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Renal Homotransplantation in Man: Follow-up of 189 Cases

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AT THE Sixth National Cancer Conference held in 1968, we discussed organ transplantation as a possible adjuvant measure in the treatment for cancer as, for example, by using liver replacement to permit the extirpation of a hepatoma that could not be resected by partial hepatectomy. Three lines of evidence were presented[2] that this concept might be at least partly self-defeating. This evidence indicated that the necessary antirejection therapy confidently could be expected to erode those immune defenses which might slow the natural growth of a malignancy in the event of incomplete removal.

The objective of the present report is quite different. It is simply to say something about the practical value of renal homotransplantation in patients with kidney failure due to nonneoplastic disease. The opinions will be based on our experience with 189 recipients who were treated long enough ago so that relatively long potential follow-ups are available in each case. Attention will be drawn again to the fact that chronic survivors after renal homotransplantation are unusually prone to the development of a variety of de novo malignant conditions. The following account has been abstracted from a much more complete description of these same cases.[1]

Survival

INTRAFAMILIAL TRANSPLANTATION

A positive judgment about the practical value of renal homotransplantation was not difficult with related cases, since even at the beginning there was a substantial benefit if homografts were obtained from family members. In Figure 11-6 is shown the graphic fate of 131 consecutive patients who received kidneys from siblings, parents, or more distantly related donors such as aunts, uncles, and cousins. The follow-

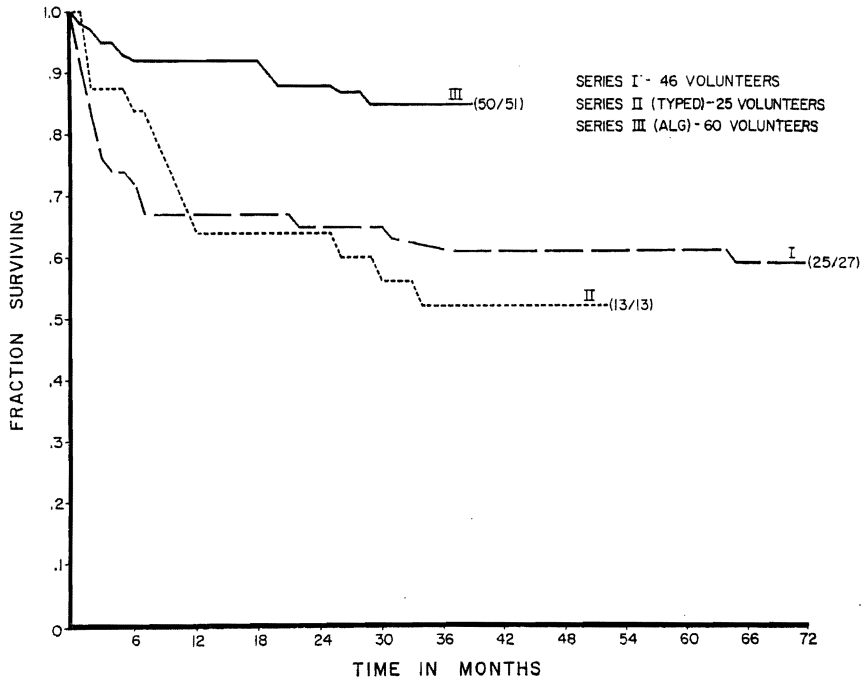


FIGURE 11–6.—Life survival curves in the three series of intrafamilial renal homotransplantations described in the text. In Series III, the patients have been studied for at least 27 months. The follow-ups in Series II and I are for a minimum of four and six and one-fourth years, respectively. At the end of each survival curve a numerator and denominator are given. The denominator tells the number of living patients, and the numerator denotes the number of original homografts that are still functioning.

up in Series I is now six and one-fourth to seven and two-thirds years, in Series II from four to five and one-half years, and in Series III from two and one-fourth to four years.

The 71 patients of Series I and II were treated with azathioprine and prednisone. About two thirds of these patients lived for at least two years and subsequent deaths have been relatively uncommon, so that 57% of the combined Series I and II survive to date after four to seven and two-thirds years. The patients of Series III had heterologous antilymphocyte globulin (ALG) in addition to azathioprine and prednisone. In the 60 cases of Series III, the survival at one year was 92%, at two years 88%, and currently, after two to four years, it is 85%.

The over-all results were not remarkably influenced by the type of donor-recipient consanguinity. The present survival is about 70% in all related recipients treated in Denver from two and one-fourth to seven and two-thirds years ago, without regard to the kinship of the donor,

TABLE 11-5.—RESULTS OF INTRAFAMILIAL TRANSPLANTATION

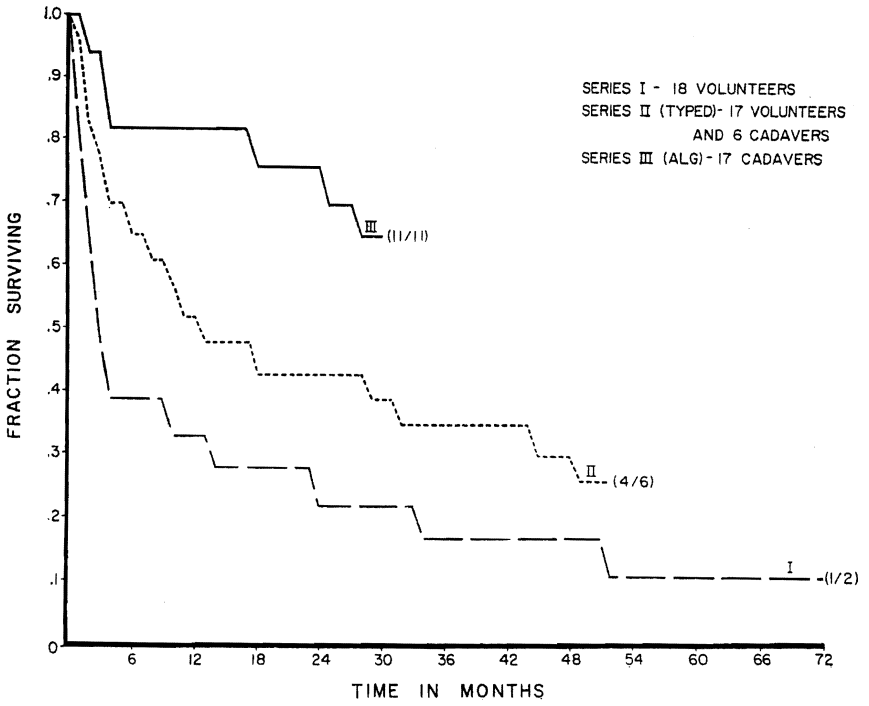
Sibling	44/66	(67%)
Parental	40/55	(73%)
Others	7/10	(70%)
	(2 to 7½ years)	

whether these were siblings, parents, or more distant relatives (Table 11-5).

UNRELATED TRANSPLANTATION

With the 58 transplantations between nonrelatives (both volunteers or cadaveric donors), the results were inferior to those with blood relatives. In Figure 11-7, the Series I, II, and III conform to the same intervals already defined above in the related cases, except that in Series III

FIGURE 11-7.—Life survival curves in the three series of nonrelated renal homotransplantations described in the text. The minimum follow-ups in Series I, II, and III are six and one-fourth, four and two-thirds, and one years. The significance of the numerators and denominators at the end of each curve is the same as in Figure 11-6.



the minimum follow-up was one rather than two years. In the 1962 and 1963 era (Series I), only 33% (six of 18) of the recipients survived for a year. From 1964 to 1966, this figure rose to 52% (12 of 23). In Series III the one-year survival in the nonrelated cases was 82%, or 14 of 17 patients. Subsequent to one year in all three series the losses continued at a rather steady rate, far more frequently than in the related cases (compare Figures 11-6 and 11-7), so that only 19 (or 33%) of these 58 recipients remain alive today. Even in the ALG-treated patients of Series III, the final survival in nonrelated cases has drifted off so that it is now 65%.

Influence of Antigen Compatibility

In most of the foregoing cases, Dr. Paul Terasaki of Los Angeles analyzed the antigens in the peripheral lymphocytes of both donors and recipients by his cytotoxicity test. The antigen compatibility as expressed by the well-known A-D scoring designation was then correlated with the clinical outcome.

In the sibling cases, the well-matched (A and B) kidneys tended to have an advantage over the combined Cs and Ds in terms of survival and function. With genetic analysis, it was then established that these well-matched organs tended to be from donors who had identity with the recipients of both haplotypes of the HL-A chromosome; 88% of all compatible organs transplanted in Denver between siblings are still functioning, as opposed to 74% in the less favored cases (Table 11-6).

The advantage of double haplotype identity in the sibling recipients was easily identified in a series of biopsies taken two years after operation, and graded on a scale of 0-4 as to the presence or absence of a number of abnormalities, including those shown in Table 11-7. The HL-A identical sibling kidneys had fewer and less severe glomerular and vascular lesions, as well as less pronounced cell invasion and immunoglobulin deposition.

With other donor-recipient relationships (even parent to offspring transplantations) there was no significant correlation between the A-D matching grades and the outcome. The same was true with the completely unrelated cases. The series of B, C, and D matched unrelated kidneys are shown in Table 11-8; the one-year survival was the same under

TABLE 11-6.—Sibling Transplantation—Haplotype vs. Outcome

		Survival (Months)			
	0	6	12	24	Current (26-86 mos.)
Double Haplotype Identity ($P \geq 0.7$)	16	15 (94%)	15 (94%)	15 (94%)	14 (88%)
All Others	35	35 (100%)	33 (94%)	31 (89%)	26 (74%)

TABLE 11-7.—DOUBLE HAPLOTYPE VS. PATHOLOGY

	No. of Cases	Glomerular	Mononuclear	Vascular	IgM
Two Haplotype Identical ($P \geq 0.7$)	13	0.60	0.39	0.39	0.55
Other Siblings	28	1.61	1.21	1.50	1.12
P	<0.013	<0.003	<0.003	<0.003	<0.01

TABLE 11-8.—UNRELATED TRANSPLANTATION MATCH VS. OUTCOME

		Survival (Months)		
Match	0	6	12	Current (12-60 mos.)
B	8	5 (62.5%)	5 (62.5%)	3 (37.5%)
C	17	12 (71%)	12 (71%)	8 (47%)
D	9	8 (89%)	6 (67%)	4 (44%)
Totals	34	25 (74%)	23 (68%)	15 (44%)

all three circumstances. The same applied to subsequent follow-ups of one to five years.

It is important to comment about these negative findings in the parent to offspring and nonrelated cases, if only to avoid the unwarranted conclusion that tissue matching is an obsolete concept. A discussion of several possible explanations for the lack of correlations has been published elsewhere,[1] but one point is worth re-emphasizing. That is that the A-D grades represent only a statement as it were in shorthand about the data available in a given case. It is probable that the alphabetical designations do not optimally express the information that can be extracted from the raw typing data. Rapaport and Dausset have recently published evidence to this effect, and in fact Rapaport has personally demonstrated to us that this may be true in our own cases. It seems clear that the first step in improving the situation with tissue matching will be re-examination of the original data so carefully collected by Terasaki and by others, with a view to its reinterpretation.

Homograft Glomerulonephritis

Another controversial question about renal transplantation concerns the frequency with which glomerulonephritis affects kidneys transplanted to recipients whose native organs were destroyed by such an autoimmune process or even to recipients with renal failure from a nonimmunologic etiology. In 105 of the homografts of our series examined with light microscopy, electron microscopy, and immunofluorescence a year or more after operation, many varieties of glomerulonephritis were seen: (1) with antiglomerular base membrane antibody (Masugi nephritis), (2) with antigen-antibody complexes deposited in the subepi-

TABLE 11-9.—GLOMERULONEPHRITIS
(105 COMPLETE STUDIES)

No Glomerulonephritis	32 (30.5%)
Possible Glomerulonephritis	23 (21.9%)
Definite Glomerulonephritis	50 (47.6%) *

* 23 examples of "transmission"

thelial location, (3) with complexes in the subendothelial location, or (4) with complexes in both locations. The findings were related to those with light microscopic examination, and a designation was made of membranous, proliferative, and lobular glomerulonephritis.

Of the 105 biopsied grafts, only 30% were completely free of glomerulonephritis as has just been defined. Half the kidneys had obvious glomerulonephritis and another 20% had this diagnosis as a possibility (Table 11-9). Thus, a high incidence of glomerulonephritis in these kidneys was a matter of fact. The etiology of the lesions was another question. Evidence will be given in another publication[1] that the majority of these glomerulonephritides developed as a form of antibody-mediated indolent rejection. For example, there was no other way to explain why glomerulonephritis developed in homografts transplanted to patients whose original disease was oxalosis, cystinosis, polycystic disease, and pyelonephritis. Conversely, there was evidence in many cases that preexisting host glomerulonephritis was "transmitted" to the transplants. In 23 such instances, the glomerulonephritis in the grafts was a faithful or nearly faithful anatomic recapitulation of the same disease that had destroyed the native kidneys (Table 11-9).

Human Thymectomy

From four to five and one-half years ago, a human thymectomy study was carried out. During that time, 24 patients had their thymus glands excised prior to transplantation, whereas a similar number of control recipients did not. The thymectomy patients have not enjoyed any kind of advantage in terms of lowered mortality or improved renal function.[1] However, somewhat surprisingly, the homografts in the thymectomy series have had less severe glomerular, arterial, infiltrative, and other lesions (Table 11-10). Thus, the question of thymectomy as an adjuvant suppressive measure in humans must be kept open at this time.

TABLE 11-10.—TYPE OF HISTOLOGIC ABNORMALITY

		GLOMERULAR	ARTERIAL	INFILTRATE	IgG
Non-Thymectomy	(22)	1.41	1.41	1.27	.93
Thymectomy	(24)	.83	.79	.63 ($P < .005$)	.14 ($P < .02$)

These figures represent the mean score in each group with grading on a 0 to 4 scale according to severity.

TABLE 11-11.—MALIGNANT TUMORS
(189 RECIPIENTS)

Epithelial	7
Cured	7
Mesenchymal	3
Cured	1
Total	10*

* Incidence (5.3%)
ALG 3/10

The Risk of Malignancy

The harmful effects of chronic immunosuppression are so well known that such things as fatal infections have not even been mentioned in this report. An increased incidence of de novo malignant disease is another less recognized penalty for chronic immunosuppression. Of the series of 189 patients presented today, seven have developed carcinomas and three have developed lymphomas for an uncorrected total incidence of 5.3% (Table 11-11). Moreover, two of the patients have died from widespread tumor metastases (both reticulum cell sarcomas). The incidence of malignant disease has been the same before and after the introduction of ALG.

The development of malignant tumors in renal transplant recipients has not been confined to the University of Colorado. In 16 other centers, 27 de novo malignant tumors (14 carcinomas and 13 mesenchymal neoplasms) have been reported[1] to an informal registry established in Denver for such cases by Dr. Israel Penn. As in our recipients, the prognostic implications of the mesenchymal tumors were grave, and only one of these patients remains alive. In contrast, nine of 14 patients with carcinomas were successfully treated.

Summary

Since most of this paper has been devoted to an exposition of the dangers and deficiencies of renal transplantation, an appropriate balance might be given by summarizing on an optimistic note. Of the 189 patients treated by kidney transplantation from more than one to seven and one-half years ago, 110 are still alive. A procedure which can result in this kind of prolongation of life can have deficiencies and still have real practical value.

Acknowledgments

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Bone Marrow Graft in Man after Conditioning by Antilymphocytic Serum

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Introduction

THE SUCCESSFUL USE of allogeneic bone marrow grafts in the treatment of accidentally irradiated persons[16] led us to believe that total body irradiation would be a good method of suppressing immunologic reactions before leukemic patients were treated with allogeneic bone marrow grafts. Since 1959, we have given 24 patients with acute leukemia allogeneic marrow grafts after total body irradiation. In 17 cases the grafts were successful, but in only five could the acute secondary disease be controlled.[17, 18, 22, 28] Secondary disease can be prevented or cured in animals by giving methotrexate[20, 31, 39, 40] or cyclophosphamide,[21, 31] by incubating the donor cells at 37 C before transfusion,[23] or by giving antilymphocyte serum.[6] In man, however, none of these methods has been really efficient.[28, 41] The two components in secondary disease are a proliferation of lymphocytes, which infiltrate many tissues, especially the skin