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Living Related and Unrelated Donors for Kidney Transplantation

A 28-Year Experience

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Objective
The objective of this study was to analyze a single center's 28-year experience with 1000 living donor transplants.

Summary Background Data
The number of potential renal transplant recipients far exceeds the number of cadaveric donors. For this reason, living related donors (LRDs) and, more recently, living unrelated donors (LURDs) have been used to decrease the cadaveric donor shortage.

Methods
From November 15, 1966, until August 5, 1994, 1000 living donor transplants were performed; 906 were living related and 94 were living unrelated transplants. Results were divided into precyclosporine (1966–1986, era I) and cyclosporine (1986–1994, era II) eras. Patient and graft survivals were compared between diabetic and nondiabetic recipients, between LRDs and LURDs, and according to human leukocyte antigen (HLA) matching. Donor mortality, morbidity, and postoperative renal function were also analyzed.

Results
The 5-, 10-, and 20-year graft survivals were 78.8%, 64.8%, and 43.4%, respectively. Patient and graft survival improved in era II (patient = 87.0% *vs.* 81.7%, p = 0.03; graft = 72.9% *vs.* 67.7%, p = 0.04). Nondiabetic patient and graft survivals were better than diabetic patient survivals in both eras. However, diabetic patient survival improved in era II (78.0% *vs.* 66.9%, p = 0.04). In era II, HLA-identical recipients had better graft survival than haploidentical or mismatched recipients (91.7% *vs.* 67.3% and 66.1%, p = 0.01). No difference between haploidentical LRDs and LURDs was seen. One donor death occurred in 1970, and 17% of donors developed postoperative complications.

Conclusion
Living related and unrelated renal donation continues to be an important source of kidneys for patients with end-stage renal disease.

Despite intensive educational efforts, cadaveric renal donation has remained essentially unchanged at 4000–5000 donors per year. The number of patients awaiting renal transplantation has risen dramatically, with more than 27,000 potential recipients waiting as of January 1995.[1] This huge disparity between donors and recipients has led to renewed interest in alternative ways to increase the donor pool. These include the use of marginal and non-heart-beating donors[2] and living related and living unrelated donors.

Although living related renal transplantation has been applied to the treatment of end-stage renal disease since the early days of transplantation,[3] controversy remains regarding the use of living related donors (LRDs). Concern centers on possible donor morbidity and mortality in the early postoperative period as well as potential long-term complications after unilateral nephrectomy. More recently, living unrelated donors (LURDs) have been utilized at several centers in an attempt to provide renal transplantation to more patients.[4] Although LURDs constitute only 1% of renal transplants performed in the United States, they are a topic of ethical as well as scientific controversy. Because it is unlikely that the number of cadaveric donors will increase significantly, LRDs and LURDs will continue to be the most likely potential sources of kidneys. This paper reviews our results in 1000 living donor transplants performed over a 28-year period.

MATERIALS AND METHODS

Patient Population

From November 15, 1966, until August 5, 1994, 1000 living donor renal transplants were performed on 964 recipients at our center (Fig. 1); 906 transplants were from LRDs and 94 were from LURDs. In this series, 916 were primary and 84 were nonprimary; 70 were second, 12 were third, and two were fourth transplants. The mean age of recipients was 31.8 ± 11.5 years; 611 patients were males and 389 were females. Complete human leukocyte antigen (HLA) matching (A, B, DR) data were available for 611 patients; 157 recipients were HLA-identical, 412 were haploidentical, and 42 were mismatched. Seven hundred two recipients (70.2%) were nondiabetic; 298 (29.8%) were diabetic. The etiology of renal failure is shown in Table 1.

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Immunosuppressive Protocols

Patients were divided into three eras based on immunosuppression; with each era there were changes regarding transfusion protocols. From 1966 until 1985 (era I), immunosuppression consisted of azathioprine (1–2 mg/kg/day) and prednisone (6–8 mg/kg/day, tapered to 0.5 mg/kg/day at 1 month and 0.15 mg/kg/day at 1 year). During era I and beginning in 1980, donor-specific blood transfusions were given in 200-cc aliquots three times at 2-week intervals before transplant. Era I was precyclosporine; 520 renal transplants were performed in that time. Era II, from March 1986 through July 1993, covered 419 renal transplants. During era II, all patients received either three donor-specific transfusions or three random-donor transfusions. During era II, a steroid-withdrawal protocol was also instituted.[5] Immunosuppression included azathioprine and prednisone, as in era I (except for patients undergoing steroid withdrawal), but also included cyclosporine, which was administered after the serum creatinine level fell to ≤3 mg/dL. The initial dose was 4 to 8 mg/kg and was adjusted to maintain whole blood cyclosporine levels by radioimmunoassay (Sandoz Pharmaceuticals, East Hanover, NJ) between 300 and 600 ng/mL. Human leukocyte antigen–identical recipients had prednisone discontinued after 14 days; haploidentical recipients, after 6 months.

Also during era II (in 1988), donor-specific transfusions were abandoned in favor of random-donor transfusions, and either Minnesota antilymphocyte globulin (10–20 mg/kg/day) or OKT3 (2.5–5.0 mg/day) was used for 7 to 10 days of induction therapy. Era III, from August 1, 1993, until August 5, 1994, included 61 renal transplants by our current protocol. Immunosuppression consisted of azathioprine, prednisone, cyclosporine, OKT3 induction, and no blood transfusions in haploidentical recipients. For purposes of this study, these patients were included in era II for calculations of patient and graft survival. Human leukocyte antigen–identical recipients received no induction therapy; LURDs and complete mismatches received both OKT3 induction and donor-specific transfusions.

Tissue Typing

Complete HLA typing was available for all recipients in the cyclosporine era (n = 480) and for 131 recipients in the precyclosporine era. Panel of reactive antibodies results were determined using the extended-incubation National Institutes of Health cytotoxicity assay. Cytotoxicity cross-matching was performed on historical sera and on sera obtained the day before transplant. T-cell cross-matches in all eras were performed by complement-dependent cytotoxicity. B-cell cross-matches were

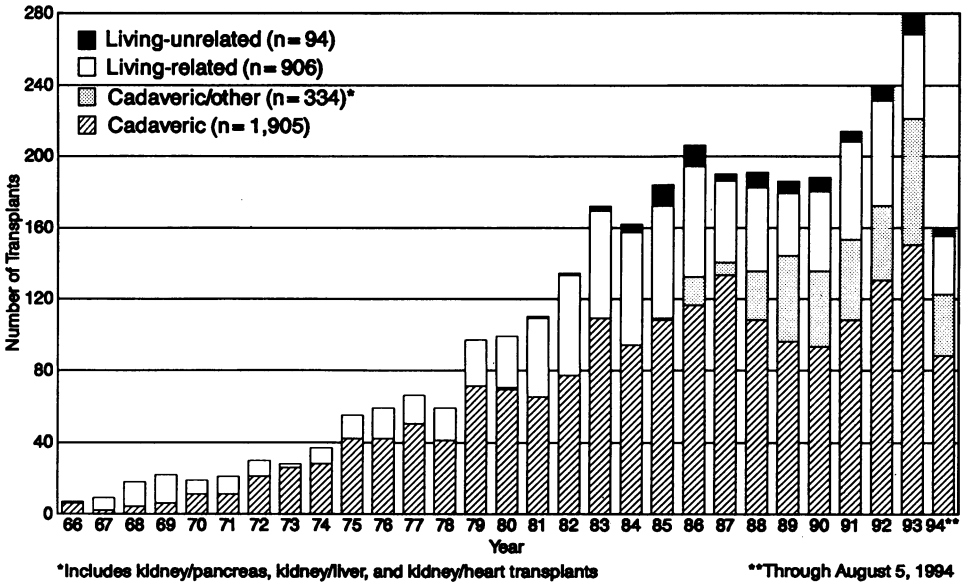

Figure 1. Number of living and cadaveric renal transplants performed from November 15, 1966, until August 5, 1994.

not performed until 1981, at which time a complement-dependent cytotoxicity assay was used. This was replaced by the antiglobulin B-cell cross-match in 1993.

Operative Procedures

All living-donor nephrectomies and all transplant procedures were performed by staff urologists and transplant surgeons, respectively. All procedures were performed in adjacent operative suites; each donor nephrectomy was started slightly before the transplant procedure. After removal of the donor kidney through a flank incision, the kidney was brought into the recipient's operating room and flushed for 1 minute with a cold solution of lactated Ringer's containing sodium bicarbonate (22.3 mEq/L), mannitol (25 g/L), heparin (10,000 U/L), and procaine 1% (5 cc/L). The donor kidney was then transplanted into either iliac fossa using standard surgical procedures.

Table 1. ETIOLOGY OF RENAL FAILURE IN 1000 RENAL TRANSPLANT RECIPIENTS

Disease	No. (%)
Glomerulonephritis	303 (30.3)
Diabetes mellitus	298 (29.8)
Unknown/other	140 (14.0)
Hereditary/pyelonephritis	125 (12.5)
Polycystic/medullary cystic	48 (4.8)
Hypertension	46 (4.6)
Systemic lupus	40 (4.0)

Rejection and Graft Loss

Graft loss was defined as nephrectomy, return to dialysis, or death with a functioning graft. All recipients were followed up indefinitely, and mortality was determined despite whether they had a functional graft.

Rejection was diagnosed by such clinical signs as fever and graft tenderness as well as by elevations of serum blood urea nitrogen and creatinine and characteristic findings on a technetium renal scan. Before 1986, renal biopsies were performed only when the diagnosis was uncertain. However, all episodes of suspected renal transplant rejection have since been confirmed by biopsy. Rejection episodes were treated with methylprednisolone (6–8 mg/kg intravenously) or an increase in oral prednisone (to 3 mg/kg, tapered over 2 weeks). After 1986, rejection episodes unresponsive to steroids were treated with OKT3 (5 mg/day intravenously for 10–14 days). More recently, mycophenolate mofetil and FK506 have also been used to treat OKT3 refractory rejection episodes.

Donor Population

The charts of 681 donors between 1971 and 1991[6] were analyzed for postoperative morbidity and mortality. Preoperative and postoperative serum creatinine and 12-hour creatinine clearances were also compared. No long-term follow-up of donors was conducted.

Waiting List and Transplant Activity Analysis

To analyze transplant activity, we compared the number of patients receiving a renal transplant, from either a

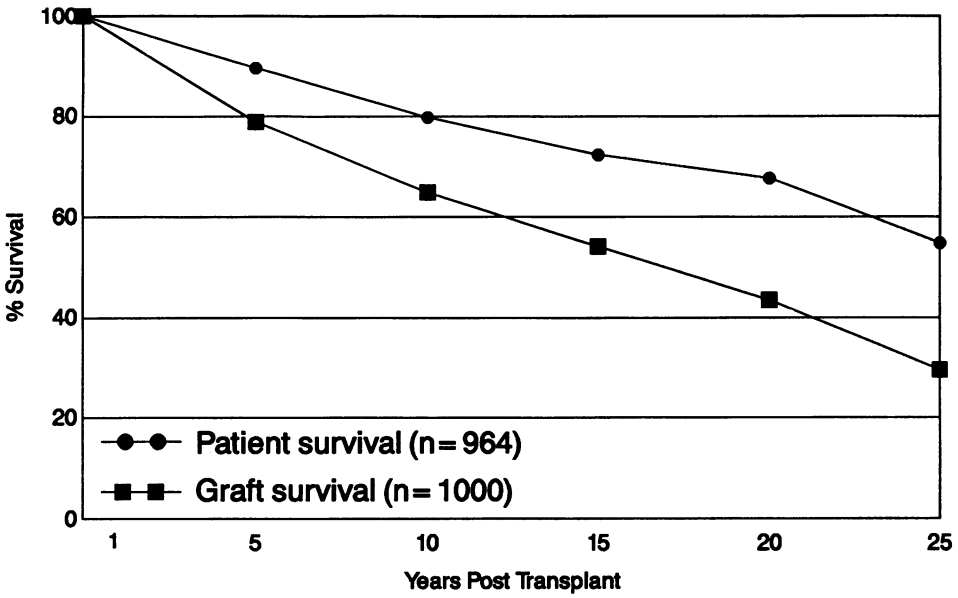

Figure 2. Overall 25-year patient and graft survival after living renal donation.

living or cadaveric donor, with the number of patients placed on our waiting list over a 6-year period. The period from January 1989 through December 1994 was chosen, because data were complete and represented our most current experience.

Statistical Analysis

Patient and graft survivals were estimated with the Kaplan–Meier product-limit estimator. The use of cyclosporine for the last 8 years provides that time period for comparisons of eras I and II. As noted, a patient death with functioning graft was treated as a graft failure. In the case of patient survival for multiple transplant recipients, the date of the first transplant was used as the origin. Comparisons between the survival curves for the various groups of interest were performed with the log-rank test. Comparisons of physiologic parameters, such as creatinine, between the groups were performed with the Wilcoxon rank-sums test. All analyses were performed with SAS statistical software (SAS Institute Inc., Cary, NC, 1989).

RESULTS

Living renal donation has increased steadily since the inception of our program in 1966 (Fig. 1). The 1000 living related or living unrelated transplants reported here represent approximately one third of all renal transplants at our center. Overall patient and graft survival have been very good, from 89.5% (patient) and 78.8% (graft) survival at 5 years to 54.7% (patient) and 29.4% (graft) survival at 25 years (Fig. 2).

When patient and graft survival were compared for precyclosporine and cyclosporine eras, both patient and graft survival improved (Fig. 3). The 1- and 8-year patient and graft survivals in the precyclosporine era were 95.3% and 81.7%, and 90.3% and 67.7%, respectively; patient and graft survivals in the cyclosporine era were 99.4% and 87.0%, and 95.3% and 72.9%, respectively.

When nondiabetic recipients were compared with diabetic recipients in the precyclosporine and cyclosporine eras, nondiabetic patient and graft survivals were significantly better. Nondiabetic patient survival did not differ between eras, but diabetic patient survival improved significantly in the cyclosporine era (Fig. 4). Patient survival for nondiabetic patients in the precyclosporine era at 1 and 8 years was 95.3% and 85.5% *versus* 94.5% and 66.9% for diabetic recipients; survival in the cyclosporine era at the same time intervals for nondiabetic recipients compared with diabetic recipients was 99.4% and 92.1% *versus* 99.3% and 78.0%.

No difference in graft survival in diabetic recipients was seen between eras. Allograft survival for nondiabetic patients at 1 and 8 years in the precyclosporine era was 89.7% and 70.1%, compared with 95.4% and 77.8% in the cyclosporine era (Fig. 5). Graft survival for diabetic patients in the precyclosporine era for the same time intervals was 90.0% and 59.9%, compared with 93.9% and 63.9% for the cyclosporine era.

Human leukocyte antigen–identical recipients in the cyclosporine era had significantly better allograft survival at 5 and 8 years than did haploidentical or mismatched recipients (Fig. 6): they held steady at 91.7%, whereas haploidentical recipients dropped to 78.2% and 67.3%, and mismatched recipients held steady at 66.1%.

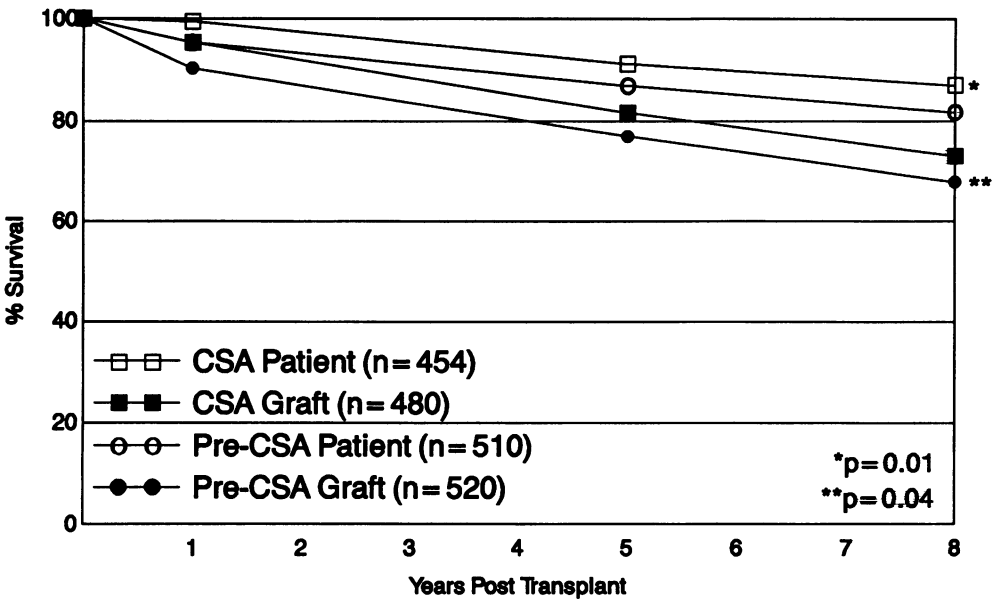

Figure 3. Eight-year patient and graft survival in the precyclosporine and cyclosporine eras.

Whereas 8-year graft survival for HLA-identical recipients improved in the cyclosporine era relative to the precyclosporine era (91.7% *vs.* 79.6%; p = 0.04), no difference was noted for recipients of haploidentical grafts, nor was any difference noted in graft survival in the cyclosporine era between patients who had panel of reactive antibodies ≥ 40% or <40% (Fig. 7).

When living unrelated transplants were compared with haploidentical recipients, no difference in allograft survival was seen at 8 years (Fig. 8). The 1- and 8-year graft survival for LURDs was 94.6% and 60.7%, and that of haploidentical recipients was 94.5% and 67.3%, respectively.

During this 28-year study period, 316 (31.6%) allografts were lost (Table 2). Also during this study period, 166 recipients died (Table 3). When rejection episodes were examined, 295 of 520 recipients (56.7%) in the precyclosporine era had one or more rejection episodes, and in the cyclosporine era, 246 of 480 recipients (51.3%) had one or more rejection episodes. The majority of rejections (80.3%) occurred within the first year of transplantation in both eras. One or more infections occurred in 298 patients (57.3%) in the precyclosporine era and in 228 patients (47.5%) in the cyclosporine era ($p < 0.05$). Unlike rejection episodes, only 45.8% of all infections occurred within the first year after transplantation.

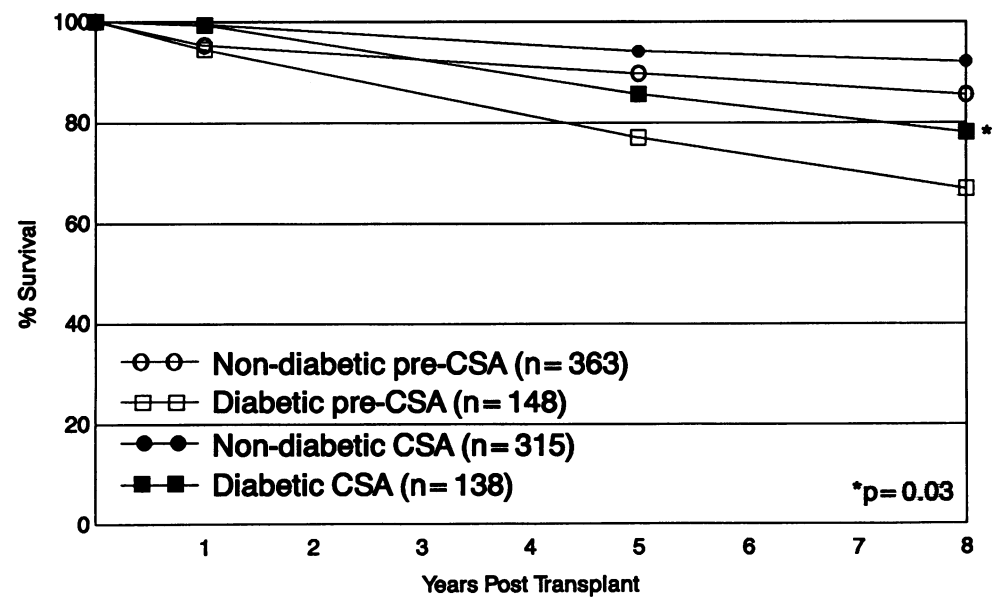

Figure 4. Patient survival of nondiabetic and diabetic recipients in the precyclosporine and cyclosporine eras.

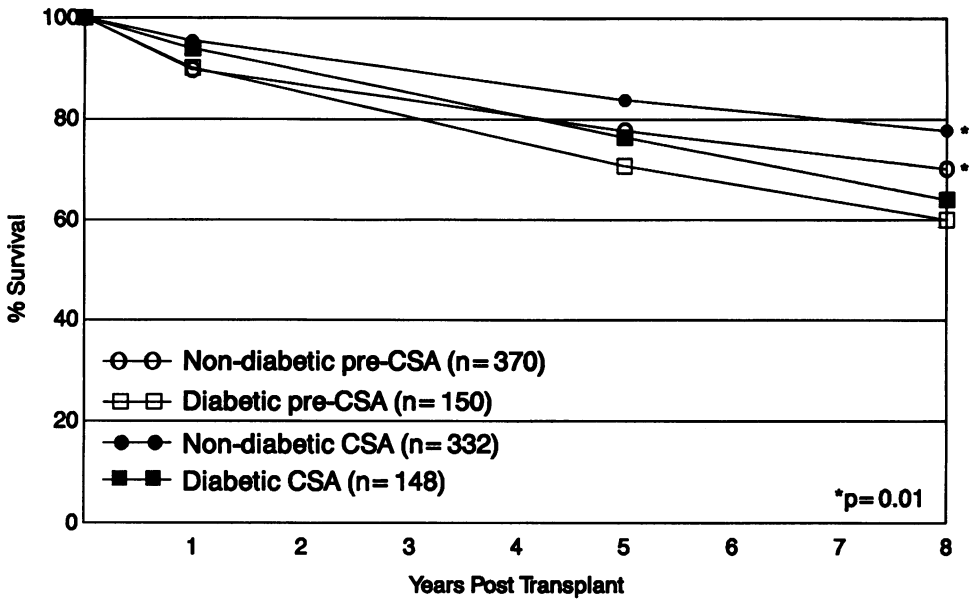

Figure 5. Graft survival of nondiabetic and diabetic recipients in the precyclosporine and cyclosporine eras.

Review of 681 charts for the 20-year period from 1971 to 1991 tracked the morbidity following donor nephrectomy (Table 4) and the preoperative and postoperative creatinine and creatinine clearance (Table 5). During the entire study period, only one death occurred in a donor, that from a pulmonary embolus in 1970.

A comparison of the number of patients receiving transplants with the number on the waiting list over a 6-year period is shown (Fig. 9). Although our waiting list increased significantly from 1989 until 1994, we were able to equally increase the number of patients receiving transplants. Some of the waiting list increase in 1994 reflected an increase in the number of multiply listed patients. Our approach has been to perform transplants for as many patients as are appropriate with living donors. We inform all potential candidates about the benefits of living related donation but certainly do not force them in this direction. The remaining patients receive transplants of cadaveric kidneys through an efficient organ procurement organization that routinely retrieves organs from 30 to 40 donors per million population.

DISCUSSION

The current cadaveric donor organ shortage has led to interest in ways to provide more transplants for the ever-

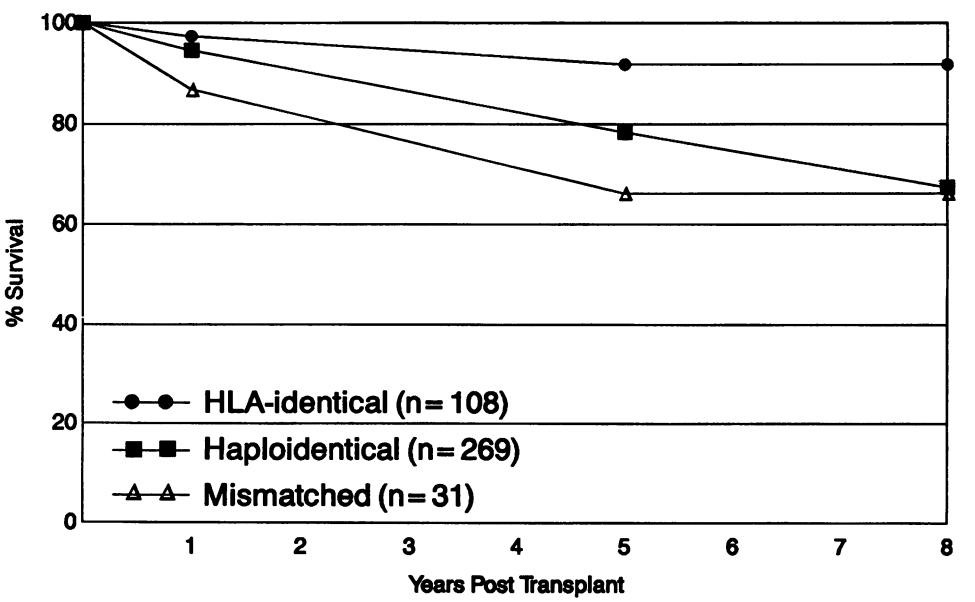

Figure 6. Effect of HLA matching on allograft survival in the cyclosporine era.

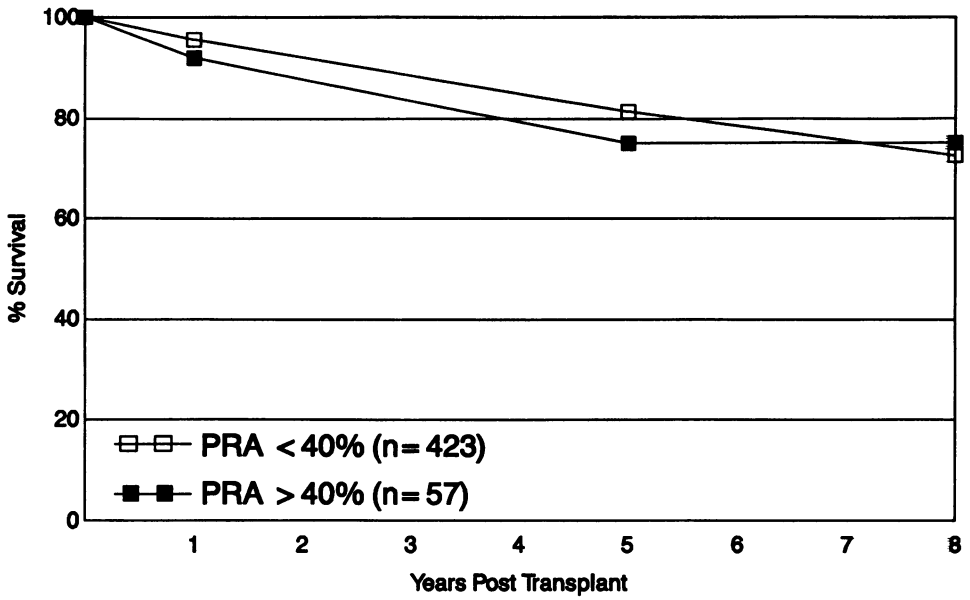

Figure 7. Effect of panel of reactive antibodies on allograft survival in the cyclosporine era.

increasing number of patients on the waiting list. For renal transplants, there are only three sources of kidneys—LRDs, LURDs, and cadaveric donors. Although xenografts may, in the future, provide enough kidneys for transplantation, currently they are not an option. The magnitude of the problem is clear: more than 27,000 potential recipients are waiting for kidneys as of January 1995,[1] whereas only 4000 to 5000 cadaveric donors are made available each year. Efforts to increase the number of organ donors should continue along with efforts at using marginal donors and non-heart-beating donors.[2] However, it is unlikely that enough cadaveric organs will ever be able to bridge the current disparity between demand and supply. Therefore, LRDs and LURDs will continue to play a significant role in the treatment of patients with end-stage renal disease.

Although many centers find LRDs and LURDs ethically acceptable, some believe we should proceed with caution, particularly with LURDs.[7] The primary concern has been over donor morbidity and mortality as well as potential long-term complications. Our series had one donor death (0.1% mortality), which occurred in 1970. In a recent review of donor deaths in the United States and Canada, Najarian et al.[8] estimated the mortality of living related donation to be 0.03%. Anderson et al.[9] and others have also demonstrated the safety and efficacy of

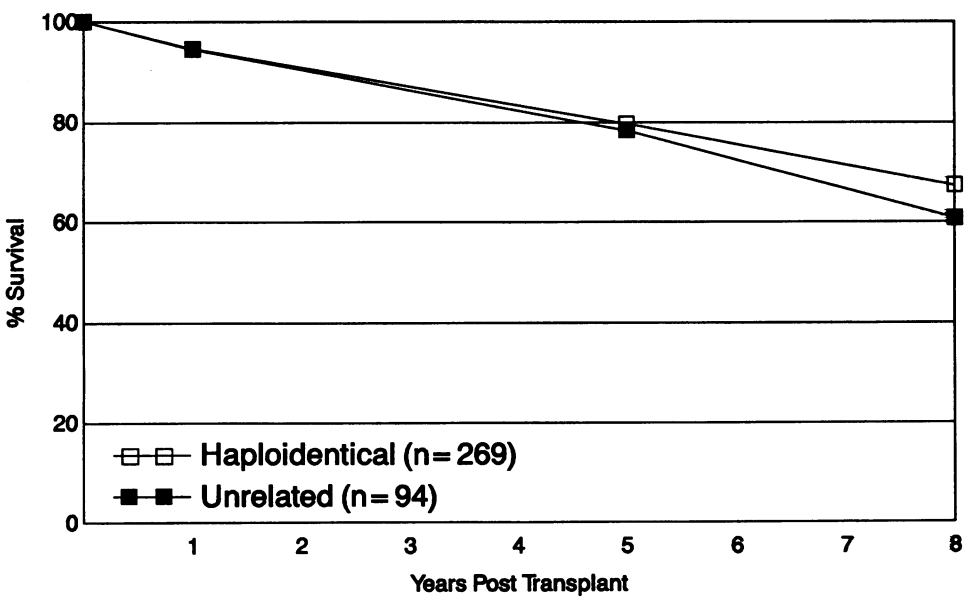

Figure 8. Eight-year graft survival in haploidentical and unrelated renal transplants.

Table 2. ETIOLOGY OF 316 GRAFT LOSSES IN 1000 LIVING-DONOR RENAL TRANSPLANTS

Etiology	No. (%)
Chronic rejection	118 (37.3)
Death with a functioning graft	106 (33.5)
Acute rejection	33 (10.4)
Unknown/other	26 (8.2)*
Vascular/urologic	13 (4.1)
Recurrent disease	10 (3.2)
Noncompliance	7 (2.2)
Infections	3 (0.9)

* All unknown causes of graft loss occurred in the precyclosporine era.

living related donation.[10-14] Likewise, our low rate of donor complications in the immediate postoperative period is similar to that reported by others.[9,15] Although we did not conduct long-term studies of our donor population, others have shown that, despite the presence of proteinuria and hypertension in some donors, this did not lead to long-term renal dysfunction.[8]

In our series, more than 30% of kidney recipients received either living related or living unrelated transplants. The percentage of living donors varies from 25% to 50% in the United States,[11,14,16] whereas Europe tends to have a lower rate of 11%.[17] Our policy is to provide transplants to as many recipients on our waiting list as we can, using all appropriate sources of kidneys. Because our organ procurement organization routinely retrieves organs from 30 to 40 donors per million population (double the national average), we had been able to match the increase in the recipient waiting list until 1993 with increases in available organs and more transplants. However, at the current rate of increase, we will outstrip our cadaveric renal supply and will need to consider increasing the percentage of recipients receiving transplants from living donors.

Table 3. ETIOLOGY OF 166 PATIENT DEATHS AFTER LIVING-DONOR RENAL TRANSPLANTS

Etiology of Recipient Death	No. (%)
Cardiac	57 (34.3)
Other	31 (18.7)
Unknown	29 (17.5)*
Sepsis	27 (16.3)
Malignancy	9 (5.4)
Pulmonary	7 (4.2)
Cerebrovascular	6 (3.6)

* All unknown causes of patient death occurred in the precyclosporine era.

Table 4. POSTOPERATIVE MORBIDITY OF 681 DONORS UNDERGOING NEPHRECTOMY

Complication	No. (%)
Pneumothorax requiring chest tube	48 (7.0)
Urinary tract infection	34 (5.0)
Wound infection	27 (4.0)
Pneumonia	5 (0.7)
Pulmonary embolus	2 (0.3)
Total	116 (17.0)

We and others[10-13] have demonstrated improved patient and graft survival in the cyclosporine era. Although nondiabetic recipients fared better than diabetic recipients in both the precyclosporine and cyclosporine eras, diabetic recipients showed significantly improved patient survival in the cyclosporine era relative to precyclosporine. This likely represents improved patient care, perhaps better patient selection, and more specific immunosuppressive therapy. Interestingly, HLA-identical recipients did better in the cyclosporine era in our series. This finding differs from other reports that demonstrate no improvement between eras in two-haplotype-matched recipients.[11] We noted no difference in haploidentical graft survival in the cyclosporine era compared with the precyclosporine era. This, too, contrasts other reported series. However, our haploidentical graft survival in the precyclosporine era (68.6% at 8 years) was higher than that reported by others in the precyclosporine era.[11,12] Perhaps donor-specific transfusions in the precyclosporine era helped to equalize results for the precyclosporine and cyclosporine eras.

Although several centers, including ours, have demonstrated the beneficial effects of donor-specific transfusions,[18-21] their use has been questioned in the cyclosporine era. Because many potential recipients become sen-

Table 5. PREOPERATIVE AND POSTOPERATIVE SERUM CREATININE AND CREATININE CLEARANCE IN DONORS UNDERGOING NEPHRECTOMY

	Preoperative	Postoperative (at discharge)
Serum creatinine (mg/dL)	1.0 ± 0.2	1.4 ± 0.3*
Creatinine clearance (mL/min)	109 ± 26	78 ± 23*

* $p < 0.05$.

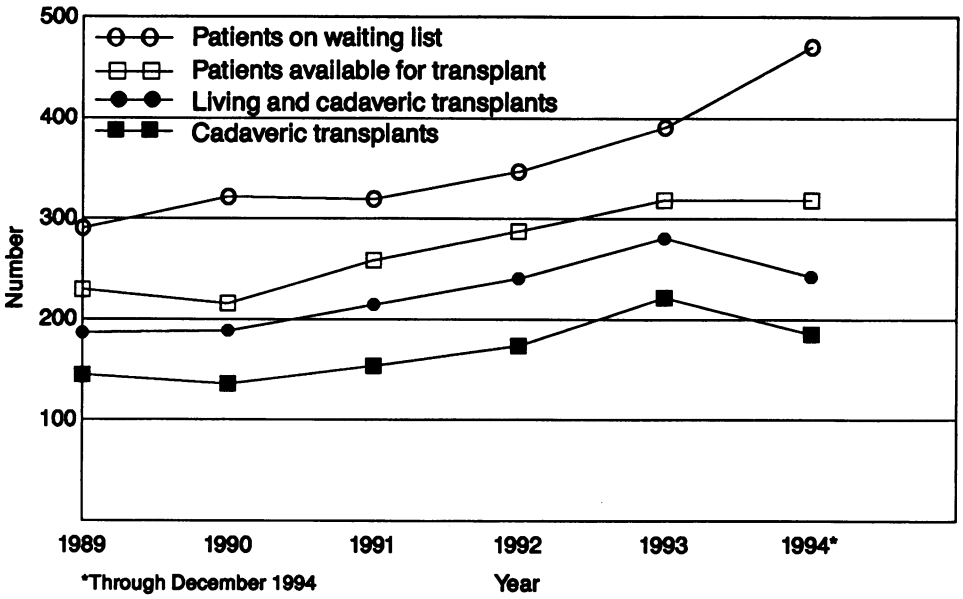

Figure 9. Summary of waiting list and transplant activity, 1989 to 1994. The figure also depicts the number of patients available for transplant; during the course of a year, some patients die, receive transplants elsewhere, or are taken off the list for medical reasons.

sitized to their donors after transfusions, we switched to a random-donor transfusion protocol in 1988. We have reported on an increased rejection rate with this protocol but no change in graft survival.[18] Because of the increased number of rejection episodes, we added induction therapy with Minnesota antilymphocyte globulin or OKT3. Because there was no difference in graft survivals with either donor-specific transfusions or random-donor transfusions in the cyclosporine era, we abandoned transfusions in haploidentical living related recipients in 1993. Our most recent protocol with haploidentical LRDs is OKT3 induction, cyclosporine, azathioprine, and no blood transfusions. Although 1-year graft survival in this group is 94%, further follow-up is necessary before we can make definitive comments about this particular protocol. As with other studies of living related transplants, panel of reactive antibodies did not appear to be relevant to LRD outcome.[10]

Our results with LURDs continue to demonstrate, as in our earlier reports,[22,23] that graft survival is similar to that for haploidentical LRDs. Despite a recent study that demonstrated a favorable attitude to LURDs,[24] only 1% of renal transplants currently performed are from LURDs.[4] The results of our study as well as others[25-27] continue to indicate LURDs are one possible means to increase the number of recipients for renal transplants. However, Starzl et al.[7] continue to caution those who would use LURDs, because there has been no truly long-term survivors with LURDs as there have been with LRDs. Likewise, fear of commercialism, particularly in developing countries, persists. As recently reported by Onwubalili et al.,[28] the outcome of bought LURDs was poor, particularly in regard to transmission of infectious diseases. Our approach to LURDs is to consider this option from spouses and from close friends who are emotionally involved with the recipient. We exclude altruistic strangers as potential donors.

We believe that this study, which chronicles the history of the living related and unrelated transplant program at our center, demonstrates the safety and superior long-term results of living related and unrelated renal donation. We have, until recently, been able to keep pace with the number of patients on our waiting list by increasing the number of cadaveric donors by using marginal donors, non-heart-beating donors, and, when appropriate, hepatitis C–positive kidneys as well as by continuing to be proponents for living related and unrelated transplantation. Until there are major breakthroughs in preventing immunologic graft loss, maximizing cadaver organ donation, and perhaps xenografting, we recommend that living related and unrelated renal donation be considered whenever possible to help reduce the disparity in numbers between potential renal transplant recipients and kidneys from cadaveric donors.

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Discussion

DR. ARNOLD G. DIETHELM (Birmingham, Alabama): I was grateful to have the opportunity to review the manuscript prior to the meeting. Dr. D'Alessandro and Dr. Belzer and colleagues have addressed an important and frustrating part of organ transplantation, and that is the organ shortage.

The manuscript is an excellent review of their results and similar to those that we have published from our own institution. They, as well as ourselves, have attempted to modify the problem of organ shortage by using living donors. In fact, they use living unrelated donors. And those results, as you have seen today, are excellent.

There are several important reasons to pursue the living donor, but the risk to the donor is ever-present. The reasons are prompt early function by the graft, which I think in turn provides better long-term graft survival, and, very importantly, the elective date of the transplant. The elective date of the transplant implies that one can preempt dialysis, perform transplantation prior to end-stage renal disease, and avoid a prolonged morbidity that occurs with chronic dialysis. I think that part of the excellent results obtained from the living unrelated donor is the opportunity to start either FK-506 or cyclosporine early in the post-transplant course and avoid nephrotoxicity.

Until the use of xenografts become a practical reality, transplant surgeons will continue to search for organs. Some of them will be living unrelated donors, some will be related donors, some will be distant relatives, and some will be what is called a marginal donor. What is marginal to one surgeon may not be marginal to another.

Now, a final comment about the problem of organ shortage. It is not unique in our country. It is unique the world over. It is really not a scientific problem. And I do not believe it is one of culture. I think it is one of education. And times are improving, but very, very slowly.

Some progress has been achieved, and certainly the Wisconsin group is one of the leaders in terms of organ procurement per million people. But until we have either the xenograft or some other major solution to the organ shortage, we will continue to look for the marginal donor, the living unrelated donor, and close relatives.

The excellent results presented today must be taken in con-