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A 14-Year Experience with Kidney Transplantation

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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.

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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.

Table 1. Denver kidney transplantation 1962–1975

Series	No. of cases: Related	Unrelated	Dates	Follow-up (years)	Characteristics of care
1	46	18	November, 1962–March, 1964	12⅓–13¾	Azathioprine/prednisone; good risk
2	25	23	October, 1964–April, 1966	10⅓–11⅚	Azathioprine/prednisone + typing; good risk
3	60	17	June, 1966–February, 1968	8½–10⅙	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

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

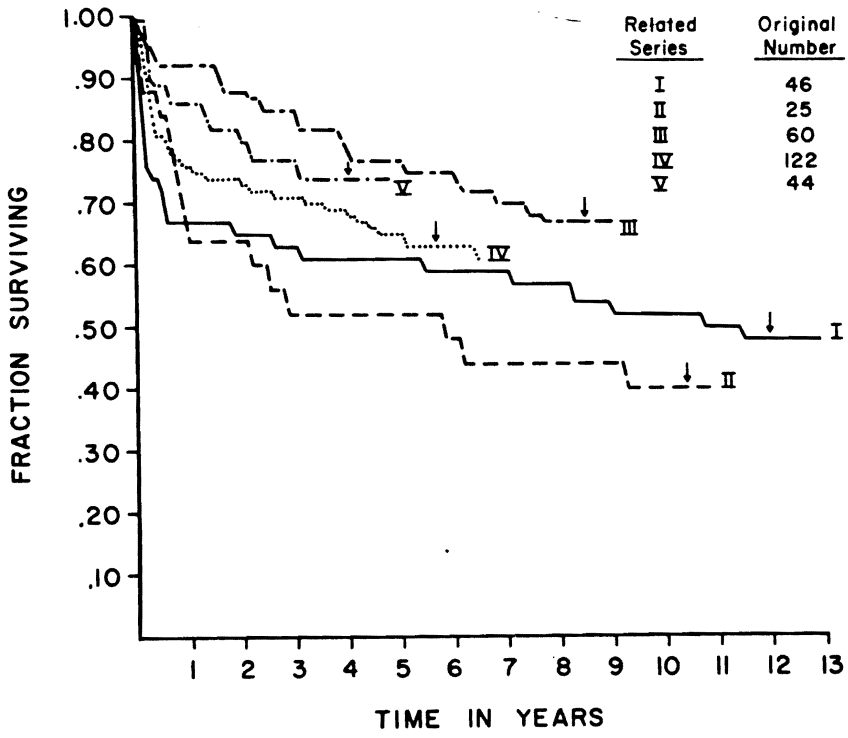

Fig. 1. Life survival curves of patients treated with primary related homografts during five intervals from 1962 to the summer of 1972. Arrows show time of minimum follow-up. Description of groups is in Table 1. (By permission of *Transplantation Proceedings*).

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	—	—	—	

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.

Table 3. Graft survival after primary related transplantation 1962–1975

Series	Time following	Present survivors*	Functioning original graft	Successful retransplantation	On dialysis
1	12⅓–13¾	22/46 (48%)	18	3	1
2	10⅓–11⅝	10/25 (40%)	7	2	1
3	8½–10⅛	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.

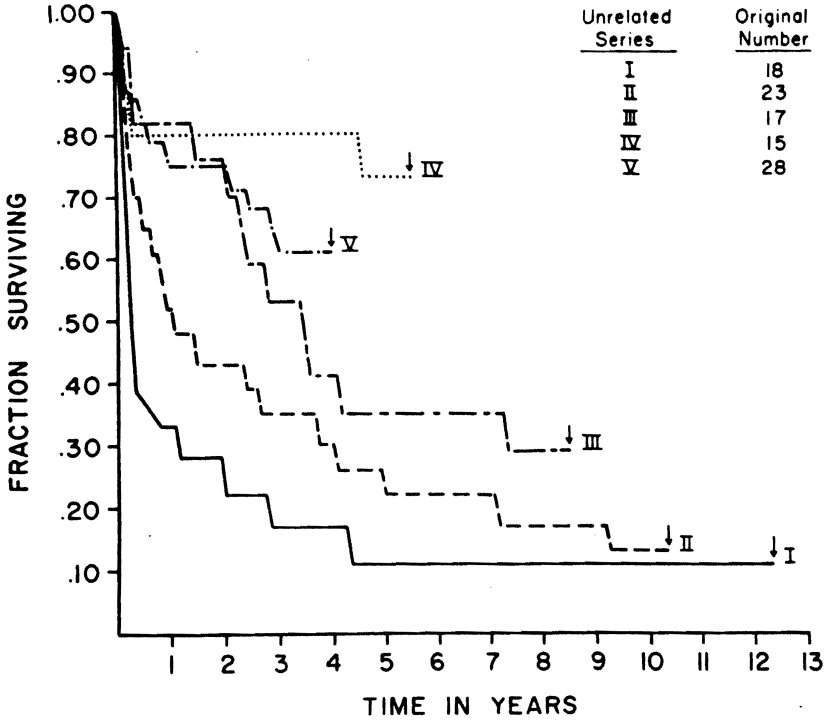

Fig. 2. Life survival curves after transplantation of nonrelated kidneys during the same five time periods as in Fig. 1. Description of groups is in Table 1. (By permission of *Transplantation Proceedings*).

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

Table 4. Patient survival after primary unrelated transplantation 1962–1975

Series	No. of cases	Percent survival				
		1 year	2 years	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	12½–13¾	2/18 (11%)	1	1	0
2	10½–11⅝	3/23 (13%)	2	0	1
3	8½–10⅛	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.

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 lym-

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 antemortem 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	1	0
Total	24	16

phocyte, 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 temperatue 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 devas-

cularization. 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.

Résumé

A Denver, Colorado, on a procédé à 668 transplantations rénales chez 556 patients entre Novembre 1962 et Août 1975. L'expérience de Denver a été divisée en 7 périodes, selon les modalités de traitement utilisées durant ces différentes périodes. Les résultats sont demeurés pratiquement les mêmes depuis 1966 dans les cas de donneurs apparentés, et depuis 1968 dans les cas de donneurs non-apparantés. Les résultats à long terme ont été meilleurs avec les donneurs apparentés qu'avec les donneurs cadavériques. Les résultats obtenus chez 57 enfants entre 3 et 18 ans ont été légèrement supérieurs à ceux obtenus chez l'adulte. Le plafonnement actuel des résultats est causé par notre impuissance à sélectionner adéquatement les patients et les greffons, et notre incapacité à contrôler avec précision le systeme immunitaire du receveur. Le rejet est responsable de la majorité des insuccès et l'infection demeure la cause principale de décès. Le progrès futurs dépendront du développement de moyens plus précis et moins toxiques pour induire la tolérance immunitaire. Cependant, même avec les moyens actuels, des milliers de patients à travers le monde ont pu être réhabilités.

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INVITED COMMENTARY

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The distinguished group at the University of Colorado have presented the results of 668 renal transplants spanning a 14-year period. Their data are of great importance, for this large experience is unencumbered by technical miscues so that the reasons for success and failure can be correlated closely with rejection or complications of immonosuppressive therapy and can be viewed as living medical history.

The single most important point emerging from this large experience is that despite 7 significant changes in the selection and management of patients for transplantation, neither transplant nor patient survival have changed radically. This observation is reflected in virtually every transplantation program. Thus, the feeling of optimism surrounding transplantation which was present in the late sixties has now been replaced quite appropriately by a realization that further progress will depend upon a breakthrough in the basic science of immunology. In essence, the belief was prevalent that our good results were on the basis of fortuitous, good, tissue matches which could be increased by creating large pools of donors and recipients; that organ preservation methodology would provide the key mechanism assuring delivery of viable organs to perfectly matched recipients; that the elimination of blood transfusions given to dialysis patients would reduce pre-existing immunity which was difficult to detect by existing serological techniques and to suppress by drugs; and that powerful, new immunosuppressive modalities including antilymphocyte globulin would drastically reduce the amount of Prednisone necessary to treat threatened rejection thereby eliminating Prednisone-related complications and further extend not only successful renal function but rehabilitation of the transplanted patient. In the ensuing years as this paper indicates, all of these factors breeding optimism have either been negated by unforeseen factors or their effects have been shown to be considerably less than originally anticipated.

Perhaps the greatest disappointment has been in the area of histocompatibility matching for unrelated transplantation. It is now clear that our good results in the past were not based on the lucky good matches. In fact, the major reason why histocompatibility matching has proved to be unrewarding practically is that the obviously mismatched recipient does extremely well too frequently. Thus, in the hemodialyzed patient, factors other than histocompatibility are of extraordinary importance in determining the outcome of the graft. Further, the discovery of B cell alloantigens which now appear responsible for the proliferative stimulus in mixed lymphocyte culture appear to be equally numerous and complex as the HLA-A,B,C antigen systems. Thus, when the B cell alloantigens are fully enumerated, a perfect match for all known antigens is likely to be a statistical possibility alone. For these reasons more and more histocompatibility laboratories have concentrated research efforts on making disease associations while providing the service of family genotyping and the performance of antibody screening to prevent hyperacute rejection. Only when the suppressive aspects

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of the normal immune response are harnessed purposely will typing labs consider transplantation a major frontier of research.

It is noteworthy that the Denver investigators who pioneered the application of ALG to recipients of kidney transplants acknowledge that the "value . . . is still not firmly established." In an extensive review of the world's experience with ALG, Monaco concludes that where adequate dosages have been used, ALG has improved long-term transplant success 10–15% [1]. The weight of evidence suggests that there are dose-response relationships in man and that batch differences still exist despite large scale efforts to standardize ALG by a multitude of tests. There is promise that immunological monitoring particularly of peripheral T lymphocyte levels may provide an index of ALG effects providing a clinical tool allowing the adjustment of dose to the individual patient. Should this prove to be correct, ALG administration may be more effective than in the past but all transplant units will have to acquire immunological sophistication to follow the patient accurately.

The finding that most patients who have rejected a transplant wish additional attempts is certainly in keeping with our experience. This fact is the best argument favoring transplantation, albeit imperfect, as the best therapy for renal failure. The brightening of intellect and the enhanced physical activity so evident in the first months following successful transplantation more than compensate for the difficulties caused by immunosuppression. These must certainly be acknowledged as real and the Denver experience reporting a 21% rate of aseptic necrosis and 5 deaths from cancer is indeed sobering. Thus, we must acknowledge that renal transplantation remains like a gifted child, full of promise and replete with problems, and that transplantation and dialysis are truly a "continuum in the treatment of end-stage kidney disease."

Hope rests in achieving greater understanding of the equilibrium that exists between recipient and successful graft. We have studied rejection too long. It is time to examine our successes, for this is the true miracle. To do this, the successful recipient of 14 years ago and his living donor provide invaluable subjects for experimentation. Applying *in vitro* methods, is it possible to find a mechanism suppressing specifically the immune response to the donor? The future of transplantation rests, first with the description of success and, second with manipulation of immunological parameters favoring the stable equilibrium associated with good graft function.

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INVITED COMMENTARY

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The extraordinary experience of the Denver group in renal transplantation under the pioneering leadership of Dr. Thomas Starzl has been presented. The data described identifies an extended experience by one group which reflects with a few differences the national experience. The Renal Transplant Registry, located in the American College of Surgeons headquarters in Chicago and funded by the National Institutes of Health has compiled statistics on over 25,000 kidney transplants. The thirteenth and final report of the Registry clearly identifies the fact that the overall functional success of renal transplants, i.e. a graft functioning well enough to keep a patient alive and off dialysis, has not significantly changed since 1968. This is true for every type of kidney donor. When living-related sibling donors were analyzed, the one-year functional graft survival for patients done in the years 1968 through 1974 was 80.2, 76.5, 80.3, 73.9, 78.6, 75.7, and 72.5% respectively. The two-, three-, and four-year survival rates showed a progressive decline, with the five-year survival for patients done in 1968, 1969, and 1970 being 61.9, 62.4, and 65.9%. When living-related parental donors were used the results for patients done in 1968 through 1974 were 72.4, 69.0, 75.2, 74.7, 72.1, 68.7, and 66.2%. The five-year survival rates were 50.5, 45.1, and 54.7%. The slightly lower survival rates for parental donors reflects the theoretical advantage in closer histocompatibility which sibling donors can achieve. Analysis of the cadaver donor results emphasized the significant decrease in functional graft survival achieved with this donor source. One-year functional graft survival from 1968 through 1974 was 46.4, 53.7, 55.4, 53.0, 50.8, 49.5 and 46.3% respectively. The five-year functional survival for patients done in 1968, 1969, and 1970 was 28.6, 35.4 and 34.6% respectively. One area of significant improvement has been in patient survival post-transplantation. Thus, survival after sibling and parental transplantation has always been approximately 90%. However, patient one-year survival after cadaveric transplantation from 1968 through 1974 has increased progressively from 58.5, 64.5, 68.5, 68.7, 69.8, 71.2 to 72.3% respectively. The decreasing mortality after cadaver transplantation is clearly related to a clear-cut shift toward early reduction of immunosuppression and reluctance to treat sustained rejection with excessive immunosuppressant drugs, thus avoiding fatal infectious complications. A second area of progress has been the exten-

sion of renal transplantation as a form of treatment to patients who are obviously non-ideal or so-called risks. These include patients over 50, as well as those with diabetes and with pulmonary, coronary, liver and/or peripheral vascular disease. One might argue that maintenance of functional graft survival in the face of increased numbers of poor risk recipients is also an area of progress. Use of increased numbers of poor risk recipients has rendered determination of the effect of new forms of treatment by retrospective analysis difficult. Thus, the best results were obtained in the Denver related transplant series in Group III (Imuran, Prednisone, ALG—Good risk patients only) whereas decreased survival was achieved in Group IV (Imuran, Prednisone, ALG—All risks). Survival in Group IV is about the same as Group I (Imuran, Prednisone—No ALG—Good risks only). Although similar survival of Group IV and I might suggest no significant effect for ALG, a more plausible conclusion might be that whatever salutory effect ALG had on functional graft survival was abrogated or obscured by the presence of high risk patients. Najarian et al. [1] have emphasized that all comparisons of treatment must take into account the presence of risk factors in treated and untreated groups with appropriate stratification of factors in both groups for major evaluation of treatment modalities.

The absence of a significant improvement in functional graft survival over the past 8 years raises a question concerning what areas of transplantation practice and/or immunobiology might be modified to improve results. Histocompatibility studies have been disappointing in regard to predicting and improving results. Knowledge of the major histocompatibility locus in man has grown steadily and has emphasized the extraordinary complexity of human histocompatibility antigens. Three series of serologically defined (SD) antigens (HL-A, B, and C) are now identified as well as one series, HL-D, of lymphocyte defined (LD), antigens. Unfortunately, in this complex series of antigens one or more major antigens has not been identified, i.e. they all seem to be of relatively equal importance, thus making significant histocompatibility matching difficult. Although extensive organ sharing will aid in decreasing histocompatibility, it seems doubtful that drastic improvement in results will be obtained from improvements in histocompatibility matching.

The role of presensitization in influencing functional graft survival of living-related and cadaver grafts is somewhat controversial. Potential recipients are evaluated as to the presence of lymphocytotoxic antibody to human histocompatibility antigens by reaction to a panel of normal lymphocytes and their degree of sensitization estimated from 1 to 100%. Prior to transplantation the recipient's serum is reacted with the potential donor's antigens (usually donor lymphocytes or splenocytes) to assure a "negative" crossmatch. The Renal Transplant Registry has identified no statistical significance in one-year functional graft survival in living related transplants when comparing patients with no presensitization with those with 1–5% sensitization (70.7% versus 75.5%). However, when living-related recipients with greater than 6% sensitization were considered, one-year survival was significantly lower, i.e. 56.6%. Similar results were obtained with cadaveric recipients. Thus, unsensitized cadaver recipients faired the same as those with 1–5% sensitization (47.9 and 48.9%), but cadaver recipients with 6% or greater sensitization had only 40.6% survival. On the other hand, several large series have emphasized that no difference in survival of sensitized and nonsensitized patients exists if accurate and elaborate crossmatch studies are performed to rule out the possibility of a positive crossmatch. This has led to the use of a number of modified crossmatch techniques in sensitized patients (analysis of most sensitized and most recent sera, prolonged crossmatch, dilutional crossmatch, antilymphocyte globulin crossmatch, etc.) to detect possible sensitivity of a recipient to a potential donor. Also, the possibility that certain positive crossmatches may be due to anti-B cell antibody (not likely to cause accelerated rejection) is currently being investigated.

To minimize or avoid the problem of presensitization, many people had adopted a policy to avoid blood transfusions whenever possible and to always use frozen (leucocyte poor) blood when necessary in all potential transplant recipients. There is no doubt that transfusions are associated with the development of detectable cytotoxic antibody against a normal lymphocyte panel, although there is not necessarily a direct relationship between the number of units transfused and the degree of sensitization generated. Nevertheless, the Renal Transplant Registry has identified a relatively unexpected relationship between the one-year functional graft survival of first cadaver transplants and the number of transfusions received prior to transplantation. Accepting that data accumulated relative to transfusion may be inaccurate and incomplete at best, it was found that cadaver recipients that received no transfusions preoperatively had a 44.4% one-year survival while those that received 1–4 units, 5–9 units, or greater than 10 units had 57.9, 60.2, and 63.8% survival, respectively. There was clearly a statistically significant improvement in survival in any patient who was transfused over those who received no transfusions. There was no significant difference between patients that received 1–4 units and those that received 5–9 or 10+ units. Reporting was done in a manner which did not

separate whole blood from packed and/or frozen cells, so a more precise anlaysis could not be done. Similarly analysis of patients who received whole blood during the transplantation operation showed that functional graft survival of those patients who received no transfusion intraoperatively was 45% at one-year while those who received transfusions was 55.5%. It must be emphasized that all groups that received transfusion prior to transplantation were smaller than those that received no transfusions, presumably because sensitization generated (or uncovered) by transfusion prevented a negative crossmatch and transplantation. Many assumed that increased survival associated with transfusion pre-transplant is due to the development of noncytotoxic, enhancing antibody. This has not been substantiated. Nevertheless, the data is so suggestive that a number of workers have proposed a minimum uniform transfusion policy to hopefully improve results. Unfortunately, it is difficult to estimate how many more successful transplants could be achieved by transfusion in relation to the possible negative effect of increased sensitization in preventing, or at least prolonging the wait for transplantation. If appropriate immunological monitoring could detect or identify the development of the postulated enhancing antibody, rational pre-transplant transfusion studies could be undertaken. This is certainly an area for intensive investigation in the next few years.

Hopefully, efforts to avoid reliance on chronic nonspecific immunosuppressive therapy as illustrated by Imuran, prednisone, and antilymphocyte globulin to prevent or control rejection will be expanded in the next few years. Several recent studies suggest that ALG has a beneficial effect in renal transplantation especially when used in good histocompatibility combinations, in good risk patients, in high dose, intravenously, for peroids of up to 28 days [2, 3, 4]. Experimentally, antilymphocyte globulin seems unusually effective in producing specific allograft survival when combined with infusion of donor antigen usually in the form of cell-free antigen preparations, lymphocytes, splenocytes, or bone marrow cells [5–7]. This kind of approach has been tried in at least one cadaveric kidney recipient with results that support the feasibility of such a therapeutic approach [8]. Recently, evidence in our laboratory suggests that platelets might be combined with a brief course of ALG therapy to achieve specific augmented allograft survival. The next several years may see renal transplantation done utilizing a brief program of intensive immunosuppression followed by infusion of donor antigen in some form. Marrow cells, platelets, or whole blood are an easily acquired and expendable donor antigen which can be derived from living-related and cadaver donors. Immunological monitoring techniques for enhancing antibody are certainly desirable but not necessarily critical to these trials. Transplantation is at the crossroads. Serious consideration should be given to carefully controlled and planned clinical trials of specific donor antigen exposure in conjunction with renal transplantation.

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