The Fate of Patients After Renal Transplantation, Graft Rejection, and Retransplantation

SAMUEL L. KOUNTZ, M.D., FOLKERT O. BELZER, M.D.

From the Department of Surgery, University of California, San Francisco Medical Center, San Francisco, California

SINCE 1964, 403 renal transplants have been performed in 336 patients at the University of California, San Francisco Medical Center. Our experience suggests that the mortality rate following transplantation is equal to or less than the mortality rate of 9% per year of patients on chronic hemodialysis.[2] However, despite the decrease in the mortality rate and the increase in the number of patients in whom transplantation is successful, the survival rate of primary grafts from related donors has not improved during the past 5 years and the survival rate of grafts from cadaver donors has not improved during the past 3 years.

Materials and Methods

Between January 1964 and January 1972, 403 transplants were performed in 336 patients. Of these 336 were primary and 54 were secondary grafts. Nine patients received three grafts, 3 patients received 4 grafts, one patient received five grafts, and one patient had an autotransplant. Donors were living related (siblings, parents, children, uncles, aunts, cousins, grandparents), and living unrelated as well as cadaver donors (Table 2). Living donors ranged in age from 21 to 60 years, and cadaver donors from newborn to 59 years. The recipients have ranged in age from 1 to 63 years (Fig. 1).

Only the presence of severe extra-renal pathologic changes excluded patients from the program. The major diagnoses were chronic glomerulonephritis (71%) and pyelonephritis (15%), but others have had diabetes, Wilm's tumors, bilateral hypernephromas, Fabry's disease, polycystic kidneys, hemolytic uremic syndrome, medullary cystic disease, malignant hypertension, cystinosis, lupus, scleroderma, and amyloidosis.

Selection of Donor-Recipient Pairs

All living donors were 21 years old or more and able to give informed consent. They were in good health prior to operation and were well hydrated during the operative procedure.[9] They were required to be ABO compatible with the recipient and the best HL-A match was chosen when several donors were available. After consent had been obtained from next of kin kidneys from cadaver donors were removed 20 to 60 minutes after cardiac arrest, and were placed on the Belzer Preservation Unit.[1] At the time of donor nephrectomy, lymph nodes were removed for tissue typing and crossmatching.[5] However, these procedures were not performed if the cadaver kidneys on the perfusion machine did not meet good viability criteria. All recipients awaiting cadaver kidneys had been previously tissue typed and were being maintained on dialysis in other centers or on home dialysis. Their ABO and phenotypes were stored in a 360/50 computer for instant selection from the donor's phenotype. All recipients were required to send a sample of serum to the tissue typing laboratory each month for cross-matching. The kidney was transplanted to the best matched recipient with a negative crossmatch against the donor's lymphocytes, kidney cells, or both.[3] All serum specimens of the recipient were used in judging the crossmatch.*

Presented at the American Surgical Society, April 28, 1972, San Francisco, California.

Supported in part by: NIH Clinical Grant AM11290, General Clinical Research Center Grant 2-M01-RR00079-08, and Organ Procurement Contract HSM110-69-394.

* Herbert A. Perkins, M.D. of the Irwin Memorial Blood Bank is the Director of our Tissue Typing Laboratory with Rose Payne, Ph.D. as Consultant.

TABLE 1. *Cause of Death After Transplantations*

		No.	% of Patients	% of Transplants
Deaths		73	21.8	18.2
I.	Due to intercurrent disease without rejection on low doses of immunosuppressive drugs	17	5.1	4.3
	Pulmonary Emboli 3			
	Malignancy 6			
	Myocardial Infarction 3			
	G.I. Problems 4			
	Suicide 1			
II.	Due to infection without rejection on low doses of immunosuppressive drugs	18	5.4	4.5
	Gram Negative Sepsis 10			
	Cytomegalovirus 1			
	Pneumocystis 2			
	Toxoplasmosis 1			
	Chicken Pox 2			
	Nocardia 2			
III.	Due to infection associated with increased doses of immunosuppressive drugs to treat a rejection crisis	30	9.0	7.5
	Gram Negative Sepsis 30			
IV.	After return to chronic hemodialysis	8	2.4	2.0
	Suicide 1			
	Vascular Accidents 7			

Immunosuppressive Therapy

The basic immunosuppressive therapy consisted of Imuran (Azathioprine), and Prednisone. Imuran was given in doses of 150 mg./day to adults and 50 to 75 mg./day to children. This dose was reduced or temporarily discontinued if the leucocyte count fell below 5000. If jaundice developed, Cytotoxin in a dose of 25 to 100 mg./day was substituted. The initial dose of Prednisone was 120 mg./day for adults and 60 mg./day for children, and reduced to 30 mg./day by the third to fifth week. Patients were maintained on 15 to 30 mg./day. A rejection crisis was treated by repeating the high dosage level of Prednisone and administering 450 rads of local irradiation as described by Hume.[4] Pulses of 1 Gm. of Methylprednisolone have been given intravenously 1 to 3 times over 36 to 48 hours.[6] Actinomycin-D was also used, but this has been discontinued. Within the last 2 years 69 patients who received cadaver grafts have also been given antilymphocyte or antithymocyte globulins obtained from the University of Minnesota, Minneapolis, Minnesota, the Hyland Laboratory, Costa Mesa, California, or from the Upjohn Company, Kalamazoo, Michigan. The ALG or ATG was given intravenously for 14 days in a dose of 10 to 20 mg./Kg./day.

After discharge, all patients were followed in the Transplant Clinic in which frequent adjustments in their immunosuppressive medication were made. The fate of the patient, graft, and donor relationship was stored in a 360/50 computer.* Actuarial survival curves were drawn using standard methods [8] and plotted directly using a Houston DP-1 Plotter. Figures are direct computer graphs.

Results

The number of transplants (primary and multiple) performed each year has increased from 15 in 1964 to 107 in 1971 (Fig. 2). The patient survival rate after transplantation from related donors improved after 1964 (Fig. 3) and after transplantation from cadaver donors

* The computer support for this research was obtained from ACME (Advanced Computer for MEdical Research) Facility at Stanford Medical Center, Palo Alto, California. ACME is supported by the Biotechnology Resources Branch of NIH, Grant No. RR00311. ACME is an IBM 360/50 time share system. Soft wave programs were developed by the ACME staff. Our own statistical and plotting programs were developed in San Francisco using a DATA-PHONE linked up to the computer in Palo Alto, California.

TABLE 2. *Distribution of donors by transplant. There were 336 primary, 54 second, 9 third, 3 fourth, 1 fifth, and 1 autotransplant. Note that the cadaver donor has accounted for about 50 per cent and is now the most frequent donor.*

First	Second	Third	Fourth	Fifth	Number
sibling					82
sibling	other related				1
sibling	living related				1
sibling	cadaver				5
sibling	cadaver	cadaver	cadaver		1
parent					61
parent	sibling				1
parent	parent				5
parent	parent	cadaver			1
parent	living unrelated				1
parent	cadaver				6
parent	cadaver	sibling			1
other related					12
other related	cadaver				1
living related					8
living unrelated	living unrelated				1
living unrelated	cadaver	cadaver	cadaver	cadaver	1
cadaver					121
cadaver	sibling	living unrelated	cadaver		1
cadaver	parent				2
cadaver	living unrelated				2
cadaver	living unrelated	cadaver			1
cadaver	cadaver				16
cadaver	cadaver	cadaver			3
self					1

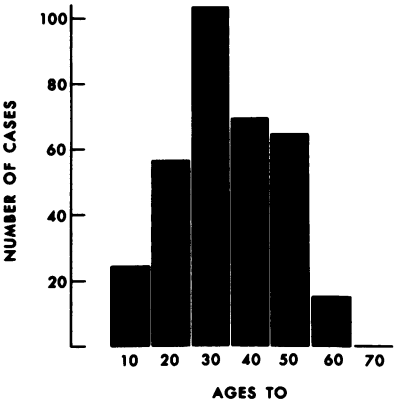

FIG. 1. Age distribution of the 336 recipients.

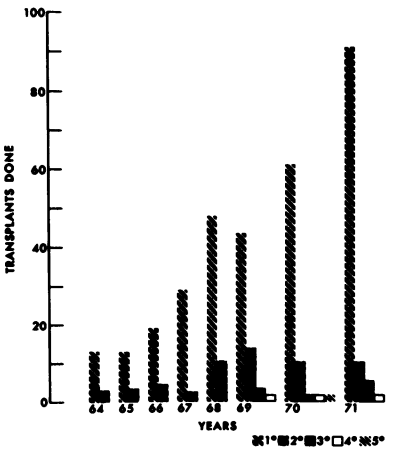

FIG. 2. Distribution of transplants by year. Note that the number of transplants have increased with time.

patient survival increased after 1968 (Fig. 4). It should be noted that the number of patients who received transplants from related and cadaver donors respectively in these years was relatively small (11 in 1964 and 20 in 1968). The average and overall patient survival after transplantation from siblings, parents, other relatives, living unrelated, and cadaver donors is shown in Figure 5. Survival of the patient was independent of the donor kidney relationship. Figure 6 shows the patient survival after the first and second transplant. In the series there was a higher mortality after the second transplant. In the last 2 years the mortality rate after first and second transplants has been the same, reflecting our increased experience.

This increased experience is further reflected in the survival of grafts. In Figure 7, all graft survivals (93 sibling donors, 85 parental donors, 14 other relatives, 17 living unrelated, and 192 cadavers) are shown. Grafts from other relatives, siblings, and parents did better than grafts from living unrelated donors and cadaver donors. Figure 8 shows the survival rate of primary grafts, and a similar finding was observed. Only a few patients received grafts from other relatives and living unrelated donors, and the numbers are too few for definitive conclusions. Therefore, if these groups are excluded, only grafts from sibling donors have a survival rate significantly better than grafts from cadaver donors after 2

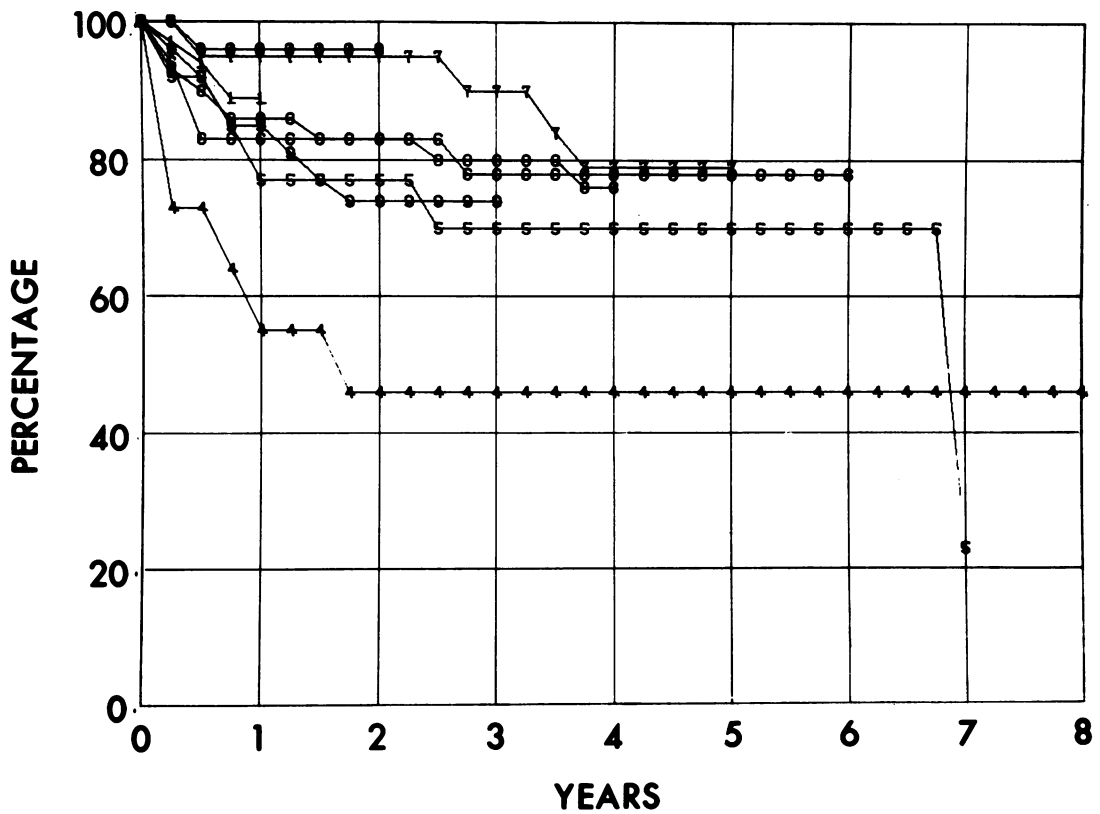

FIG. 3. Patient survival from related donors by year. The number of patients by year starting with 1964, i.e. 4 are: 4 = 11, 5 = 13, 6 = 18, 7 = 19, 8 = 29, 9 = 26, 0(70) = 24, 1(71) = 36.

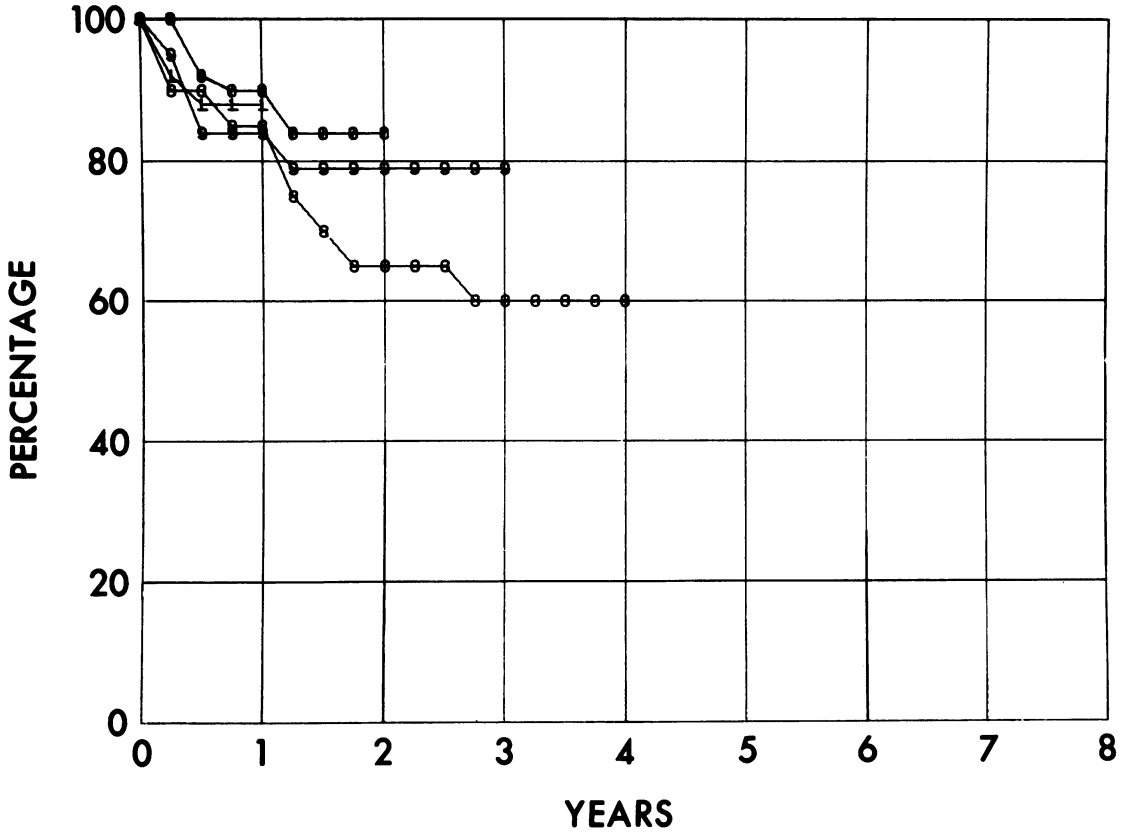

FIG. 4. Patient survival from cadaver donors by year. The number of transplants by year starting with 1968, i.e. 8 are: 8 = 20, 9 = 19, 0(70) = 38, and 1(71) = 55.

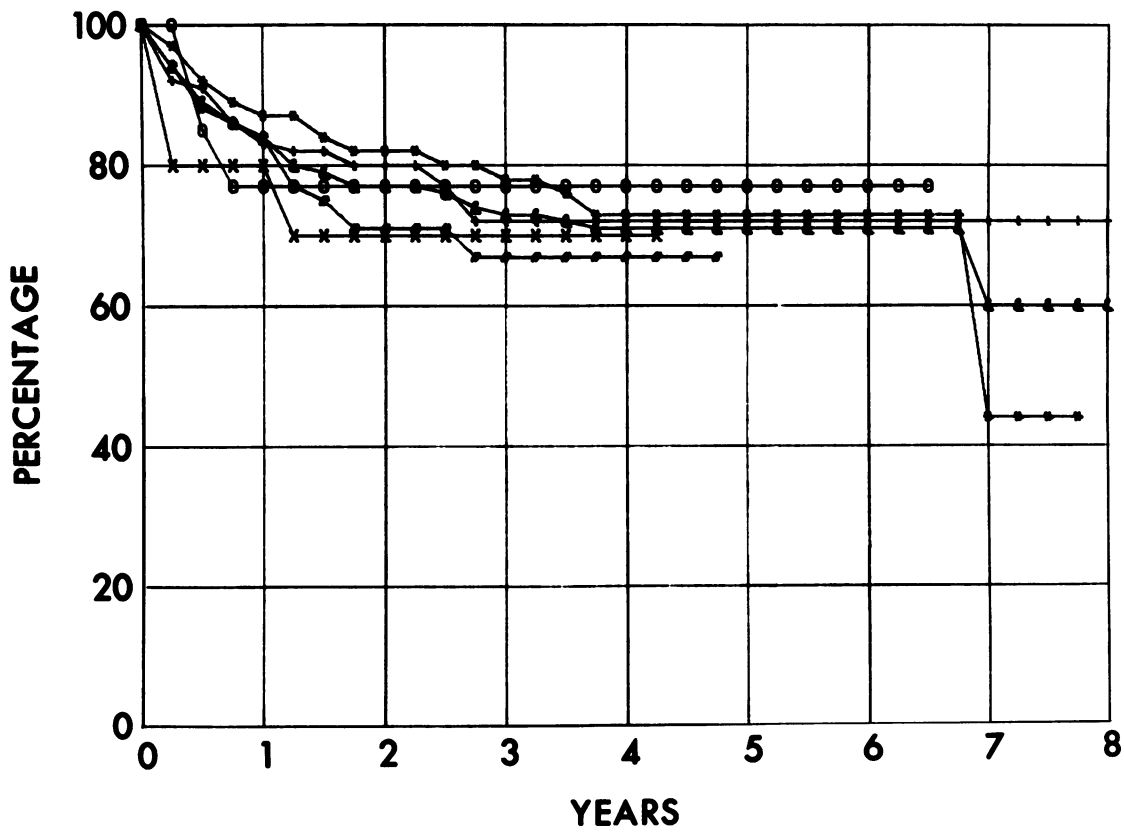

FIG. 5. Patient survivals compared with donor relationships.
& = overall-336
* = sibling-90
+ = parent-76
0 = other related-13
× = living unrelated-10
= cadaver-146
Note that survival of the patient is independent of the donor relationship.

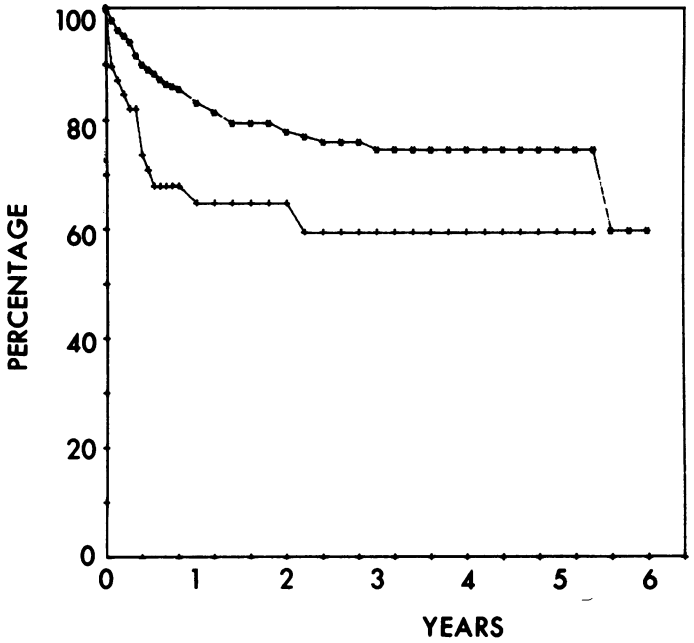

FIG. 6. Patient survivals after first * = 336, and second + = 54 transplant.

years (Fig. 8). Moreover, if the 32 HL-A identical sibling grafts in whom the survival is 100% are excluded, there is no significant difference after 2 years between the survival of grafts from HL-A non-identical siblings, parent-child, and cadaver donors.[7]

Figures 9 and 10 show that improvement in clinical management reached its peak after 1964 in related donor grafts and after 1968 for cadaver donor grafts.

Secondary graft survival was slightly better if the donor was related to the recipient, than it was if the donor was unrelated (Fig. 11). However, the related group included several HL-A identical siblings. Graft survival was not influenced by waiting for an interval after primary transplant nephrectomy (Fig. 12). Since 1964, more and more retransplants have been performed, which has increased the number of patients who have been successfully treated by transplantation (Figs. 2 and 13).

Discussion

The mortality was 21.8% during the 8-year period. The causes of death can be divided into four categories: 1) intercurrent disease in patients with a serum creatinine or less than 2 mg./100 ml. who are on maintenance immunosuppressive therapy, 2) infections in patients without a clinical rejection crisis in whom the serum creatinine was less than 2 mg./100 ml. and who were on maintenance immunosuppressive therapy, 3) infections in patients treated for a rejection crisis by increased dosage of steroids, and 4) death after returning to chronic hemodialysis (Table 1). Death from infections in patients on either low or high doses of immunosuppressive drugs usually occurred within the first year, but 50% of

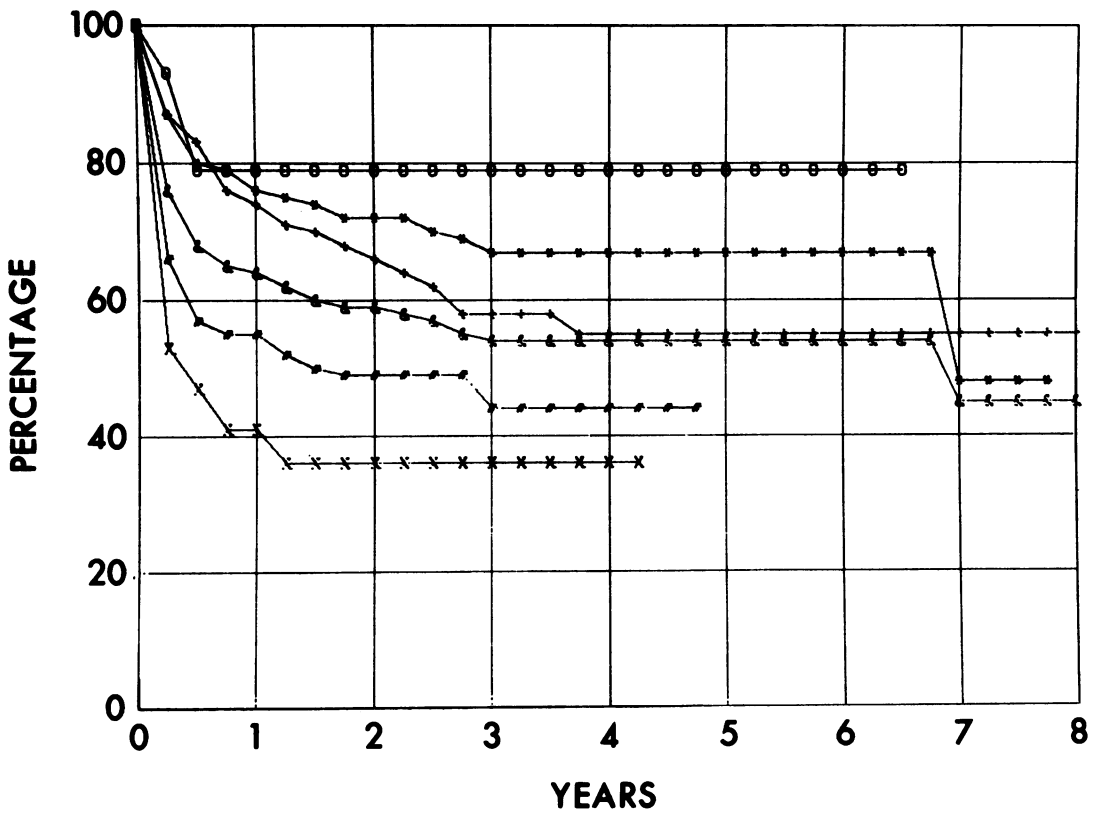

FIG. 7. Graft survivals compared with donor relationships.
& = overall-403
* = siblings-93
+ = parents-85
0 = other relatives-14
× = living unrelated-17
= cadaver 192

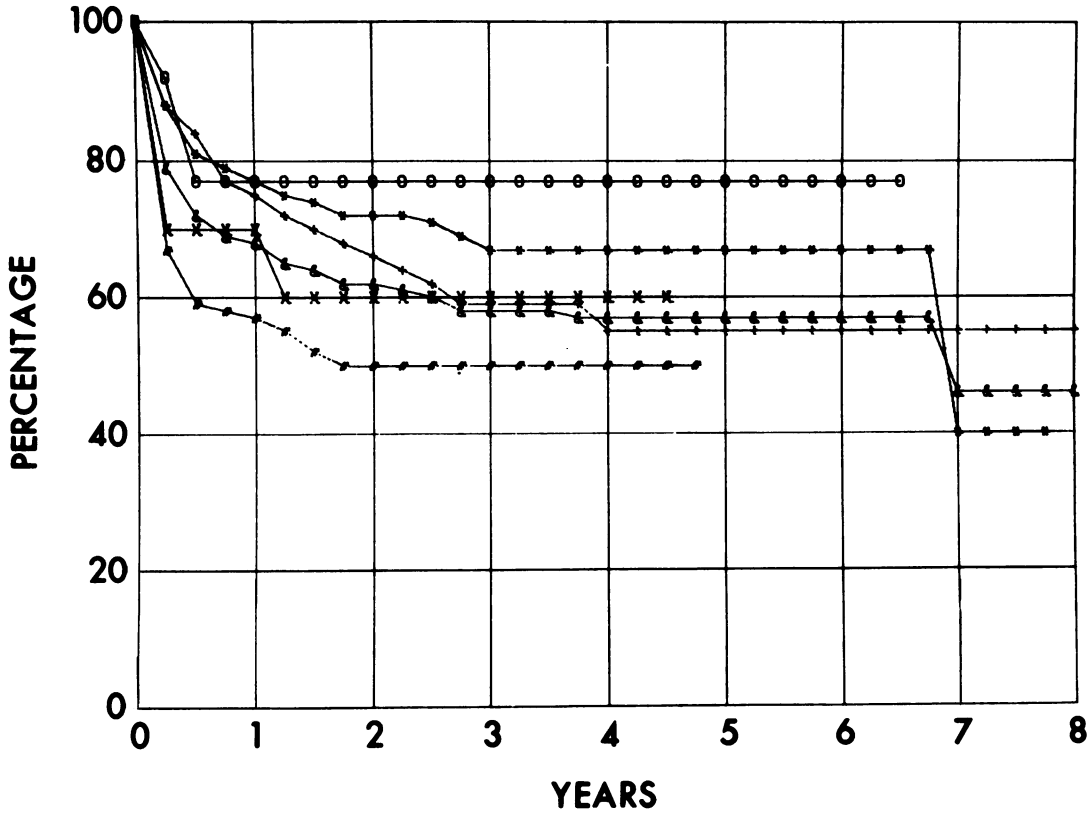

FIG. 8. Primary graft survivals compared with donor relationships.
& = overall-336
* = sibling-90
+ = parents-76
0 = other relatives-13
× = living unrelated-10
= cadaver-146

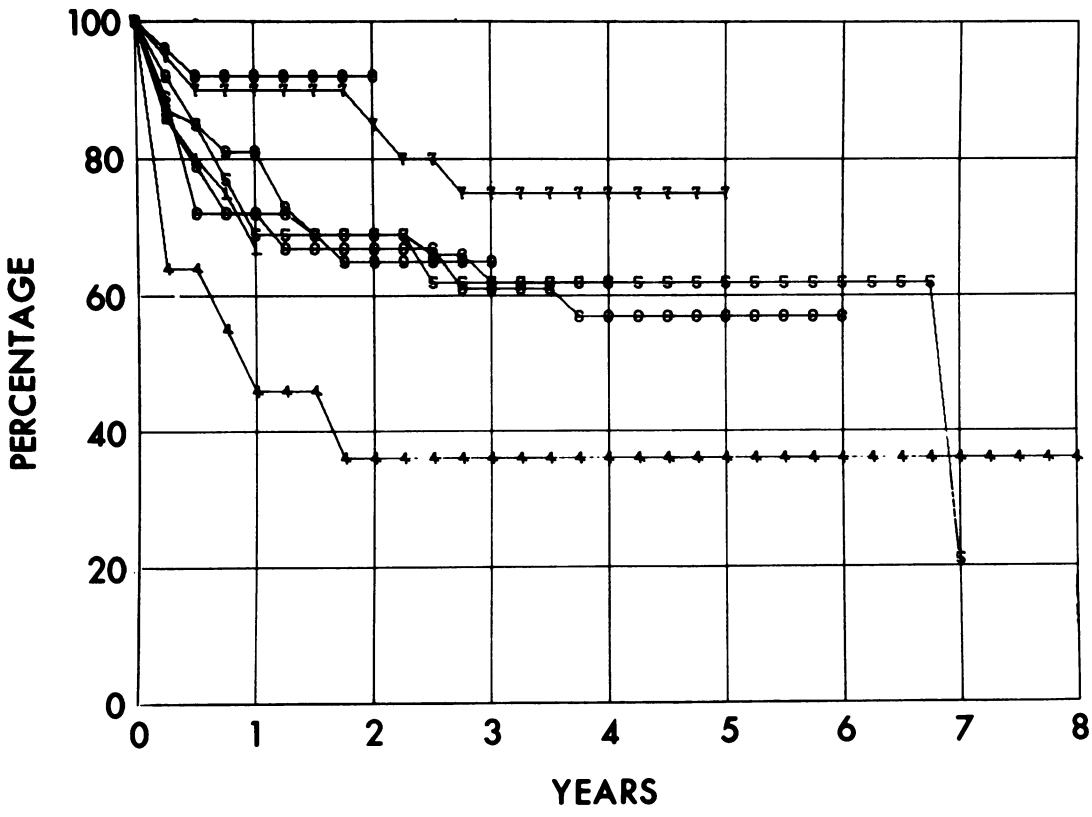

FIG. 9. Primary graft survival from related donors by year. The number of grafts by year starting with 1964, i.e. 4 are: 4 = 11, 5 = 13, 6 = 18, 7 = 20, 8 = 29, 9 = 26, 0(70) = 24, and 1(71) = 36.

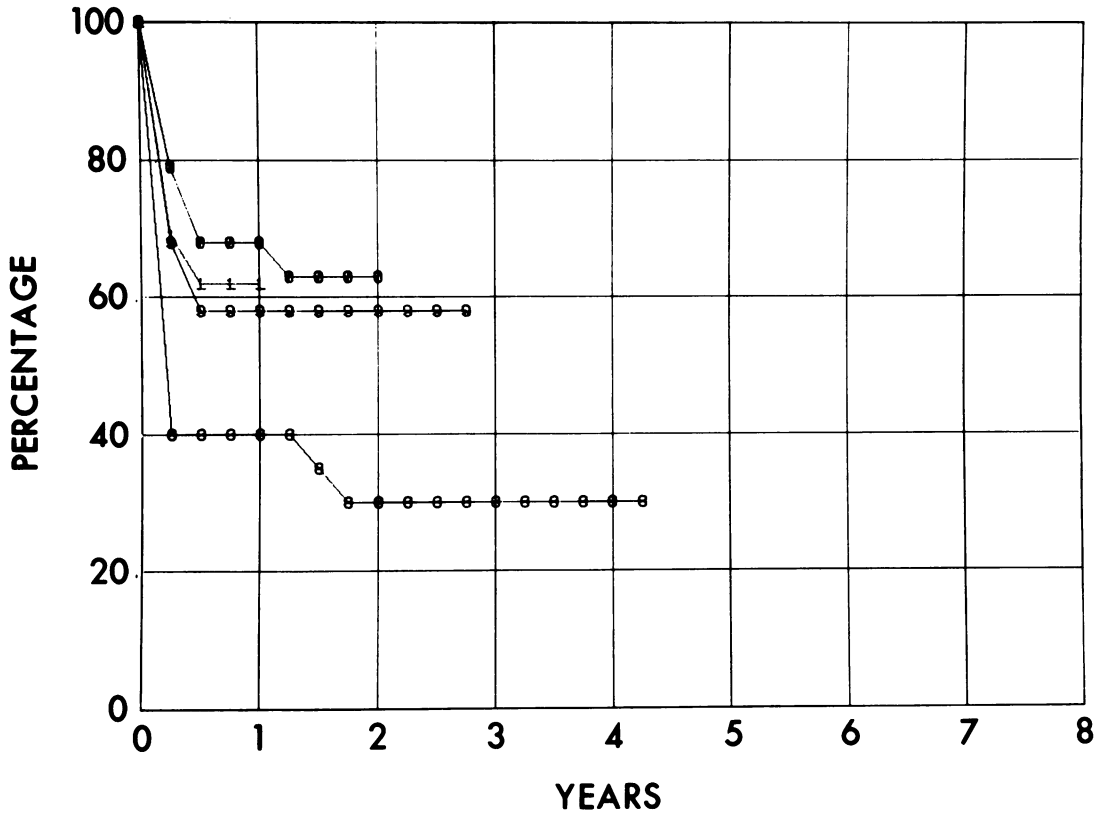

FIG. 10. Primary graft survival from cadaver donors by year. The number of transplants by year starting with 1968, i.e. 8 are: 8 = 20, 9 = 10, 0(70) = 38, and 1(71) = 55.

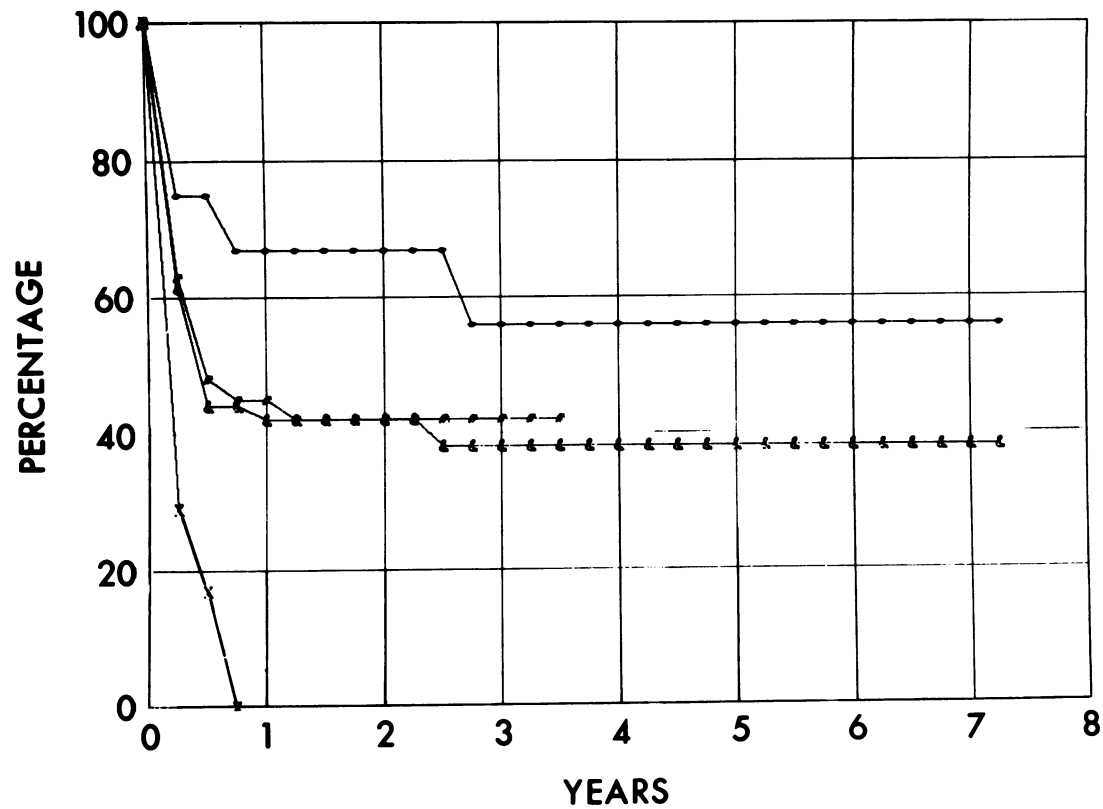

FIG. 11. Secondary graft survivals compared with donor relationships.
& = overall-54
0 = related-12
× = living unrelated-7
= cadaver-35

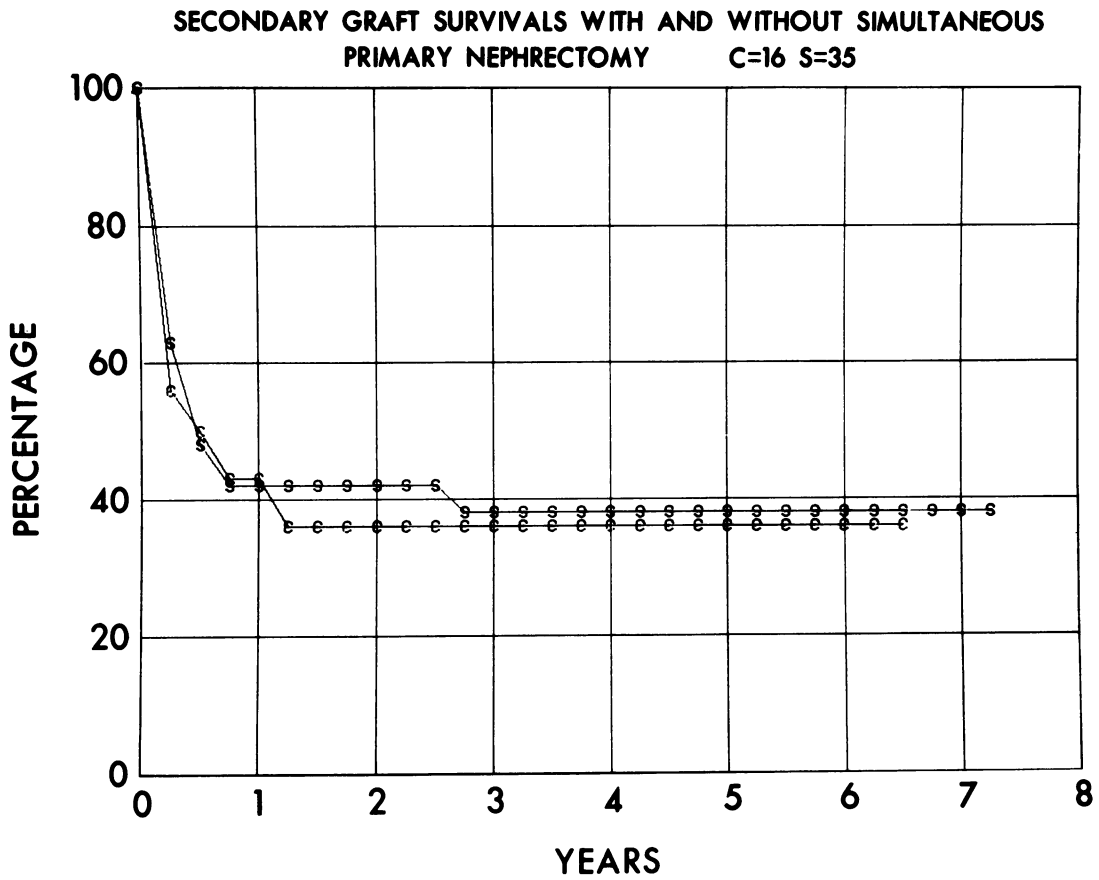

FIG. 12. Secondary graft survivals with and without simultaneous primary nephrectomy.
C = with simultaneous primary nephrectomy
S = interval after primary graft removed

the deaths due to intercurrent disease occurred after 1 year (Fig. 14). It is in category III that improvements in patient survivals must be made. The key is to remove the graft early if large doses of immunosuppressive drugs are required to maintain graft function. Adopting this approach has reduced the mortality rate from infections from 30% in 1964 to 7% in 1971 (Fig. 15). Patient survival following retransplantation was slightly worse than after primary grafting, but this was due almost exclusively to our early lack of experience. As with rejecting primary graft, rejecting retransplants that require large doses of immunosuppressive drugs to maintain graft function should be removed early as this would be a threat to patient survival.

Improvement in graft survival has not paralleled the improvement in patient survival. Survival of grafts from related donors did improve after 1964, but this was due mainly to an increase in patient survival. After 1968 there was an improvement in graft survival from cadaver donors. We believe this is due to the development of a reliable method of procurement, preservation, transportation, and viability testing of cadaver kidneys.[1] This makes cadaver transplantation, except for donor nephrectomy, an elective procedure.

In our earlier experience retransplantation was associated both with a high mortality rate and a low rate of graft survival. However, if retransplants are removed because large doses of immunosuppressive drugs are required, the mortality rate is no greater than for primary transplants. Although graft survival after secondary transplants is not as good as with primary grafts in our series, which might be expected since these patients have been sensitized, this difference becomes less significant if the early experience is excluded. The occurrence of hyperacute rejection was infrequent (two cases in the secondary group, and three cases in the primary group), suggesting that crossmatching can adequately

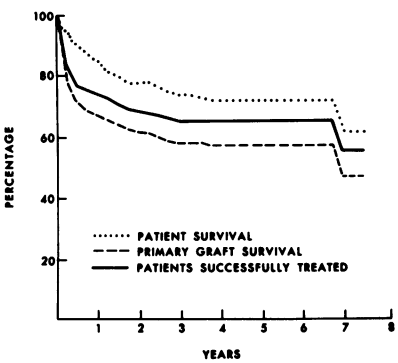

FIG. 13. Survival time of patients grouped by categories of deaths from Table 1.

detect preformed antibodies after graft rejection. Supporting this hypothesis is the observation that the results of retransplantation are the same if it is done simultaneously with transplant nephrectomy or at a later time.

Although we have added intravenous Methylprednisolone and antilymphocyte (ALG) and antithymocyte (ATG) globulin serum to the standard immunosuppressive therapy, adequate control of the rejection reaction has not been accomplished. When IV pulse doses of Methylprednisolone are used, a rejection reaction may be dramatically reversed, while in others it seems to have no effect. Our experience with ALG and ATG is too short and the number of patients studied too few to draw definitive conclusions, but our impression at the present time is that use of these materials may decrease the number and severity of the early rejection episodes. In treating a rejection crisis, our experience indicates that the mortality is greatly increased if more than two are treated within the first 3 months, which is the time of greatest risk. Likewise, chronic rejections should not be repeatedly treated. It is safer to perform another transplant or to remove the graft and return the patient to chronic hemodialysis.

Our experience parallels that of the recent report from the Transplant Registry showing that a plateau has been reached for graft survivals.[10] Our series does differ from the Registry in that our 1 and 2-year survival rate of grafts from cadaver donors is higher. Our results further differ in that our graft survival of kidneys from related donors excluding HL-A identical siblings, is not significantly different from HL-A non-identical siblings, parent-child, or cadaver donors after 2 years. However, the Registry did not exclude the HL-A identical siblings. Further in this series, the rate of graft losses after 1 year is low for all categories of donors, except parents. This could be explained by our policy of removing grafts early if large doses of immunosuppressive drugs are required to maintain graft function. These observations

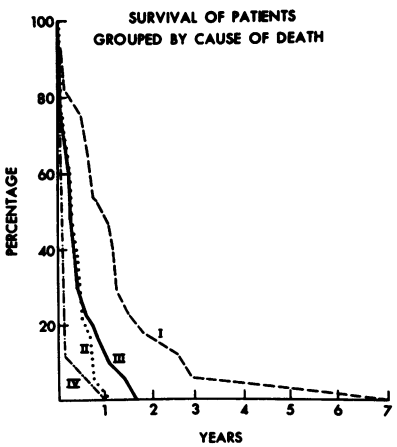

FIG. 14. Percentage of deaths due to infections by year.

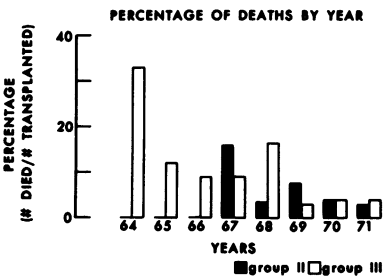

FIG. 15. Patient and primary graft survivals in relationship to percentage of patient successfully treated by use of retransplantation.

have led us to the conclusion that the only donor superior to a cadaver donor is an HL-A identical sibling.

Since graft survival has not improved despite increased experience with current immunosuppressive technics, the only way to transplant more patients successfully is to perform more retransplants. The success of such a program depends on an adequate supply of cadaver kidneys as well as hemodialysis facilities. An adequate supply of cadaver kidneys allows both optimal primary transplantation and retransplantation. In this series, one patient has normal renal function after a fifth transplant performed 2 years ago at the time of removal of his fourth transplant. Within the last 18 months 81% of patients have been successfully treated by employing retransplantation.

Summary

Over the last 8 years 336 patients have received 403 transplants and the overall mortality was 21.8%. Patient survival was independent of the donor kidney relationship. Graft survival was 100% in 32 HL-A identical sibling pairs. There was no statistically significant difference after 2 years in the graft survival in HL-A non-identical siblings, parents, children, or cadaver donors.

Immunosuppressive drugs have not improved the survival of grafts from related donors during the past 5 years nor of cadaver grafts in the last 3 years. Nevertheless, 81% of patients in the last 18 months have been successfully treated by employing retransplantation with a mortality equal to or less than that for chronic hemodialysis.

Acknowledgments

We wish to express our thanks to the many nephrologists who have supported our transplant program, and the physicians who have supported the cadaver program. The help of the tissue typing staff at the Irwin Memorial Blood Bank, under the direction of Herbert A. Perkins, M.D., is gratefully acknowledged. We also express our appreciation to J. Englebert Dunphy, M.D., who has supported and encouraged us in our efforts. The contributions of the technical staff in preservation and phenotyping are also appreciated. We are grateful for the support of the many interns, residents, and fellows who have participated in the care of these patients.

Special thanks are given to James Bauriedel, M.D., who has written all of our computer programs for the last 4 years and performed the computer analysis of these data.

References

1. Belzer, F. O. and Kountz, S. L.: Preservation and Transplantation of Human Cadaver Kidneys: A Two Year Experience. Ann. Surg., **172**:394, 1970.
2. Burton, B. T., Krueger, K. K. and Bryan, F. A.: National Registry of Long-Term Dialysis Patients. JAMA, **218**:718, 1971.
3. Douglas, K., Perkins, H. A., Cochrum, K. C. and Kountz, S. L.: Comparison of the HL-A Phenotypes of Lymphocytes and Kidney Cells Determined by the Fluorochromasia Assay. J. Clin. Invest., **50**:274, 1971.
4. Hume, D. M., Lee, H. M., Williams, G. M., White, H. J. O., Ferre, J., Wolfe, J. S., Prout, G. R., Slapak, M., O'Brien, J., Kilpatrick, S. J., Kauffman, H. M. and Cleveland, R. J.: The Comparative Results of Cadaver and Related Donor Renal Homografts in Man and the Immunological Implications of the Outcome of Second and Paired Transplants. Ann. Surg., **164**:352, 1966.
5. Kountz, S. L., Cochrum, K. C., Perkins, H. A., Douglas, K. S. and Belzer, F. O.: Selection of Allograft Recipients by Leucocyte and Kidney Cell Phenotyping. Surgery, **68**:69, 1970.
6. Kountz, S. L. and Cohn, R.: Initial Treatment of Human Renal Allografts with Large Doses of Intrarenally Administered Immunosuppressive Drugs. Lancet, **1**:338, 1969.
7. Kountz, S. L., Payne, R., Kidd, K. K., Perkins, H. A. and Belzer, F. O.: Selection of Cadaver Donors with HL-A Phenotypes Identical to Patients Awaiting Kidney Transplantation. ASAIO, (In Press).
8. Merrell, M. and Shulman, L. E.: Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematous. J. Chronic Dis., **1**:12, 1955.
9. Najarian, J. S., Gulyassy, P. F., Stoney, R. J., Duffy, G. and Braunstein, P.: Protection of the Donor Kidney During Homotransplantation. Ann. Surg., **164**:398, 1966.
10. The Ninth Report of the Human Renal Transplant Registry. JAMA, **220**:253, 1972.

Discussion

Dr. Richard E. Wilson (Boston): The manuscript of Dr. Kountz and Dr. Belzer is certainly a frank, complete, and very important review of the present status of renal transplantation in man.

I would say that, generally, our opinions and findings at the Peter Bent Brigham Hospital concur with those expressed by the authors; certainly most transplant groups have embarked on this concept of retransplantation, rather than death by overtreatment.

I would like to just ask the authors one question, which might help in the point of selection of patients for retransplantation once their first kidney has failed. That question has to do with the sensitization to the nonspecific pool.

Our group and others have recently noted a much higher failure rate in second and third transplants when recipients have been shown to carry antibody against a pood of nonspecific individuals. We have found that people with cytotoxic antibodies against Lymphocytes of greater than 10% of a pool of 40 normal people, had a 36% graft survival at 6 months. Five of 15 of these patients showed hyperacute rejection; whereas those who do not have such nonspecific antibodies had an 89% 6-month survival, with no hyperacute rejections.

I think that this may be an important way of selecting these patients who are considered for retransplant at this time, and retransplant those who are most likely to have a successful out come.

Dr. Thomas C. Moore (Torrance): As I read this manuscript, I was impressed by the importance of an ample supply of kidneys, which gave the authors many options, including the option of early removal of kidneys not functioning satisfactorily, with early retransplantation. The preservation unit of Dr. Belzer has helped make this possible. They have had more kidneys of better quality available, which has given them the opportunity of doing this. Impressed by this option which has been developed here in San Francisco, those of us from Los Angeles in the transplant field have organized a community-wide preservation effort, using Dr. Belzer's model, machines and a mobile unit. This unit serves ten transplant centers, affiliated with four medical schools, in a metropolitan area of 10.2 million. It is based in my laboratory at UCLA-Harbor. Though operational for only 13 months, 187 cadaveric human kidneys have been preserved from 110 donors, and from this group of kidneys 156 have been transplanted.

This has made it possible for us to have a threefold increase in the level of cadaveric transplantation in the Metropolitan Los Angeles area during the past year.

It has also made possible a great improvement in the life of the periodically harassed transplant surgeon. More and better kidneys have been made available, and the operation, as Dr. Kountz has stressed, has been carried out in a planned and orderly, rather than a crisis atmosphere, as heretofore. This is one of the major contributions of this study and effort.

Dr. Davad M. Hume (Richmond): In presenting transplant figures, it is very important to separate patient survival from transplant survival, as Dr. Kountz did. If one retransplants freely and stops treating rejections early, the patient survival will improve, as so nicely demonstrated by Dr. Kountz, and this has also been our own experience.

Retransplantation is not always possible in immunized patients, however, and may leave a residue of untransplantable, nephrectomized, living patients, which make the patient survival figures somewhat misleading.

In our own series, which now includes patients treated 10 years ago, there continues to be a difference in primary graft survival between related living donor and cadaver donor transplants. This difference can even be seen when one considers only the group of patients who have survived for at least 2 years, and were then followed for a minimum of 4 to 10 years. The difference is not accounted for entirely by HLA identical sibs. We agree that histocompatibility matching is important primarily for HLA identical transplants, but typing is important to avoid sensitizing patients who lack commonly occurring antigens, such as HLA-2, which occurrs in 50 per cent of the population, and attention to this will improve transplant survival on retransplantation.

Dr. Kountz's point about the similarity of patient survival regardless of kidney source is an important one, but it should not lead to his further conclusion that HLA identical sibs are the only donor source which is superior to cadaver donor transplants. This does not take into account the untransplantable patient, the increased incidence of retransplantation, which ultimately leads to increased incidence of fatalities, nor the long-term results of cadaver donor recipients when followed for from 4 to 10 years.

Dr. Joseph E. Murray (Boston): This careful, complete report brings out three points of discussion.

First, Drs. Kountz and Belzer have practically no restrictions at all in selection of recipients regarding age or the type of disease, and thus their experience truly reflects the role of an active transplant center in the deliverance of health care. This is an important attribute when considering the role of transplant centers in relationship to health care and society.

Secondly, I enjoyed their analysis of the differential between