

Eight- to Ten-Year Follow-up in Early Cases of Renal Homotransplantation

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THIS report will be concerned with a medical, social, and psychiatric follow-up on a group of patients treated by renal homotransplantation from 8½ to 10 yr ago at the Denver Veterans Administration and Colorado General Hospitals.

CASE MATERIAL

The 64 patients who underwent transplantation between November, 1962 and March, 1964 have been extensively described in journals and in a book based almost entirely on these cases.^{1,2} There were 46 recipients of consanguineous kidneys from 23 siblings, 20 parents, one aunt, one uncle, and one cousin, and 18 recipients of nonrelated kidneys donated by healthy volunteers. Immunosuppression was with azathioprine and prednisone, using two regimens. In 45 cases azathioprine was started alone; prednisone was added in 43 of these 45 patients with the appearance of clinically obvious rejection. In the other 19 recipients both drugs were administered from the outset.

Typing procedures were not available when this series was compiled. Consequently, the donor-recipient matching was not by any kind of immunologic guidelines except for the avoidance in all cases after case 23 of the kind of red blood cell type incompatibility that can lead to hyperacute

rejection.¹ Parenthetically, one of our earliest recipients is still alive with perfect graft function 9 yr 8 mo after transplantation from a B+ type donor to A+ type recipient, a combination which would no longer ever be used.

All of the recipients had splenectomy. The first eight (of whom four are still living) had pretransplantation thymectomy. Nine additional patients had thymectomy 8½ to 17 mo after transplantation in the hope of being able to reduce immunosuppression. Five of the nine recipients are still alive but three of them have undergone retransplantation. Although thymectomy may have a beneficial effect in humans², it is no longer performed in our center.

SURVIVAL

The 46 Related Cases

After a heavy mortality (33%) in the first 6 mo, subsequent deaths have been uncommon (Fig. 1). Of the 31 recipients who survived for a half year, 29 and 28 lived for 3 and 5 yr, respectively, and 24 are still alive after 8½ to almost 10 yr. No one is now on dialysis and 21 of the 24 have function of their original grafts; the other three had retransplantations 5½, 5¾, and 7 yr after the first procedure and the secondary kidneys have subsequently functioned for 4½, 3¾, and 1½ yr.

The outcome was not strikingly influenced by the nature of the relationship whether this be parental, sibling, or other (Table 1). The parent-to-offspring results were amazingly stable in terms of recipient survival. At the end of 6 mo, 14 of 20 recipients (70%) were alive. By 8½-10 yr

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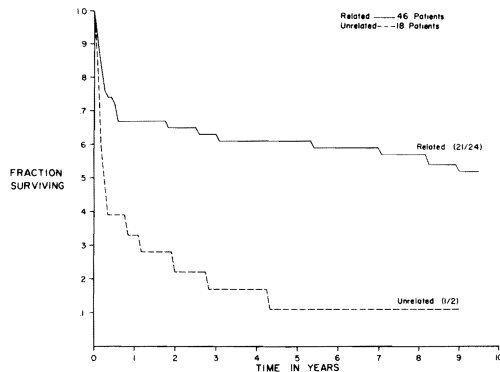


Fig. 1. Life survival curves of 64 patients treated from November, 1962 to March, 1964. The denominators in the related and nonrelated curves refer to patient survival and the numerators to survival of the original homograft. Thus, 22 of the 26 living recipients still bear primary grafts; the other four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

there were still 13 (65%) alive, although three of these were by virtue of retransplantation. Also of interest was the fact that all of the three distantly related renal grafts (aunt, uncle, and cousin) were providing superb function, nearly a decade after their insertion (Table 1).

The causes of mortality in the first 5-yr follow-up of this series have been exhaustively reported^{1,2} for which reason only the four deaths in the second 5 yr will be mentioned. Two patients with adequate renal function 8 $\frac{1}{4}$ and 9 yr posttransplantation died of chronic aggressive hepatitis of several years' duration; one was Australia-antigen positive. A third patient had

a fatal myocardial infarction after 7 $\frac{1}{3}$ yr. The fourth patient had a technically unsuccessful retransplantation in the sixth year, and then committed suicide by refusing to be placed back on hemodialysis.

The 18 Nonrelated Cases

Two-thirds of the recipients died in the first year with a mortality that continued until only two patients were left at the 5-yr mark (Fig. 1). These two are still alive after 8 $\frac{1}{2}$ and 8 $\frac{2}{3}$ yr but in the second instance a second homograft from a mother has supported life for the last 6 yr of the total survival.

GRAFT FUNCTION AND IMMUNOSUPPRESSION

In Table 2 are shown the average current renal functions of the 26 survivors, these values representing 22 primary kidneys that have functioned for 8 $\frac{1}{2}$ to nearly 10 yr and four retransplants that have functioned for 1 $\frac{1}{2}$ –4 $\frac{1}{3}$ yr. On the average, the older grafts are performing better than the more recent ones. The chronic immunosuppression being given those patients is also listed. The average daily doses of prednisone are small enough so that only one patient (the most recent retransplant) has a Cushing's facies.

Arterial hypertension is an almost universal finding in the immediate posttransplantation period and even for several years afterwards.^{1,2} This problem has tended to become less with longer follow-up. Only

Table 1. The Influence of Consanguinity upon Present Survival in 46 Cases After 8-1/2 to 9-5/6 Yr

Donor	1 Yr		3 Yr		5 Yr		Now	
	Patient	Graft	Patient	Graft	Patient	Graft	Patient	Graft
20 Parents	14	14	14	14	14 (70%)	14 (70%)	13 (65%)*	10 (50%)
23 Siblings	14	14	12	12	11 (48%)	11 (48%)	8 (35%)	8 (35%)
3 Aunt, uncle, or cousin	3	3	3	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)

*Retransplantation was carried out after 5 $\frac{1}{2}$, 5 $\frac{3}{4}$, and 7 yr.

one of the survivors (and this the retransplant of 1½ yr ago) has severe hypertension. Five other patients receive small daily doses of a combination of antihypertensives. Fourteen recipients require no antihypertensive therapy, and six are receiving only chlorothiazide. With the generally low steroid doses, there are no examples of steroid-induced diabetes.

THE QUESTION OF CANCER

Six of the 64 recipients (9%) including four who are still alive developed carcin-

omas, the features of which are summarized in Table 3. All were skin cancers and treatment was by standard surgical measures. So far cancer has not been a cause of death in this original group of patients although we have had two deaths from de novo reticulum cell sarcomas in patients treated since 1964.²

THE QUALITY OF LIFE

The degree of rehabilitation in this group has been truly remarkable. All those who were adults at the time of transplantation

Table 2. Average Current Renal Function and Immunosuppression in 26 Recipients of Renal Homografts Surviving 8½–10 Yr Posttransplantation

Patient	BUN (mg 100 ml)	Serum Creatinine (mg 100 ml)	Creatinine Clearance (ml/min)	Azathioprine (mg/day)	Prednisone (mg/day)
LD 1*	22	1.6	90	125	15
LD 2	16	1.7	70	100	0
LD 3	11	1.1	130	150	0
LD 6	20	1.3	105	200	10
LD 12	18	1.4	70	100	15
LD 13	19	1.4	90	87.5	7.5
LD 14	10	0.9	120	200	0
LD 17	9	0.8	70	100	2.5
LD 22	17	0.8	90	137.5	10
LD 25	22	1.6	80	50	10
LD 33	12	1.2	90	125	0
LD 34	31	1.5	60	50	0
LD 37	11	1.0	94	150	15
LD 39	17	1.0	80	125	10
LD 41*	60	3.0	20	5	30
LD 42	18	1.1	75	125	7.5
LD 49	25	1.1	70	87.5	5
LD 50*	49	2.0	45	75	20
LD 51	21	1.3	85	125	10
LD 52	17	0.8	110	150	5
LD 53	25	1.6	55	100	5
LD 54* †	25	1.1	85	125	15
LD 55	27	1.4	40	150	20
LD 58	16	1.4	65	137.5	10
LD 60	46	3.3	40	87.5	20
LD 63†	27	1.4	80	125	15
Mean ± SD					
22 Original grafts	19.8 ± 8.3	1.3 ± 0.5	80.4 ± 22.9	121.0 ± 38.8	8.1 ± 6.3
Four retransplantation	39.0 ± 18.5	1.9 ± 0.8	60.0 ± 33.4	82.5 ± 56.8	20.0 ± 7.1
All 36 patients	22.7 ± 12.2	1.4 ± 0.6	77.3 ± 25.2	115.1 ± 43.1	9.9 ± 7.7

*Patients surviving after retransplantation (LD 1, 4½ yr, LD 41, 1¾ yr, LD 50, 3 yr, LD 54, 6 yr).

†Surviving recipients of living unrelated renal homografts.

heave returned to some kind of full time work ranging from menial through technical to highly intellectual.

Twelve of the survivors were younger than 18 yr (3–17) at the time of the original operation. They all returned to school, half graduated from college, eight now support themselves fully in adult work, and nine have married. The only one who has spent an excessive amount of time in the hospital is a child originally treated at the age of 3, whose original homograft failed, and who subsequently required retransplantation. He is now 12 years old and is stunted in growth. His prognosis to reach emotional and physical maturity is doubtful.

At the time of this original series, potential recipients were screened with great care to rule out those with possible important psychiatric problems. Because of this, it has not been surprising to find exceptional

emotional stability among those who were accepted and who are still surviving. Excellent adjustments have been made in spite of such serious early postoperative complications as aseptic necrosis of one or both of the femoral heads in three of the adolescents. These latter patients have learned to walk adequately in spite of their handicaps. Many of the young patients were stunted in growth before and after transplantations and have had catch-up growth spurts late in their teens.

Nine of the 64 patients of the original series have had children of their own, including three by two female and 10 by seven male recipients. One of these offspring had a meningomyelocele which required surgical correction. It is of interest that all the children issuing from this transplant population came from those 26 still surviving. Thus, no orphans have so far

Table 3. Features of Cancers in Original Colorado Transplant Recipients

Patient Number	Time of Onset After Transplant (Mo)	Type of Tumor	Treatment	Outcome	Follow-up After Initial Diagnosis of Tumor (Mo)
LD 63	66	Squamous cell carcinoma lower lip	Wide excision	No recurrence	35
LD 30	32	Squamous cell carcinoma skin of ear	Wide excision	No recurrence; died of perforated diverticulitis	20
LD 6	75	Basal cell carcinoma nasolabial fold	Wide excision	No recurrence	38
LD 48	74	Squamous cell carcinomas forearms, right arm, and scalp	Multiple excisions	Died of myocardial infarction	14
LD 60	78	Squamous cell carcinomas—two of left hand and one of face	Excisions and skin graft of hand	No recurrence	24
LD 55	87	Squamous cell carcinoma face	Wide excision and skin graft	Eight months later had radical neck dissection for lymph node metastases	15

been created by the premature death of a transplant patient.

DISCUSSION

It is axiomatic that some degree of immunologic weakening must be accepted as the price of success after whole organ transplantation under immunosuppression. Because of this, it was once feared that a real margin of safety might not exist which would permit effective graft protection without killing the host. The fallacy of this assumption as it applies to the early post-operative course has long since been proved. Now, there is evidence that immunosuppression may be tolerated for intervals that will extend beyond a decade in many instances.

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

the effectiveness of treatment by transplantation.

Instead, with each passing year the case is strengthened that transplantation represents one of the greatest, although as yet incompletely exploited, therapeutic achievements of modern medicine. It has become clear that about half of the original series of related kidney recipients are going to move into the second decade of their convalescence. The poorer results in non-related transplantation would have been discouraging if it were not for the great progress made in many centers including our own with cadaver transplantation since the spring of 1964, when the presently reported series was completed.

SUMMARY

Sixty-four consecutive patients underwent renal homotransplantation 8½ to almost 10 yr ago, 46 from related and 18 from nonrelated living donors. Twenty-four (52%) of the 46 consanguineous recipients survive to date, in 21 cases with function of the original grafts. Only two of the 18 recipients of nonrelated kidneys survive and one of these patients has undergone retransplantation. The patients who are alive have had a high and continuing degree of rehabilitation.

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