HEART TRANSPLANTATION

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CONTENTS

Introduction

Thirteen and a half years ago Christiaan Barnard performed the first human heart transplant (1). The patient lived only eighteen days before dying from a pseudomonas pneumonia. However, a month later Barnard performed a second operation. This recipient lived for nearly two years before dying from chronic rejection of the transplanted heart.

The initial enthusiasm following Barnard and Shumway's early cases heralded a wave of misplaced enthusiasm. Between 1968 and 1970, more than 100 transplants were performed by 58 teams in all parts of the world, and many surgical teams had their reputations tarnished by embarking on heart transplantation without a proper understanding of the complex issues involved. A combination of generally low survival rates and sensational publicity resulted in the work being abandoned in all but a few centers, specifically, Stanford University, the University of Cape Town, South Africa, the Medical College of Virginia and Hôpital de la Pitié, Paris, by the early 1970s.

During the past 2-3 years interest in heart transplantation has been revived because both the Stanford (2) and Cape Town (3) teams have reported 1 year survival rates in excess of 60%. These results are comparable to those achieved with cadaver kidney transplants (4). Heart transplantation has recommenced in England (5) with the blessing of the National Health Service after being outlawed for nearly a decade. Although the Secretary of the Department of Health and Human Services has not yet followed suit, there are now 8 centers in this country and 14 centers world-wide where heart transplantation is being actively pursued.

During the next hour I plan to discuss the factors that have made heart transplantation a feasible proposition at certain specialized centers and to indicate some of the problems that remain to be resolved.

I. PRE-CLINICAL HEART TRANSPLANTATION

Heart transplantation is performed in one of two ways: Orthotopic transplantation, which is placement of the heart in the normal intrathoracic position, or heterotopic transplantation, placement of the donor heart outside the normal intrathoracic position.

The first heart transplantation procedure was performed by Carrel and Guthrie in 1905 (6). They performed a heterotopic transplantation on a canine heart to the neck vessels of another dog. This transplanted heart beat for approximately two hours before clotting. During the next 55 years heterotopic cardiac transplants were placed in the neck, abdomen and thorax by a number of surgeons (7).

The next major contribution to heart transplantation was made in 1960 by Lower and Shumway (8, 9). They described a simple technique for orthotopic transplantation of the canine heart. The method they described entailed excision of the recipient heart at the level of the atrioventricular groove, thus leaving the majority of the left and right atria of the recipient in situ. The donor heart was then implanted by joining the atrial walls and septum to the corresponding recipient structures with a single continuous suture. This technique obviated the need for multiple posterior venous anastomoses (two caval and 4 pulmonary venous) and was faster, simpler and more effective. These investigators also used cold saline (4°C) for topical cooling of the donor heart to a myocardial temperature of 12 to 15°C. This provided protection for the ischemic organ until coronary reperfusion was established. In a series of 8 consecutive canine transplants, 5 of the recipient animals survived for 6 to 21 days. This canine model of orthotopic cardiac transplantation formed the basis for subsequent work on human transplantation in the late 1960s, and the basic surgical technique of orthotopic cardiac transplantation has not changed substantially since that time.

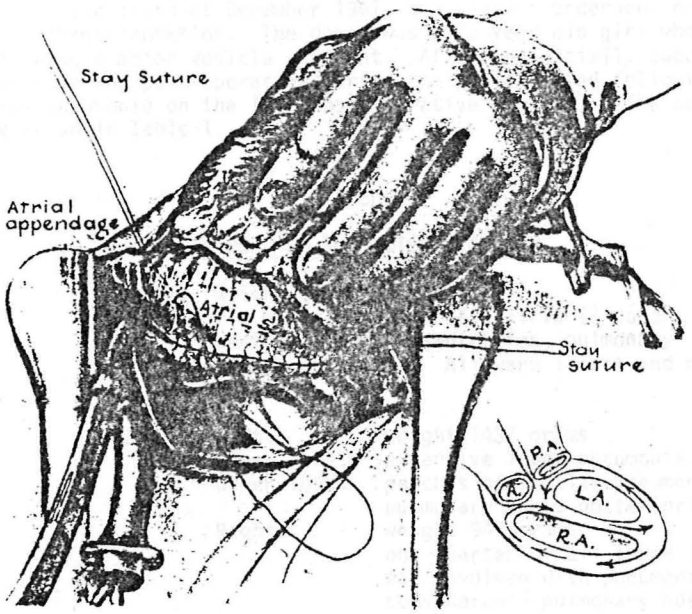

Figure 1. Implantation of a donor heart. The inset at the bottom right hand corner illustrates the remnant of the recipient heart and the great vessels. (from Reference 9).

II. HUMAN HEART TRANSPLANTATION

The first human heart transplant was performed in December, 1967 by Dr. Christiaan Barnard, at Groote Schuur Hospital in Cape Town (1). The recipient was a 54 year old white man with diabetes since 1955, and three previous documented myocardial infarctions with resultant intractable congestive heart failure despite maximal medical therapy. His electrocardiogram revealed evidence of old anterior and inferior infarction, first degree AV block and right bundle branch block. His chest x-rays revealed cardiomegaly with pulmonary congestion. Cardiac catheterization revealed a mean right atrial pressure of 10 mm Hg, pulmonary artery pressures of 75/38, mean pulmonary artery wedge pressure of 35 and an aortic pressure of 125/75 mm Hg. His cardiac output was 2.36 L/min. Selective coronary angiography revealed that the left anterior descending artery was attenuated and beaded throughout its course, the circumflex coronary artery was totally occluded and the right coronary artery was partially occluded 2 cm from its ostium. Left ventricular angiography revealed diffuse left ventricular impairment but no obvious mitral regurgitation (10).

On the third of December 1967, the patient underwent orthotopic heart transplantation. The donor was a 22 year old girl who died following a motor vehicle accident. After an initially successful operative and post-operative period the patient died following pseudomonas pneumonia on the 18th post-operative day (11). The autopsy data are shown in Table 1.

TABLE I

REPORT ON THE AUTOPSY OF L.W.

Heart:	Weight 350 grams. The major portions of 4 atria (2 donor, 2 recipient) and 2 ventricles, pulmonary artery and aorta. All were intact and not dilated.	
Lungs:	Left:	weight 1432 grams
	Lower lobe:	extensive lobar pneumonia
	Upper lobe:	patches of similar pneumonia pulmonary edema posteriorly.
	Right:	weight 943 grams one quarter of all three lobes was involved with pneumonia. considerable pulmonary edema.
	Pulmonary arteries:	dilated with considerable atheroma.
Remaining organs:		Unremarkable

(from Reference 11)

The second human heart transplantation (and first in the United States) was performed by Dr. Adrian Kantrowitz in an infant with tricuspid atresia, but the patient died within the first 12 hours. The first human heart transplant procedure at Stanford was performed on January 6, 1968. Since that time Stanford University has performed more than 200 human heart transplants, or approximately half of all the human heart transplants in the world (2). This group has consequently contributed most to the literature on this subject and I shall focus mainly on their experience in the field. However, I shall draw attention to some major differences between heart transplantation as it is performed at Stanford and other centers, where appropriate.

III. SELECTION OF THE RECIPIENT.

Greater care in the selection of a potential recipient is one of the factors that has contributed substantially to the improvement in results following heart transplantation. A fundamental prerequisite for selection is that the patient should have irremediable terminal cardiac disease, not amenable to any other form of cardiac surgery, and should have a poor prognosis for surviving the next 6 to 12 months. Documentation of a progressive recent decline in the patient's cardiac function facilitates such a projection. Selection criteria vary somewhat from one center to another but are in general fairly similar. Thus, while Columbia Presbyterian Hospital (12) has performed heart transplants in patients dependent on aortic balloon counterpulsation for support, the Stanford group have not regarded such patients as suitable recipients.

In the Stanford series the presenting diagnosis in 55% of the patients was congestive heart failure due to coronary atherosclerosis. The remaining patients had idiopathic, viral or rheumatic cardiomyopathy. Their medical regimen generally included digitalis, high dose furosemide, afterload reduction, antiarrhythmic agents and anticoagulants.

Based on their experience in over 200 cases, the Stanford team (2) has defined the following primary selection criteria, and absolute contraindications to heart transplantation:

TABLE II

PRIMARY RECIPIENT SELECTION CRITERIA

1. Irremediable terminal cardiac disease
2. Age under 55 years
3. Non-cardiac organ function: normal or reversible.
4. Absence of systemic illness that would limit recovery or survival.

(from Reference 2)

TABLE III

ABSOLUTE CONTRAINDICATIONS TO CARDIAC TRANSPLANTATION

1. Active infection
2. Recent pulmonary infarction
3. Diabetes mellitus (requiring insulin)
4. Pulmonary vascular resistance > 8 Wood units unresponsive to vasodilators.
5. Psychosis or mental deficiency, unrelated to low cardiac output or metabolic status
6. Drug addiction

(from Reference 2)

Many of these contraindications are self-evident. However, particular mention must be made of the pulmonary vascular resistance. The normal right ventricle is unable to function against a considerably elevated pulmonary vascular resistance. Transplantation of a normal right ventricle in this setting, results in acute early right heart failure, leading to generalized hypoperfusion, morbidity and mortality. It is thus generally held that a pulmonary vascular resistance in excess of 8 Wood units despite vasodilator therapy constitutes an absolute contraindication to orthotopic heart transplantation (but not necessarily to heterotopic heart transplantation). Measurement of the pulmonary vascular resistance in the potential recipient is thus crucial.

Many other additional criteria for selection have been used since 90% of referrals to the Stanford program have been refused transplantation. Thus, for example, in a typical year 234 patients were referred to the Stanford group but only 23 patients were finally accepted as potential recipients. (Table IV).

TABLE IV

REFERRALS FOR CARDIAC TRANSPLANTATION DURING A ONE-YEAR PERIOD (STANFORD UNIVERSITY)

	NO OF PATIENTS
Initial Evaluation	234
Rejected	188
Too old	66
Inadequate finances	10
Premature referral	7
Psychosocial problems	24
Other medical contraindications	45
Died while under consideration	32
Referred elsewhere for transplant	4
Further Evaluation	46
Rejected	23
Other therapy attempted	14
Died during evaluation	6
Psychosocial problems	2
Other medical contraindications	1
Accepted	23
Died while awaiting donor	3
Deselected	0
Transplanted	14
Waiting transplantation	6

(from Reference 13)

Psychosocial problems and other medical contraindications accounted for about 25% of the rejections. In addition, 41 of these patients died during the selection process or after being selected, 7 were considered premature referrals and other therapy was attempted in 14 patients. Potential recipients are also required to have strong emotional support from a family member and adequate financial support or insurance since Medicare may not cover this procedure.

Certain criteria have also been established for matching the donor-recipient pair (Table V).

TABLE V

MATCHING REQUIREMENTS WITH DONOR

1. ABO compatibility
2. Absence of donor-specific lymphocyte cytotoxicity
3. Appropriate size match
4. (HLA-A_2 compatibility)

(from Reference 2)

First, the donor and recipient must be ABO compatible - the "ABO-barrier" has not been crossed by any group performing heart transplants. Second, the lymphocyte cytotoxicity test (incubation of donor lymphocytes with recipient serum) is performed to avoid transplanting a donor heart into a recipient who possesses preformed antibodies against donor histocompatibility antigens. (Hastillo et al (14) of the Medical College of Virginia group feel this is not important). Third, the donor and recipient should preferably be of comparable size:a small donor heart should not be transplanted into a large recipient but a large donor heart may be transplanted into a small recipient, within certain limits. Finally, HLA typing has been found to be of little importance in heart transplantation, as opposed to kidney transplantation. The one possible exception relates to compatibility of the HLA-A_2 antigen (2).

IV. SELECTION OF A DONOR

Irreversible functional and structural changes occur in the normothermic heart after 20 to 30 minutes of anoxia (15). Removal of a donor heart after cessation of the heart-beat would thus lead to a damaged organ which would in turn jeopardize the survival of the recipient. Recognition and acceptance of the concept of brain death by the medical profession, the courts and the public has thus been a prerequisite to successful heart transplantation.

A. Brain Death

The "Harvard Criteria," a product of the ad hoc committee of the Harvard Medical School (16) to examine the definition of brain death, were outlined in August 1968 and have been accepted widely in the past years. The fundamental tenet is the following: "It is generally recognized that when satisfactory scientific evaluation has established that the brain is dead, that person is in fact dead, whether the heart or other vital organs continue to function or not".

Several other definitions of brain death have been proposed. Most recently The University of Arizona Health Science Center (2) proposed the following criteria:

TABLE VI

BRAIN DEATH CRITERIA (UNIVERSITY OF ARIZONA)

1. Deep coma with unresponsivity and unreceptivity
2. No movement (except deep tendon reflexes) and no spontaneous breathing.
3. No brain stem reflexes e.g. pupils are fixed in diameter and do not respond to sharp changes in the intensity of incident light; there is no corneal reflex; the vestibulo-ocular reflexes are absent; there is no reflex response to pharyngeal or bronchial stimulation.
4. A condition which can cause brain death must be diagnosed (depressant drug effects, profound metabolic disturbances or hypothermia must be excluded).
5. A "flat" EEG provides confirmatory evidence but is not essential.
6. Cerebral angiography showing absent blood flow for more than 30 minutes is acceptable evidence of brain death.

To avoid conflict of interest, these evaluations should be performed independently by 2 neurologists or neurosurgeons, (not by the cardiologists or cardiac surgeons) and repeated at intervals if necessary to exclude observer error.

Once the potential donor has been declared "cerebrally dead", and the patient's family has signed permission for removal of organs, the County Medical Examiner should be notified and the potential donor's case may be turned over to the surgical team. After organ removal, the respirator and all other supportive means are discontinued. The County Medical Examiner should again be informed and a complete autopsy should

then be performed.

B. Choosing an Appropriate Donor

Not all patients who meet the brain death criteria are suitable donors. In particular, the potential donor should be fully screened for any suggestion of a cardiac abnormality, infection or carcinoma. A detailed history should be taken and physical examination performed. Male cardiac donors should preferably be under the age of 35 and female donors under 40 years of age. In older potential donors, or where any question of cardiac disease in the donor is seriously raised, cardiac catheterization with coronary angiography is recommended. Most potential donors have suffered traumatic head injuries and initial evaluation should include a careful search for evidence of thoracic or cardiac trauma, including intracardiac injections during resuscitation procedures.

Abnormalities of the electrocardiogram are not uncommon in potential donors and may present a diagnostic dilemma, since many of these abnormalities may be secondary to the intracranial catastrophe, the effect of vasopressors or hypothermia. Griepp et al (17) reported ECG abnormalities in 22 cardiac donors, including abnormalities of ST segments (elevation and depression), atrial arrhythmias, prolongation of the QT interval, left ventricular hypertrophy, and intraventricular conduction delay. All these abnormalities were considered to be compatible with intracranial trauma, vasopressors or hypothermia. The Stanford group considers ECG diagnosis of previous myocardial infarction (on the basis of pathologic Q waves) an absolute contraindication to acceptance of the donor heart.

Once the potential donor has been fully screened and appears to have a normal, functioning heart, has no evidence of infection or carcinoma, is ABO compatible with the recipient, has a negative lymphocyte cross-match with the recipient serum, and is a reasonable size match with the recipient, he or she is usually accepted. The period of time between pronouncement of brain death and cessation of heart beat with maximal medical support may range from 6 hours to several days (18).

C. Support of the Donor

Brain death is usually accompanied by derangements of homeostatic control mechanisms. Thus, maintenance of cardiovascular stability in the potential heart donor requires meticulous attention.

Extreme fluctuations in arterial blood pressure occur with advancing intracranial hypertension (17) and severe hypotension usually accompanies tonsillar herniation and brain stem compression. Such physiologic abnormalities are related to neurologic injury and have been the subject of numerous investigations (19-23). In an analysis of the Stanford experience with potential cardiac donors, Griepp (24) found that decreases in arterial pressures to unobtainable levels at any time prior to

cardiectomy correlated with poor post-operative graft function. Thus, intensive care and vigorous support of blood pressure with fluid replacement and vasopressors, with appropriate invasive monitoring, is necessary. A second major problem following brain death is diabetes insipidus, which usually develops after infarction of intracranial contents and complicates management of fluid balance (13). Marked diuresis resulting from loss of pituitary function may be effectively controlled by administration of vasopressin, in doses of 10 units intramuscularly every 4 hours. This also contributes to maintenance of peripheral vasomotor tone. Despite meticulous attention to fluid homeostasis, and monitoring of arterial blood gases and electrolytes, pulmonary edema occurs in some patients. This may be neurogenically mediated (25). .Finally, patients with a total loss of brain function have loss of thermoregulatory mechanisms and usually require active warming to maintain body temperatures above 35° C (13).

Since pneumonia is a constant threat, particularly in the face of neurogenic pulmonary edema, the donor is commenced on high-dose broad-spectrum antibiotics after obtaining a tracheal aspirate, blood and urine cultures (2). Vigorous pulmonary care with frequent suctioning and position change, and positive end-expiratory pressure are also instituted.

D. Distant Heart Procurement

One of the major factors limiting heart transplantation is the availability of suitable donor hearts at the required time. This has led the Stanford group (13), the Medical College of Virginia group (26, 27) and others (5) to institute a program of distant heart procurement. Most of the hearts used by these teams are now obtained elsewhere. Hearts removed at a distant site are arrested by aortic root perfusion with a hyperkalemic electrolyte solution, placed in sterile containers filled with normal saline at 4° C, and surrounded with ice for the period of transport. The safe period for cardiac storage is not known. However, Thomas et al (26) from the Medical College of Virginia report a successful transplant following 5 hours and 20 minutes of ischemia, with an average ischemic time of 3 hours. Cardiotonic support of the graft with isoproterenol may be necessary. Several investigators have used "extracellular" (28) or "intracellular" (29) solutions for coronary perfusion in experimental animals to extend the preservation time to more than 24 hours, but the results are not sufficiently reliable for application to human transplantation. The feasibility, and indeed necessity, of distant graft procurement has thus been demonstrated and has contributed largely to the increasing number of heart transplants being performed.

V. ORTHOTOPIC CARDIAC TRANSPLANTATION

A. Operative Technique

Lower and Shumway (8, 9) described the key technical aspects of successful orthotopic cardiac transplantation. Procedures for removal of the donor heart and implantation in the recipient, as described by Baumgartner et al, (13) are illustrated in Figures 2 and 3.

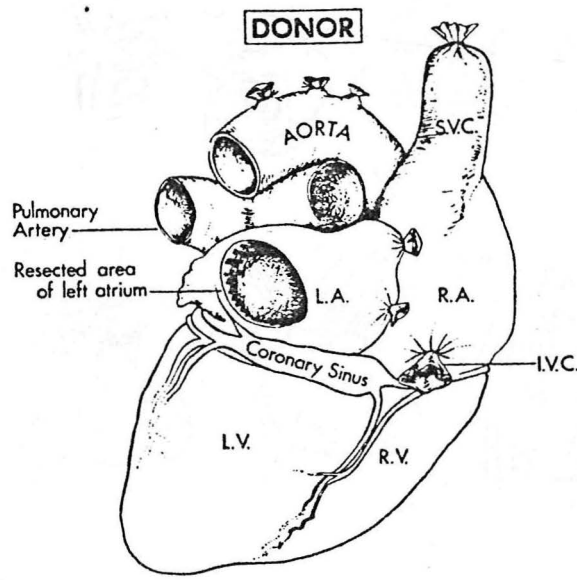

Figure 2. The donor heart (from Reference 58)

The donor heart is excised through a midline stenotomy incision. Heparin is administered intravenously to the donor heart in a dose of 300 u/kg, the heart is electrically fibrillated and the superior vena cava is doubly ligated and divided immediately below the entrance of the azygos vein. The inferior vena cava is also doubly ligated and divided, thus maintaining a relatively bloodless field for subsequent exposure. The aorta is then transected at the origin of the innominate artery and the pulmonary artery is transected at its bifurcation. The

heart is then elevated out of the pericardium and the pulmonary veins are divided individually at the level of their pericardial reflection. The donor heart is then immediately immersed in saline at 3 to 4° C and transferred to the recipient's operating room.

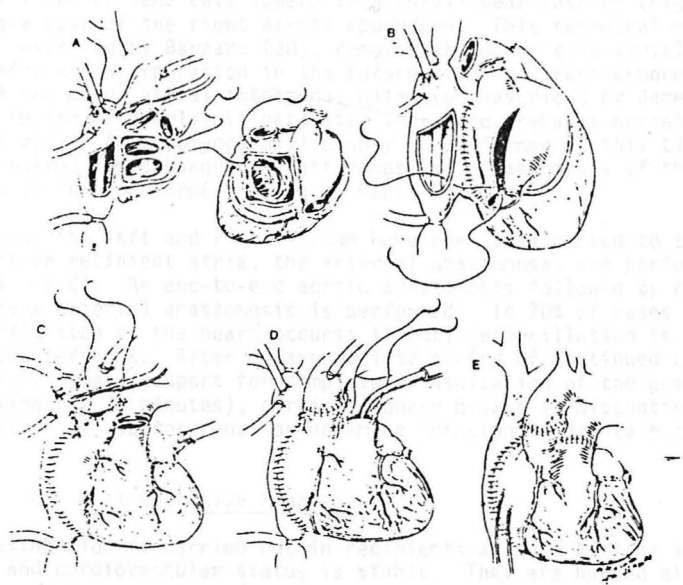

Figure 3. Operative technique for human orthotopic cardiac transplantation - see text for details. (from Reference 13).

Cannulation of the recipient for cardiopulmonary bypass is similar to standard techniques for most open cardiac surgical procedures. After institution of cardiopulmonary bypass and exclusion of the atrial cannulae with snares placed around the superior and inferior vena cavae (Fig 3, Panel A) the ascending aorta is cross-clamped and both great vessels are then divided at the level of the commissures of the semilunar valves. The aorta and main pulmonary artery are separated by division of the

visceral pericardium to provide maximum exposure and mobility. The atria are transected immediately above their atrio-ventricular grooves, but posterior to the level of the atrial appendages, since these structures constitute potential sites of post-operative thrombus formation.

Implantation of the graft begins with the left atrium (Fig 3, Panel B) using a running suture. As soon as feasible, continuous pericardial lavage with cold saline at 3 to 4° C is initiated during the left atrial anastomosis in order to maintain myocardial hypothermia. The donor right atrium is then opened by an incision extending from the orifice of the inferior vena cava upward in a curvilinear fashion (Fig 3, Panel B) into the base of the right atrial appendage. This technical modification, first described by Barnard (30), removes the donor sino-atrial node from proximity or incorporation in the suture line and, furthermore preserves two of the major atrial internodal pathways (described by James). The sinus rhythm of nearly all patients, therefore, remains normal post-operatively. An endomyocardial biopsy is performed at this time to serve as a control for subsequent graft biopsies. Anastomosis of the right atrium is then performed. (Fig 3, Panel C).

Once the left and right atrium have been anastomosed to their respective recipient atria, the arterial anastomoses are performed (Fig 3, Panels D & E). An end-to-end aortic anastomosis followed by end-to-end pulmonary arterial anastomosis is performed. In 70% of cases spontaneous defibrillation of the heart occurs: if not, defibrillation is accomplished with countershock. After an appropriate period of continued cardio-pulmonary bypass support for complete resuscitation of the graft (usually approximately 30 minutes), cardiopulmonary bypass is discontinued after initiation of isoproterenol or dopamine infusion to maintain cardiac output.

B. Post-operative Management

Extubation is carried out in recipients as soon as they are awake and cardiovascular status is stable. They are nursed either in an intensive care unit with full reverse isolation for a period of one to three weeks, or at some centers in a separate transplantation intensive care unit. Rehabilitation efforts, including physical therapy, occupational therapy and psychosocial counselling are commenced during the first post-operative week. After an initial period of 3 to 4 weeks in the intensive care unit, the patient is transferred to a less restricted area for an additional 2-4 weeks prior to discharge.

Immunosuppression in cardiac recipients is usually initiated immediately before operation. The Stanford therapeutic regimen, which is similar to that used by other major centers, is shown in Table VII.

TABLE VII

THERAPEUTIC REGIMEN FOR TRANSPLANT RECIPIENT (STANFORD)

1. Pre-operative Period
   - Azathioprine: 4 mg/kg p.o.
   - RATG: 2.5 mg IgG/kg per dose I.M.

2. Immediate Post-operative Period
   - Methylprednisolone: 500 mg I.V. immediately post-operatively, 125 mg I.V. 8 hourly x 3 doses
   - RATG: 200 mg IM every other day x 6 doses
     50-100 mg IM, alternated with IV, x 6 doses
   - Inotropic support: Isoproterenol, dopamine or dobutamine

3. When Oral Intake Starts
   - Prednisone: 100 mg p.o. per day → 1-2 mg/kg/day x 2 months → 0.25 mg/kg/day by 4-6 months
   - Azathioprine: 200 mg/day, according to bone marrow and hepatic tolerance
   - Dipyridamole: 400 mg/day
   - Aspirin: 325 mg/day

(from Reference 2)

The cornerstones of immunosuppressive therapy at present comprise corticosteroids, azathioprine and rabbit antithymocyte globulin (RATG). Immediately pre-operatively, the recipient is given azathioprine 4 mg/kg orally and RATG in a dose of 2.5 mg of IgG per/kg intramuscularly. In the immediate post-operative period methylprednisolone 500 mg intravenously is administered followed by 125 mg intravenously 8 hourly for 3 doses. RATG is then given in a dosage of 200 mg intramuscularly every other day for 6 doses followed by RATG 50 to 100 mg IM, alternating with IV for 6 doses. Inotropic support with isoproterenol, dopamine or dobutamine is maintained for as long as is deemed necessary and heparinization is commenced on the 3rd or 4th day.

When oral intake starts prednisone 100 mg p.o. per day is commenced and gradually tapered to 1 to 2 mg/kg per day by 2 months, and 0.25 to 0.5 mg/kg per day by 4 to 6 months. Azathioprine in a dosage of 100-200 mg/day is given according to bone marrow and hepatic tolerance. Dipyridamole 400 mg/per day and aspirin 325 mg per day are commenced and continued indefinitely.

(i) Anti-human Thymocyte Globulin

Heterologous antisera prepared in horses against either human splenocyte or thoracic duct lymphocytes were used as an immunosuppressive agent during the initial years of clinical transplantation. Subsequently,

human thymocytes were used as the antigen source because of evidence that these cells produced a more effective antibody (31-33). Bieber et al (34) compared the efficacy of rabbit antithymocyte globulin (RATG) and horse ATG in modifying allograft rejection. They showed that in those patients who received the rabbit preparation there was a significant delay in the onset of the first rejection episode and a significant decrease in total number of rejection episodes. Adverse reactions to both horse and rabbit ATG including fever, chills, hypotension and the development of significant infection with bone-marrow depression have occurred. In addition, since rabbit ATG must be administered intramuscularly, repeated injections often cause local inflammation and severe pain. The experience of both the Stanford group (13) and others suggests that when properly used, this agent can be an effective adjunct to azathioprine and corticosteroids.

(ii) Other Therapeutic Modalities

Kahn et al (36) suggested that total lymphatic irradiation and bone marrow infusion might allow decreased immunosuppressive drug therapy, and, perhaps actively create tolerance. However, this group's results with heart transplantation do not lend support to their suggestion. A number of other agents have been or are being evaluated for immunosuppression in animal heart allograft models. Cyclosporin A, a cyclic polypeptide extracted from 2 species of fungi, has attracted the most interest. This agent appears to suppress T-lymphocytes selectively (unlike corticosteroids) and may prevent graft rejection without increasing the recipients susceptibility to infection (37). However, major side-effects of this agent include hair loss, nephrotoxicity and hepatotoxicity (2). There also seems to be an increased incidence of malignant lymphoma in recipients (37 , 38). The search for an agent that will selectively inhibit T-cells, which mediate graft rejection, thus continues.

C. Physiology of the Transplanted Heart

The transplanted heart can support a virtually normal functional existence (39-41). Resting hemodynamics are normal in most instances, but the transplanted heart responds atypically to exercise (42 , 43), and to certain cardioactive drugs, due primarily to the lack of direct neural control of the allograft. Cardiac auto-transplantation in dogs and lower primates has suggested that graft reinnervation can occur within 30-120 post-operative days (44) and parasympathetic reinnervation usually precedes sympathetic reinnervation. Partial reinnervation has also been demonstrated in a few canine homografts; however, numerous studies of human cardiac recipients, extending to 8 years, have failed to demonstrate any evidence of post-operative reinnervation (13).

The surgical technique used in cardiac transplantation results in the retention of a small portion of the recipient's posterior left and right atria, including the sino-atrial (SA) node, which retains sympathetic and parasympathetic innervation. The transplanted heart rate is faster than normal (45). Since the transplanted heart no longer receives direct input from the autonomic nervous system, this observation is consistent with the concept that cholinergic influences predominate at the sinus node at rest in normal individuals. These observations have been further elucidated by electrophysiological studies (46), since electrical activity can be recorded from both the donor and recipient SA nodes. A reflex increase in recipient SA node rate occurs in response to atropine or hypotension while a decrease in recipient SA node rate occurs in response to induced hypertension; the donor heart's rate remains unchanged during these interventions (47).

(i) Response to Exercise

The Stanford group (48) recently reported the results of studies performed during exercise in 9 long-term (more than one year) survivors of orthotopic heart transplantation. Their observations confirmed and amplified the work of earlier investigators (49). The transplanted human heart is able to increase its cardiac output appropriately in response to an increase in oxygen demand. However, the manner in which this increase in cardiac output is achieved differs markedly from the normal physiological response: at low workloads of 45 watts, heart rate increases only slightly and the increment in cardiac output is produced mainly by an increase in stroke volume (Fig 4). End-diastolic volume increases and end-systolic volume falls.

Conversely, with strenous exercise to 90 watts, a further increase in cardiac output occurs, despite a fall in stroke volume, because of a marked increase in heart rate, which parallels a marked increase in circulating norepinephrine level (Fig 5).

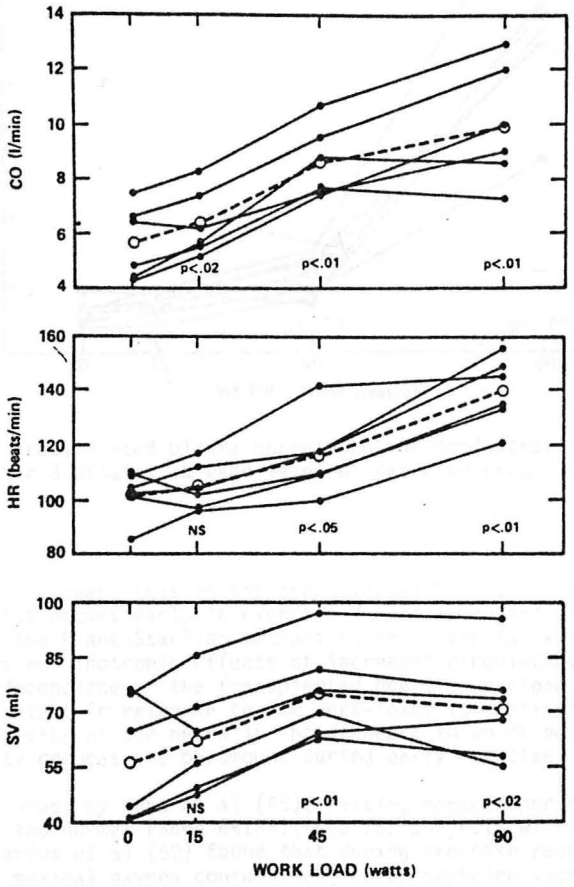

Figure 4: The response to exercise of patients with long-term orthotopic heart transplants. Cardiac output (CO) heart rate (HR) and stroke volume (SV) before and after 3 minutes of exercise at work loads of 15, 45 and 90 watts. (from Reference 48).

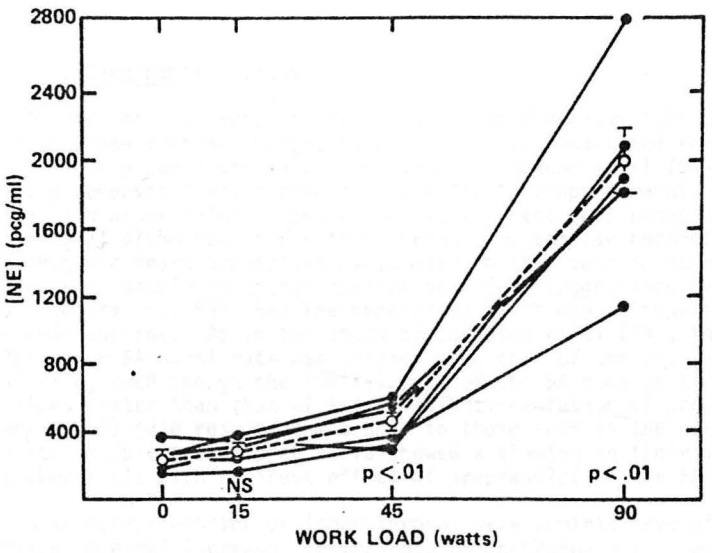

Figure 5. Fractionated plasma norepinephrine concentration (NE) before and after 3 minutes at each level of exercise (from Reference 48).

Thus, it appears that in the transplanted heart, an increase in cardiac output occurs early in exercise due to augmented left ventricular stretch and the Frank-Starling mechanism, and later in exercise due to chronotropic and inotropic effects of increased circulating catecholamines. The unique dependence of the transplanted heart on preload as a means of increasing output in response to low work-loads is distinctly different from the behavior of the neurally intact heart in which heart rate and contractility changes are paramount during early exercise.

In the study by Pope et al (48), resting norepinephrine levels were within the normal range established for subjects with intact neural control. Davies et al (50) found that during exercise requiring less than 75% of maximal oxygen consumption, norepinephrine increased slowly, then increased rapidly at the maximal and supramaximal loads in subjects with a normal heart. Patients with a denervated heart subjected to multistage exercise show a similar relation between norepinephrine levels and the work load imposed. Thus, both the increment in circulating catecholamines and the response to circulating catecholamines appears to be similar in normal subjects and patients with orthotopic heart transplants. The major difference in their response both to supine and erect exercise relates to the lack of direct cardiac innervation and the concomitant early increase in inotropic and chronotropic effects that are neurogenically mediated.

(ii) Cardioactive Drugs

Studies of a variety of cardiac drugs in the transplanted human heart indicate that adrenergic receptors remain intact and remain responsive to exogenously administered catecholamines. Cannom et al (51) demonstrated that the denervated heart responds normally to isoproterenol, norepinephrine and propranolol. Isoproterenol, a direct beta receptor agonist with minimal alpha receptor effects produced a similar chronotropic effect in orthotopic heart transplant recipients to that seen in normals. These workers were unable to either confirm or refute suggestions by other investigators (52, 53) that the denervated heart may be hypersensitive to norepinephrine. As in the study of Carleton et al (49), the response of the donor SA nodal rate was greater than that of the recipient's SA nodal rate, even though the initial rate of the SA node of the donor heart was faster than that of the recipient. Infusion of propranolol (7 mg/10 min) gave results comparable to those seen in the normal heart. Both the recipient and donor atria showed a slowing in their intrinsic rate compatible with a direct effect of propranolol on the SA node.

When norepinephrine or isoproterenol were administered after beta blockade, minimal increases in the rate of the donor atrium were produced. Similarly, the AH interval was not changed by infusion of norepinephrine or isoproterenol after propranolol, whereas this interval had previously been shortened by both agents. Competitive inhibition at the beta receptor site in both the SA and AV nodes best explains these findings.

VI HETEROTOPIC HEART TRANSPLANTATION

A. Operative Technique

Heterotopic heart transplantation refers to placement of an allograft heart in any position other than that normally occupied by the recipient heart. The use of auxillary hearts in the intrathoracic position was extensively investigated by Demikhov (54) during the 1950s and subsequently by other investigators (55-58). Barnard and Losman (58) reported on two patients in 1975 who had undergone heterotopic heart transplantation with the cardiac homograft placed in the right side of the recipient's chest. This procedure has been advocated by the Cape Town team since November 1974 (59, 60).

The initial procedure performed by the Cape Town group constituted a bypass of the left heart only so that the recipient's right heart continued its normal physiological role. The transplanted heart was connected in parallel with the left heart of the recipient, left atrium to left atrium, aorta to aorta, with the donor pulmonary artery anastomosed end-to-side to the recipient's right atrium. This procedure was designated a 'left ventricular bypass' (See Figures 6 and 7).

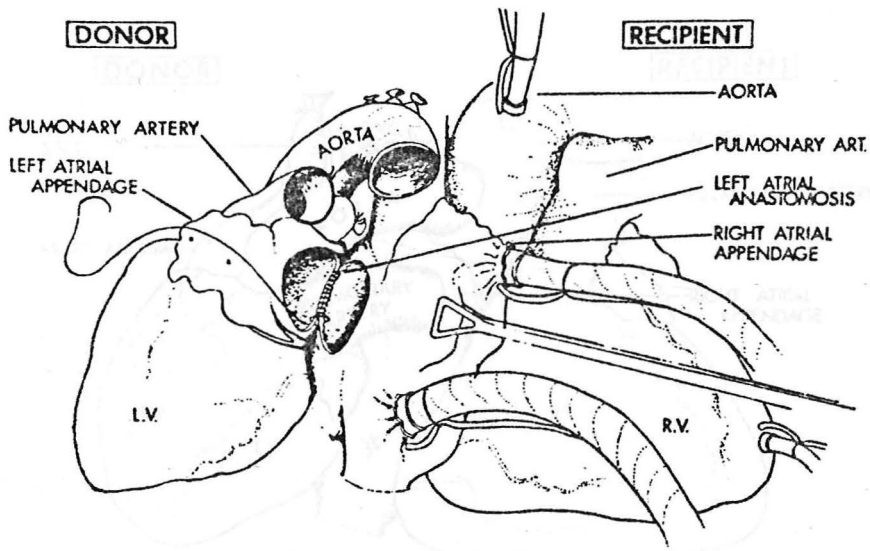

Figure 6. Heterotopic heart transplantation. The diagram illustrates the connection between the left atria of the donor and recipient. (from Reference 58).

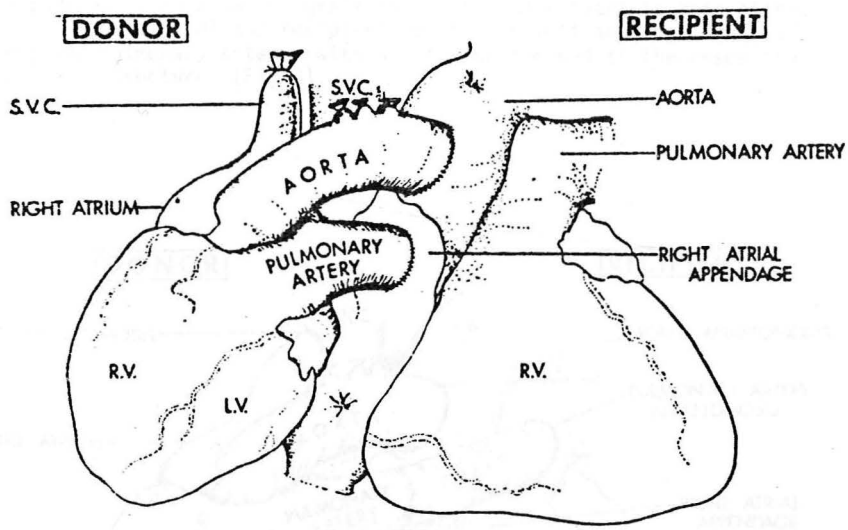

Figure 7. Heterotopic heart transplantation (left ventricular bypass only). The donor and recipient left atria are connected, and the donor aorta is anastomosed to the recipient aorta. The donor right atrium forms a blind pouch. The donor pulmonary artery is anastomosed to the right atrium. (from Reference 58).

The heterotopic transplant procedure has subsequently been modified so that in patients undergoing placement of such "piggy-back" hearts, both right and left ventricles are bypassed by performing donor to recipient right atrial anastomoses as well as pulmonary arterial anastomoses using a dacron graft (61). The donor heart is then placed on the right side of the recipient heart with left and right atria, aorta and pulmonary artery (with graft) anastomosed to the respective recipient structures (Fig 8).

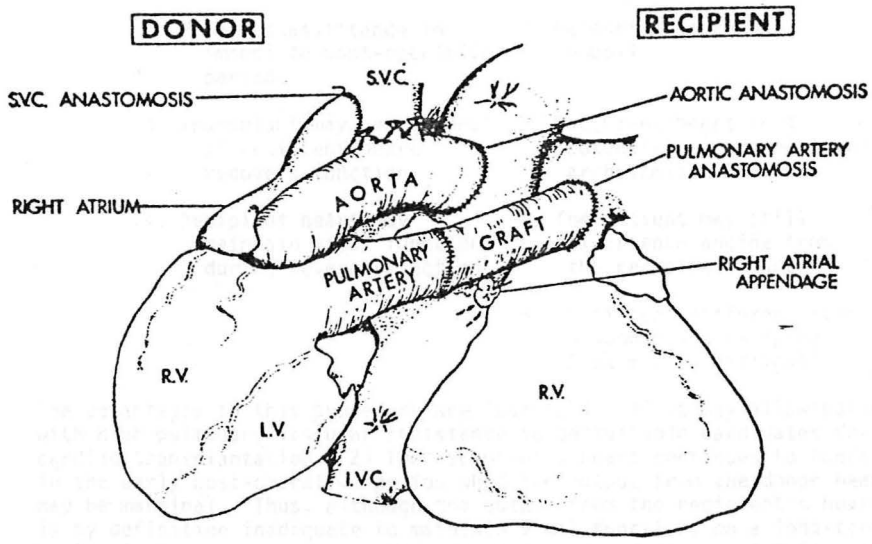

Figure 8. Heterotopic heart transplantation. Both the patient's left and right ventricles are bypassed by use of the cardiac allograft. The donor right atrium is now anastomosed to the recipient superior vena cava (SVC) and the donor pulmonary artery is connected to the recipient pulmonary artery by means of a dacron graft. (from Reference 58).

The major rationale for the "piggy-back" heart technique is to permit heart transplantation in patients with high pulmonary vascular resistance in whom an orthotopic transplantation would lead to early right heart failure and death. The relative merits and demerits of this procedure are indicated in Table VIII.

TABLE VIII

HETEROTOPIC TRANSPLANTATION

ADVANTAGES	DISADVANTAGES
1. P.V.R> 8 Wood units not a contraindication	1. Possible compromise of pulmonary function
2. Provides assistance in immediate post-operative period	2. Potential source of emboli
3. Transplant may be removed if recipient heart recovers function	3. Recipient heart is a potential source of lethal arrhythmias
4. Recipient heart may maintain vital functions during severe rejection	4. The patient may still experience angina from the recipient heart
	5. Consistent differentiation of donor and recipient ECGs may be difficult

The advantages to this procedure are four-fold: 1) it may allow patients with high pulmonary vascular resistance to be suitable candidates for cardiac transplantation. 2) The recipient's heart continues to function in the early post-operative period when the output from the donor heart may be marginal. Thus, although the output from the recipient's heart is by definition inadequate to maintain vital functions on a long-term basis, it is able to augment the output from the donor heart following the period of relative ischemia that occurs during the operative procedure. The Cape Town group have had no perioperative deaths since commencing heterotopic transplantation while other groups who perform orthotopic transplants continue to experience perioperative deaths (62). 3) In some patients the recipient heart may recover function in which case the piggy-back heart may be removed. Such a case occurred in Cape Town where the recipie heart recovered function, presumably following severe myocarditis, while the piggy-back transplanted heart developed evidence of late rejection necessitating removal 9 months following the initial procedure (3). 4) The presence of the recipient heart connected in parallel with the donor heart provides a back-up device; thus, acute severe rejection or

potentially lethal arrhythmias in the donor heart may not be catastrophic since the recipient heart maintains vital functions for a period of time (3, 63).

Several theoretical objections have been raised to the heterotopic technique (2, 13, 64): 1) The heterotopically placed heart may compromise respiration. Bronchograms performed in one patient revealed the donor heart situated to the right of the recipient heart and anterior to the lung, causing no right lung collapse. 2) The malfunctioning dilated recipient heart may serve as a potential source for thromboemboli. This has occurred in 1 patient in the Cape Town experience, immediately following cardiac catheterization and left ventricular biopsy. 3) The recipient heart may be the source of malignant arrhythmias. While this was a considerable problem when the left ventricle alone was bypassed, it appears not to be a major problem with total heterotopic transplantation. 4) The patient may still experience angina from the recipient heart. This appears not to be an important problem. 5) It may be difficult to consistently differentiate the recipient and donor complexes on the electrocardiogram. 6) Can the parallel donor heart function effectively to support the circulation without co-ordinated contraction between the two hearts? This question is discussed in detail below.

B. Post-operative Management

Post-operative management of heterotopic heart transplant recipients in Cape Town is essentially similar to that outlined for orthotopic transplant recipients by the Stanford group. Corticosteroids, azathioprine and RATG form the cornerstones of management; total lymphatic irradiation is not practiced and cyclosporin A is investigational (62).

C. Physiology of the Heterotopically Transplanted ("Piggy-back") Heart.

One of the proposed advantages of heterotopic transplantation over orthotopic transplantation is that the recipient heart continues to provide circulatory support during the early post-operative period, at which time the transplanted heart may be functioning suboptimally because of pre-and intraoperative hypoxemia. Barnard et al (3) have demonstrated this supportive role graphically (Fig 9) when a hypoxic donor heart was used.

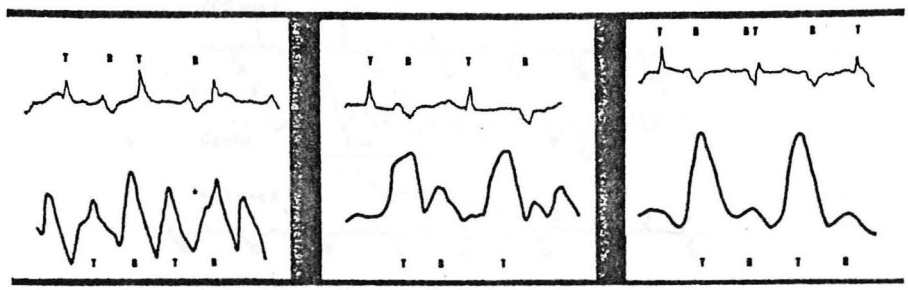

Figure 9. Electrocardiogram (upper tracing) and carotid pulse recordings (lower tracing) showing transplant (T) and recipient (R) tracings when a hypoxic donor heart was used. Left: Immediately after operation; center: Recovery of donor heart 4 days later; right: Further increase in the donor/recipient ratio 11 days post-operatively. The recipient QRS complex is wide and notched (from Reference 3)

The first panel illustrates the electrocardiogram and carotid pulse tracings generated by both the recipient (R) and transplanted (T) hearts in the immediate post-operative period. At this time the recipient heart plays the dominant role in maintaining forward output and hence produces the major deflection on the carotid pulse tracing. The second set of tracings showsthe electrocardiogram and carotid pulse tracing in the same patient 4 days post-operatively. At this time the transplanted heart has assumed a dominant role but the recipient heart still makes some contribution to forward output. Finally, the third set of tracings recorded 11 days post-operatively showsa further increase in the contribution from the transplanted heart and a decrease in contribution from the recipient heart.

One of the other proposed advantages of heterotopic transplantation over orthotopic transplantation suggested by the Cape Town team is that the recipient heart may provide some support during periods of rejection.

This allegation is borne out by the following series of recordings (Fig 10).

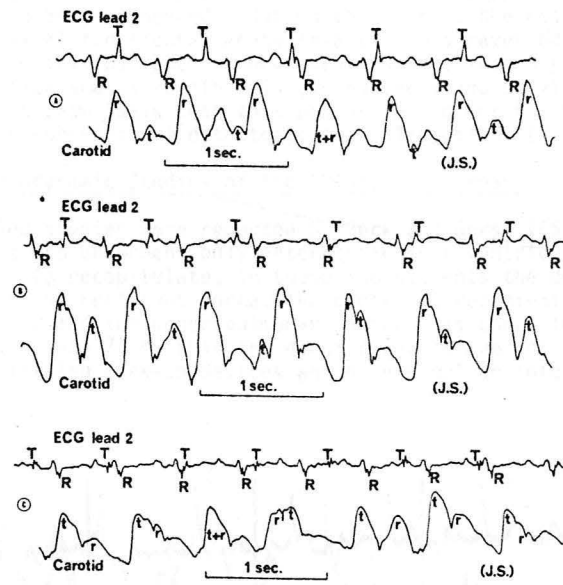

Figure 10. Electrocardiographic and carotid pulse tracings in a patient with a heterotopic heart transplant (A) during a rejection episode (B) following 3 days of antirejection therapy and (C) one month later. The recipient (R) electrocardiogram is wide and notched compared to the transplant (T) electrocardiogram. The progressive increase in the contribution from the transplanted heart as the rejection episode subsides is demonstrated by the carotid pulse tracing. (from Reference 63).

The electrocardiogram and carotid pulse tracing at the time of rejection in one patient are shown in Panel A. At this time both the recipient (R) and transplant (T) hearts make a contribution to the carotid pulse tracing, but the recipient heart is dominant. Panel B illustrates the situation after 3 days of antirejection therapy. There is now an increase in the contribution from the transplanted heart. Panel C illustrates the situation one month later at which time the transplanted heart is making the major

contribution to the stroke volume (as reflected by the carotid pulse tracing). This particular patient with a heterotopic heart transplant discontinued his immunosuppressive treatment and rejection progressed to the extent that the transplanted heart fibrillated before immunosuppressive therapy could be recommenced. During this period the recipient heart maintained vital functions. Acute rejection was reversed with adequate treatment and this patient has now survived more than 4 years after transplantation and is running his own business and playing squash. The Cape Town team feels that this patient would not now be alive had he undergone conventional orthotopic transplantation. (3)

(i) Hemodynamic Studies of the "Piggy-back" Heart

Detailed studies were reported by Beck and Gersh (65) on the first two patients who underwent only heterotopic left ventricular bypass operations. To recapitulate, in these two patients the donor aorta was connected to the recipient aorta, the donor and recipient left atria were connected and the donor pulmonary artery was connected to the right atrium (Figs 6 and 7) so that the donor right atrium and right ventricle merely constituted back-up devices which were not an integral part of the circuit.

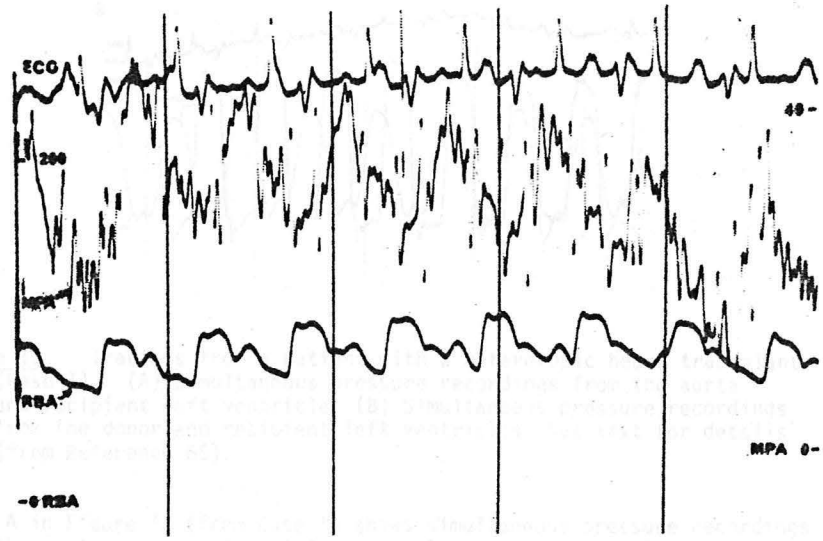

Figure 11. Simultaneous pressure tracings from the pulmonary artery (above) and brachial artery (below) in a patient who received a left ventricular bypass heterotopic heart transplant. The recipient electrocardiogram has broad notched QRS complexes while the donor heart has narrow QRS complexes (See text for details) (from Reference 65).

Simultaneous pressure recordings from the pulmonary and brachial arteries of Case 1 are shown in Figure 11. The electrocardiogram shows a composite record of the donor heart with narrow QRS complexes and the recipient heart with wide QRS complexes. The pulmonary arterial wave (MPA) is related to the recipient QRS complex, whereas the brachial arterial pressure (RBA) follows the donor electrocardiogram. During sequential beats a very small pressure wave is visible on the nadir of the brachial pressure tracing caused by ejection from the recipient heart. The situation is further illustrated by Figure 12 from the same patient.

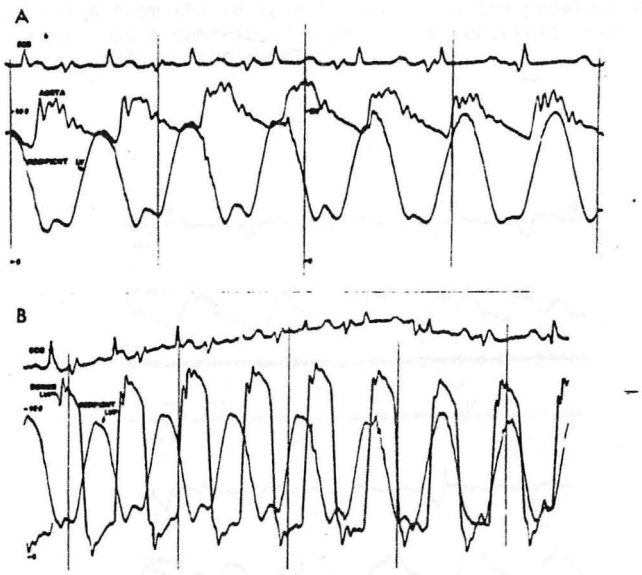

Figure 12. Tracings from a patient with a heterotopic heart transplant (Case 1). (A) Simultaneous pressure recordings from the aorta and recipient left ventricle. (B) Simultaneous pressure recordings from the donor and recipient left ventricles. See text for details (from Reference 65).

Panel A in Figure 12 (from Case 1) shows simultaneous pressure recordings from the aorta and recipient left ventricle. Left ventricular systolic pressure is less than aortic during synchronous contractions, which are thus probably isovolumic. During sequential contractions, some ejection occurs and a small aortic pressure pulse becomes visible. Panel B shows

simultaneous pressure tracings from the donor and recipient left ventricles. The donor left ventricle has the greater systolic pressure, the greater left ventricular dp/dt, the greater increment in diastolic pressure and the shorter duration of systole. During synchronous contractions the recipient ventricle has an increased systolic pressure and no increment in diastolic pressure in keeping with an isovolumic systole and diastole; during sequential contractions, the systolic pressure decreases and the diastolic pressure increment is seen suggesting that ejection and filling have occurred.

The second case studied by Beck and Gersh (65) had a relatively larger contribution from the recipient heart than the previous case. In this patient there was a contribution from both ventricles even when the heart beats were nearly synchronous.

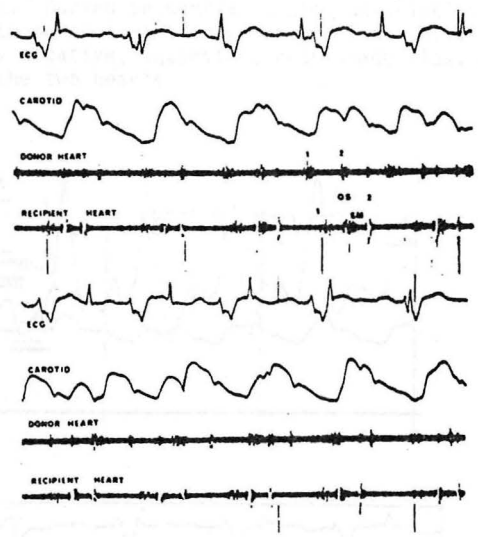

Figure 13. Tracings from a patient with a heterotopic heart transplant (Case 2). The electrocardiogram, carotid pulse tracing and phonocardiograms from the donor and recipient hearts are shown. In this case there was a contribution from the recipient left ventricle even when the hearts were beating nearly synchronously. (from Reference 65).

The electrocardiogram, carotid pulse tracing and phonocardiogram from Case 2 are shown in Figure 13. The donor heart again has narrow QRS complexes while the recipient heart has broad notched QRS complexes. The carotid pulse tracing reveals that the donor heart still makes the dominant contribution to the pulse contour and hence the forward output (this is most easily seen on the lower set of tracings).

These authors also measured instantaneous blood flow velocity in Case 2 using a specially-constructed electromagnetic velocity catheter which was passed into the ascending aorta of both the donor and recipient aortas (Fig 14). Panel A shows the electrocardiogram, aortic pressure signal and the flow velocity signal in the donor aorta. As in the previous figures the narrow QRS corresponds to the donor heart, while the wide QRS complex corresponds to the recipient heart. There is a major positive deflection in the flow velocity signal which does not vary in amplitude during synchronous or sequential beats. This represents major forward flow in the donor aorta due to the contribution from the donor heart. Recordings made from the recipient aorta are illustrated in Panel B. Both the amplitude and wave form of the flow velocity signals are markedly different. During sequential beats the velocity signal is reduced in amplitude compared to the previous tracing, while the velocity signal becomes frankly negative, suggesting retrograde flow, during synchronous beats of the two hearts.

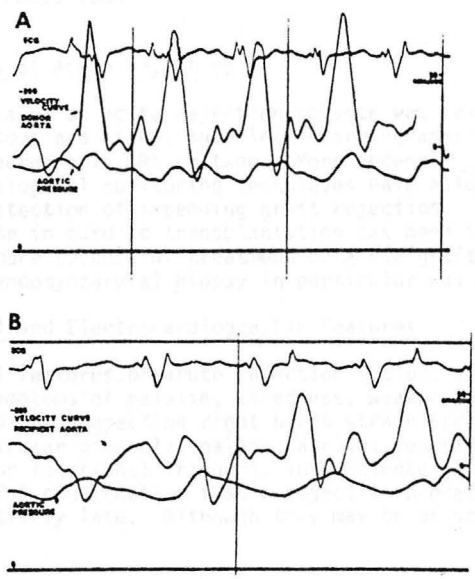

Figure 14. Aortic flow velocity recordings (A) in the donor ascending aorta and (B) in the recipient ascending aorta. See text for details. (from Reference 65).

These data indicate that forward output is optimised when the hearts beat sequentially. Both these cases illustrate the point that the contribution to flow made by the recipient ventricle may be minimal and contractions are at times isometric when hearts beat synchronously. It is thus possible that the greatly reduced blood flow through the large dilated recipient ventricle could lead to intracavitary thromboses with attendent serious sequellae. This led the Cape Town team to investigate the use of a double atrial-triggered standby pacemaker system to minimize the degree of stasis and to achieve maximal function from the recipient heart by stimulating the donor heart electrically after an appropriate delay. This system has been described in detail by Kennelly et al (66) but its use has been limited.

The rationale for simultaneous bypass of the right ventricle at the time of left ventricular bypass (Fig 8), which is the standard operation now performed in Cape Town, is that this procedure might prevent the onset of acute right heart failure during serious arrhythmias (67) arising in the recipient heart. Thirty-four biventricular bypass procedures have now been performed by the Cape Town team (62) but detailed physiological studies have been reported in only 2 of these patients (68). The donor and recipient right ventricles act in concert with each other to a greater or lesser degree, in the same way that the donor and recipient left ventricles interact. Thus, depending on the particular state of the patient, either the donor or recipient heart may dominate the circulatory system.

VII ACUTE REJECTION

A. Diagnosis of Acute Rejection

The diagnosis of an acute rejection episode was initially based on clinical symptoms and signs, and electrocardiographic changes, particularly a decrease in QRS voltage. More recently, endomyocardial biopsy and immunological monitoring techniques have allowed earlier more sensitive detection of impending graft rejection. The major advance in the past decade in cardiac transplantation has been in the earlier recognition and more successful treatment of acute graft rejection episodes, which endomyocardial biopsy in particular has enabled.

(i) Clinical and Electrocardiographic Features

The clinical features of acute rejection include generalized constitutional symptoms of malaise, tiredness, weakness and anorexia and physical findings suggesting right heart strain and failure, such as a right ventricular diastolic gallop, a right ventricular lift, raised venous pressure or functional tricuspid incompetence (2). Although these features are useful confirmation that a rejection process is occurring, they appear relatively late. Although they may be of some value in a

patient with an orthotopic transplant, they are of little value in the patient with a heterotopic biventricular transplant as the presence of the patient's own right heart will prevent the right sided failure even in advanced rejection (61).

Pre-clinical studies of heart transplantation revealed that rejection was heralded by decreases in QRS voltage (69) and histological findings consisting of myocardial edema and serous infiltration (70). The ECG findings in patients with allograft rejection were studied in the late 1960s (71). A decrease in QRS voltage was the most reliable finding and preceded the onset of clinically apparent heart failure. This permitted treatment at a time when the rejection process could be stopped and voltage then reverted to normal. Other ECG abnormalities associated less consistently with rejection include: the onset of atrial arrhythmias, right axis deviation, and first degree heart block progressing to nodal rhythm.

The Stanford group currently measure the sum of the peak to peak QRS voltage for leads 1, 2, 3, V1 and V6; a fall of 20% or more is an indication for heart biopsy. Decreases in voltage 3 months or more following heart transplantation are treated first with an increase in the prednisone dosage. If this does not lead to a prompt rise in QRS voltage, myocardial biopsy is performed. Although ECG voltage is highly sensitive, it is not entirely specific for rejection. Technical factors such as lead placement and variability in electrode contact may account for voltage drops. Changes in thoracic impedance from pneumonia, pneumothorax and pleural or pericardial effusion may lower QRS voltage in surface leads. Finally systemic changes such as a fall in hematocrit, a sudden rise in body weight (from fluid retention) and sepsis with fever can decrease voltage (2).

The Cape Town group also place great reliance on the QRS voltage, changes in conduction and the onset of atrial and ventricular arrhythmias, but in addition record carotid pulse tracings, as discussed previously. Since the heterotopically transplanted heart is situated in the right side of the thoracic cavity, these workers measure the sum of the voltage in 1, 2, and 3 and leads V3R, V4R and V5R. In patients with heterotopic heart transplants, the relative amplitude of the recipient and donor heart inflections on the carotid pulse tracing provide further valuable information (3).

(ii) Transvenous Endomyocardial Biopsy

Percutaneous transvenous biopsy of both right and left ventricles with a specially designed biopsy forceps was first described by Sakakibara and Konno (72). This technique was modified for use in cardiac transplantation by Caves and Billingham in 1973 (73,74). The biopsy forceps, modified and designed to provide greater mechanical versatility,

ease of sterilization and a minimum number of moving parts (Fig 15) was employed and a safe technique for repetitive biopsy via a percutaneous approach was developed (75) .

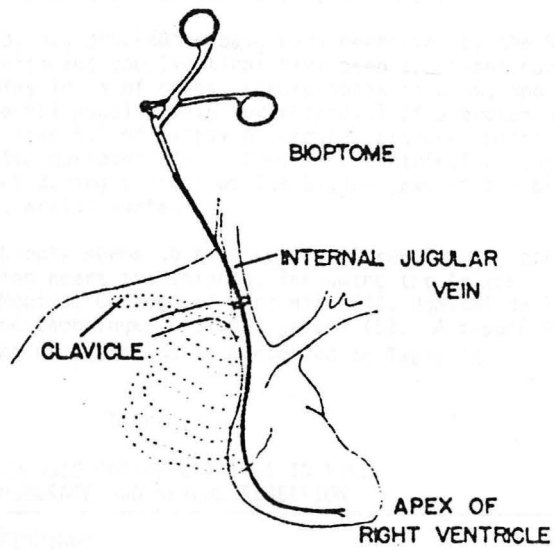

Figure 15. A diagram illustrating the use of the endomyocardial bioptome, introduced via the right internal jugular vein (from Reference 13).

The procedure takes 10 to 15 minutes and is performed under local anesthesia in the operating room with fluoroscopic control. The Stanford and Richmond groups use the right internal jugular vein which is cannulated with a cardiac catheterization sheath using the standard Seldinger technique. Biopsy forceps are then passed through the sheath and advanced under fluoroscopic control to the region of the apex of the right ventricle where 2 or 3 specimens, 2 to 3 mm in size may be obtained from different sites on the right ventricular side of the interventricular septum. The Cape Town group prefers to use a long sheath as a conduit passed from the right femoral vein up the inferior vena cava into the right ventricle through which an Olympus bioptome is passed. The same technique can be used on the arterial side, which allows biopsies to be taken of both the donor and recipient left ventricles.

More than 1200 biopsy procedures have been performed by the Stanford group. The only significant complications have been transient supra-ventricular arrhythmias in 3% of cases, pneumothorax in 0.4%, and dissection of an internal jugular vein for retrieval of a broken bioptome in one patient. More than 95% of biopsy procedures produce specimens suitable for diagnostic purposes (13). Premature ventricular contractions occur and are expected during contact of the biting jaws of the biopsy forceps with the endocardial surface.

Endomyocardial biopsy seems to have been well received by other institutions performing heart transplants, including the Arizona Health Science Center (2), Medical College of Virginia (64), Hôpital de la Pitie (Paris) (76) and Cambridge (England) groups (5). A resumé of the histologic grading of rejection is presented in Table IX.

TABLE IX

HISTOLOGIC CHARACTERISTICS IN MILD, MODERATE AND SEVERE REJECTION

HISTOLOGIC FINDINGS IN REJECTION	MILD	MODERATE	SEVERE
Myocardial interstitial edema	+	++	+++
Mononuclear cell infiltrate in myocardium	+	++	+++
Mononuclear pyroninophilic cell infiltrate in endocardium	+	+	++
Perivascular cuffing	+	+	++
Polymorphonuclear infiltrate in myocardium	-	-	+
Hemorrhage in myocardium	-	-	+
Myocytolysis	-	+	++

(from Reference 13)

Lymphocytic infiltration of the graft is generally required for the diagnosis of acute rejection. Other histologic changes, such as myofibrillar edema or necrosis, may be observed that characterize, in a semi-quantitative fashion, the severity of the rejection episode. Interstitial graft fibrosis is sometimes seen and may reflect the degree of irreversible damage sustained by the graft during previous rejection episodes (77). The methylpyronin stain has been particularly helpful in mild rejection. It identifies so-called "turned-on" lymphocytes in the myocardial interstitium by staining increased RNA in the cytoplasm.

Criticism of the biopsy technique has focused primarily on the possibility of sampling error and the subtlety of histologic changes in diagnosing rejection (64). However, Rose et al (78) from the Cape Town group examined biopsy samples taken with the bioptome from formalin fixed transplanted hearts from human transplant recipients and compared these in a blinded fashion with standard histological sections taken from the same hearts. Using a scoring technique to grade severity of rejection, they found agreement of results between the bioptome biopsies and routine sections in 86% of the cases. More important was the fact that in 285 biopsy samples, only 2 false negative results were obtained.

The principal value of cardiac graft biopsies is that it enables the physician to diagnose objectively the activation of the efferent immune response before functional graft impairment develops. Frequently a routine biopsy reveals morphologic evidence of mild rejection in patients who are entirely asymptomatic and exhibit no clinical signs of rejection. Because of the diffuse distribution of pathologic changes during rejection of cardiac grafts, histologic diagnosis by right ventricular biopsy has proven highly reliable for diagnosis (75). Since the procedure can be performed percutaneously, rapidly and safely, it can be repeated as often as necessary to assess graft histology serially. The Stanford group (13) perform routine biopsies weekly for the first 4 to 6 weeks after transplantation, or any time impending rejection is suspected and the Cape Town group have adopted a similar strategy (3). In addition to its role in the diagnosis of cardiac graft rejection, endomyocardial biopsy has also proven highly useful in the assessment of histologic response to anti-rejection therapy. The duration and intensity of treatment for rejection can therefore be individualized on the basis of direct examination of graft histology.

(iii) Immunologic Monitoring

Although endomyocardial biopsy often provides earlier diagnosis and more precise therapy for rejection episodes, it has two major limitations. First, it is impractical to perform biopsies more frequently than every 3-5 days. The data provided about the status of the host immune response are thus relatively discontinuous, and the onset of mononuclear cell infiltration of the graft may not be immediately detected by this means. Second, the histologic diagnosis of rejection requires the presence of cellular infiltration or other histological changes. By the time these

changes appear, some degree of irreversible graft damage may already have occurred. Each additional rejection episode may be presumed to add some further increment in damage to the graft which is bound to affect the long-term functional capacity of the transplanted organ (79).

An assay based on the measurement of circulating thymus-derived lymphocytes (T-cells) has thus been instituted by several groups (3, 77, 79, 80). This approach allows activation of the rejection process to be detected before morphological alterations in the graft occur and can be performed on a daily basis.

When transplant recipients are given rabbit anti-thymocyte globulin (RATG) as part of their immunosuppressive regimen, T-cell levels are markedly and uniformly reduced within 5 days post-operatively. T-cells normally number 1000-2000 per cu mm (or approximately 65% of the circulating lymphocyte pool). Following RATG therapy, their numbers fall to 5-20 per cu mm or 5-10% of the circulating lymphocyte pool. A sudden large rise in T-cell numbers during the first 30 days after transplantation in patients treated with RATG, correlates closely with histologically detectable rejection, which it precedes by 1-3 days (81).

The major limitation of the T-cell assay is that after 6 weeks post-operatively, T-cell levels tend to rise toward normal, irrespective of the presence or absence of graft rejection. Before this time, however, the sensitivity and specificity of this assay is good: a false negative rate of 4% and false positive rate of 13% has been reported (77).

Transplant recipients who eliminate RATG rapidly from their serum develop more episodes of early acute rejection, which tend to be more severe, and they have a significantly lower 1-year survival rate. Measurement of the half-life of RATG in serum and prolonged RATG administration may enhance long-term survival in these patients, but this remains to be proven.

Several other immunologic evaluations, including the phytohemagglutinin blastogenesis test (80) modified reactive leucocyte blastogenesis test (82), B cell levels, ATG-coated lymphocyte levels, T-cell reactivity to mitogens, B-cell reactivity to a staphylococcal strain, spontaneous lymphocyte blastogenesis, "K"-cell cytotoxicity, and mixed lymphocyte culture have been proposed (13). None of these have found widespread favor.

With current therapy, about 3 rejection episodes can be expected during the first 3 post-operative months and 1 in 10 patients will experience no rejection. In subsequent months, approximately 1 acute rejection episode per year is expected (83). It is not yet possible to predict accurately pre-operatively which recipients are likely to be rejection prone. Contrary to earlier reports (84), it now appears that pre-operative blood transfusions do not improve 1-year survival (2).

B. Treatment of Acute Rejection

The first prerequisite for successful treatment of acute rejection is diagnosis at the earliest possible time. Thus, in addition to careful daily physical examination and recording of electrocardiographic QRS voltages both the Stanford and Cape Town groups perform endomyocardial biopsy on a weekly basis, while varying degrees of reliance are placed on the immunological monitoring techniques. The schema for treatment of early acute rejection used by the Stanford group (77) is shown in Figure 16.

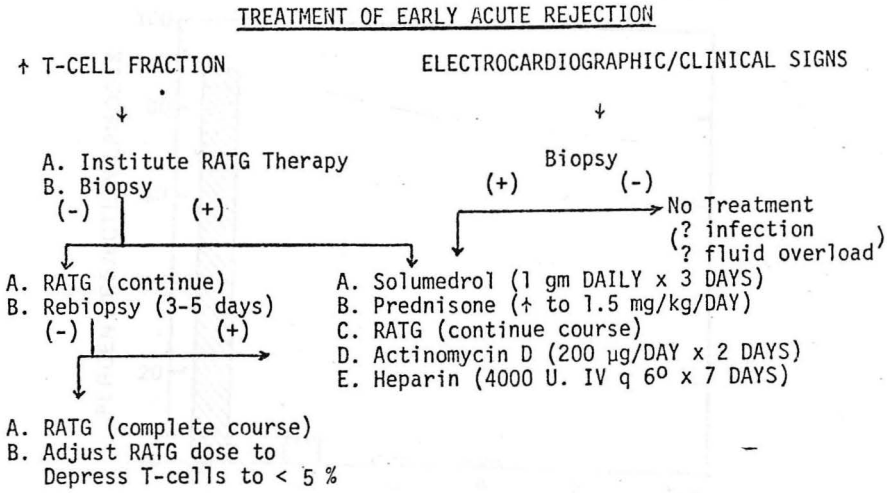

Figure 16. (from Reference 77)

If an increase in T-cell fraction (>10%) occurs in the early post-operative period, RATG therapy is reinstituted and endomyocardial biopsy is performed. If the biopsy is negative, RATG therapy is continued and the patient is re-biopsied at 3 to 5 days. If the biopsy remains negative, RATG dosage is continued to complete the course and adjusted to depress T-cells to less than 5% of normal. If either the first or second endomyocardial biopsy shows evidence of rejection, formal anti-rejection therapy is commenced.

If electrocardiographic or clinical signs of rejection occur, biopsy is performed. If the biopsy is negative, rejection therapy is not commenced; however, if it is positive, therapy is commenced with methyl-prednisolone (solumedrol, 1 gram daily for 3 days), prednisone is increased to 1.5 mg/kg/day, actinomycin D (200 micrograms/day x 2 days) and heparin 4000 units intravenously 6 hourly x 7 days are instituted, and RATG is continued. A standard course of RATG usually lasts 7-10 days. Actinomycin D is generally given for all first rejection episodes. During a period of heightened immunosuppressive therapy, even closer attention to diagnosis and treatment of infections is necessary.

The criteria used in the diagnosis of late acute rejection (rejection occurring more than 3 months after transplantation) are similar to those described for early acute rejection, with the exception of T-cell levels. The incidence of acute rejection decreases markedly after the first 3 months, as shown in Figure 17.

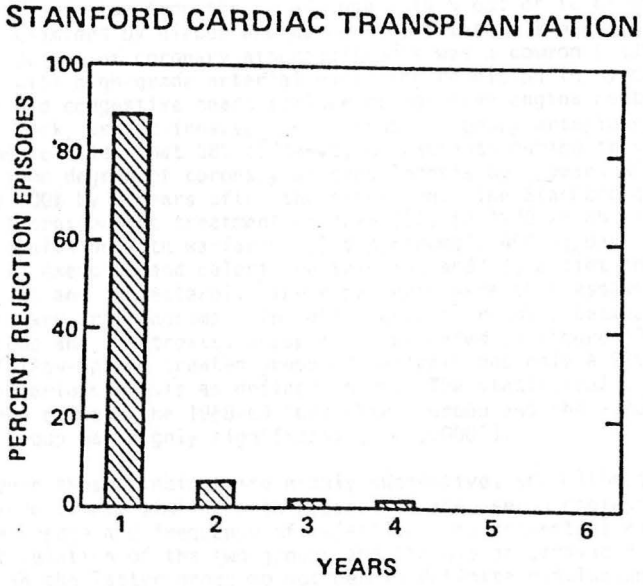

Figure 17. Incidence of acute rejection episodes following transplantation. (from Reference 13).

The Stanford group reports that 50% of all late acute rejection episodes can be successfully treated by an increase in oral prednisone alone (13). The remainder require hospitalization and institution of therapy as shown in Figure 16.

VIII. CHRONIC REJECTION--GRAFT ATHEROSCLEROSIS

An accelerated form of atherosclerosis was first reported by Thomson (85) from Cape Town in 1969 in a cardiac homograft transplant recipient who died 19½ months post-operatively. Severe atherosclerosis of the coronary arteries of the donor heart, with marked luminal narrowing, was considered responsible for the death. Similarly, the first long-term survivor in the Stanford program died 21 months after heart transplantation from the same cause. In 8 out of 12 cardiac recipients examined by Bieber and co-workers between 1968 and 1970 (86) a variable degree of coronary atherosclerosis was a common finding. Recipients with high-grade arterial narrowing resulting in myocardial infarction and congestive heart failure do not have angina pectoris since they lack cardiac innervation. Annual coronary arteriographic examination revealed that 58% of surviving patients during this period developed some degree of coronary atherosclerosis by 1 year, 88% by 2 years, and 100% by 3 years after the operation. The Stanford group thus commenced a prospective treatment program (87) in 1970 which included 1) anticoagulation with warfarin 2) dipyridamole 400 mg/day 3) weight control with exercise and caloric restriction and 4) a diet low in saturated fat and cholesterol. These patients were then assessed with yearly coronary arteriograms. The difference in results between the earlier group and the treated group is illustrated in Figure 18. After a 4 year follow-up the treated group of patients had only a 22% incidence of graft arteriosclerosis as defined above. The statistical difference in incidence between the 1968-69 "untreated" group and the 1970-74 "treated" group was highly significant ($p < 0.0001$).

Although these findings are highly suggestive, and although the 2 groups were fairly similar with respect to age, serum cholesterol, prednisone dosage and frequency of rejection, the sequential rather than concurrent relation of the two groups and the use of cardiac biopsy and RATG only in the latter group do not permit definite conclusions as to which single factor has been responsible for the reduction in graft atherosclerosis. The study does, however, document a rapidly progressive form of arteriosclerosis in transplant recipients and a marked reduction in incidence from the early (1968-69) to the later (1970-74) group. The Stanford group has thus continued this therapeutic regimen, to which they have now added aspirin 325 mg daily (13). Other groups performing heart transplantation have been sufficiently impressed with these data to follow a similar regimen. The reduction in graft atherosclerosis is in part responsible for the increased survival of patients at Stanford since 1970.

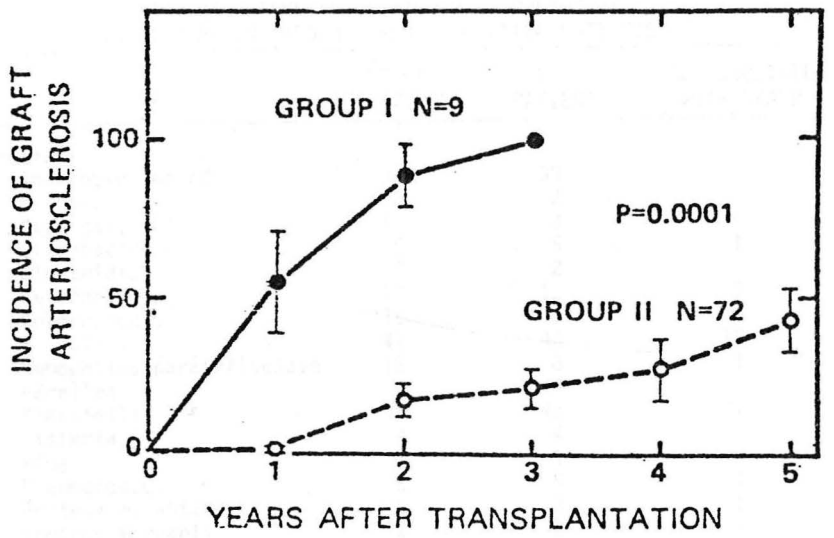

Figure 18. Incidence of graft atherosclerosis following transplantation in patients who received no specific therapy (Group 1) and in patients who were treated prophylactically with anti-platelet agents, diet and exercise (Group II). (from Reference 13).

Bieber et al (88) recently analyzed the effect of a variety of factors on the incidence of graft arteriosclerosis by multivariant analysis. Incompatibility of the HLA-A2 antigen was associated with a higher incidence of graft arteriosclerosis ($p < 0.0003$). Similarly, serum triglyceride levels greater than 280 mg/dl were significantly associated with the development of arteriosclerosis ($p < 0.0002$).

IX. INFECTION

Infection is the most common cause of death after cardiac transplantation accounting for 62% of all deaths in the first post-operative month and 46% of deaths after the first 3 months in the Stanford experience (2) and 47% of deaths in the Cape Town experience (3). The agents responsible for infection in the Stanford experience are shown in Table X. The mean incidence of infectious episodes is 3 per patient which drops markedly after the first year to one episode per 455 patient days.

TABLE X

MICROORGANISMS ASSOCIATED WITH PULMONARY INFECTIONS IN CARDIAC TRANSPLANTATION PATIENTS

	NO OF INFECTIONS	NO OF PATIENTS	NO ASSOCIATED WITH DEATH
Bacterial			
Anaerobic, mixed	36	30	
Arizona	2	2	
Atypical, AFB	11	9	
Citrobacter	5	5	1
Clostridia	2	2	
Enterobacter	14	12	7
Enterococcus	15	14	6
E. coli	49	40	18
Hemophilus parainfluenzae	13	8	1
Herellea	4	4	
Klebsiella	44	42	21
Listeria	4	4	
Mima	1	1	
Pneumococcus	5	5	1
Proteus mirabilis	5	3	1
Proteus morganii	2	2	1
Pseudomonas	28	22	11
Salmonella	1	1	
Serratia	17	16	5
Staphylococcus	30	25	8
Streptococcus	15	11	3
Viral			
Cytomegalovirus	9	9	2
Hepatitis	4	4	1
Herpes simplex	48	42	1
Herpes zoster	30	29	3
Influenza A	3	2	
Undefined	3	3	1
Fungal			
Aspergillus	39	39	20
Candida	12	12	6
Coccidioides	1	1	
Cryptococcus	10	9	3
Mucor	1	1	1
Rhizopus	2	2	
Protozoan			
Pneumocystis	22	21	6
Toxoplasma	6	6	5
Trichomonas	1	1	1
Nocardial	22	22	3

(from Reference 2)

Nearly every organ system may be involved but pulmonary infections (47%) have been most common. In decreasing order of frequency, other sites of involvement have included blood stream (10%); urinary tract (6%), central nervous system (4%), disseminated viral (2%), pleural cavity (2%), disseminated fungal (2%), liver (1%), retina (1%), bone (0.2%) and a number of other rarely involved sites (25%). Bacterial organisms have predominated followed by viral, fungal, protozoan and nocardial. Aspergillus and the gram negative bacteria (E coli, Klebsiella, and Pseudomonas) have been most commonly associated with a fatal outcome. Although the risk of infection is highest in the first 3 months, any time an acute rejection episode is treated with a pulse of methylprednisolone (1 gram daily/3 days) and anti-thymocyte globulin, there is a 3-fold increase in the incidence of serious infection. However, there appears to be no significant increase in the incidence of infection when the dosage of prednisone is merely increased.

Care in the selection of the recipient is imperative if later morbidity and mortality from infections is to be avoided. In particular, recurrent chronic infections (e.g., urinary tract, sinusitis or otitis) or previous tuberculosis make a recipient less attractive. Rand et al (89) also found that cardiac transplant recipients who were pre-operatively sero-negative for cytomegalovirus (CMV) had a higher incidence of pulmonary infections post-operatively than those who were seropositive pre-operatively. In all cases, the pulmonary infections occurred during the second and third month after transplantation, at a time when CMV infections were serologically detected. It was thus proposed that pulmonary infections occur as superinfections following CMV pneumonitis.

Preventive measures commonly used in the post-operative period include prophylactic antibiotics, reverse isolation or isolation in a separate transplantation intensive care unit, and special nursing care. Prophylactic antibiotics (cephalosporin and gentamicin) are generally administered prior to transplantation and for 48 hours post-operatively. Careful hygiene is emphasized and additional room cleaning precautions are enforced. The Stanford team (2) has also used increased pressure air conditioning in transplant rooms to prevent air inflow through the door and high-grade medical filters for the inflow ducts into the room. They also use alternating tetracycline and amphotericin B mouth-washes for the first several weeks and oral nystatin three times daily. In addition, the patient is encouraged to wear a mask, which serves as a reminder to avoid sources of respiratory contimination. Cultures and titers, aside from baseline titers, are obtained only when clinically indicated. Chest x-rays are obtained daily for about 2 weeks, then 2 or 3 times per week until discharge. When infiltrates are noted on chest x-ray, transtracheal aspiration often yields a culture positive for the infecting organism. When the transtracheal aspirate is non-diagnostic, percutaneous pulmonary needle aspiration is performed by the Stanford group (2) while bronchoscopy is favored by the Virginia group (64).

The treatment of infections differs little from their treatment in any patient population. However a tendency to treat with higher doses, multiple drugs and for more prolonged periods has been a natural outgrowth of witnessing the devastating results of infection in transplant recipients (2). For bacterial infections two bacteriocidal antibiotics are usually administered concomitantly until complete resolution of the process has occurred. Fungal infections require therapy with amphotericin B, (occasionally in combination with 5-fluorocytosine), and nocardial infections are usually treated with sulfa derivatives combined with a brief course of an appropriate aminoglycoside (90). Pneumocystis carinii infections are treated with pentamidine isothionate trimethoprim-sulphamethoxazole combination, or both, while toxoplasma infections are treated with pyrimethamine and triple sulfa. Intrathecal administration of antibiotics is sometimes required for treatment of certain central nervous system infections, such as those caused by coccidiodes or cryptococcus.

The incidence of infectious episodes in the Stanford experience has remained constant throughout the program (88). Thus, improvement in survival in their patients has related primarily to an improved recognition and treatment of acute and chronic rejection (graft arteriosclerosis) episodes.

X. MALIGNANCY

Cardiac transplant patients, like immunosuppressed recipients of other human organ grafts, are subject to a substantially higher risk of malignancy. In the Stanford experience 8 carcinomas, 10 lymphomas, and 1 leukemia have occurred in 124 cardiac recipients at risk 3 months or longer post transplantation (88). Seven of the 8 carcinomas were squamous cell lesions of the skin which were resected without recurrence. The remaining epithelial lesion was an adenocarcinoma of the colon, metastases from which caused the recipient's death 12 months following transplantation. The ten lymphomas occurred in the following sites: Central nervous system (4), lung (2) soft tissue (2) and systemic (2). Despite aggressive therapy, only 2 patients with CNS lymphoma and the 2 patients with pulmonary lymphoma survived.

Three factors in particular appear to be associated with the occurrence of lymphoma, namely, younger age, re-transplantation (88), and treatment with cyclosporin-A (91). The occurrence of lymphoma in recipients according to presenting disease, age and transplant order (88) is shown in Table XI. Since patients with cardiomyopathy were generally younger than other recipients, age rather than presenting disease probably represents the primary association with the occurrence of lymphoma. Lymphoma has also occurred at the site of intramuscular injection in 2 patients who happened to have received the highest number of RATG injections at the tumor site in the Stanford series.

TABLE XI

LYMPHOMA/LEUKEMIA INCIDENCE IN CARDIAC RECIPIENTS
AT RISK 3 MONTHS OR LONGER

	Patients	Cumulative Risk (Years)	Lymphoma/ Leukemia	Percent Lymphoma/Yea
By presenting disease				
Idiopathic cardiomyopathy	53	129.6	9	6.9
ASHD, CHD	71	217.3	2	0.9
By age of recipient (years)				
11-20	7	14.3	3	21.1
21-30	12	36.5	2	5.5
31-40	26	102.3	3	2.9
41-50	61	154.3	3	1.9
51 +	18	36.5	0	0.0
By transplant order				
First transplant	124	336.3	7	2.1
Second transplant	10	12.5	4	32.1

(from Reference 88)

XI RE-TRANSPLANTATION

When the transplanted heart fails, either due to unremitting or recurrent acute rejection or arteriosclerosis, the only viable long-term alternative is re-transplantation. Although considerable progress has been made in the development of a total artificial heart (92), even the best device has a limited life-span (less than 1 year) due to material failure, and requires an external source of power. A normal ambulant life-style is thus not possible, although these devices may serve as useful interim support measures while a second donor heart is being acquired.

Re-transplantation has been performed in at least 10 patients at Stanford (88). The operative risk associated with the second transplant appears to be similar to that of the initial procedure but there is an increased incidence of lymphoma following re-transplantation. Other groups (3) have also performed successful re-transplantation. Since the lack of graft innervation precludes the development of angina in heart transplant recipients, the Stanford group (2) recommends annual coronary angiography to assess the extent of atherosclerosis. They consider a patient with critical coronary lesions, in the absence of overt graft dysfunction, a candidate for elective re-transplantation.

XII. CURRENT RESULTS OF CARDIAC TRANSPLANTATION

A. Survival

There are few therapeutic modalities that have enjoyed both the initial euphoria and subsequent disillusionment that heart transplantation has known. More than 13 years have now passed since the first human heart transplantation. It therefore seems appropriate to synthesize what has been learned over this time period, and to assess the feasibility of this procedure.

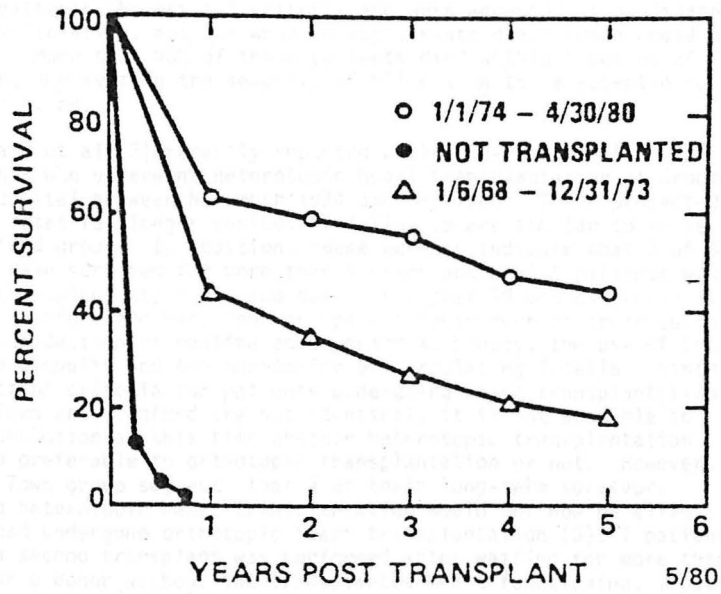

Figure 19. Actuarial survival rates for orthotopic heart transplant recipients at Stanford University. Survival rates for patients operated upon after 1973 are compared to those operated on before this time. The survival probabilities among those patients for whom appropriate donors could not be found are also shown. (from Reference 93).

(1) Orthotopic versus Heterotopic

The feasibility of heart transplantation is attested to by the results recently reported by Stanford University (93) for orthotopic cardiac transplantation. Their survival data are summarized in Figure 19. This figure compares survival in patients who received transplants between 1974 and 1980 with those who were transplanted during the initial 5 years of clinical experience. The major change has been an improvement in survival in the first 3 months due to both more careful patient selection and improved recognition and treatment of rejection. At the present time these workers project that 65% of patients undergoing orthotopic transplantation at Stanford may be expected to survive for 1 year, and between 45 and 50% for at least 5 years. These results are eminently comparable to survival statistics for patients undergoing renal transplantation (4). The therapeutic nature of the procedure is illustrated by comparison of these data with the observed survival rate of patients who met all criteria and were accepted as candidates for transplantation, but for whom an appropriate donor organ could not be found. More than 90% of these patients died within 3 months of selection, emphasizing the severity of illness in those accepted for transplantation.

Barnard et al (3) recently reported a 61% one-year survival in 30 patients who underwent heterotopic heart transplantation at Groote Schuur Hospital between November 1974 and May 1980. Their projected survival rates for longer periods of follow-up are similar to those of the Stanford group. In addition, these workers indicate that 3 of 6 patients have survived for more than 4 years and 8 of 9 patients whose initial transplant was performed during the past 18 months remain alive. Both the Stanford and Cape Town groups attribute much of their success to the introduction of routine endomyocardial biopsy, the use of anti-thymocyte globulin and the monitoring of circulating T-cells. Since the selection criteria for patients undergoing heart transplantation in Cape Town and Stanford are not identical, it is not possible to draw a conclusion at this time whether heterotopic transplantation is indeed preferable to orthotopic transplantation or not. However, the Cape Town group suggest that 4 of their long-term survivors following heterotopic heart transplantation would not now be alive if they had undergone orthotopic heart transplantation (3): 1 patient in whom a second transplant was performed after waiting for more than 2 months for a donor without the transplanted heart functioning, 1 patient with myocarditis in whom the recipient heart regained function at the time that the donor heart developed evidence of rejection and was removed, a third patient who awaits a second heart transplant following rejection of a heterotopic heart, and a final patient who discontinued immuno-suppressive therapy resulting in rejection which progressed to the extent that the transplanted heart fibrillated. In addition, it appears that the Cape Town group is more flexible about operating on patients with elevated pulmonary vascular resistance. Thus, at least 2 patients with pulmonary vascular resistance in excess of 8 Wood units have received

heterotopic heart transplants and survived. In both these patients the donor right ventricle apparently provided no substantial forward output to the pulmonary arterial system until several months after heart transplantation (62, 94).

(2) Age of Recipient

There is a very marked inverse correlation between patient age at operation and survival rate following heart transplantation. This is graphically demonstrated by Figure 20 taken from the Stanford experience. (24). Patients over the age of 50 have a 15% three year survival compared to a 25% 3-year survival for patients 41 to 50 years old and a 55% 3-year survival for patients 11 to 40 years old. Infection has been responsible for the majority of deaths in older recipients and these patients tend to be more intolerant of the effects of immunosuppression than their younger counterparts.

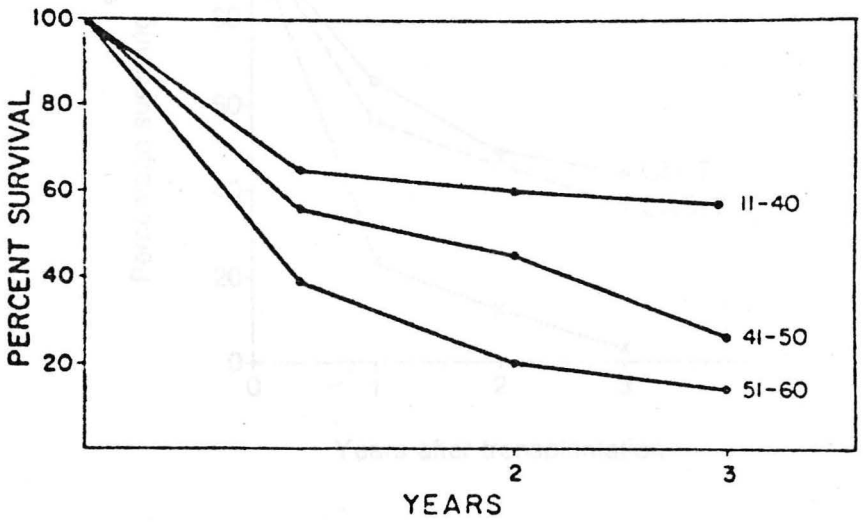

Figure 20. The effect of age on survival rate following orthotopic heart transplantation. (from Reference 24).

(3) Etiology of Heart Failure

Patients with a congestive cardiomyopathy, rather than atherosclerosis, were initially thought to fare less well following transplantation (95). Hassell et al (96) from Stanford recently suggested that this is not the case. They found that the 1 year survival for forty-six patients who underwent transplantation because of congestive cardiomyopathy was 64% compared to 55% for a similar group of 59 patients whose underlying disease process was atherosclerosis. In contrast, in 36 similarly ill patients with cardiomyopathy who did not undergo transplantation, the 1 year survival rate was 23% (and 3 year survival rate 4%). The overall three year survival rate was similar for those with cardiomyopathy or atherosclerosis who underwent transplantation (43 versus 38%). These data are shown in Figure 21.

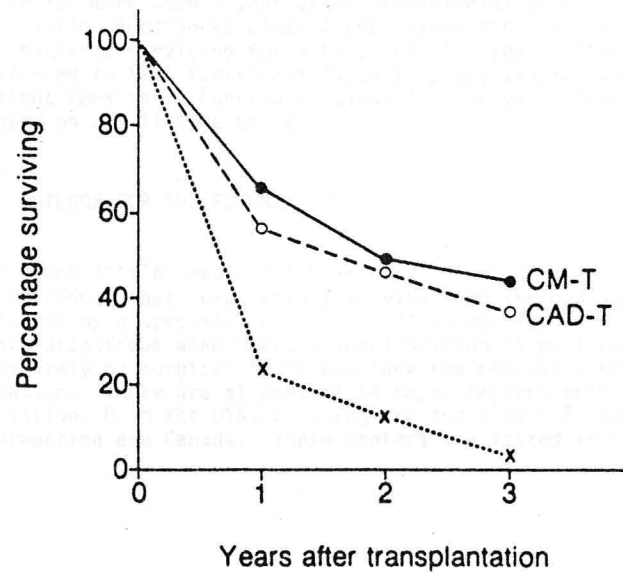

Figure 21. Actuarial survival rates for patients with end-stage cardiomyopathy (CM-T) or coronary artery disease (CAD-T) following orthotopic heart transplantation at Stanford. The group with cardiomyopathy who did not undergo transplantation is represented by the crosses. (from Reference 96).

B) Rehabilitation Following Heart Transplantation

The efficacy of a therapeutic procedure should be judged not only by survival statistics but also by the quality of life following the procedure. Christopherson et al (97) reported on the physical and social status of 56 patients who survived 6 or more months after cardiac transplantation at Stanford University. Fifty-one patients (91%) were classified as successfully rehabilitated, 4 (7%) retained substantial physical disability and 1 (2%) experienced psychiatric disability. Specifically, 26 of the 51 rehabilitated recipients returned to full-time work following transplantation, 13 recipients chose active retirement, 8 recipients returned to school full-time while 4 were classified as home-makers after transplantation. In 4 of the 6 patients classified as disabled, physical limitations were responsible for their inability to achieve rehabilitation. Rottembourg et al (76) from Paris recently reported similar favorable results in 11 patients more than 1 year after heart transplantation. These workers have concluded that 80% of patients who survive for more than 1 year after transplantation return to New York Heart Association Functional Class I and resume their previous activities. Of the 11 patients surviving for a total of 33.3 years after transplantation, 7 have returned to NYHA Functional Class I, 3 are stable NYHA Class II and 1 patient remains in Functional Class III. Five of these patients are employed on a full-time basis.

XIII. OUTLOOK FOR THE FUTURE

There seems little doubt that heart transplantation is a successful, feasible procedure that can improve survival and the quality of life, when performed by a specialized center. It is equally clear that the results are disastrous when heart transplantation is performed indiscriminately by surgical teams who lack the necessary expertise and dedication. There are at present 14 major centers performing heart transplantation: 8 in the USA, 2 in England and 1 each in South Africa, France, Argentina and Canada. These centers are listed in Table XII.

TABLE XII

CURRENT HEART TRANSPLANTATION CENTERS

Stanford University Medical Center
University of Cape Town, South Africa
Medical College of Virginia
Hôpital Pitié-Salpetriere, Paris, France
Columbia University College of Physicians + Surgeons, New York
State University of New York, Downstate Medical Center, Brooklyn
University of Arizona, Tucson
University of Wisconsin, Madison
University of Cambridge, England
Harefield Hospital, London, England
Sanatorio Guemes Hospital Privado, Buenos Aires, Argentina
University of Minnesota, Minneapolis
Mayo Clinic, Rochester, Minnesota
Montreal Heart Institute, Montreal, Quebec

Several major centers are at present weighing the pros and cons of heart transplantation. It is significant that the regents of the Massachusetts General Hospital recently voted against the introduction of a heart transplantation program at that institution (98), despite the request from the chief of surgical services to launch a "limited" cardiac transplant program (99, 100). At much the same time, the Mayo Clinic announced that it would initiate a cardiac transplantation program (101). The National Health Service in Britain has also recognized that this procedure is no longer experimental and has thus far agreed to fund two centers to perform a limited number of transplants annually. The Department of Health and Social Security in Britain has made certain recommendations that seem generally applicable, namely: "a centre planning a programme in heart transplantation should satisfy the following criteria: 1) a centre should already be a centre for advanced cardiac surgery, and preferably, renal transplantation should already be taking place at the same centre; 2) donor hearts of high quality should be available; 3) sufficient medical, surgical, nursing and technical personnel and equipment must be available to maintain both the transplantation programme and the regular cardiac surgical programme; and 4) adequate support services in pathology, immunology, and microbiology must be readily available at all times". This British body more recently added a further criterion, namely, that "a centre performing cardiac transplantation should already have carried out experimental work in immunology, circulatory support, and organ preservation systems with and without animals" (102).

At the present time, the United States Department of Health and Human Services (HHS) has taken the view that heart transplantation is experimental at centers other than Stanford University, and thus Medicare has been instructed not to pay for the procedure at other centers (13). The HHS is at present examining the data on the more than 200 heart transplants that have taken place in the United States during the past 13 years, will carefully examine the data on patients who receive transplants during the next several years, and has invited detailed applications from other centers contemplating or engaged in heart transplantation. The single factor which concerns the HHS most is the potential cost of indiscriminate, or at very least, widespread introduction of a new technology, which, like its predecessor renal transplantation, may burgeon and consume a considerable fraction of the annual health care budget.(103). The present cost of a heart transplantation is not known, but during the first year the cost is probably at least 3 times that of more conventional open-heart surgery (99).

The reigning imperative of American Medicine has been: "If it works, do it". Until the present time, the government has adopted a similar stance and has asked only three questions about a procedure before deciding whether or not to pay for it out of Medicare and Medicaid funds: Is it safe? Is it effective? Does it have widespread acceptance in the Medical community? However, on June 12, 1980 the HHS stated that it will require new technologies to pass muster on the basis of their "Social consequences" before financing their wide distribution(103). It thus seems highly probable that the fate of heart transplantation as a therapeutic modality will be decided not by its inherent merits or demerits alone but by factors beyond the control of Medical Science.

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