

Long-Term (25-Year) Survival After Renal Homotransplantation—The World Experience

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At the beginning of 1962, renal transplantation, except with an identical twin donor, was not a promising means of treatment. Total body irradiation^{1,2} 6-mercaptopurine,³⁻⁶ its analogue, azathioprine⁷ and steroids⁸ had been shown in dogs and/or rodents to have immunosuppressive qualities, but prolonged survival of skin or kidney grafts in experimental animals was a relatively uncommon achievement. Similarly, the first clinical trials with these agents, alone or in combination, had been almost universally unsuccessful.⁹⁻¹⁴

METHODS

It was known from our own unpublished canine experiments that steroids and azathioprine had synergistic immunosuppressive effects. As it turned out, this kind of multimodality therapy allowed the prevention or reversal of rejection of renal homografts in most clinical cases.¹⁵ Consequently, an extensive and encouraging clinical experience (Table 1) with 64 patients was quickly acquired at the University of Colorado.¹⁶ Forty-six patients were given kidneys from blood relatives other than identical twins. The other 18 received kidneys from nonrelated volunteer donors. Fifteen of the recipients survived for 25 years and 14 are still living after 25½ to 27 years. These long-surviving recipients are the principal basis of this report.

In addition, with the help of colleagues at 6 other centers which were active in these early years, 9 more patients have been found who have survived to date after treatment with renal homotransplantation during this same time frame.

RESULTS

Forty-Six Recipients of Living Related Kidneys

Fourteen (30%) of 46 recipients of living related kidneys in the original University of Colorado series are still alive after 25½ to 27 years (Table 2). The 25-year survival rate in this group was 15/46 (33%), but one of the patients died after 25.3 years with function of his original maternal graft (Cr 2.0 mg %). Ten of the 14 survivors have their original

grafts (Table 2), and all have serum creatinines less than 2 mg %.

Recipients of Sibling Kidneys. Only 3 (13%) of the 23 recipients of sibling kidneys are alive (Table 1). They have good function of their original transplants, the first two of which are the longest surviving homografts in the world. These 3 patients are males. Their grafts were placed on 31 January 1963 (from a sister), 9 February 1963 (brother), and 15 January 1964 (sister) (Table 2). The first of these recipients was A blood type and received a B kidney, a blood group incompatibility that is generally avoided today. The last 2 of the 3 surviving recipients stopped all therapy 25 and 23 years ago because of mental illness and religious convictions respectively. Renal function has been perfect throughout. Why treatment could be stopped permanently is not known. Noncompliance of this kind often has been described in the literature as an important cause of graft loss.

Recipients of Parental Kidneys. Nine (45%) of the 20 recipients of parental kidneys are alive (Table 1) and 5 still have adequate function of their original grafts. Two more have undergone successful retransplantation with related donors and two are on dialysis (Table 2).

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Table 1. Living Donor Renal Transplants From November 1962 to March 1964

	Number	Alive in Years					Function Now of Original Graft	Off Dialysis Now
		5	10	20	25	Now		
Non-Twin Relatives	46	28	24	17	15	14	10	12
Sibling	23	11	8	4	3	3	3	3
Parental	20	14	13	11	10	9	5	7
Other*	3	3	3	2	2	2	2	2
Non Related	18	2	2	1	0	0	0	0

*Aunt, Uncle, or Cousin.

Table 2. Fourteen Surviving Patients From 1962 to 1964 (March) Series

LD	Tx Date	Donor	Age/Sex	Renal Function	Dialysis
1	11-24-62 5-21-68	Mother Father	12/M		Since 1982
2	1-31-63	Sister	38/M	Good	
3	2-9-63	Brother	21/M	Good	
13	7-3-63 7-27-87	Mother Brother	15/M	Good	
17	7-19-63	Mother	15/F	Good	
33	10-07-63	Mother	18/F	Good	
34	10-11-63 9-14-82	Mother Brother	8/F	Good	
39	11-13-63	Mother	17/M	Good	
42	11-27-63	Father	19/F	Good	
49	1-15-64	Sister	32/M	Good	
50	1-25-64 11-07-69 10-30-85	Father Mother Cadaver	16/F		Since 1987
51	2-10-64	Aunt	18/M	Good	
52	2-17-64	Father	15/F	Good	
53	2-22-64	Uncle	15/M	Good	

Recipients of Grafts From an Aunt, Uncle, and Cousin. One graft from an aunt and one from an uncle are still functioning well (Tables 1 and 2). A kidney from a second cousin was chronically rejected after 15 years and the recipient died not long after.

Pediatric Vs Adult Recipients of Related Grafts. Of 16 patients who were 18 years-old or younger at the time of transplantation, 10 (63%) are still alive, 8 are dialysis free, and 6 have good function of their original grafts (Table 3). In contrast, only 4 (13%) of 30 adults are alive, all with function of their original grafts of which 3 were from siblings, and the other from a parental donor.

Table 3. Pediatric Versus Adult Recipients in 46 Related Transplantations

	Number	Alive	Original Graft	Dialysis Free
Pediatric (3-18 years)	16	10 (63%)	6 (38%)	8 (50%)
Adult (19-55 years)	30	4 (13%)	4 (13%)	4 (13%)

Table 4. Outcome of Pediatric Recipients Treated From November 24, 1962 to March 23, 1964, Follow-up to September 1, 1989

LD	Age at Tx	Patient Survival	Donor	Tx Dates	Function	
					CR	BUN
1	12	Alive	Mother Father	11-24-62 5-21-68	Dialysis	Since 9-2-82
13	15	Alive	Mother Brother	7-03-63 7-27-87	Failed	Normal
17	15	Alive	Mother	7-19-63		Normal
19	17	109d	Mother* Unrel M	7-26-63 8-09-63		
20	6	201d	Mother*	7-29-63		
22	15	11y 169d	Mother	8-12-63		
26	16	1d	Father	8-29-63		
33	18	Alive	Mother	10-07-63		Normal
34	8	Alive	Mother Brother	10-11-63 9-14-82	Failed	Normal
39	17	Alive	Mother	11-13-63		Normal
41	3	14y 16d	Mother Cadaver M Cadaver F Cadaver F Cadaver F	11-23-63 1-22-70 6-29-70 2-27-71 12-29-72		
50	16	Alive	Father Mother Cadaver	1-25-64 11-07-69 10-30-85	Dialysis	Since 1987
51	18	Alive	Aunt	2-10-64		Normal
52	15	Alive	Father	2-17-64		Normal
53	15	Alive	Uncle	2-22-64		Normal
61	5	36d	Mother	3-23-64		

Tx = transplantation; ReTx = retransplantation.

* A to O transplants.

Because of the disproportionately high 25-year survival observed in infants and pediatric recipients, all 16 cases were examined retrospectively (Table 4). Four of the 6 deaths occurred early from 1 to 201 days after transplantation. Only 2 more deaths occurred in the next 25 years.

Eighteen Colorado Recipients of Nonrelated Volunteer Kidneys

None of these patients are alive (Table 1). The longest kidney survival was 16 $\frac{2}{3}$ years (LD63) and the longest patient survival (LD54) was 24.8 years (Table 5).

Table 5. Causes of 12 Deaths That Occurred After 10 Years

LD*	Donor	Date of Tx	Age	Date of Death	Survival	Last Kidney Function		Cause of Death
						CR	BUN	
6	Brother	4-17-63	23	9-24-87	24.4	5.0	73	Coronary artery disease
12	Brother	6-07-63	48	7-15-80	17.1	1.7	16	Cancer of prostate
14	Brother	7-05-63	42	4-06-82	18	1.2	19	Coronary artery disease
22	Mother	8-12-63	15	1-28-75	11.6	—	—	Renal failure, stopped medications
25	Brother	8-21-63	33	5-09-81	17.7	1.6	18	Suicide
37	Mother	10-18-63	21	2-10-89	25.3	2.0	40	Coronary artery disease
41	Mother Cadaver Cadaver Cadaver Cadaver	11-23-63 1-22-70 6-29-70 2-27-71 12-29-72	3	12-08-77	14	—	—	Renal failure
54	Unrelated Cadaver Cadaver	2-24-64 9-26-66 11-17-74	21	11-25-88	24.8	1.2	20	Coronary artery disease
55	Father	2-26-64	21	9-02-84	20.5	1.5	25	Cancer of lung
58	Sister	3-13-64	27	10-10-74	10.6	1.2	13	Liver failure from chronic active hepatitis
60	2nd Cousin	3-17-64	21	5-29-79	15.2	—	—	Renal failure, multiple skin cancers

Causes of Late Death in the Colorado Series

At the end of 10 years, 24 (52.2%) of the 46 patients given living related kidneys, and 2 (11.1%) of 18 recipients of nonrelated kidneys were still alive. Twelve of these 26 survivors died subsequently for reasons summarized in Table 5. Heart disease from coronary arteriosclerosis and cancer (4 examples each), were the principal reasons for the late deaths. Two patients stopped immunosuppression in what may have been covert suicides. They rejected their kidneys, and died of inadequately treated renal failure. Another patient with perfect renal function 17.7 years posttransplantation committed suicide with carbon monoxide inhalation. One patient developed chronic active hepatitis and died of liver failure 10.6 years posttransplantation.

It was particularly distressing to have 3 patients die a few months before or just after the twenty-fifth anniversary of their transplantation. Two of these patients (LD6 and LD37) still had life supporting although subnormal renal function. One (LD6) was under consideration for heart transplantation and kidney retransplantation.

Survivors From Other Centers Before 31 March 1964

Nine additional survivors from this early era of renal transplantation are being followed in 6 centers (Table 6), 4

in the United States and 2 in Europe. All 9 were recipients of kidneys from blood relatives. In 7 of the 9 cases, the original grafts are still functioning. In the other 2, retransplantation many years later has made or kept the patients dialysis free; these patients who were treated in Paris (1962) and Edinburgh (1962) are the longest survivors in the world.

DISCUSSION

There are no patients left from the era preceding 1962 in which immunosuppression was with total body irradiation. However, the long survival of two fraternal twin recipients from this earlier time provided an exceptional incentive for continuing efforts during an otherwise bleak period. The first of these twins whose operation was in Boston on 24 January 1959,^{11,12,17} died in August 1979 of arteriosclerotic heart disease (personal communication, Dr Robert Kirkman, August 1989). The second fraternal twin underwent transplantation in Paris on 29 June 1959,¹⁸ and died on 13 July 1985 of carcinoma of the bladder (personal communication, Dr Henri Kreis, August 1989).

The subsequent wave of successes that began in 1962 was made possible by the availability of azathioprine and by its combination with prednisone. March of 1964 was a natural demarcation point defining the end of this remark-

Table 6. Nine Other Non-Twin Recipients From Before March 31, 1984

Number	Date Tx	Where Done*	Donor	Age/Sex	Principal Physician	Earlier Late Reports	Follow-up by	On Dialysis	Dialysis Free Now	
									With 1st Graft	With RTx
1	2-12-62 3-28-77	Paris	Cousin Sister	18 M	J. Hamburger	—	H. Kreis	—	No	Yes
2	7-27-62 1-86	Edinburgh	Father Cadaver	12 M	M. Woodruff	22	M. Woodruff	1-83 to 1-86	No	Yes
3	3-18-63	Richmond	Brother	22 F	D. Hume	25	G. Mendez-Picon, H.M. Lee	—	Yes	—
4	5-06-63	Boston	Father	30 M	J. Murray, J. Merrill	20, 21	R. Kirkman	—	Yes	—
5	5-16-63	Richmond	Mother	14 F	D. Hume	25	G. Mendez-Picon, H.M. Lee	—	Yes	—
6	7-16-63	Cleveland	Brother	41 M	W. Kolff	26	W. Braun	—	Yes	—
7	8-14-63	Minneapolis	Mother	12 M	W.D. Kelly, R. Lillehei	27	J. Najarian	—	Yes	—
8	12-27-63	Minneapolis	Aunt	7 F	W.D. Kelly, R. Lillehei	27	J. Najarian	—	Yes	—
9	2-03-64	Richmond	Sister	35 F	D. Hume	25	G. Mendez-Picon, H.M. Lee	—	Yes	—

*Paris—Hopital Necker; Edinburgh—Western General Hospital; Boston—Peter Bent Brigham; Richmond—Medical College of Virginia; Cleveland—Cleveland Clinic; Minneapolis—University of Minnesota.

able new phase. The cases compiled to that time at the University of Colorado provided the basis for the first textbook on renal transplantation.¹⁶ In addition, this same time frame was used for a collection of all 342 renal homotransplantations done in the world up to March 1964.¹⁹ This latter extraordinary labor of love had been undertaken by the great transplantation pioneer, Dr Joseph E. Murray of Boston, following a meeting on 26 and 27 September 1963 in Washington DC of about 20 early workers (surgeons, physicians, and pathologists) in this embryonal new specialty. The meeting was sponsored by the National Research Council and the National Academy of Science.

Almost all of the survivors in the world at the time of the September 1963 meeting and up through the following March were treated at the same centers in Boston, Cleveland, Denver, Edinburgh, Minneapolis, Paris, and Richmond where more than 25 years later the residual group of patients can be found today. Late reports from most of these centers have been published²⁰⁻²⁷ but not for a number of years. The presence of these survivors continues to justify an effort which once was perceived by many as the height of folly.²⁸

Ever since 1964, there was a growing uneasiness in the University of Colorado team about our dependence on living related donors; this is a concern which continues to

haunt us to the present day. In addition, the failure to do better at the end of our 24-month trial than at the beginning of it had already convinced us that fundamental improvements in tissue matching, in immunosuppression, or both would be necessary before renal transplantation would be truly practical. Consequently, a moratorium on renal transplantation was declared at the University of Colorado from March 1964 until the following October. When efforts were resumed, they included the first trial (with Dr Paul Terasaki at the University of California, Los Angeles) of prospective tissue matching.²⁹

By 1964 it became evident that the quality of life provided by nonrelated kidneys was inferior to that provided under the same conditions by living-related donor transplants. Furthermore, progress in the results of cadaver donor renal allografts appeared to be a clear prerequisite to extension of clinical transplantation to nonrenal organs, which uniformly require cadaveric donors. It is worthy of note that none of the world's currently surviving 23 long-term recipients was given an unrelated donor kidney. The longest continuous function of an unrelated kidney allograft in the University of Colorado series was 16.7 years. There is no report, as yet, in the world of a 25-year survival of a cadaveric kidney allograft, although a recipient in Paris who has maintained perfect renal function is expected to breach this barrier on 12 October 1989

(personal communication, Dr Henri Kreis, August 1989). This female recipient was 31 years-old at the time of her transplantation in 1964.

A disquieting note in this series of patients is the continuing late mortality, which appears to bear no relationship to the organ source. In the University of Colorado series, 12 of the 26 patients alive at 10 years²⁴ died subsequently. The higher rate of cancer seems to be related to chronic immunosuppression as was predicted from the beginning of this experience.³⁰ Cardiovascular disease seen in these patients may also have been a consequence of chronic immunosuppression, and particularly of the use of steroids. It is of interest in this regard that the two patients who stopped their own immunosuppression more than 20 years ago remain free of these complications. These recipients have behaved almost as identical twin recipients studied during this era. Less than complete satisfaction with the outcome of transplantation may be inferred from the suicide of one patient and the occult suicide of 2 other subjects, who refused to return to chronic dialysis after their kidney grafts had failed.

At the time, the results observed during this era ending in March 1964 were considered revolutionary. A new field was deemed to have been opened with staggering scientific and social ramifications. The follow-up provided in this report is less of a justification of the technology than available than a sobering description of its limitations. The treatment options available today continue to have many of the same risk factors for truly long survival as the methods of 25 years ago. The results provide a stark warning against complacency regarding what we have to offer to transplant recipients today.

SUMMARY

A follow-up is provided for 64 patients treated with renal transplantation at the University of Colorado before 31 March 1964. The 25-year survival was 15/64 (23.4%) and 14 patients (22%) are still alive after 25½ to 27 years. There are 9 other survivors in the world from this era, distributed in 4 American and 2 European centers. All of the 25-year survivors received their grafts from living related donors.

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