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KIDNEY TRANSPLANTATION:

Modern Trends in Kidney Transplantation

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IT IS OBVIOUS that the so-called modern trends in kidney transplantation represent an evolution based on actual experience that began about 15 years ago and from which much of a very practical nature has been learned. To trace the development of the present-day attitudes and practices, we reviewed the results and adjustments in our own program, which began in 1962, obtaining follow-ups on all the 556 consecutive patients treated at the University of Colorado from 1962 until 1 year ago. In addition, we surveyed the abstracts on renal transplantation submitted to this year's program committee of the Transplantation Society in order to gain insight into what was perceived as important by others working in this field.

COLORADO CASE MATERIAL

During the 13 years from 1962 to 1975, our program has profited from the efforts of many talented members of this society, a number of whom now run their own units elsewhere. The direct involvement of the senior author (T.E.S.) ceased almost completely in the summer of 1972. From 1972 to 1974, Drs. Jacques Corman (now of Montreal) and Bo Husberg (now in Malmo) directed the effort on a locem tenens basis of 1 year each. The directorship was filled (by R.W.) in the summer of 1974. These arrangements illustrate an important trend worth noting; namely, that major input by a well-trained chief is obligatory for the success of a kidney transplant program. Attempts to maintain transplant sideshows without such a major commitment have usually failed.

The features of each of seven periods in our renal transplantation program are summarized in Table 1 in terms of immunosuppression. The cases in the first five series encompassing the decade 1962–1972 have been reported before.[1–4] Double-drug therapy with azathioprine and prednisone was used until 1966. Since then, triple-agent therapy including antilymphocyte globulin (ALG) has been employed. In series 5, cyclophosphamide was substituted for azathioprine during the first several postoperative months. Although the results were not different than with azathioprine, we have returned to the routine use of azathioprine because of our much greater experience with the latter drug and because of our high degree of satisfaction with its use.

The cases were consecutive. At the beginning, an effort was made to treat younger patients who were free from disease of other organ systems. About 7 years ago, the conditions for transplantation were relaxed to permit the treatment of older recipients and of patients with concomitant diabetes mellitus, coronary heart disease, previous malignancies, and a variety of other disorders that had previously been considered contraindications.

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RELATED TRANSPLANTATIONS

Series 1

The genuine therapeutic potential of consanguineous transplantation was evident from 1962 to 1975. Even in series 1, compiled $12\frac{1}{3}$ to almost 14 years ago, two-thirds of the recipients of related kidneys lived for at least 1 year (Fig. 1 and Table 2). Between 1 and 5 years, this survival only dropped from 67% to 61%, and between the 5- and 10-year interval it declined to 52%. To put it differently, a patient in the consanguineous series 1 who lived for a year had an 80% chance of surviving a decade. Two more deaths occurred in the 11th and 12th postoperative years so that today 22 (48%) of the original 46 original recipients are alive. The mortality of the original patients averaged throughout the full period of observation has been almost exactly 4% per year.

The related kidneys have proved to be highly durable. After a minimum follow-up of $12\frac{1}{3}$ years, 18 of the 22 present survivors in series 1 still have good function of their original transplants (Table 3). Two more are living on second grafts and one is living on a fifth graft. Both of the second transplants that now have been functioning for more than 8 years were donated by parents when a primary kidney from the other parent was rejected after more than 5 years. The second to fifth retransplants in the other recipient were from cadavers. Only one patient is anephric (Table 3). Renal function ceased in this case more than 11 years after receipt of a cousin's kidney, when immunosuppressive treatment had to be stopped because of systemic cryptococcosis.

Subsequent Series

An attempt in series 2 to select donors by prospective tissue typing[5] was not fruitful, since the pattern of heavy early and lighter delayed mortality was not altered. After $10\frac{1}{3}$ to almost 12 years, 10 (40%) of these 25 consanguineous recipients are still alive, 7 with the original kidneys.

A reduction in early mortality was obtained in series 3, begun in 1966. The 1-year survival in that series of a decade ago rose to 92%. After $8\frac{1}{2}$ to 10 years, 67% of these patients are still alive (Fig. 1 and Table 2) for an average loss from the original population of about 3.5% per year. Series 3 was the last one in which candidacy was generally restricted to good-risk recipients. Although the restrictions were relaxed in series 4 and 5, the 1-year survivals were 76% and 86%, respectively, with a similar gradual subsequent loss rate (Fig. 1 and Table 2). The results in series 6 and 7 are probably going to follow the same pattern (Table 2).

In series 2–6, the need for retransplantation has been approximately the same as in series 1 (Table 3), and only a handful of the survivillg patients in these groups are anephric (Table 3). This reflects an aggressive policy of retransplantation in our center.

NONRELATED TRANSPLANTATION

Series 1

Although the majority of recipients of related kidneys survived chronically even in 1962 and 1963, the same was not true if unrelated kidneys were used.

The 1-year mortality after unrelated transplantation in our series 1 was 67% (Fig. 2 and Table 4). By 5 years, only 2 (11%) of an original 18 recipients were still alive. Both patients

still survive after $12\frac{1}{3}$ and 13 years, but only one has an original graft. That exceptional organ (in a patient identified in past publications by the code LD 63) is probably the longest functioning nonrelated kidney transplant in the world. The other patient who remains alive (LD 54) now has a well-functioning cadaveric graft after rejecting first a kidney from a nonrelated living donor and next a transplant of maternal origin. Five of the 13 years of his survival have been on dialysis.

Subsequent Series

A substantial and lasting improvement of survival for recipients of nonrelated kidneys was late in coming in our experience. In series 2, which was completed in April 1966, the 1-year survival was upgraded to 52%, but after 5 years only 5 (22%) of 23 patients were alive. Now after $10\frac{1}{3}$ to almost 12 years, only 3 (13%) are left, in 2 cases with original kidneys. In series 3, in which all of our nonrelated organs were obtained from cadavers, the 1-year survival had increased (Fig. 2 and Table 4) to 82% (14 of 17). Unfortunately, deaths continued at a steady rate so that at 5 years only 6 (35%) of the recipients of series 3 were left. Now, after $10\frac{1}{2}$ to 10 years, 5 (29%) remain. In 4 of these 5 survivors of series 3, the original cadaveric kidneys are still functioning. In the combined nonrelated series 1–3, the average actual patient loss rate over the first decade after transplantation was the unacceptable figure of approximately 8% of the original population per year.

However, beginning in 1968 and continuing throughout series 4 and 5, patient survival sharply improved throughout the first 4 or 5 years and beyond (Fig. 2 and Table 4). Three-fourths or more of the recipients were alive at 1 year and from then until 4 and 5 years, the further deaths were reduced. However, a different attitude about the primacy of the transplants was obvious. Now, the grafts were being abandoned, and the patients were being treated by return to dialysis and aggressive retransplantation. For example, in series 4 after a minimum follow-up of almost 6 years, 73% of the original patient group (11 of 15) are still alive but only 4 of the 11 have original cadaveric grafts. Five others have had successful retransplantation, and two are back on dialysis (Table 5).

From all of the first six periods of our experience, relatively few surviving patients are anephric. In the nonrelated series 1–6, only 10 of the 70 surviving patients are anephric. Thus, the potential administrative spectre of developing a pool of nontransplantable recipients by virtue of unsuccessful primary transplantation has not materialized.

The improved survival after cadaveric transplantation has been maintained in the more recent series 7 (Table 4).

CAUSES OF DEATH AFTER 5 YEARS

Twenty-four patients from series 1–4 died from 60 to 137 months after their original kidney transplants. A study of their fate provided insight about the late risks that are apt to be encountered in future cases. Nine of these 24 recipients had undergone retransplantation after failure of the primary kidney. In 16 of the 24 cases, renal function from a primary or secondary graft was still adequate just before the final illness.

The single most common delayed lethal factor was pneumonitis caused by a virus in four cases, *Pneumocystis carinii* in one case, and a mixed bacterial flora in the other. Four of the six patients who died of pneumonitis were healthy with function of the original transplant until the fatal acute respiratory crisis. The other two had failedor failing kidneys and both

had recently undergone retransplantation. Two other patients died with complications of disseminated cytomegalovirus infections.

Four other patients, *all* with well-functioning renal homografts, died of chronic aggressive hepatitis. Thus, kidney transplantation under today's circumstances is generating candidates for liver transplantation. Among our own renal recipients who died of hepatic failure, consideration of liver transplantation was delayed for too long. However, we have attempted liver and kidney transplantation for combined hepatic and renal failure in one renal recipient who was referred from another center. The patient died 5 weeks postoperatively.

Three patients committed suicide, one by stopping medication, one by refusing to return to dialysis, and the third by shotgun injury. The other causes of late death are self-explanatory (Table 6). One patient died of disseminated carcinoma of the jaw; two more whose deaths were caused by a mesenteric infarction and pneumonitis, respectively, had an incidental carcinoma of the lung and a hepatoma. The fact that only one late death was caused by malignancy was encouraging in view of the incidence of de novo malignancies that has been reported at about 10% in our chronic survivors.[4] The low death rate from tumors reflects the effectiveness of the cancer therapy that can be applied in immuno-suppressed recipients, especially if repeated and careful examinations are made by physicians who are conscious that this is a special problem.

Three patients eventually died from mesenteric vascular occlusion (two arterial and one venous) and bowel necrosis. An abnormal incidence of vascular disease was also reflected in two deaths from myocardiai infarction. Finally, a patient with hyperparathyroidism developed widespread metastatic calcification in small vessels and consequent massive skin and subcutaneous fat infarction. Another of our recipients survived a less severe variant of this dreadful complication but at the price of more than a year's continuous hospitalization and only after the amputation of both hands and forearms.

NOTATION OF TRENDS

The trends in our own experience are also easy to identify in most other programs today. This is not surprising, since essentially all of the immunosuppressive and other techniques being used now have been generally available for a decade or more. The failure of radically new methods to be developed in the last 8–10 years has relegated progress to the shuffling of details and to the adjustment of earlier attitudes and policies.

For one thing, there has been a recognition of the impermanence of nonrelated kidneys compared to consanguineous organs. At the International Transplantation Conferences convened by the New York Academy of Sciences in 1964 and 1966, there was much talk that cadaveric organs that were functioning well at 1 or 2 years would probably be good for a decade. Our results and those of many others have shown this expectation to be unrealistic.

Fortunately, the conditions for treatment of renal failure have also changed, making possible a second shift in attitude about both cadaveric and consanguineous transplantation. Throughout the 1960s, transplantation was usually carried out on a research ward as a desperate administrative alternative to the financial ruin caused by the necessity for prolonged dialysis. The prospect of homograft failure with return to dialysis was a grim and unacceptable one for many people. Consequently, aggressive immunosuppressive treatment was too often persisted in after all reasonable hope had been lost for continuing graft function. This was the main explanation for the high mortality in our cadaveric series 1–3. In recent years, the proper interlocking, as opposed to competing, roles of dialysis and transplantation have been recognized and exploited. In large part this was made possible by the Federal H.R. Bill amending Medicare-Medicaid. This legislation provided the necessary

financial backing for complete treatment. The new ground rules have permitted either transplantation or dialysis to be considered part of the same continuum of care for renal failure in which the transition from one to the other modality is of minimum economic concern.

The mortality should be less and the quality of life should be greater with combined dialysis and transplantation than with either treatment alone. The data from our experience suggest that a patient today who has adequate dialysis support should have about a 75% chance of living at least 5 years if either a related or unrelated transplantation is performed, providing there is a willingness to abandon and remove failed grafts early, especially cadaveric ones. The risks of dialysis alone are probably greater than this, as has been exemplified by the Public Health Service collected statistics showing a 4-year dialysis mortality of about 40%.[6]

It is self-evident that neither technique is perfect for chronic care. However, it is recognized that the causes of late death are somewhat different in transplant and dialysis recipients. The profound susceptibility of dialysis patients to vascular disease and to neurologic complications is well known, whereas the chief causes of late death after transplantation will probably continue to be infections (mainly affecting the lungs and liver) and possibly malignancy in the long run. The imperfections of both transplantation and dialysis are underscored by the high incidence of suicide and serious emotional disorders in patients treated by either method.

Efforts to improve transplantation are reflected in the abstracts for this year's program, and from these more trends that are worth mentioning can be seen. Typing is not dead, as was illustrated by a total of about two dozen abstracts with variable but generally fuzzy correlations of HL-A match and outcome and better correlations with MLC tests. The effects of chronic dialysis and transfusions prior to transplantation were said to be usually not harmful. Most authors conceded that preformed recipient antibodies were prognostically bad even without demonstrable antidonor specificity.

Efforts to make the treatment on a rational rather than an empirical basis were illustrated by many abstracts directly concerned with preoperative or postoperative monitoring, most commonly with immunologic measures, but also with other sophisticated techniques such as radio-nuclide scanning. A small number of papers was concerned with further defining pathologic changes in rejecting grafts or with the physiologic performance of transplants.

The subject of organ preservation was covered in 11 abstracts. For 2- or 3-day periods, the perfusion methods pioneered by Belzer were shown to have a demonstrable advantage. But from a practical point of view, the simple flush techniques of Collins and Sacks have yielded about comparable results providing transplantation could be completed within 24–36 hr. The result has been a movement away from the perfusion approach.

The dead-center position of immunosuppression was evident from the fact that almost all the clinical abstracts concerned with rejection therapy were reexaminations of older techniques. Questioned were the value of graft irradiation, the value of antilymphocyte globulin, the usefulness of alternating day steroid therapy, and the efficacy of high-dose pulse steroid administration.

At the same time, the sometimes devastating effectiveness of all forms of treatment now in use was attested to by 22 abstracts detailing the complications of chronic immunosuppression. These included cancer; gastrointestinal ulcerations; viral, bacterial, and fungal infections; hypersplenism; hyperparathyroidism; cataracts; bone disease; liver malfunction; hyperlipidernia; and vascular disease. The central objective of research in our

specialty remains the achievement of graft acceptance with lesser penalties than are now exacted.

SUMMARY

Trends in renal transplantation stem from recognition of the virtues and drawbacks of this kind of treatment and from a better appreciation of the interrelationship between transplantation and dialysis.

Acknowledgments

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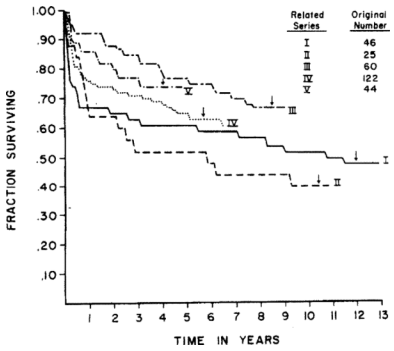

Fig. 1.

Life survival curves of patientr treated with primary related homografts during five intervals from 1962 to the summer of 1972. Arrows show time of minimum follow-up. Description of sofibs is in Table 1.

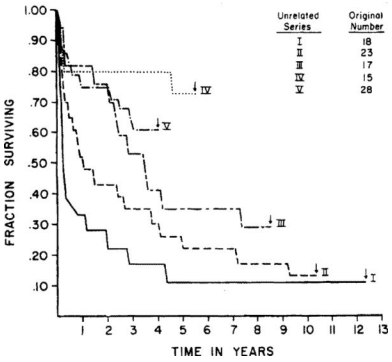

Fig. 2.

Life survival curves after transplantation of nonrelated kidneys during the same five time periods as in Fig. 1. Description of series is in Table 1. Arrows show time of minimum follow-up.

Table 1

Experience With Renal Transplantation at the University of Colorado, 1962–1975

Series	Number of Cases		Dates	Follow-Up (Years)	Main Feature
	Related	Unretated*			
1	46	18	November 1962 to March 1964	$12\frac{1}{3} - 13\frac{3}{4}$	Azathioprine/prednisone; good risk
2	25	23	October 1964 to April 1966	$10\frac{1}{3} - 11\frac{5}{6}$	Azathioprine/prednisone + typing; good risk
3	60	17	June 1966 to February 1968	$8\frac{1}{2} - 10\frac{1}{6}$	Azathioprine/prednisone/ALG; good risk
4	122	15	March 1968 to March 1971	$5\frac{1}{2} - 8\frac{1}{2}$	Azathioprine/prednisone/ALG; all risk
5	44	28	March 1971 to August 1972	$4 - 5\frac{1}{2}$	Cyclophosphamide/prednisone/ALG; all risk
6	65	49	August 1972 to August 1974	2– 4	Azathioprine/prednisone/ALG; all risk
7	27	17	September 1974 to August 1975	1– 2	Azathioprine/prednisone/ALG; all risk

*Since late 1965, all unrelated kidneys have come from cadavers. Before then, nonrelated volunteer donors were used.

Table 2

Actual Survival at 1 Year and Thereafter in Patients Given Primary Related Grafts From 1962 to 1975

		Percent Survival				
Series	**Number of Cases**	**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

Number of Survivors in Related Series With Functioning Original Transplants or Subsequent Grafts

Series	Time Following	Present Survivors*	On Original Graft	Successful After Retransplantation	Anephric
1	$12\frac{1}{3} - 13\frac{3}{4}$	22/46 (48%)	18	3	1
2	$10\frac{1}{3} - 11\frac{5}{6}$	10/25 (40%)	7	2	1
3	$8\frac{1}{2} - 10\frac{1}{6}$	40/60 (67%)	30	8	2
4	$5\frac{1}{2} - 8\frac{1}{2}$	75/122 (61%)	67	6	2
5	$4 - 5\frac{1}{2}$	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

Actual Survival at 1 Year and Thereafter in Patients Given Primary Nonrelated Grafts From 1962 to 1975

		Percent Survival				
Series	**Number of Cases**	**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

Number of Survivors in Nonrelated Series With Functioning Original Transplants or Subsequent Grafts

Series	Time Following	Survivors	On Original Graft	Successful After Retransplantation	Anephric
1	$12\frac{1}{2}-13$	2/18 (11%)	1	1	0
2	$10\frac{1}{2}-11\frac{5}{6}$	3/23 (13%)	2	0	1
3	$8\frac{1}{2}-10\frac{1}{2}$	5/17 (29%)	4	1	0
4	$5\frac{1}{2}-8\frac{1}{2}$	11/15 (73%)	4	5	2
5	$4-5\frac{1}{2}$	17/28 (61%)	11	5	1
6	2–4	32/49 (65%)	20	6	6
7	1– 2	14/17 (82%)	8	1	5

Table 6

Causes of Death 5 Years or More After Primary Kidney Transplantation

Causes of Death	Number of Patients	Number of Patients With Adequate Antemortem Kidney Function
Pneumonia	6	4
Liver failure	4	4
Mesentric 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