The Period and Nature of Hazard in Clinical Renal Transplantation:

III. The Hazard to Transplant Kidney Survival

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RENAL transplant survival is influenced by factors which affect both patient survival and transplant kidney function. A functioning transplant kidney may be lost in three ways: 1) uncontrollable transplant rejection or loss for technical reasons and its removal from the living patient with the hope and potential of subsequent successful transplantation, 2) progressive transplant failure occurring in the dying patient and contributing to death and 3) loss of a well-functioning kidney transplant due to patient death from non-renal causes.

Transplant Kidney Survival Data

Three of our patients are living with transplant kidneys that have been functioning more than 5 years. Two of these patients have related living donor (RLD) first kidney transplants and one has a cadaver donor (CD) second kidney transplant. Three additional patients are surviving on functioning second, third and fourth CD kidney transplants more than 5 years after the initial kidney transplant.

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Twenty-seven other patients have had functioning kidney transplant survival in the 3- to 5-year period. Twenty-five of these patients are still living with function of these same kidney transplants from 3 to 5 years after transplantation. Twenty-one of these patients have RLD first transplants, two have CD first transplants, one has a RLD second transplant and one has a CD third transplant. The average period of functional survival for RLD first kidneys in the 3- to 5-year survival group has been 47 months and that for the CD first kidneys 43 months. Two functioning transplant kidneys have been lost after 3 years of function. One patient, still living, had received total body radiation prior to the first RLD transplant and lost this kidney at 52 months from slowly progressive failure in transplant function. The other loss of a functioning transplant was in a patient who had had hepatitis and who died in hepatic coma 43 months after transplantation.

The current hazard to first transplant kidney survival is best presented with recent survival data for consecutive transplants at risk a minimum of 12 months (Table 1). It may be seen that the CD transplant survival at 1 year is somewhat less than the one year CD patient survival given in the first article of this series and

TABLE 1. *First Transplant Kidney Survival in Most Recent Group of 25 CD and 42 RLD Patients Managed During the Same Period and At Risk a Minimum of 12 Months*

Group	1 Yr. Survival		2 Yr. Survival	
	Kidneys	%	Kidneys	%
CD	19/25	76	10/21	48
RLD	36/42	86	28/34	82.4

that there is a substantial fall off in CD transplant kidney survival between 1 and 2 years. There was little difference between the 1- and 2-year survival of RLD kidneys. Indeed, had one RLD transplant kidney, long in trouble, failed at 24 rather than 23 months, the 1- and 2-year survival percentages would have been identical. One RLD ABO mismatched transplant kidney that was hyperacutely rejected and removed at the time of the transplant operation and one CD kidney which was removed at the original operation because of technical difficulties in placement are excluded from these and subsequent data relating to transplant kidney survival. Both patients are still alive.

When the RLD and CD first transplant kidney survival data is studied with each interval of follow-up being used as its own control for 1-, 2-, 3- and 4-year survival as was done for patient survival in the first article in this series, findings similar to the patient survival differential between RLD and CD transplants are encountered (Tables 2 and 3). CD transplant survival fell off after 1 year while that of RLD transplants changed comparatively little. Survival percentages in both groups involvin longer periods of follow-up and including earlier cases reflect the greater hazard to patient and transplant kidney survival from less knowledgeable and sophisticated transplant kidney and patient management in the early part of this experience. This type of data presents a truer picture of transplant kidney survival and periods of hazard than is obtained from the use of actuarial tables.

As with patient survival, the data for transplant kidney survival shows little difference in RLD recipients between those who received transplants from parents and those who received them from siblings. In a consecutive group of 57 RLD first kidney transplants at risk a minimum of 1 year, the 1 year survival for parent donor kidneys was 77 per cent (24/31) and for sibling donor kidneys it was 81 per cent (21/26). For those from this group at risk a minimum of 2 years, the 2-year survival for parent donor kidneys was 73 per cent (19/26) and for sibling kidneys it was 74 per cent (17/23).

Factors in Transplant Kidney Loss

Forty-nine of the 113 RLD and CD first kidney transplants in this study have failed to survive and function in a living patient. Twenty of these kidneys have been lost through transplant nephrectomy, two of

TABLE 2. *Transplant Kidney Survival Results in 29 Consecutive Cadaver Donor First Kidney Transplants at Risk a Minimum of 12 Months*

Minimum Period Pts. At Risk	1 Yr. Survival		2 Yr. Survival		3 Yr. Survival		4 Yr. Survival	
	Kidneys	%	Kidneys	%	Kidneys	%	Kidneys	%
1 yr.	19/29	66						
2 yr.	16/25	64	10/25	40				
3 yr.	7/15	47	4/15	27	3/15	20		
4 yr.	2/6	33	1/6	17	1/6	17	0/6	0

TABLE 3. *Transplant Kidney Survival Results in 57 Consecutive RLD First Kidney Transplants At Risk a Minimum of 12 Months*

Minimum Period Pts. At Risk	1 Yr. Survival		2 Yr. Survival		3 Yr. Survival		4 Yr. Survival	
	Kidneys	%	Kidneys	%	Kidneys	%	Kidneys	%
1 yr.	46/57	81						
2 yr.	39/49	79.6	36/49	73.3				
3 yr.	23/31	75	22/31	71	21/31	68		
4 yr.	13/19	68	13/19	68	12/19	63	12/19	63

them from hyperacute rejection associated with ABO mismatching and one was removed at first transplant operation because of technical difficulties. The remaining 17 were removed because of rejection and loss of function. Fifteen of these patients received second transplants, three received third transplants and one a fourth. Ten of these 20 transplants nephrectomized first RLD and CD transplant patients are still living.

Only six transplants were lost with severe, progressive renal transplant functional failure leading to patient death, whereas nearly one half of the transplant loss was from patient death when transplant function was adequate to maintain life. This was true for both RLD and CD groups of patients (Table 4). It is of interest and significance that death rarely occurred in recipients whose transplant was functioning at or below the 20-1.2 (BUN-creatinine) excellence level of function.

In both the RLD and CD groups of patients the incidence of transplant kidney loss due to patient death with a functioning transplant was substantially greater in the first half of the series of RLD and CD first transplants as compared with the second half (Table 5). Although the relative incidence of loss due to transplant nephrectomy was greater in the second half of the series, the actual number of transplants lost in this way was essentially the same in the first and second halves in both RLD and CD groups.

The lesser intervals from transplantation to transplant nephrectomy in the second halves of both RLD and CD groups doubtless reflects to a degree the longer periods of follow-up in the first halves. The longer interval to transplant nephrectomy in the RLD first half of the series in comparison to the CD first half may be due in part to a lesser degree of histoincompatibility in the RLD group. Two of the RLD first half

TABLE 4. *Factors in RLD and CD Kidney Transplant Loss*

Type of Transplant	Transplant Nephrectomy		Transplant Failure—Patient Death		Patient Death—Functioning Transplant	
	No. Transplants	%	No. Transplants	%	No. Transplants	%
RLD	11/28*	39	4/28	14	13/28**	47
CD	9/21†	43	2/21	9	10/21	48

* Two of these transplant nephrectomies included ABO mismatches and hyperacute rejection.
** One of these deaths occurred at first transplantation operation.
† One of these transplants was removed at first transplanatation operation for technical reasons.

TABLE 5. *Comparison of First and Second Half of Series with Respect to Incidence and Period of Factors in RLD and CD Kidney Transplant Loss*

Type of Transplant		Transplant Nephrectomy			Transplant Failure—Patient Death			Patient Death—Functioning Transplant		
		No. Transplants	%	Average Interval Transplant-Nephrectomy (mo.)	No. Transplants	%	Average Interval Transplant-Death (mo.)	No. Transplants	%	Average Interval Transplant-Death (mo.)
RLD	First half of series	5/19	26	24	3/19	16	0.5	11/19	58	3.8
	Second half of series	6/9	67	6.8	1/9	11	13*	2/9	22	5.5
CD	First half of series	5/15	33	8.0	2/15	13	4.8	8/15	54	17.3
	Second half of series	4/6	67	5.5	0/6	0	—	2/6	33	9.5

* Death of this patient with decreasing transplant function was precipitated by operation for gastrointestinal bleeding and failure of a hepatitis damaged liver.

patients had transplant nephrectomies carried out 52 and 30 months after transplantation. These were the only two patients in the entire series who were transplant nephrectomzied more than 24 months after transplantation. The patient with the 52-month transplant survival had received total body irradiation and the 30 month survival patient had received isonicotinic acid hydrazide for tuberculosis. Isonicotinic acid hydrazide is known to produce a relative pyridoxine deficiency and is closely related chemically to a compound, semicarbazide, which has been found by one of us to have an immunosuppressive effect when used in combination with a pyridoxine deficient diet in animals.[1-3] These two unusual circumstances of irradiation and drug administration, in addition to the routine immunosuppression, may have been factors in the prolonged survival of these two rejecting kidneys.

The greater interval to death with a functioning transplant in the CD group is due largely to the greater incidence and delayed lethality in CD recipients of such complications as hepatitis, transplant nephrectomy site sepsis and gastrointestinal ulceration and bleeding.

Conclusions

Transplant kidney survival is a composite of the interplay of factors influencing transplant patient survival and transplant kidney function.

Related living donor renal transplant results clearly are superior to those obtained when non-related cadaver organs are used. The results in this clinical experience suggest that random (untyped and unmatched) first RLD transplants with current immunosuppression may be expected to have an 85 to 90 per cent one year functioning trans-

plant survival and that little or no attrition may be expected in the second and subsequent years. One also may expect approrimately 36 per cent of RLD transplants to achieve the 20-1.2 (BUN-creatinine) excellence level of function in the early days after transplantation, one half within the first 7 days, and to retain this steady-state level of function indefinitely.

The picture is less encouraging in the case of random selected CD first transplants. Although 76 per cent of these transplants were functioning at 1 year; the fall-off at 2 years to 48 per cent was disappointing and worrisome. An important part of this fall-off was due to recipient mortality with a functioning kidney. An even more disappointing observation was that only six per cent of the random selected CD first transplants achieved early and maintained 20-1.2 excellence level of function. Donor organ ischemia and greater degrees of histoincompatibility doubtless are factors here.

Clues as to the ultimate outcome of transplant function and survival generally are present in the early days after transplantation and they mark this early period as one of particular importance in determining the ultimate fate of transplant survival.

Major improvement in results, particularly in CD transplants, hopefully may be expected from the routine use of histocompatibility typing and careful selection of transplant donor and recipient on the basis of well matched histocompatibility antigenic profiles. In addition, reduction in the incidence and risk of major specific recipient fatality hazards such as hepatitis, transplant nephrectomy site abscess formation and gastrointestinal ulceration and bleeding also may lead to improvement of results.

The degree of histoincompatibility between donor and recipient in some matches may be too great to be overcome by currently available means of immunsuppression with reasonable assurance of freedom from undue hazard to the patient's life or transplant function. This problem is greatest in cadaver donor transplant recipients.

Although much has been accomplished in the field of histocompatibility matching, it is recognized that much more needs to be done to clarify the number and significance of human histocompatibility antigenic barriers.

While better antigenic matching to transplant donor and recipient is likely to reduce the hazards associated with current means of immunosuppression, more specific and subtle means of immunosuppression hopefully will expand the limits of the histocompatibility antigenic barriers which may be breached with safety, and may even open the way to successful heterotransplantation.

References

1. Moore, T. C.: Histidine Decarboxylase Inhibitors and the Survival of Skin Homografts. Nature, **215**:871, 1967.
2. Moore, T. C.: Role of Histidine Decarboxylase Inhibitors in the Suppression of Transplant Rejection. Proceedings of the International Symposium on Pharmacological Treatment in Organ and Tissue Transplantation, Feb. 28 and March 1, 1969, Milan, Italy, Exerpta Medica, Amsterdam (In Press).
3. Smellie, W. A. B. and Moore, T. C.: Effect of Semicarbizide and Pyridoxine Deficiency on the Survival of Canine Renal Homografts. Surg. Gynec. Obstet., **128**:81, 1969.