976. During the almost 13-year period from November, 1962 until August, 1975, 668 kidney transplants were done at the University of Colorado Medical Center and the Denver Veterans Administration Hospital. Follow-up data have been obtained on each of the 556 consecutive patients treated during this interval, with a minimum period of 1 year of post-transplant observation in the most recent cases. The Denver experience is presented to illustrate the development of kidney transplantation and as an example of current trends in the field.

Methods: Denver Conditions of Care

Case Material and Immunosuppression

The Denver kidney transplantation experience between 1962 and 1975 has been divided into seven periods according to the conditions of care rendered during these times. The characteristics of these periods are summarized in Table 1. Prior to March, 1968, when series 4 was started, certain high-risk cases were advised not to undergo transplantation; since 1968 all patients who have desired transplantation have been accepted, except for very rare instances where it was thought that the patient could probably not tolerate anesthesia or immunosuppression. In recent years transplantation has been carried out with increasing

frequency in patients with advanced age, coronary artery disease, diabetes mellitus, and other systemic disorders.

Between November, 1962 and April, 1966 (series 1 and 2), immunosuppression consisted of prednisone and azathioprine. In June, 1966 (series 3), antilymphocyte globulin (ALG) was added to azathioprine and prednisone. The same conditions applied in series 4. Between March, 1971 and August, 1972 (series 5), cyclophosphamide was substituted for azathioprine in the triple-drug immunosuppressive program; since August, 1972 azathioprine rather than cyclophosphamide has been used because cyclophosphamide was found to have no advantage over azathioprine.

Donor Selection

From 1962 until late 1965 volunteer living unrelated donors were used in some cases; since 1965 all unrelated kidneys have been obtained from cadaver donors. During the period October, 1964 until April, 1966 (series 2), related and cadaver kidney recipients were selected according to the results of human leukocyte antigen (HLA) matching; since 1966 HLA matching has been used mainly for the selection of HLA-identical sibling donors. During almost all of the 14-year period, an effort has been made to prevent hyperacute graft rejection by the use of a sensitive direct cytotoxicity crossmatch test. Recently, donor lymph node cells have been used as a target cell in most cases, and two samples of recipient's serum—the most current serum sample and the sample with the highest percentage of antibodies against a random panel of lymphocytes—have been tested for the presence of preformed antibodies.

Cadaver Kidney Preservation

From 1962 to 1968, cadaver kidneys were harvested after cardiac standstill or from heart-beating cadavers or from cadaver donors whose circulation was being maintained by cardiopulmonary bypass. The removed organs were further cooled by infusion with chilled electrolyte solutions with or without low molecular weight dextran. From 1968 to 1971, some of the cadaver kidneys were stored in a hyperbaric oxygen chamber. From 1971 through 1975, cadaver kidneys were preserved by Belzer's machine pulsatile perfusion method using cryoprecipitated plasma. Since the beginning of 1976, cadaver kidneys which were expected to be reimplanted within 24 hours after removal from the donor have been stored in modified Collins-2 solution (Travenol®), without procaine, at 4°C.

Results

Related Transplants

Patient survival after primary related transplantation has not improved since 1966 (Figure 1, Table 2). Patient survival 2 years after transplants done between 1962 and 1966 was 65%; in cases done between 1966 and 1974, the 2-year patient survival ranged from 73 to 88%. In fact, patient survival was less in subsequent series than in the cases done between 1966 and 1968, the last period when only "good-risk" patients were accepted. This decline in patient survival is probably attributable to a progressively more bold approach to recipient selection.

The durability of primary related grafts is illustrated by the high percentage of survivors from the 1962 to 1964 patients (series 1) whose original grafts are still functioning (Table 3). Of the original group of 46 patients transplanted 12 to 14 years ago, 22 (48%) are still living, and 18 of these 22 patients (82%) have functioning original grafts. Of the 22 current survivors, 3 have had successful retransplantation, and 1 patient is back on dialysis after 11 years of function of the original graft, which was donated by a cousin and eventually was lost because of chronic rejection. Retransplantation has not yet been carried out in this patient because of the presence of multiple low-grade skin neoplasms, which have been regressing steadily since

discontinuation of immunosuppression, and because of the development of preformed cytotoxic antibodies associated with resumption of dialysis and a need for blood transfusions.

Although the risks of retransplantation are higher than with primary transplantation [1], our patients have been reluctant to return to chronic hemodialysis after experiencing the rehabilitation which can be provided by a successfully functioning transplant, and most of our patients have been retransplanted repeatedly until a successful graft could be obtained. Of the entire group of 229 survivors after primary related transplants from series 1 through 6, only 10 (4%) are currently on dialysis, and some of these patients are waiting for retransplantation. Of the 22 survivors in the most recent series 7, a total of 6 are now on dialysis and all are hoping to be retransplanted, but high titers of preformed antibodies have prevented us from carrying out this treatment to date.

Unrelated Transplants

Volunteer living unrelated donors have not been used since 1965 because with rare exceptions such donors offer the patient no significant advantage over a cadaver donor. The long-term patient survival after primary unrelated transplantation (Figure 2) was distinctly lower than after primary related transplantation (Figure 1). In series 1 and 2 the 10-year patient survival after unrelated transplantation was 12% (Table 4), compared with 48% (Table 2) after related transplantation. However, in the more recently treated cases since March, 1968 (series 4 through 7), the patient survival following unrelated transplantation is not significantly different from the results after related transplantation; this improvement in patient survival followed our recognition between 1966 and 1968 that excessive immunosuppression in an effort to save a cadaver graft represents an unreasonably high risk to the life of the patient. Since 1968, cadaver grafts which have demonstrated a repeated and relentless propensity for rejection have been abandoned.

In spite of this willingness to abandon immunologically difficult cadaver grafts, an aggressive attitude toward retransplantation has made it possible to provide most of the surviving patients with a functioning graft (Table 5). Of the 38 surviving patients who received primary unrelated grafts between 1962 and August, 1972 (series 1 through 5), only 4 (11%) are back on dialysis. Of the 46 survivors from series 6 and 7, a total of 11 are currently on dialysis, but almost all of these patients are waiting for retransplantation.

Transplantation in Children

The results of pediatric kidney transplantation in Denver were brought up to date several months ago and are comparable to the results of adult kidney transplantation [2]. Of 57 children (67%), 35 were alive 6 to 13 years after original transplantation. The patient survival was the same for recipients of related and unrelated grafts. In all, 10 of the 35 surviving patients have been retransplanted. In spite of the burdens imposed on these children by their illness, transplantation, and immunosuppression, most of them were able to develop into well-adjusted young adults. One 23-year-old woman who received a transplant 13 years ago from her mother married a transplant surgeon.

Causes of Late Death

Of the 326 patients transplanted more than 5 years ago (series 1 through 4), 24 died more than 5 years after the original kidney transplant. Nine of these 24 patients had undergone retransplantation; 16 died with adequately functioning original grafts (Table 6).

Infection, the leading cause of early post-transplant death [3], was also the major cause of late death. There were 6 deaths from pneumonia and 2 deaths from disseminated cytomegalovirus. The role of viral infection in the 4 deaths from liver failure is uncertain, but probably viral

hepatitis was contributory in at least some of these cases. Therefore, half (12/24) of the late deaths may have been related to infection. Five deaths were due to cardiovascular disease (3 mesenteric vascular occlusions, 2 coronary occlusions). The remaining 7 deaths were due to varied causes (3 suicides, 2 colon perforations, 1 hyperparathyroidism, 1 cancer). The man who died of cancer more than 5 years after transplantation had multiple squamous cell epitheliomas of the skin of the head and neck, one of which recurred on the external ear and eventually metastasized to liver and bone, in spite of re-excisions, radical neck dissection, and drastic reduction of immunosuppression. The risks of cancer under immunosuppression will be discussed below.

Discussion

It is clear from the Denver kidney transplantation experience that the results with this treatment have improved little during the last decade. The patient and graft survival of patients receiving their grafts in recent years differ remarkably little from the results obtained by patients transplanted in 1966 (Tables 2 through 5). During the last decade a great deal has been done to try to improve the results of kidney transplantation, but there has been no advance in knowledge which could be translated into a major therapeutic advantage for the patients. Nevertheless, it is appropriate to examine the current status of the central issues in the field.

Histocompatibility Matching

The ABO blood group antigens are expressed on kidney cells, and kidney transplantation in the presence of donor-recipient ABO incompatibility probably carries more than a 50% likelihood of early irreversible graft rejection [5]. The Rh system is not important in organ transplantation.

The histocompatibility test which carries the greatest predictive value is the direct crossmatch, which identifies preformed antibodies (mostly cytotoxic) in the recipient's serum against antigens of the donor. The donor target cell is usually a lymph node lymphocyte, but peripheral blood lymphocytes or kidney cells obtained by biopsy can also be used [6]. If preformed antibodies against a donor are detected in a recipient by this test, transplantation from that donor to that recipient carries approximately a 75% likelihood of early irreversible rejection [7], and a different donor is therefore sought for the patient.

In 1964, HLA typing began to be used clinically for donor selection in Denver. This serologically defined system initially appeared to hold great promise for the identification of the optimal organ donor for each patient. In Denver HLA typing was used regularly for donor selection during the 1964 to 1966 period (series 2), and the results of transplantation were not significantly improved by this tool. HLA typing has been done for all Denver cases since then, but since 1966 the results have been used as a selection instrument only to identify perfectly matched sibling donors. In the United States HLA typing has had limited value for the selection of cadaver and nonsibling related donors [3], although in Europe better correlations between HLA match and graft survival have been claimed by some [8].

Lymphocyte-defined histocompatibility testing similarly has had little impact on the results of kidney transplantation. Donor and recipient lymphocyte stimulation in mixed lymphocyte culture (MLC), with or without mitomycin inhibition of donor or recipient cells, has had at least some degree of correlation with graft outcome in many reports [9,10], but the test as usually done requires about 5 days for its completion and is, therefore, of only retrospective value for cadaver transplantation since organ preservation is at present not feasible for this length of time. A more rapid MLC test has been developed [11], but its value is not yet established.

It remains to be proven that matching a cadaver organ donor with a large pool of prospective recipients will significantly help patient or graft survival. If matching could be improved, cadaver kidney survival would increase and the decreased amount of immunosuppression required for graft survival would reduce the morbidity of immunosuppression. The HLA matching as carried out today is not likely to accomplish these objectives.

Kidney Preservation

The feasibility of organ storage, even for only a few hours, changed the operative procedure of cadaver kidney transplantation from an emergency operation requiring the facilities of 2 or 3 operating rooms simultaneously to a procedure which could be carried out less hurriedly using less operating facilities at one time. Organ storage also made it possible to carry out postmortem examination of the cadaver donor prior to organ transplantation in order to discover occult infection or malignancy in the cadaver which might be transferred to the recipient of the organ. During organ storage, histocompatibility matching could be completed and the recipient could have time for travel from home to the hospital and for optimal preparation for operation, including preoperative hemodialysis if necessary.

The major characteristic of organ preservation is a reduction of temperature to 4°C. Organ freezing to permit prolonged storage has been attempted experimentally [12] but is not yet feasible without serious damage to the organ. Hyperbaric oxygen systems are not now in wide clinical use.

The two methods of kidney storage most often used are infusion with and cold storage in intracellular electrolyte solution [13] and continuous pulsatile cold perfusion with oxygenated cryoprecipitated plasma [14]. Cold storage is simpler and is probably as effective as more complex machine perfusion for 18 to 24 hours [3]. For periods of preservation from 24 to 48 hours, the oxygenated machine preservation appears superior [15]. The use of human albumin rather than cryoprecipitated plasma is currently under investigation in an effort to eliminate the possibility of kidney damage by antibodies contained in the cryoprecipitated plasma.

Although direct transfer of the kidney from a heart beating donor to the recipient without interval storage (as is done with living related transplantation) is probably the optimal method of organ transfer from a physiological standpoint, the advantages of short-term organ preservation seem to outweigh its disadvantages.

The Transplant Operation

The techniques of vascularization and restoration of urinary drainage are fairly standardized [16,17]. In patients weighing more than approximately 20 kg, the kidney is placed in the extraperitoneal iliac fossa; in children weighing less than 20 kg, the kidney is placed transperitoneally in a retrocecal position, attaching the renal vessels to aorta and vena cava. Vascular or urinary complications are uncommon but not rare. In a recent review of the experience at the Peter Bent Brigham Hospital in Boston, investigators observed arterial stenosis in 6% of cases [18], some of which may have been related to immunologic damage to the donor artery distal to the anastomosis. Renal vein thrombosis is observed much less frequently. Early urinary leak almost always requires prompt reoperation. Late stricture of the donor ureter has been seen in less than 5% of the Denver cases; this complication may be caused by periureteral adhesions or by intrinsic narrowing due to devascularization. Late reconstruction by conversion of the ureteroneocystostomy to ureteroureterostomy usually provides a satisfactory result [19]. Lymphocele in the transplant wound occurred in 4% of Denver cases in series 1 through 5. External drainage was done for all of these cases, but recently internal drainage via a peritoneal window has been found satisfactory, eliminating the need for prolonged wound irrigations.

Although the techniques of renal transplantation are quite straightforward, technical complications continue to account for an important loss of grafts. The ACS/NIH Registry observed that about 10% of failed identical twin grafts, in which rejection was not operative, were lost from technical complications [3].

Immunosuppression

Most of the complications of kidney transplantation are related to the immunosuppression, which is required for all cases except identical twin transplants. Early experience at the Peter Bent Brigham Hospital in Boston suggested that immunosuppression should be used in identical twin transplants done for glomerulonephritis to reduce the frequency of recurrent glomerulonephritis in the graft [20]. However, 3 identical twin transplants done for glomerulonephritis at Denver in 1962, 1963, and 1972, without immunosuppression at any time, all are now functioning well. A fourth recipient of a twin transplant, done without immunosuppression for probable chronic pyelonephritis, is also functioning well after 10½ years.

The mainstays of immunosuppression have been corticosteroids and azathioprine. In series 1 in Denver (1962 to 1964), only azathioprine was used prophylactically, reserving corticosteroids for rejection episodes. Corticosteroids have been used routinely since 1964, often beginning intraoperatively. Antilymphocyte globulin (ALG) was added to the double-drug program in 1966 and continues to be used in Denver, but the value of this agent is still not firmly established. It is possible that biologic differences among different batches of ALG may account for apparent variability in the effectiveness of this agent in different centers [21]; prospective trials are currently in progress to attempt to finally answer the question of whether or not ALG combined with corticosteroids and azathioprine can provide better immunosuppression than corticosteroids and azathioprine alone.

The complications of immunosuppression include the complications of excess adrenal corticosteroid levels, hypertension, acne, obesity, diabetes mellitus, peptic ulcer, osteoporosis, and ocular cataract. Aseptic necrosis of bone has been observed in 21% of our patients studied 4 to 146 months after transplantation [22]. Markedly increased susceptibility to infection is found in immunosuppressed patients, including susceptibility to a variety of opportunistic infections caused by bacteria, viruses, protozoa, and fungi. Sepsis is the chief cause of death in kidney transplant patients [3]. Hyperlipidemia has been observed in more than 50% of dialysis and transplant patients [23]. Cancer occurs approximately 100 times more frequently in kidney transplant patients than in a control population, a frequency of 6% in the Denver patients (4). Many of these malignancies are cutaneous and easily treated, but there have been 5 deaths from malignancy in the 556 patients transplanted between 1962 and 1975 in Denver; 4 of these 5 deaths occurred less than 5 years after transplantation, and 1 occurred later. Of the 4 earlier deaths, the causes were lymphoma in 3 and leukemia in 1.

It is urgent that a more specific and less toxic form of immunosuppression be developed. Immunologic enhancement and tolerance induction, or combinations of these approaches, are being studied experimentally in many centers [24,25], but it is not yet possible to control and manipulate the immune system sufficiently well to be able to produce immunologic protection or immunologic killing in a predictable and reliable manner. Methods of immunologic monitoring are being developed by means of which immunosuppressive medications can be adjusted appropriately before the graft is rejected because of inadequate immunosuppression or before the patient dies of sepsis due to excessive immunosuppression [26].

It is not possible to know from which direction research will produce a major change in clinical immunosuppressive management. It seems likely that any major change will come from approaches that are not now clearly envisioned. After more than 10 years of speculation and

after myriads of conferences about the clinical application of tolerance induction and iatrogenic enhancement, the limitations of these approaches as they have so far been tried are evident.

Trends

Transplanted kidneys are impermanent. Cadaver kidneys are less permanent than related kidneys. Nevertheless, kidney transplantation and retransplantation, with careful individualization of care for each patient, are capable of providing a quality of life for most patients with end-stage renal disease which is not possible with chronic hemodialysis. In addition, the mortality of transplantation is not different from the mortality of chronic hemodialysis: the 4-year mortality of chronic dialysis in a recent National Dialysis Association report was 40% [27].

Transplantation and dialysis are a continuum of therapy for end-stage renal disease [28,29]. As a result of the Federal HR 1 Bill passed in 1972, both forms of treatment are now available to almost every citizen of the United States with chronic renal failure. It is the obligation of physicians and surgeons caring for these patients to use both treatments to their maximum advantage for each patient.

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Fig. 1. Life survival curves of patients treated with primary related homografts during five intervals from 1962 to the summer of 1972. Arrows show time of minimum follow-up. Description of groups is in Table 1. (By permission of *Transplantation Proceedings*).

Fig. 2.
Life survival curves after transplantation of nonrelated kidneys during the same five time periods as in Fig. 1. Description of groups is in Table 1. (By permission of *Transplantation Proceedings*).

Table 1

Denver kidney transplantation 1962–1975

No. of cases				Dates	Follow-up (years)	Characteristics of care
Series	Related	Unrelated				
1	46	18		November, 1962–March, 1964	12½–13¾	Azathioprine/prednisone; good risk
2	25	23		October, 1964–April, 1966	10½–11½	Azathioprine/prednisone + typing; good risk
3	60	17		June, 1966–February, 1968	8½–10¼	Azathioprine/prednisone/ALG; good risk
4	122	15		March, 1968–March, 1971	5½–8½	Azathioprine/prednisone/ALG; all risk
5	44	28		March, 1971–August, 1972	4–5½	Cyclophosphamide/prednisone/ALG; all risk
6	65	49		August, 1972–August, 1974	2–4	Azathioprine/prednisone/ALG; all risk
7	27	17		September, 1974–August, 1975	1–2	Azathioprine/prednisone/ALG; all risk

Table 2

Patient survival after primary related transplantation 1962–1975

Series	No. of cases	Percent survival				
		1 year	2 years	4 years	8 years	10 years
1	46	67	65	61	57	52
2	25	64	64	52	40	40
3	60	92	88	78	67	
4	122	76	73	68	—	
5	44	86	80	74	—	
6	65	77	75	—	—	
7	27	89	—	—	—	

Table 3

Graft survival after primary related transplantation 1962–1975

Series	Time following	Present survivors *	Functioning original graft	Successful retransplantation	On dialysis
1	12½–13¾	22/46 (48%)	18	3	1
2	10½–11½	10/25 (40%)	7	2	1
3	8½–10½	40/60 (67%)	30	8	2
4	5½–8½	75/122 (61%)	67	6	2
5	4 – 5½	33/44 (75%)	28	4	1
6	2–4	49/65 (75%)	40	6	3
7	1–2	22/27 (81%)	16	0	6

* July, 1976.

Table 4

Patient survival after primary unrelated transplantation 1962–1975

Series	No. of cases	Percent survival				
		1 year	2 year	4 years	8 years	10 years
1	18	33	22	17	11	11
2	23	52	43	30	17	13
3	17	82	76	41	29	—
4	15	80	80	80	—	—
5	28	75	75	61	—	—
6	49	82	71	—	—	—
7	17	94	—	—	—	—

Table 5

Graft survival after primary unrelated transplantation 1962–1975

Series	Time following	Present survivors	Functioning original graft	Successful retransplantation	On dialysis
1	12½–13¼	2/18 (11%)	1	1	0
2	10½–11½	3/23 (13%)	2	0	1
3	8½–10½	5/17 (29%)	4	1	0
4	5½–8½	11/15 (73%)	4	5	2
5	4–5½	17/28 (61%)	11	5	1
6	2–4	32/49 (65%)	20	6	6
7	1–2	14/17 (82%)	8	1	5

* July, 1976.

Table 6

Causes of late death more than 5 years after primary kidney transplantation

Causes of death	No. of patients	No. of patients with adequate ante-mortem kidney function
Pneumonia	6	4
Liver failure	4	4
Mesenteric vascular occlusion	3	2
Suicide	3	1
Disseminated CMV infection	2	1
Coronary occlusion	2	2
Colon perforation	2	1
Cancer	1	1
Hyperparathyroidism and skin gangrene	<u>1</u>	<u>0</u>
Total	24	16