Cardiac Transplantation in Man

VI. Prognosis of Patients Selected for Cardiac Transplantation

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Between July 1967 and March 1970 we considered 49 patients with end-stage heart disease for cardiac transplantation. After complete cardiologic evaluation to exclude all patients who could benefit from other modes of therapy, 34 patients were selected as potential recipients. Twenty of these underwent cardiac transplantation; 14 did not. While receiving optimal medical therapy before a donor became available, two of the 14 nontransplanted patients improved significantly and were removed from the waiting list. The other 12 died within 2 to 90 days (average, 28 days) while awaiting a suitable donor. Clinical data on both groups are presented. Actuarial statistics show a survival after cardiac transplantation, in our series, of 55% at 3 months, 43% at 6 months, and 36% at 1 year. Six patients are alive at more than 1 year after transplantation. In a select group of carefully evaluated patients cardiac transplantation appears to prolong life.

ALTHOUGH more than 160 patients have received cardiac allografts in medical centers throughout the world since December 1967, the early experience with this procedure has produced few long-term survivors (1). It is important, therefore, that patients considered for this operation undergo careful cardiologic evaluation with particular attention to establishing the exact etiology of the cardiac disorder, quantitating the severity of the circulatory alterations, and estimating the prognosis for survival. We describe our experience at Stanford University Hospital, Palo Alto, Calif., with evaluating and selecting cardiac transplant recipients and describe the subsequent clinical courses of those patients selected as potential recipients. The operative procedure and postoperative program for managing patients undergoing cardiac transplantation at Stanford have been described extensively in other publications and will not be presented in this communication (2-5).

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Patient Selection

Patients referred as possible cardiac transplant recipients are generally those considered by their physicians to have end-stage heart disease that cannot respond further to conventional medical or surgical therapy. These patients are studied carefully to determine the precise cause and quantitative severity of their heart disease. Evaluation includes complete medical history, physical examination, and appropriate laboratory studies. In most patients right heart catheterization and retrograde left heart catheterization with exercise studies are carried out. Coronary arteriography is performed on patients with coronary artery disease when the patient's clinical status permits it. Left ventricular angiography is done in patients with suspected localized dysfunction of the ventricle, aneurysm of the left ventricle, or unexplained and refractory heart failure.

Those patients whose comprehensive cardiologic evaluation suggests a poor prognosis for more than short-term survival are studied further to detect diseases of other organs or psychiatric illness that would preclude a successful postoperative recovery. Acceptance into the transplant program as a potential recipient then depends on informed consent of the patient after we have thoroughly discussed with the patient and his family the patient's disease, the

Table 1. Accepted Recipients Not Undergoing Cardiac Transplantation

Case Number	Age	Cardiac Diagnosis	Length of Known Disease	Length of Severe Disease	ECG*	Cardiac Catheterization**		
						PAW or LAM	PVR	Cardiac Index
	yr		*yr*	*months*		*mm Hg*	*units*	*liters/min/m²BSA*
1	28	Radiation cardiomyopathy	7 months	2	IVCD	17	1.2	2.0
2	51	Cardiomyopathy	2	5	IVCD	—	—	—
5	20	Cardiomyopathy	2	½	LVH, LAE	14	1.0	2.9
6	9	Cardiomyopathy	2	12	LVH, RVH	25	2.5	4.3
8	51	Cardiomyopathy	2	6	LVH, LAE	27	6.0	1.3
9	47	Coronary artery disease	4	5	AMI	29	6.2	1.6
12	46	Coronary artery disease	6	½	AMI, IMI	27	4.9	1.6
15	53	Coronary artery disease	4	7	AMI, IMI	23	6.1	1.1
17	20	Cardiomyopathy	6	2	LVH, LAE	25	7.8	1.4
19	59	Coronary artery disease	12	8	LAD	25	1.3	2.8
26‡	30	Cardiomyopathy	2	2	LAE, IVCD	28	4.0	1.9
28	50	Cardiomyopathy	7	7	IVCD, PAT, flutter	31	12.0	1.0
30	55	Coronary artery disease	7	8	IVCD, LAD	—	—	1.0
34	43	Coronary artery disease, acute myocardial infarction	10	1	IMI, IVCD	—	—	—
Average	§43.6		5.2	4.3		24.2	5.2	1.67
	‡42.5		4.9	4.26		24.6	5.0	1.69

* IVCD = intraventricular conduction delay; LVH, RVH = left and right ventricular hypertrophy; LAE = left atrial enlargement; AMI = anterior myocardial infarction; IMI = inferior myocardial infarction; LAD = left axis deviation; LBBB = left bundle-branch block; ALMI = anterolateral myocardial infarction; ASMI = anteroseptal myocardial infarction; PAT = paroxysmal atrial tachycardia.
** PAW = pulmonary artery wedge; LAM = left atrial mean; PVR = pulmonary vascular resistance.

prognosis without transplantation, and the present experience with cardiac transplantation at Stanford. The postoperative course is discussed in detail; we emphasize full commitment of the patient and his family to the procedure by insisting that the patient either reside in the San Francisco Bay Area or move to the area after successful cardiac transplantation, so that meticulous postoperative follow-up will be possible. Once the patient has accepted his status and is a definite candidate, lymphocyte typing is performed for future matching with potential donors (6, 7). Acceptance as a potential recipient is based on review of the objective data and the patient's clinical condition at that time. The medical cardiology team continues to evaluate the patient clinically to ensure that there is no unexpected improvement while the patient is receiving optimal medical therapy. Should such improvement of the patient's clinical condition occur, he may be removed from the active recipient list. This alternative is especially important in patients with cardiomyopathy and its occasional unpredictable course.

Results

Forty-nine patients were considered as candidates for cardiac transplantation at Stanford between July 1967 and March 1970. After complete cardiologic evaluation, as described, 34 patients were selected as potential recipients. For this report these patients are divided into two subgroups: those not receiving cardiac allografts because of unavailability of a suitable donor and those who were matched with an appropriate donor and received an allograft.

In the former group, consisting of 14 patients, 12 died awaiting transplantation. Relevant clinical data for these 14 patients are summarized in Table 1. Ten of the 14 were men, 3 were women, and 1 was a child. Adult ages ranged from 20 to 59, with an average age of 42.5 years. The average length of known cardiovascular disease in these patients was 4.9 years, with an average interval of incapacitating symptoms of 4.3 months. It should be emphasized that although these patients do not compose a true control group to compare with patients who have undergone cardiac transplantation, they do represent a series of similar patients considered to have end-stage irremediable heart disease by the same criteria as the group that was transplanted.

Two patients initially selected as potential recipients were subsequently removed from the active list

Table 1 (Continued)

Angiogram	Coronary Arteriogram†	Blood Urea Nitrogen	Bilirubin	Date Considered	Date Accepted	Date of Natural Death	Days Awaiting Transplant
		mg/100 ml					
—	—	15	0.4	7/26/67	11/15/67	1/13/68	49
—	—	21	2.1	1/1/68	1/2/68	1/7/68	5
↓ Left ventricular contraction	—	16	1.1	5/4/68	5/10/68	5/27/68	17
↓ Left ventricular contraction	—		—	6/10/68	—	—	—
—	—	32	1.6	7/25/68	8/1/68	9/9/68	40
↓ Left ventricular contraction	Occl R, 3+ LAD, Circ	19	1.1	8/2/68	8/9/68	11/1/68	84
—	—	32	0.8	9/17/68	9/17/68	9/24/68	7
—	—	57	0.9	9/21/68	9/27/68	9/27/68	1
↓ Left ventricular contraction	—	13	1.6	10/12/68	10/28/68	12/2/68	35
↓ Left ventricular contraction	Occl LAD, 3+ R, Circ	12	0.7	11/13/68	11/18/68	12/24/68	36
↓ Left ventricular contraction	—	19	1.0	4/13/69	5/1/69	8/21/69‖	111
↓ Left ventricular contraction	—	45	4.0	5/5/69	7/14/69	8/17/69	34
—	—	40	0.9	8/15/69	8/23/69	9/7/69	15
—	—	50	0.7	1/21/70	1/21/70	2/1/70	12
		29.3	1.4				27.9
		28.5	1.4				34.3

† Occ = completely occluded, R = right coronary artery; 3+ = 90% occlusion; LAD = left anterior descending; Circ = left circumflex coronary artery; 2+ = 60% occlusion; 1+ = less than 25% occlusion.
‡ = Averages of adult patients including the patient in Case 26, who was removed from active recipient list (*see* text).
§ = Averages of adult patients who died awaiting transplantation.
‖ = Date removed from active recipient list.

of patients awaiting transplantation. One patient (Case 6) was a 9-year-old girl with a history of chronic heart failure and intermittent pulmonary edema, requiring repeated hospitalizations. Evaluation with left ventriculography and cardiac catheterization showed findings consistent with a cardiomyopathy. The patient's clinical course subsequently stabilized, and her name was removed from the list of potential recipients. Without any significant change in her clinical course the patient died suddenly 14 months later. This patient's young age presented unique problems, both in assessing the severity of her

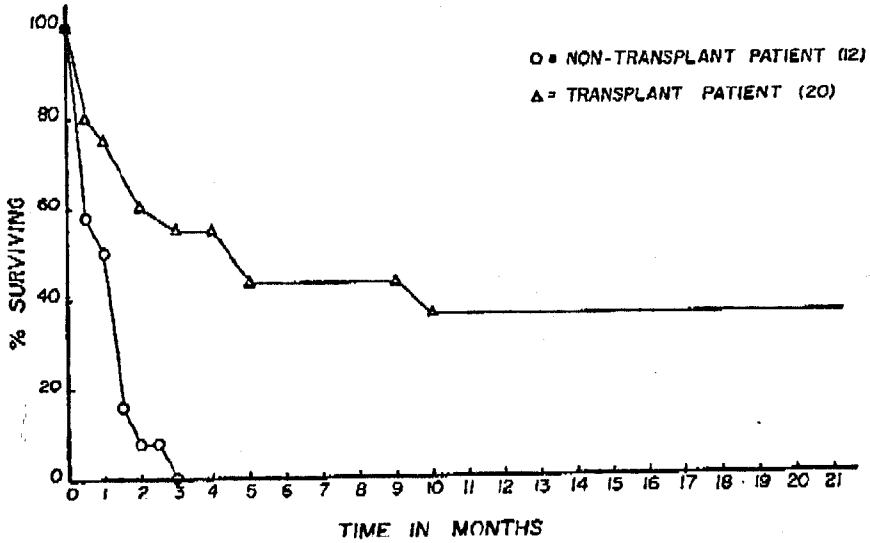

Figure 1. Survival calculated by the life table method. Survival for transplanted patients is calculated from the time of operation; survival of nontransplented patients is calculated from the time of selection for transplantation.

heart disease and in determining indications for operation. The other patient (Case 26), a 35-year-old man, when initially evaluated, presented with severe congestive heart failure with ascites and anasarca secondary to cardiomyopathy, which had been totally unresponsive to conventional therapy during a 2-month observation period. After being selected as a recipient he improved with comprehensive medical therapy, to which he had been unresponsive previously. This prompted his removal as an active recipient candidate 3 months after selection. His clinical condition is now quite stable 16 months later, and he is being followed closely in the Cardiology Clinic. Of the 12 patients who died while continuously at risk of dying or transplantation, the maximum survival after selection was 84 days, with an average survival of 27.9 days (Figure 1). Death was in each case caused by progressive heart failure. Addition of the adult patient who was initially selected and at risk of transplantation or dying but then removed from the active waiting list at 3½ months, as described above, increases the average "survival" to 34.3 days.

The clinical data and pertinent laboratory results

Table 2. Patients Undergoing Cardiac Transplantation

Case Number	Age	Cardiac Diagnosis	Length of Known Disease	Length of Severe Disease	ECG*	Cardiac Catheterization			Angiogram†
						PAW or LAM	PVR	Cardiac Index	
	yr		*yr*	*months*		*mm Hg*	*units*	*liters/min/m² BSA*	
3	54	Cardiomyopathy	10	2	LAD, IVCD	—	—	1.6	—
4	40	Coronary artery disease	7	13	ASMI	28	8	1.7	↓ Left ventricular contraction
10	42	Coronary artery disease	12	36	ASMI	10	1	3.2	↓ Left ventricular contraction
7	51	Coronary artery disease	4	12	IMI	20	1.3	2.7	↓ Left ventricular contraction
11	48	Coronary artery disease	2	1	AMI	28	2.7	1.3	↓ Left ventricular contraction, left ventricular aneurysm
13	54	Coronary artery disease	9	4	AMI, IMI	23	7	1.5	↓ Left ventricular contraction
14	54	Coronary artery disease	5	12	AMI, IMI	34	4.9	1.3	—
18	56	Coronary artery disease	10 months	7	AMI, IMI, ventricular tachycardia	12	—	—	↓ Left ventricular contraction
16	49	Cardiomyopathy	3	8	Abnormal ST-T	25	2.4	1.7	—
21	43	Coronary artery disease, acute myocardial infarction	3	3 weeks	Acute AMI	—	—	—	—
20	55	Coronary artery disease	18	4	AMI	20	—	2.9	↓ Left ventricular contraction, 2+ myocardial infarction
22	42	Cardiomyopathy	7	7	IVCD	—	—	—	↓ Left ventricular contraction, 2+ aortic insufficiency
23	58	Coronary artery disease	15	4	AMI, IVCD	28	8.5	1.2	↓ Left ventricular contraction
25	33	Coronary artery disease	4	12	AMI, IMI	—	—	—	↓ Left ventricular contraction
24	51	Coronary artery disease	½	6	ALMI	28	1.5	1.6	↓ Left ventricular contraction, 2+ myocardial infarction
27	54	Coronary artery disease	11	6	LBBB, LAE	36	16.0	1.0	↓ Left ventricular contraction, 2+ myocardial infarction
29	46	Cardiomyopathy	3	3	IVCD, LAE	39	10.3	1.1	2+ myocardial infarction
31	64	Cardiomyopathy	6	12	IVCD, LBBB	24	5.4	1.8	↓ Left ventricular contraction
32	40	Coronary artery disease	2.5	5	ALMI	26	3.3	1.2	↓ Left ventricular contraction
33	48	Coronary artery disease, ventricular aneurysm	½	3	ALMI, LAE	36	4.0	1.9	Large left ventricular aneurysm
Average	49.1		6.15	7.89		26.1	5.45	1.69	

* *See* Table 1 for explanation of ECG abbreviations.
† *See* Table 1 for explanation of angiogram and arteriogram abbreviations.

obtained on the first twenty patients who have undergone cardiac transplantation at Stanford are presented in Table 2. At present seven of these patients are alive. Survival from the actual date of operation, calculated by actuarial methods, is 55% at 3 months, 43% at 6 months, and 36% at 1 year (Figure 1). Six patients are alive more than 1 year after transplantation; the patient who has survived the longest in our series was transplanted more than 20 months ago.

The clinical data presented in Tables 1 and 2 show no significant differences between the transplanted and nontransplanted patients in respect to age, sex, primary cardiac diagnosis, or duration of severe cardiac symptoms. Cardiac catheterization and angiographic findings, as well as laboratory data, are similar in the two groups.

Survival for the group not undergoing transplantation is calculated from the date of acceptance as a potential recipient to the date of death, except for the two patients removed from the waiting list. Survival in the transplanted patients is calculated from the date of operation to the date of death, or to the present time. The time awaiting transplantation is

Table 2. (Continued)

Coronary Arteriogram†	Blood Urea Nitrogen	Bilirubin	Date Considered	Date Accepted	Date Transplanted	Date of Postoperative Death	Cause	Days Awaiting Transplant	Days Survived‡	Months Survived‡
	mg/100 ml									
—	26	3.3	1/5/68	1/6/68	1/6/68	1/21/68	Hepatic failure	1	15	0.5
—	20	1.8	3/7/68	3/28/68	5/2/68	5/5/68	Pulmonary hypertension	34	3	0.1
Occl R, LAD	17	0.6	6/11/68	8/11/68	8/22/68	10/7/68	Infection-rejection	11	46	1.5
Severe diffuse disease	12	0.5	3/29/68	7/12/68	8/31/68			49	[608]	[20.3]
—	19	1.2	7/30/68	8/15/68	9/9/68	1/14/68	Hepatitis	24	127	4.2
Occl Circ, 3-+ LAD	17	1.9	9/16/68	9/19/68	10/5/68	12/5/68	Infection	16	61	2.0
—	22	0.5	9/10/68	9/20/68	10/26/68			36	[552]	[18.4]
Occl Circ, 3-+ LAD	19	0.4	10/15/68	11/1/68	11/20/68	12/14/68	Cerebral vascular accident	19	24	0.8
—	14	2.2	10/23/68	10/26/68	11/22/68	8/30/69	Chronic rejection	26	281	9.3
—	50	2.3	1/30/69	2/1/69	2/8/69			7	[447]	[14.9]
—	28	1.6	1/18/69	1/29/69	2/18/69	2/25/69	Acute rejection	17	10	0.3
—	37	2.9	3/14/69	3/18/69	3/29/69	5/7/69	Acute rejection	11	39	1.3
—	33	2.8	3/11/69	4/11/69	4/13/69			2	[383]	[12.8]
Occ R, Circ, 3-+ LAD	18	2.3	4/23/69	4/28/69	5/22/69			24	[344]	[11.5]
Occ LAD, 1-+ Circ	40	0.8	4/12/69	4/25/69	7/16/69	11/29/69	Chronic and acute rejection	81	136	4.5
—	12	2.0	5/28/69	6/7/69	6/16/69	6/17/69	Pulmonary hypertension	69	1	0.03
—	19	1.5	8/12/69	8/19/69	9/3/69			15	[240]	[8.0]
—	65	2.0	8/25/69	8/29/69	9/14/69	11/13/69	Infection	17	60	2
Severe 3-vessel disease	17	0.9	12/2/69	12/12/69	1/9/70			22	[118]	[3.9]
—	12	0.5	11/23/69	11/27/69	1/16/70			50	[104]	[3.5]
	24.8	1.6						26.5	All 199.9 +66.9 [349.3]	All 5.99 +2.23 [11.65]

‡ + = patients who died; [ ] = patients alive.

not included in the survival figures for transplanted patients, and the average time awaiting transplant (26.5 days) approximates the average survival of patients without transplant (27.9 days). The range of days awaiting transplant (1 to 81 days) is likewise comparable with the life expectancy of nontransplanted patients.

Discussion

The present results of clinical cardiac transplantation at Stanford suggest that significant qualitative improvement in and prolongation of life is possible in certain selected patients with end-stage, irremediable heart disease. Our experience demonstrates that the cardiologic indications for operation, as well as other medical factors influencing postoperative survival, must be carefully evaluated. All patients presented in this report had end-stage heart disease and appeared to be in imminent danger of dying at the time of medical and hemodynamic evaluation. Twenty of these patients underwent cardiac transplantation; fourteen did not.

One patient who presented unique problems in planning therapeutic management (Case 33) was a 48-year-old man who, 3 months before referral, suffered a massive myocardial infarction and subsequently developed a ventricular aneurysm. Evaluation showed a massive left ventricular aneurysm involving the entire apex of the left ventricle and a resting cardiac index of 1.9 liter/min per m^2 body surface area. Careful study of the cardiac catheterization data and left ventricular angiograms suggested that aneurysectomy would leave insufficient myocardium to provide a functional left ventricle. Surgery was therefore postponed until a standby donor became available. Exploration at operation showed that the entire anterolateral and apical portions of the left ventricle, including the anterior half of the interventricular septum, were included in the aneurysmal formation. The remaining portion of the left ventricle exhibited poor contractions. Cardiac transplantation was thus selected as the only available means of therapy for this patient; the availability of a donor heart probably saved his life.

Recent experience with direct coronary artery bypass surgery (8, 9) has allowed us to expand standard operative indications considerably for patients with severe coronary artery disease. These new operative approaches emphasize the importance of full angiographic evaluation of the coronary arteries and left ventricle in patients who have known or suspected coronary artery disease. At present, however, patients exhibiting diffusely poor and asynchronous left ventricular contractions and evidence of extensive fibrosis, in addition to severe diffuse coronary disease, may be considered for cardiac replacement. Once myocardial scar has been formed, increasing the coronary flow by vein bypass grafts probably cannot restore ventricular capacity.

Messmer and Leachman's experience (10) regarding survival of nontransplanted candidates appears to differ from ours. Of their 42 potential recipients who were not transplanted, 14 survived more than 3 months, and 12 of the patients were still alive at the time of their report. Their reported mean survival at 74 days included many patients who had not yet died or undergone transplantation, giving a mortality rate of 35%. Their transplanted patients had a mean survival time of 89 days (including the waiting period). Thus, improved survival could be considered as 15 days as a result of transplant. This appears to contrast with our ongoing experience of essentially 100% mortality rate in patients awaiting transplant and an average survival of 42 days if transplantation was not accomplished. At Stanford overall mortality in cardiac transplantation decreases to 35%, with average survival of 200 days and six survivors for more than 1 year. With a small series of patients statistics can only partially help to assess progress in such a new field as cardiac transplantation. Although the 6-week survival rates are similar, 14 of 42 potential recipients in Messmer's report survived longer than 3 months without transplantation. Except for the two previously discussed patients who improved on medical therapy (Cases 6 and 26), none of the 34 patients accepted at Stanford as a potential recipient has survived longer than 3 months without transplantation. It should be emphasized that technical differences exist between Messmer's data and ours—namely, they include the time awaiting transplant in their survival times, and they mention no measures taken to remove patients from the active recipient list. These specific differences and the general absence of published reports of criteria for recipient selection by other centers make it impossible to compare our data with the worldwide experience. The short survival of nontransplanted patients, in addition to rendering it impossible to have a true control group, confirms the severity of the underlying heart disease present in patients fulfilling our criteria for recipient selection for cardiac transplantation.

Figure 1 compares the survival of the 12 nontransplanted candidates with the survival of transplanted patients. Survival statistics themselves do not convey the improved quality of life afforded long-term surviving patients after successful transplantation, but this aspect of the procedure is a significant factor in

assessing postoperative results. The activity and well-being of successfully transplanted patients stand in clear contrast to the terminal existence of nontransplanted candidates.

To date none of the preoperative studies performed in these patients has served to predict accurately the long-term postoperative results. Apparently, however, severe secondary organ dysfunction related to chronic congestive heart failure may contribute significantly to early postoperative morbidity and mortality. Our general experience with postoperative infectious complications in patients managed on a broad immunosuppressive program also emphasizes that significant preoperative infection is a relative contraindication to transplantation (11, 12).

Although further experience is necessary to confirm the indications for recipient selection and to define those diagnostic criteria that preclude successful cardiac transplantation, we believe that our experience to date justifies continuing clinical investigation of this procedure in carefully evaluated and highly selected patients.

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Does Cardiac Transplantation Prolong Life?

A Reassessment

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Analysis of survival data from two studies on cardiac transplantation suggests that the assignment method used favored the transplanted group and that the improved survival in the transplanted group could be explained solely in terms of selection bias. Several alternative experimental designs are proposed.

Two recent reports of experience with cardiac transplantation conclude that this procedure appears to prolong life in carefully selected patients (1-2). In our opinion, the data do not warrant even this guardedly optimistic assessment, since the observed differences in survival can be explained in terms of probable selection bias.

Methods and Results

Figure 1 contains four survival curves calculated by applying the actuarial methods in Cutler and Ederer (3) to the data of Messmer and associates (1) and Clark and colleagues (2). All time is measured in months from when the patient was first accepted as a potential transplant recipient. Percent survival is plotted on a log scale so that the force of mortality (slope of the log survival plot) can be seen. The data of Messmer and associates (1) (hereafter called study 1) are represented by solid symbols, and those of Clark and colleagues (2) (hereafter called study 2) are represented by open symbols. For both studies circles depict survival of the transplanted group and triangles that of the nontransplanted group. The median survival of the transplanted group exceeds that of the nontransplanted group by about 4 months in study 1 and 8 months in study 2. We now ask if this difference in survival is an effect of treatment or only reflects bias in the assignment of subjects to the transplanted or nontransplanted groups.

In both study 1 and study 2 the patient is assigned to the nontransplant group by default. That is, a potential transplant recipient becomes a member of the nontransplant group because no suitable donor becomes available before the potential recipient dies (or before the end of the study). We now present a hypothetical example that illustrates how this assignment method biases the results in favor of the transplanted group.

Dr. Edgeworth decided to conduct a study of the efficacy of cardiac transplantation, and he accepted three patients, A, B, and C into his pool of potential recipients. Patient A was agonal with, at most, days to live; Patient B was a bad operative risk, having had debilitating cardiac disease for years; and Patient C was comparatively healthy. Unfortunately no allograft became available for 40 days. Patient A had died 3 days after acceptance into the recipient pool; he was assigned to the nontransplanted group. Patient B, too, had died, after 31 days, and was assigned to the nontransplanted group. Only Patient C survived the 40-day waiting period. He received a transplant and had an uncomplicated postoperative course until he died during a rejection crisis 100 days later (which was 140 days after his initial acceptance as a potential transplant recipient). Although Dr. Edgeworth was tempted to compare the survival of Patient C, the transplantee, with that of Patients A and B, the nontransplanted group, he reasoned as follows:

"My assignment procedure introduced important

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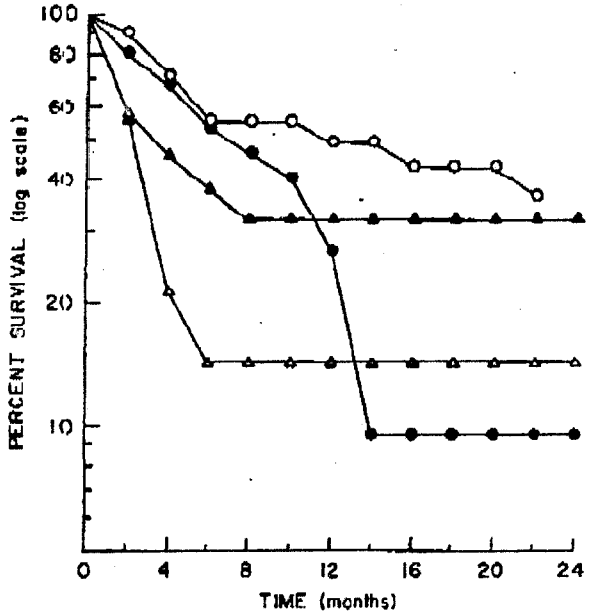

Figure 1. Percent survival (log scale) versus time in months from initial acceptance into the recipient pool. Solid symbols depict data of Messmer and associates (1) and open symbols those of Clark and colleagues (2). Circles represent transplanted groups and triangles nontransplanted groups. (All 14 patients in the nontransplanted group described by Clark are included.)

biases. After all, A, the sickest patient, never had much chance to be transplanted anyway. And in general, most of my sickest subjects will get thrown into the nontransplanted group. Also, this waiting period will tend to filter out the bad risks like Patient B, so I'll only have to operate on comparatively healthier patients like C. This should at least reduce my early mortality, and maybe it will help in the long run too. And if I had randomized the initial assignment to the transplant group, surely some of the patients in this group would have died while awaiting a donor. In effect I have given my transplantee survival curve an artificial boost by guaranteeing survival at least to the time of transplantation."

This example emphasizes the types of biases inherent in the assignment method used in study 1 and study 2 by depicting a very inhomogeneous recipient pool and a long waiting period. But, although this example was chosen mainly to highlight the biases, the biases are real enough, and it is the experimenter (not the gadfly) who must prove that adequate precautions were taken to eliminate bias. Indeed, since the average waiting time was about 20 days in study 1 and 26 days in study 2, and since the initial attrition rate is so high (Figure 1), these biases are undoubtedly important.

We summarize Dr. Edgeworth's objections as follows: [1] the survival time of the nontransplanted group is shorter than would have been observed with a random assignment method, because the method used assigns an unfair proportion of the sicker patients to this group (bias); [2] the survival time of the transplanted group is longer than would have been observed with a random assignment method for two reasons. First, an unfairly large number of good-risk patients have been assigned to this group, introducing a bias. Second, the patients in this group are guaranteed (by definition) to have survived at least until a donor was available, and his grace period has been implicitly added into the survival time of the transplanted group.

Discussion

Messmer and co-workers (1) and Clark and colleagues (2) conclude that cardiac transplantation "appears" to increase survival in suitably selected patients. Figure 1 shows an "apparent" increase in median survival (in comparing transplanted and nontransplanted groups) of about 4 months for study 1 and 8 months for study 2. Our analysis of selection bias allows us to state with some assurance that these figures overestimate the "true increase" in survival attributable to transplantation. (By "true increase" we mean the increase in survival that would have been observed had the original pool of potential recipients been *randomly* assigned to the transplantation and nontransplantation groups at the outset.) Part of the apparent increase in survival (perhaps 2 to 4 weeks) is a waiting period before transplantation. Part of the apparent increase is probably caused by selection bias, as described above. Indeed, the transplantation procedure may contribute nothing to the survival increase in the transplanted group. Clark pointed out that the nontransplanted group was not a "true control" group, but he failed to note, as we have, that the patient assignment method used in these studies almost certainly introduced a selection bias that favored survival of the transplanted group.

Since the difference in survival times between the transplanted and nontransplanted groups is not striking, and since a part of this difference probably results from selection bias and not from treatment method, further large-scale evaluation of the efficacy of cardiac transplantation may not be deemed necessary. Should such studies be planned, however, we suggest three alternative approaches, each answering a slightly different question.

One could pair potential recipients at their mutual time of acceptance as transplant candidates and immediately—and at random—assign one to the transplant group and one to the control group. Survival should be measured from time of acceptance into the

study. This study would measure the overall effectiveness of transplantation therapy, including the practical difficulty of waiting for a suitable donor.

If one were interested in assessing survival from the time of transplantation (rather than from the time of admission as a transplant candidate), one could randomly assign an available heart to one of a pair of living recipients (perhaps that pair that had waited longest). Then the survival of the two groups, transplantees and control subjects, could be measured from the time of operation. This design partially answers the ethical imperative of giving available hearts on a first-come, first-served basis, and it is acceptable if one is prepared to disregard histocompatibility studies in assigning the heart.

If suitable histocompatibility matching is a *sine qua non* of transplantation, one could define several cohorts of transplant candidates, each cohort consisting of subjects accepted as candidates at approximately the same date. A newly available heart would then be assigned to a cohort on a next-in-line basis. From that cohort the two members with best histocompatibility to the donor would be selected, and one would be randomly chosen for transplantation, the other becoming a control. Survival would be measured from the time of operation. If the cohorts were large enough, the two best matches would almost certainly be "suitable" for transplantation.

Each of the previous designs has distinctive desirable (and undesirable) features. The first measures the effectiveness of transplantation in current practice, and the last two the effectiveness of the operation itself in prolonging life. The second alternative partially preserves a first-come, first-served queuing discipline. The third alternative sacrifices this discipline to assure suitable histocompatibility. Other designs are conceivable, but they must all share with these three the feature of randomization to guard against selection bias.

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