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## IMPROVED GRAFT SURVIVAL AFTER RENAL TRANSPLANTATION IN THE UNITED STATES, 1988 TO 1996

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### ABSTRACT

**Background** The introduction of cyclosporine has resulted in improvement in the short-term outcome of renal transplantation, but its effect on the long-term survival of kidney transplants is not known.

**Methods** We analyzed the influence of demographic characteristics (age, sex, and race), transplant-related variables (living or cadaveric donor, panel-reactive antibody titer, extent of HLA matching, and cold-ischemia time), and post-transplantation variables (presence or absence of acute rejection, delayed graft function, and therapy with mycophenolate mofetil and tacrolimus) on graft survival for all 93,934 renal transplantations performed in the United States between 1988 and 1996. A regression analysis adjusted for these variables was used to estimate the risk of graft failure within the first year and more than one year after transplantation.

**Results** From 1988 to 1996, the one-year survival rate for grafts from living donors increased from 88.8 to 93.9 percent, and the rate for cadaveric grafts increased from 75.7 to 87.7 percent. The half-life for grafts from living donors increased steadily from 12.7 to 21.6 years, and that for cadaveric grafts increased from 7.9 to 13.8 years. After censoring of data for patients who died with functioning grafts, the half-life for grafts from living donors increased from 16.9 years to 35.9 years, and that for cadaveric grafts increased from 11.0 years to 19.5 years. The average yearly reduction in the relative hazard of graft failure after one year was 4.2 percent for all recipients ( $P < 0.001$ ), 0.4 percent for those who had acute rejection ( $P = 0.57$ ), and 6.3 percent for those who did not have acute rejection ( $P < 0.001$ ).

**Conclusions** Since 1988, there has been a substantial increase in short-term and long-term survival of kidney grafts from both living and cadaveric donors. (N Engl J Med 2000;342:605-12.)

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THE number of patients with end-stage renal disease is increasing at the rate of 7 to 8 percent per year in the United States.<sup>1</sup> Renal transplantation is the treatment of choice for most of these patients, but the number of kidneys available for transplantation is limited.<sup>2</sup> Since 1988, there has been a growing discrepancy between the number of transplantations performed and the number of patients awaiting transplantation, underscoring the need to maximize graft survival.<sup>2</sup>

The short-term outcome of renal transplantation has improved substantially in the past 15 years. The introduction of cyclosporine for the prevention of acute and chronic rejection in the early 1980s and the introduction of muromonab-CD3 (OKT3 monoclonal antibody) for the treatment of acute rejection in the early 1980s have increased the rate of graft survival at one year.<sup>3,4</sup> In recent years, use of newer immunosuppressive drugs such as mycophenolate mofetil and tacrolimus has been associated with further reduction in the incidence of acute rejection episodes.<sup>5,6</sup>

However, there has not been a noticeable improvement in long-term graft survival.<sup>7</sup> Long-term graft failure is usually due to death with a functioning graft, chronic rejection, or recurrent kidney disease.<sup>8</sup> Cyclosporine is nephrotoxic and has been thought to aggravate graft failure. Among these causes of long-term graft failure, the most important and the most potentially remediable is chronic rejection.<sup>9</sup> Graft failure due to chronic rejection is a common reason for placing a patient on a waiting list for retransplantation.

The relation between acute and chronic rejection is not clear. Although acute rejection is considered the most important predictor of chronic rejection,

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**TABLE 1.** CHARACTERISTICS OF RENAL-TRANSPLANT DONORS AND RECIPIENTS, 1988 TO 1996.

CHARACTERISTIC	YEAR OF TRANSPLANTATION									OVERALL*
	1988	1989	1990	1991	1992	1993	1994	1995	1996	
No. of transplants	9038	8985	9870	10,119	10,219	10,979	11,228	11,730	11,766	93,934
Black race (%)										
Recipient	20.4	20.0	19.7	19.8	20.3	20.3	22.2	21.1	21.5	20.6
Donor	8.9	9.1	9.4	10.2	11.1	12.1	12.1	11.7	11.6	10.7
Prior transplantation (% of recipients)	14.2	14.0	13.7	13.8	13.1	11.4	11.7	11.6	11.2	12.7
Living donor (% of recipients)	20.0	21.2	21.2	23.6	24.8	25.9	26.3	27.5	29.2	24.4
Cadaveric donor's age >50 yr (% of recipients)	10.4	12.2	13.5	14.3	16.1	16.4	16.9	17.4	18.2	15.0
Mean cold-ischemia time (hr)	24.2	23.5	23.6	24.1	22.8	21.9	20.5	20.7	20.4	22.4
Mean serum panel-reactive antibody in recipients (%)†										
Graft from living donor	13.2	10.3	10.0	8.6	8.5	8.5	8.5	8.6	7.3	9.3
Graft from cadaveric donor	21.5	20.5	17.2	16.6	16.8	14.7	14.9	14.1	14.2	16.7
Mean no. of HLA matches										
Cadaveric donor	2.0	2.0	2.1	2.2	2.2	2.3	2.3	2.4	2.4	2.2
Living donor	3.7	3.6	3.6	3.6	3.5	3.5	3.4	3.3	3.1	3.5
Mean wait for cadaveric graft (yr)	2.6	2.6	2.7	2.8	2.8	2.8	2.9	2.8	3.0	2.8
Antibody therapy (% of recipients)	25.0	27.4	26.9	25.6	24.3	26.2	47.3	48.3	38.2	32.1
Delayed graft function (% of recipients)	24.1	22.3	21.5	19.6	19.7	18.6	18.6	18.1	18.4	20.1
Mycophenolate mofetil at time of transplantation (% of recipients)	<0.1	<0.1	0.1	0	<0.1	0.1	0.2	14.9	48.7	—
Tacrolimus at time of transplantation (% of recipients)	0.1	0.1	1.6	1.6	2.6	1.9	6.1	9.4	13.9	4.1
Clinical acute rejection in first year (% of recipients)										
Living donor	35.8	34.9	34.6	30.8	29.9	31.7	27.0	25.8	23.4	30.4
Cadaveric donor	43.3	45.5	44.6	40.2	38.9	37.8	33.3	28.6	23.9	37.3

\*With the exception of the number of transplants, all overall values are means.

†The value is the degree of reactivity to random donor cells.

no studies have demonstrated that a reduction in the incidence of acute rejection is associated with a reduction in the incidence of chronic rejection and an improvement in long-term graft survival. We conducted a study to determine the rate of long-term renal-allograft survival, as estimated on the basis of the projected half-life, and to identify factors that may affect graft survival.

### METHODS

We studied all adults with available follow-up data who underwent primary or repeated transplantation with a graft from a living or cadaveric donor in the United States between 1988 and 1996. The data were obtained from 276 renal-transplantation centers through the United Network for Organ Sharing.

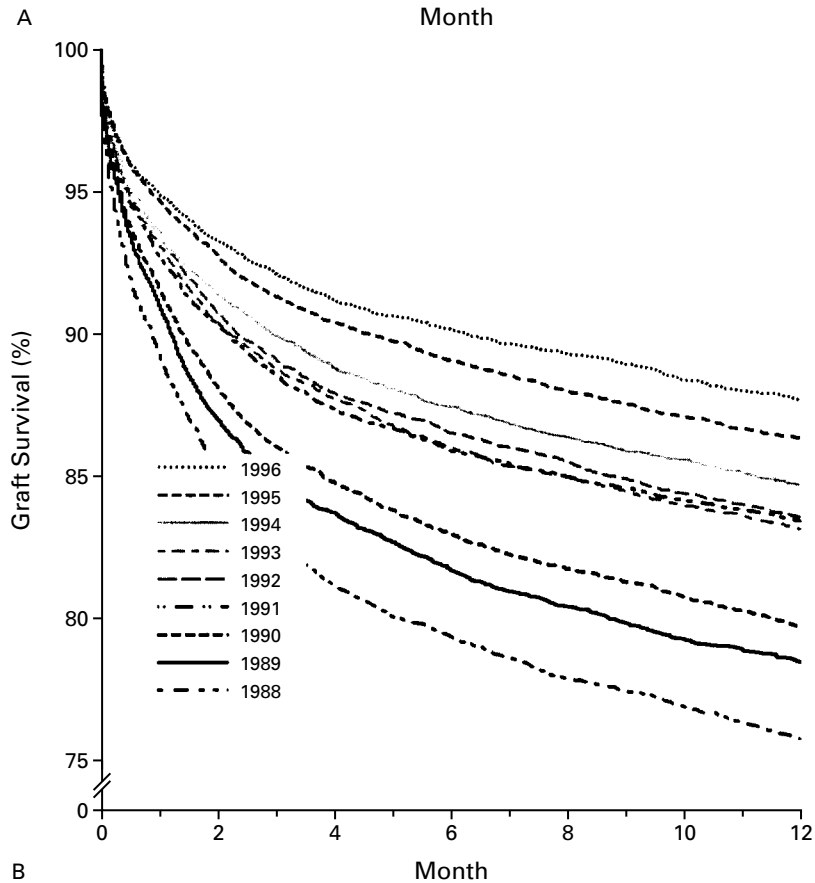
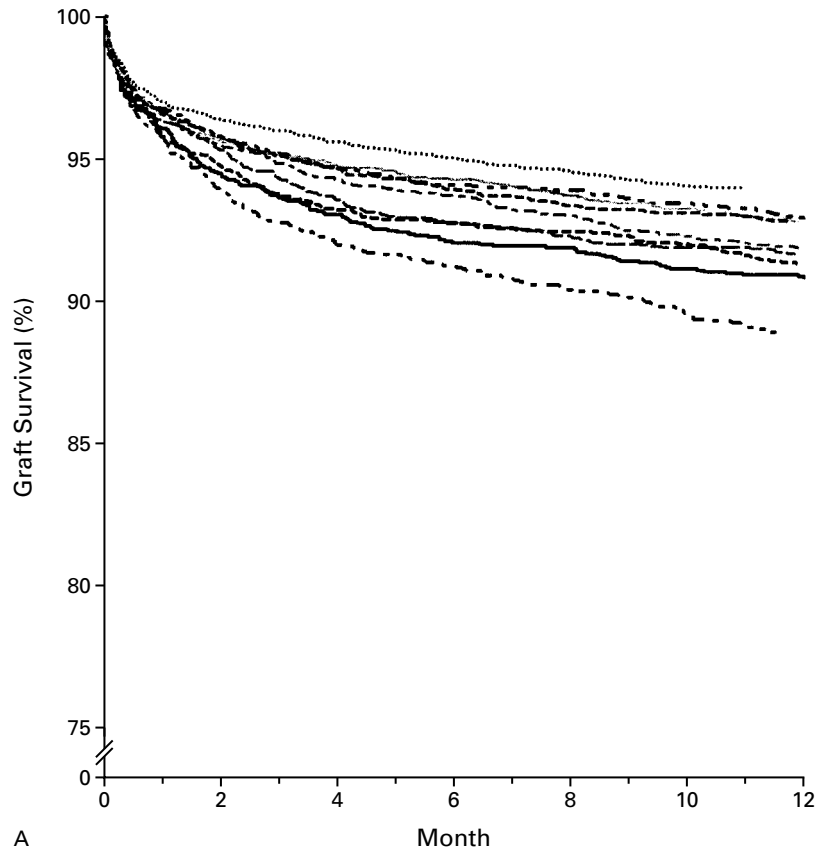
The Kaplan–Meier method was used to estimate the survival of the transplants for each year.<sup>10</sup> A maximum-likelihood estimate of the projected half-life (median value) was calculated with the assumption of exponentially distributed graft-survival times. Graft loss was defined by the need for permanent dialysis, repeated transplantation, or death. We performed an additional analysis after censoring data on patients who died while their grafts were functioning. The analysis of short-term graft survival (defined as survival for one year or less) included all patients who received transplants between 1988 and 1996, and the analysis of long-term graft survival (defined as survival for more than one year) included all patients who received transplants between 1988 and 1995. To avoid a reporting bias associated with rapid notification of critical events (death or graft failure) and delayed notification of continued survival, follow-up time was restricted to two years before November 1998.

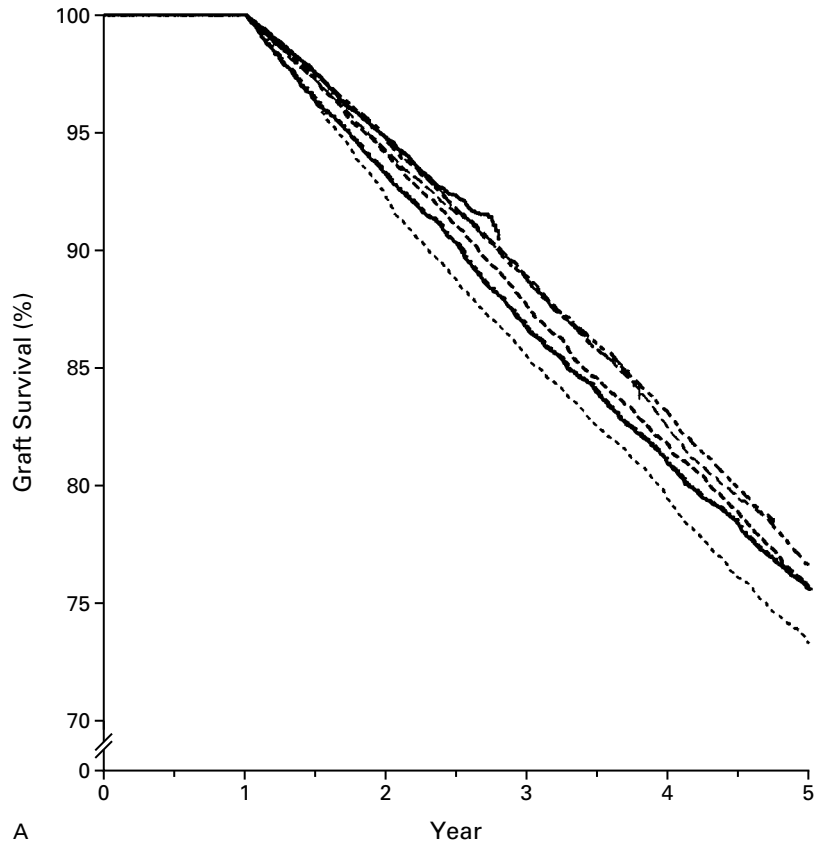
The demographic characteristics used for covariate-adjusted analyses included the age of the recipient and of the donor at the time of transplantation and the recipient's race and sex. Transplant-related variables included the source of the organ (living or cadaveric donor), the titer of serum panel-reactive antibody in the recipient, the duration of cold ischemia, and the extent of HLA matching. We also included a variable for the volume of transplantations at the center. Clinical variables at the time of transplantation were the presence or absence of multiple-organ transplantation, previous transplantation or blood transfusion, and an associated medical condition.

Post-transplantation variables included the presence or absence of delayed graft function; treatment with antibody such as muromonab-CD3, antithymocyte globulin as induction therapy, or mycophenolate mofetil and tacrolimus for the prevention of acute rejection; and clinical acute rejection within one year after transplantation. Mean values were used for missing data. Clinical acute rejection was defined as confirmed or suspected acute rejection in patients who received antirejection treatment.

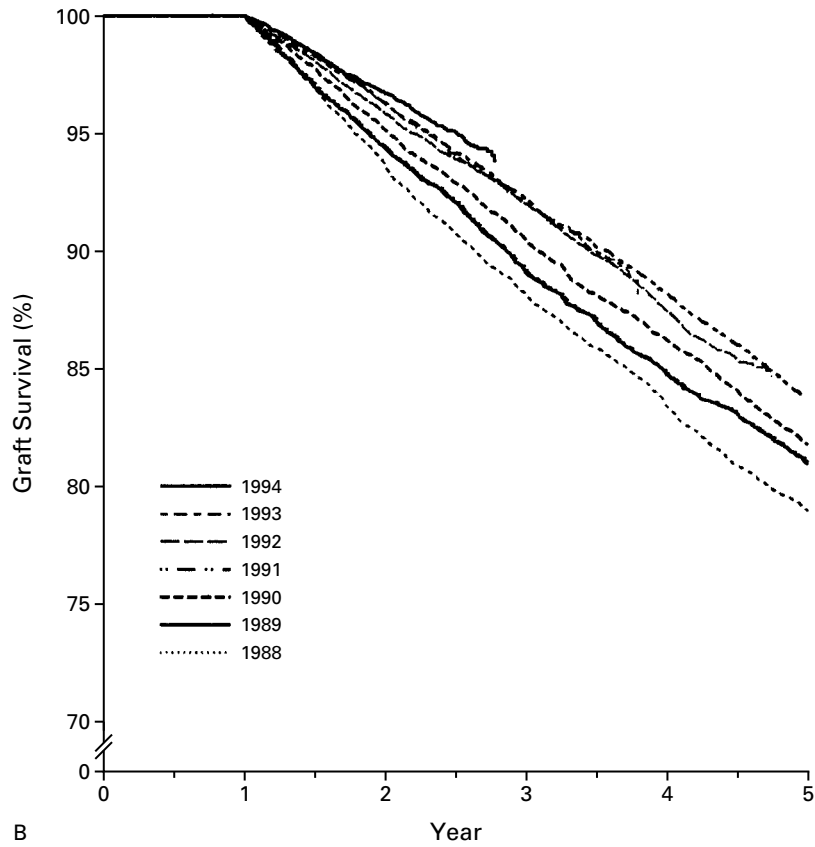
The variables listed above were included in models with the year of transplantation as an indicator variable, in order to assess their effect on short-term and long-term graft survival. The statistical analysis was performed with the use of proportional-hazards regression models with adjustment for potential prognostic variables; post-transplantation variables were included only in the long-term analysis. The relative hazard of graft failure was estimated separately for the first year (short-term survival) and more than one year

**Figure 1 (facing page).** Kaplan–Meier Estimates of Graft Survival during the First Year after Transplantation for Grafts from Living Donors (Panel A) and Cadaveric Donors (Panel B) from 1988 to 1996.





A



B

**TABLE 2.** PROJECTED HALF-LIFE OF RENAL TRANSPLANTS, 1988 TO 1995, BEFORE AND AFTER THE CENSORING OF DATA ON PATIENTS WHO DIED WITH FUNCTIONING GRAFTS.

DONOR	PROJECTED GRAFT HALF-LIFE (95% CI)*							
	1988	1989	1990	1991	1992	1993	1994	1995
<b>Before censoring</b>								
Living	12.7 (11.5–13.9)	15.0 (13.5–16.5)	14.8 (13.3–16.3)	14.8 (13.3–16.4)	16.9 (14.8–18.9)	16.7 (14.5–19.0)	21.8 (17.7–26.0)	21.6 (13.8–29.3)
Cadaveric	7.9 (7.6–8.3)	8.7 (8.3–9.0)	8.8 (8.4–9.2)	9.7 (9.2–10.1)	9.6 (9.1–10.1)	10.3 (9.7–11.0)	11.0 (10.1–11.9)	13.8 (11.2–16.4)
<b>After censoring</b>								
Living	16.9 (15.1–18.7)	20.8 (18.3–23.2)	19.9 (17.5–24.1)	21.5 (18.8–24.1)	21.9 (18.9–24.9)	22.9 (19.3–26.5)	35.0 (26.5–43.5)	35.9 (19.3–52.5)
Cadaveric	11.0 (10.5–11.5)	12.0 (11.4–12.6)	12.5 (11.8–13.2)	14.5 (13.6–15.4)	14.2 (13.2–15.1)	15.1 (13.9–16.3)	17.4 (15.5–19.3)	19.5 (15.1–23.8)

\*CI denotes confidence interval.

(long-term survival) after transplantation. The annual change is reported as 1 minus the relative hazard per year.

**RESULTS**

All 93,934 renal transplantations performed in the United States were included in the study. Selected variables at the time of transplantation and transplant-related and post-transplantation variables are shown in Table 1.

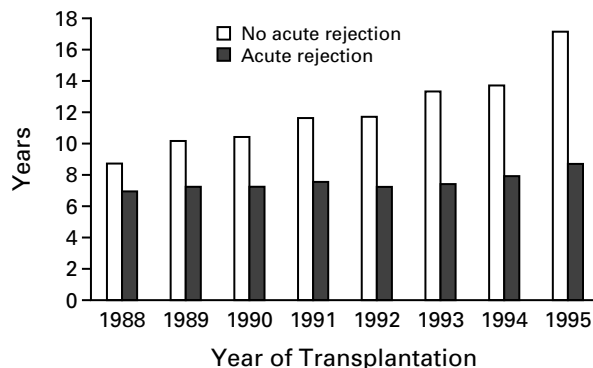
Figure 1 shows Kaplan–Meier estimates of survival one year after the transplantation of a renal graft from a living or cadaveric donor during the period from 1988 to 1996. The survival rate at one year for transplants from living donors increased from 88.8 percent in 1988 to 93.9 percent in 1996, an increase of 5.1 percentage points. The corresponding rates for transplants from cadaveric donors were 75.7 percent and 87.7 percent, with an increase of 12.0 percentage points from 1988 to 1996. After the censoring of data for transplants in patients with incomplete follow-up (15,386 transplants), a total of 13,455 transplants had failed and 65,093 were still functioning one year after transplantation. Of the 65,093 functioning transplants, 12,562 (19.3 percent) subsequently failed. The long-term survival of cadaveric transplants that were functioning at the end of the first year is shown in Figure 2. The survival curves are shorter for transplants received in recent years than for those received earlier because there are fewer follow-up data for recent years. The curves show a continuous trend toward improved long-term graft survival in recent years.

Table 2 shows the projected half-life of all transplants, with and without the censoring of data for patients who died with functioning grafts, from 1988 to 1995. The projected half-life for transplants from

living donors was 12.7 years in 1988 and 21.6 years in 1995, representing an increase of 70 percent in 1995. After the censoring of data for patients who died with functioning grafts, the respective values were 16.9 years in 1988 and 35.9 years in 1995, representing an increase of 112 percent. The projected half-life for transplants from cadaveric donors was 7.9 years in 1988 and 13.8 years in 1995, representing an increase of 75 percent in 1995. After the censoring of data for patients who died with functioning grafts, the respective half-lives were 11.0 years and 19.5 years, representing an increase of 77 percent. The difference in the projected half-life between 1988 and 1995, with and without the censoring of data for patients who died with functioning grafts, was greater for transplants from living donors (42 percent) than for those from cadaveric donors (2 percent). The projected half-life for transplants in nonblack recipients increased from 9.1 years to 13.3 years from 1988 to 1995, an increase of 46 percent. The corresponding values for transplants in blacks were 5.1 years and 7.2 years, an increase of 41 percent.

Clinical acute rejection within the first year after transplantation had a detrimental effect on long-term graft survival (Fig. 3). Among patients who had an episode of clinical acute rejection, the projected half-life of cadaveric transplants was 7.0 years in 1988 and 8.8 years in 1995, an increase of 25 percent. In contrast, the projected half-life for cadaveric transplants in patients who did not have an episode of clinical acute rejection in the first year after transplantation was 8.8 years in 1988 and 17.9 years in 1995, an increase of 103 percent. After the censoring of data for patients who died with functioning grafts, the projected half-life increased from 9.1 to 11.9 years, an increase of 31 percent, in patients who had an episode of clinical acute rejection, and from 12.9 to 27.1 years, an increase of 110 percent, in those who did not have acute rejection. The proportion of transplants from cadaveric donors who were more than

**Figure 2 (facing page).** Kaplan–Meier Estimates of Cadaveric Graft Survival after One Year for All Grafts from Cadaveric Donors (Panel A) and after the Censoring of Data for Patients Who Died with Functioning Cadaveric Grafts (Panel B).



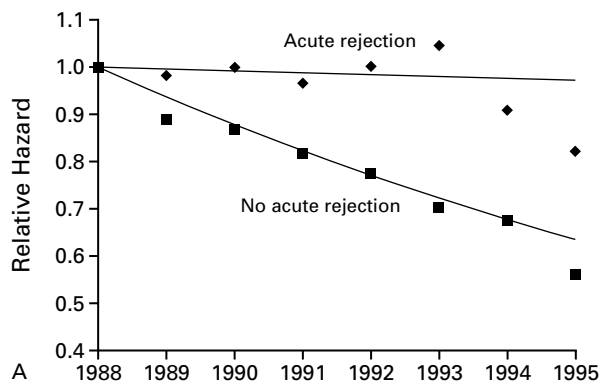
**Figure 3.** Projected Half-Life of Grafts from Cadaveric Donors According to the Presence or Absence of Clinical Acute Rejection during the First Year after Transplantation.

50 years old increased from 10.4 percent in 1988 to 18.2 percent in 1996 (Table 1), and the projected median half-life of the grafts from these donors was 5.5 years in 1988 and 7.5 years in 1995, an increase of 36 percent.

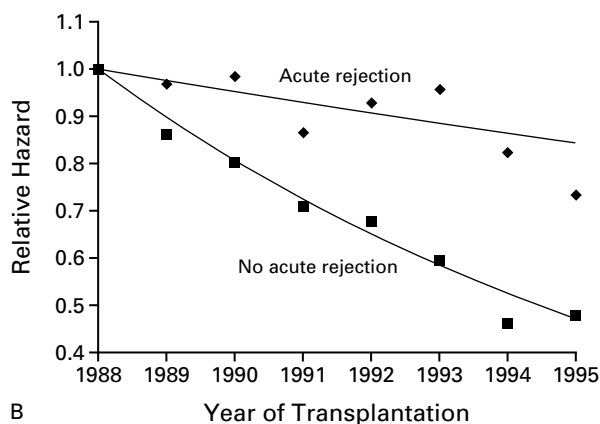
After adjustment for the prognostic variables listed in the Methods section, the reduction in the relative hazard of graft failure during the first year after transplantation was 7.1 percent per year from 1988 to 1996 ( $P < 0.001$ ). After the first year, the mean reduction in the relative hazard of graft failure was 4.2 percent per year ( $P < 0.001$ ). The analysis was further stratified according to whether there was clinical acute rejection during the first year after transplantation. Among patients with an episode of clinical acute rejection, the reduction in the relative hazard of graft failure was 0.4 percent per year ( $P = 0.57$ ), whereas among those without acute rejection, the reduction in the relative hazard was 6.3 percent per year ( $P < 0.001$ ) (Fig. 4A). After the censoring of data for patients who died with functioning grafts, the reduction in the relative hazard of graft failure was 2.4 percent per year among patients who had an episode of clinical acute rejection ( $P = 0.005$ ) and 10.2 percent per year among those who did not have acute rejection ( $P < 0.001$ ) (Fig. 4B).

### DISCUSSION

Renal transplantation is the treatment of choice for patients with end-stage renal failure. Since the first report on renal transplantation, in 1955, there has been a continuing effort to improve the short- and long-term survival of renal transplants.<sup>11</sup> Graft failure during the first year after transplantation is due to acute rejection, primary nonfunction, graft thrombosis, recurrent kidney disease, or the death of a patient with a functioning graft. The main obstacle to the success of transplantation has been acute rejection. The introduction of cyclosporine in the early 1980s



**A**



**B**

**Figure 4.** Relative Hazard of Graft Failure after the First Year, According to the Presence or Absence of Clinical Acute Rejection in the First Year.

For all grafts, the reduction in the relative hazard of graft failure was 0.4 percent per year for patients with acute rejection and 6.3 percent per year for those without acute rejection (Panel A). After the censoring of data for patients who died with functioning grafts, the reduction in the relative hazard was 2.4 percent per year for patients with acute rejection and 10.2 percent per year for those without acute rejection (Panel B).

for the prevention of acute rejection reduced the rate of acute rejection and significantly improved graft survival at one year.<sup>3</sup> Nonetheless, even after the advent of cyclosporine-based immunosuppressive therapy in the mid-1980s, the prevalence of acute rejection after the transplantation of a kidney from a cadaveric donor ranged from 40 to 60 percent.<sup>12</sup>

Although treatment with cyclosporine has improved the rate of graft survival at one year, it has not substantially improved long-term graft survival.<sup>7</sup> We found that from 1988 to 1996, the survival rate at one year improved by 5.1 percentage points for transplants from living donors and by 12.0 percentage points for those from cadaveric donors. The reduction in the relative hazard of graft failure within one

year after transplantation was 7.1 percent per year, after adjustment for multiple variables. We also found that since 1988, there has been steady improvement in long-term graft survival. The improvement is not due to a reduction in the number of deaths, because the results of analyses performed before and after the censoring of data for patients who died with functioning grafts were similar.

Chronic rejection remains the most important cause of graft loss in long-term studies. The prevalence of chronic rejection ranges from 10 percent to 80 percent, depending on the duration of follow-up.<sup>9,13,14</sup> The most important predictor of chronic rejection is a previous episode of acute rejection.<sup>13,15-18</sup> Apart from clinical acute rejection, patients may have subclinical rejection that causes ongoing immunologic injury, leading to chronic rejection.<sup>19,20</sup> Black transplant recipients are more likely than white recipients to have chronic rejection, a finding that may be due to differences in immunologic responsiveness, HLA matching, or control of blood pressure.<sup>21-23</sup> Our study shows an improvement in the projected half-life of grafts in blacks as well as in other patients, but graft survival in blacks continues to be poor.

Our study also shows the decline in the relative hazard of graft failure during long-term follow-up — a reduction of approximately 4.2 percent per year from 1988 to 1995. Among patients who had one or more episodes of clinical acute rejection, the reduction in the relative hazard of graft failure was only 0.4 percent per year, as compared to 6.3 percent per year among those who did not have clinical acute rejection. Among patients who underwent transplantation in recent years, the projected half-life of grafts in patients who did not have an episode of clinical acute rejection was nearly double that for those who did have such an episode. Thus, it seems clear that the reduction in the rate of acute rejection from 1988 to 1996 has resulted in lower rates of graft failure due to chronic rejection. These results indicate that the long-term toxicity of cyclosporine does not blunt its short-term benefit.<sup>24</sup>

Data from various studies make it clear that immunologic factors such as higher values for serum panel-reactive antibody, prolonged cold-ischemia time, and nonimmunologic factors, including delayed graft function, can increase the incidence of acute rejection and reduce long-term graft survival.<sup>25-27</sup> We found that the cold-ischemia time and the titer of serum panel-reactive antibody in recipients have decreased over time, which may have contributed to the lower rate of acute rejection in the recent cohorts of patients, but there has been little change in either the racial distribution of recipients or the extent of HLA matching.

The limited availability of organs has prompted many centers to use organs from older cadaveric donors. Kidneys from such donors have a lower survival rate than those from younger cadaveric donors.<sup>2,28</sup>

From 1988 to 1996, the proportion of grafts from older cadaveric donors increased from 10.4 to 18.2 percent.

The introduction of mycophenolate mofetil and tacrolimus in the 1990s has also been associated with a reduction in the incidence of acute rejection during the first year after transplantation.<sup>5,6</sup> This finding does not explain the results reported here, however, because the overall proportion of patients in our study who received either drug was small. The drugs may have been introduced at a later date after transplantation, but in the group of patients who had an episode of clinical acute rejection — those who may have been switched to these drugs — there was no substantial improvement in the graft half-life. Long-term follow-up studies of treatment with mycophenolate mofetil in the United States have not revealed any effect of this drug on graft survival or the prevalence of chronic rejection.<sup>29</sup> Higher doses of cyclosporine improve graft survival,<sup>30</sup> and the increased bioavailability of cyclosporine has been correlated with a reduction in episodes of acute rejection.<sup>31</sup> However, data on cyclosporine doses and blood concentrations were not available for the patients in our study, so we could not determine whether this factor contributed to the improvement in graft survival.

In conclusion, between 1988 and 1996, there was a steady improvement in the short-term and long-term survival of renal grafts from both living and cadaveric donors.

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## CORRECTION

**Improved Graft Survival after Renal Transplantation in the United States, 1988 to 1996**

*To the Editor:* It was heartening to learn that the outcome of kidney transplantation has improved since 1988, as reported by Hariharan and colleagues (March 2 issue).<sup>1</sup> When one discusses treatment options with a patient, however, it is frequently helpful to estimate the chance that a kidney graft will be functioning 5 or 10 years after surgery. With other diseases, such as cancer and heart disease, data on survival at five years, determined from the date of the intervention, are widely available. Although appropriate scientifically, the approach that Hariharan and colleagues used — analysis of graft survival at one year and then derivation of the half-life of the graft, with events during the first year excluded — does not readily provide such information.

On the basis of the data before censoring, reported by Hariharan and colleagues in Table 2 of their article, we estimate that the survival rate at five years for cadaveric grafts transplanted in 1988 was approximately 56 percent. In contrast, the projected five-year survival rate for cadaveric grafts transplanted in 1995 was approximately 74 percent. Thus, the modest improvement in long-term graft survival (approximately 6 percent at five years) shown in Figure 2 of the article translates into a large improvement in long-term survival (an absolute difference of 18 percent), when differences during the first year are factored into the analysis.

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*To the Editor:* We were pleased to see that long-term renal graft survival increased from 1988 to 1996 in the United States. However, a few points in the report by Hariharan et al. need clarification. It would have been useful if they had stated the percentage of patients who were receiving cyclosporine each year. Without this information, it is difficult to attribute any improvement in short-term or long-term graft survival to treatment with cyclosporine, since the drug was being used even in 1988. Second, there was a substantial decrease in the mean value for serum panel-reactive antibody in the recipients during the study period. Was the decrease due to a decreased rate of blood transfusion, and to what extent does the decrease explain the improvement in long-term graft survival? Third, the authors state, “The

projected half-life for transplants in nonblack recipients increased from 9.1 years to 13.3 years from 1988 to 1995, an increase of 46 percent. The corresponding values for transplants in blacks were 5.1 years and 7.2 years, an increase of 41 percent.” However, according to Table 2 of the article, the overall projected half-life of grafts from living donors (i.e., in blacks and nonblacks) transplanted in 1995 was 21.6 years, and the overall half-life of cadaveric grafts was 13.8 years. Even if only patients with cadaveric transplants are considered, how could the projected half-life in 1995 be 13.3 years for whites and 7.2 years for blacks but 13.8 years overall?

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The authors reply:

*To the Editor:* Parikh and Ellison correctly note that from the patient's perspective, improvement in the short-term and long-term survival of renal transplants is additive and directly affects the prognosis.

We found that there has been steady improvement in the survival of renal transplants since the introduction of cyclosporine in the 1980s. Over 90 percent of the 1988 cohort received cyclosporine, and therefore the improved outcomes in later cohorts could be related to changes in doses or timing.<sup>1</sup> However, the improvement is probably not related to cyclosporine alone. The causes of this improvement cannot be pinpointed, but they include a reduction in episodes of acute rejection and improvements in the control of hypertension and in the prevention and management of infections. The decrease in panel-reactive antibodies is probably due to a reduction in the transfusion rate (15 percent with more than 10 prior transfusions in 1988 vs. less than 4 percent after 1992), a decrease that is correlated with the introduction of erythropoietin.

Sam and Leehey raise a question about discrepancies between the text and Table 2 of our article with respect to the improvement in the projected half-life of transplants in blacks, nonblacks, and all recipients. The projected half-life values given in the text (7.2 years for blacks and 13.3 years for nonblacks) were for 1994, not 1995; the value of 11.0 years for all recipients of cadaveric transplants, shown in Table 2, is correct.

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