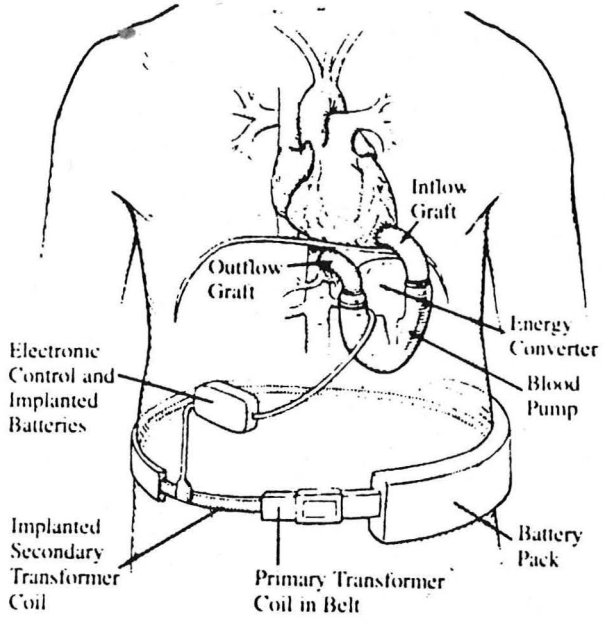
REPLACEMENT OF THE FAILING HEART



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MEDICAL GRAND ROUNDS

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AT DALLAS
SOUTHWESTERN MEDICAL SCHOOL

"The transplantation of organs will be assimilated into ordinary clinical practice --- and there is no need to be philosophical about it. This will come about for the single and sufficient reason that people are so constituted that they would rather be alive than dead".

Sir Peter Medawar, at the Second International Congress of the Transplantation Society, September 11, 1968, New York City.

I. HEART TRANSPLANTATION

In December, 1967, Professor Christiaan Barnard performed the first human heart transplant in Cape Town, South Africa (1). During the past eighteen and a half years, this procedure has passed from the realm of the esoteric and highly experimental to being an accepted therapeutic modality in certain patients with end-stage congestive heart failure. It seems appropriate at this time to review the present status of heart transplantation and the major advances that have occurred in this arena during the past two decades.

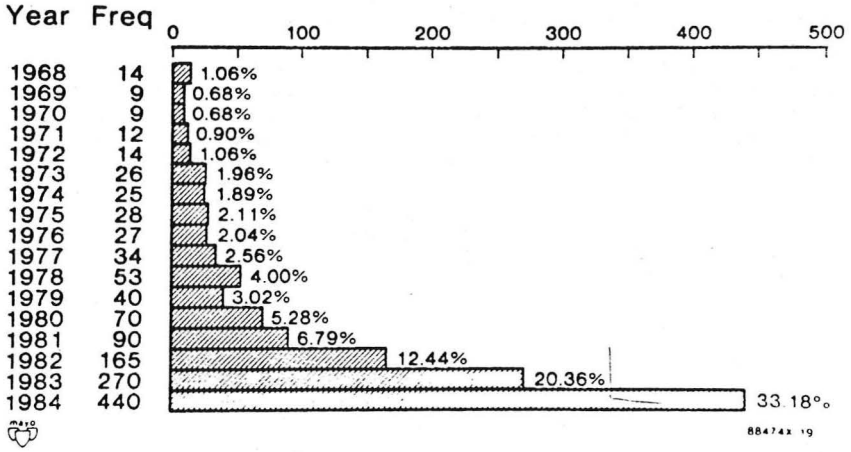
1. Current Status of Heart Transplantation

After the initial success of Barnard and his colleagues, heart transplants were performed very enthusiastically but with generally dismal results at a large number of centers world-wide. Therefore, by the early 1970s, the procedure had been abandoned by virtually all centers except four, namely, Stanford University, the University of Cape Town, South Africa, the Medical College of Virginia, and Hôpital de la Pitié, Paris. However, by 1978-80, both Stanford University and the University of Cape Town, reported greater than 60% one year survival rates following heart transplantation i.e. a survival rate very comparable to that of cadaver kidney transplants at that time (2,3). As a result of these favorable results an ever-increasing number of heart transplants are being performed world-wide (Figure 1) (4). The data presented in Figure 1 represent only the centers that participate in the International Heart Transplantation Registry. It is estimated that at least 800 heart transplants were performed world-wide in 1985.

The International Heart Transplantation Registry in 1984, included 29 centers in the USA, 4 in France, 4 in Canada, 2 in West Germany, and 1 each in the United Kingdom, South Africa, Norway, Belgium, and Spain (Table I). Several additional centers, including Dr. Magdi Yacoub's center in London, which is the major center for heart transplantation in Europe, are apparently not currently participating in this registry.

Figure 1

NUMBER OF TRANSPLANTS PERFORMED EACH YEAR (1968 - 1984)



Reference 4

Table I

REGISTRY PARTICIPANTS (1984)

INTERNATIONAL SOCIETY FOR HEART TRANSPLANTATION:

USA:	**29 centers**
France:	**4 centers**
Canada:	**4 centers**
W. Germany:	**2 centers**
U.K.:	**1 center**
South Africa:	**1 center**
Norway:	**1 center**
Belgium:	**1 center**
Spain:	**1 center**

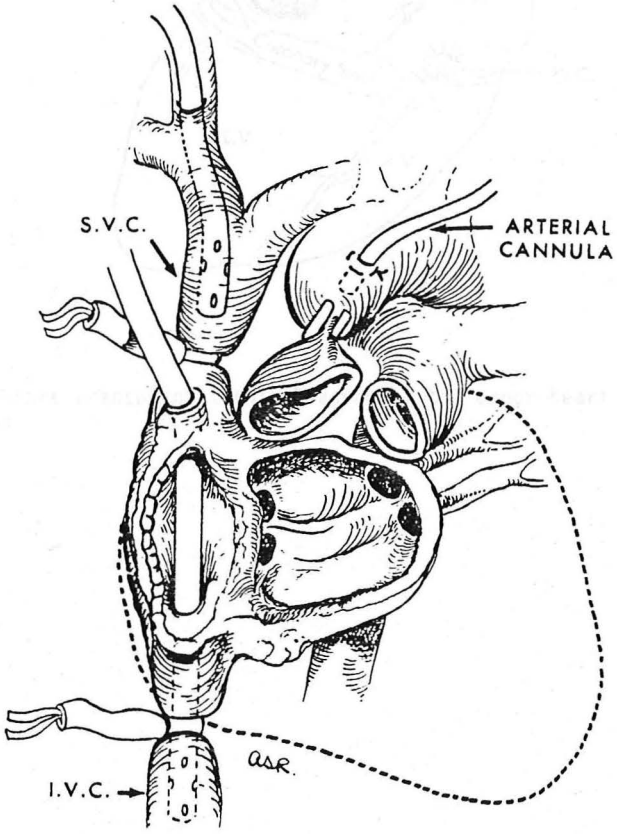
Reference 4

At the present time, the 1 year survival rate is greater than 80% and the 5 year survival rate is approximately 50% at major heart transplant centers (4).

2. The Transplant Procedure

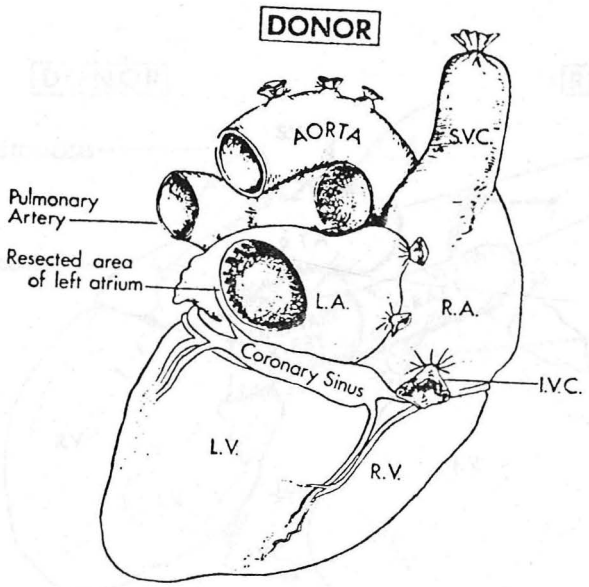
Heart transplantation may be performed in one of two ways: orthotopically or heterotopically (5,6). Orthotopic transplantation refers to placement of the donor heart in the normal intrathoracic position following removal of the native heart (Figures 2 & 3). Conversely, heterotopic transplantation refers to placement of the donor heart in a position other than the normal intrathoracic position. In practice, this usually implies that the donor heart is placed to the right of the native heart as shown in Figure 4.

Figure 2



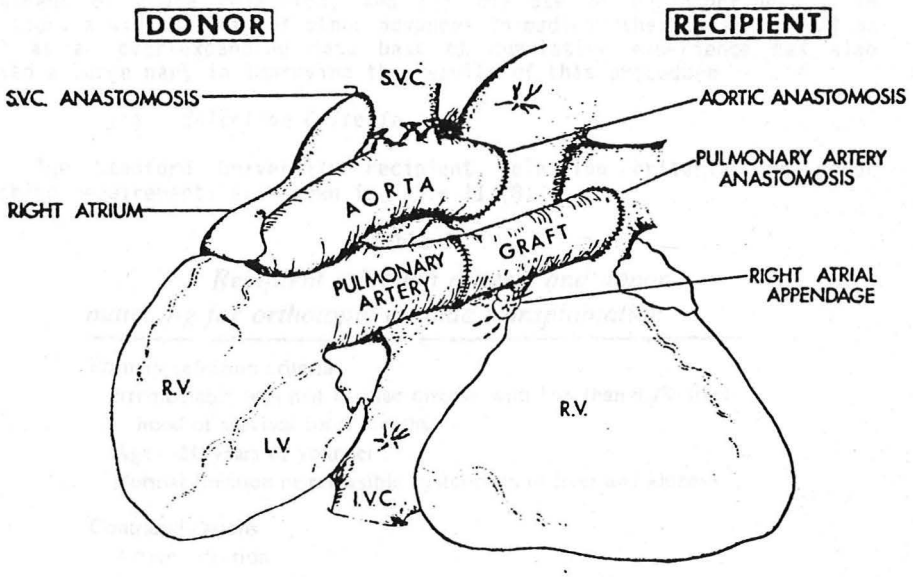
Orthotopic heart transplantation. Diagram of the recipient prior to implantation of the donor heart.

Figure 3



Orthotopic heart transplantation: Diagram of the donor heart ready for implantation.

Figure 4



Heterotopic heart transplantation. Reference 5.

The relative advantages and disadvantages of heterotopic versus orthotopic heart transplantation, as well as a detailed account of the physiological consequences of these procedures, have been exhaustively reviewed previously (7). The reader is referred to this source for additional information.

3. Major Advances in Heart Transplantation During the Past Two Decades

There have been three major advances in the field of heart transplantation that have led to a marked improvement in survival, namely, (1) refinement of selection criteria, (2) aggressive diagnosis and treatment of acute rejection, and (3) the use of cyclosporine-A. In addition, a wide variety of other advances in medical therapy in general as well as an ever-expanding data base of cumulative experience has also played a large part in improving the results of this procedure.

(1) *Selection Criteria*

The Stanford University recipient selection criteria and donor matching requirements are shown in Table II (8).

Table II

Recipient selection criteria and donor matching for orthotopic cardiac transplantation

Primary selection criteria
Irremediable terminal cardiac disease with less than 10% likelihood of survival for 6 months
Age—50 years or younger
Normal function or reversible dysfunction of liver and kidneys
Contraindications
Active infection
Recent pulmonary infarction
Diabetes mellitus necessitating insulin
Pulmonary vascular resistance greater than 8 Wood units and unresponsive to vasodilator drugs
Symptomatic or documented severe peripheral or cerebrovascular disease
Active peptic ulcer disease
Drug addiction
Psychosis or mental deficiency unrelated to low cardiac output or metabolic status
Alcoholic cardiomyopathy
Absence of adequate external psychosocial support
Presence of any systemic illness that would limit recovery or survival
Donor matching
ABO compatibility
Absence of donor-specific lymphocyte cytotoxicity
Appropriate size match
HLA-A2 compatibility

Reference 8

The criteria laid down by Stanford University have generally been adhered to by other centers. However, some of these criteria have been liberalized by other centers (9-12).

a. Age

It is now fairly common practice at several centers to consider patients for transplantation who are over 50 years of age. Nevertheless, the data from the International Heart Transplantation Registry (1984), clearly suggest that increasing age is a significant risk factor (Table III). In this series, patients aged more than 50 years had a 28% chance of surviving 6 years as compared to a 59% 6 year survival in those aged 20-29 years.

Table III

AGE AS A RISK FACTOR

Chance of survival at 6 years

20-29 years:	59%
30-39 years:	51%
40-49 years:	34%
50+ years:	28%
0-19 years:	Inadequate numbers

International Heart Transplantation Registry (1984)

Reference 4

b. Recent pulmonary infarction

While it has been the general practice to wait at least 6 weeks after a pulmonary infarction before proceeding to heart transplantation, several centers (University of Pittsburgh, Harefield Hospital, England) have recently verbally reported on heart transplants in a few near-terminal patients soon after pulmonary infarction. Although several of these patients survived, they all had a stormy post-operative course and this approach is not generally recommended.

c. Diabetes mellitus necessitating insulin

Patients with insulin-dependent diabetes mellitus are now being considered for heart transplantation by several centers, providing they do not have any evidence of a diabetic nephropathy.

d. Pulmonary arterial hypertension

A pulmonary vascular resistance greater than 8 units (620 dynes-sec-cm^{-5}) is still generally considered to be an absolute contraindication to orthotopic, but not heterotopic, heart transplantation. With lesser degrees of pulmonary hypertension, for example a pulmonary vascular resistance of 2-8 units (160-640 dynes-sec-cm^{-5}), the Stanford University investigators place great reliance on the response to vasodilator agents (nitroprusside or prostacyclin) (13). However, other investigators are skeptical about the utility of this approach and will instead either use an oversized heart or proceed to heterotopic heart transplantation, depending on the severity of the pulmonary hypertension.

e. Presence of any systemic illness that would limit recovery or survival

In addition to the exceptions already mentioned, several other specific exceptions to this general rule have been made. Thus, patients with sarcoidosis, a limited malignancy (particularly a superficial malignancy), and those with a history of peptic ulcer disease or ulcerative colitis may now be considered with the advent of cyclosporine-A. However, severe systemic arterial hypertension, chronic infection (particularly deep-seated infections), significant renal or hepatic failure, malignancies other than those mentioned, and extensive systemic atherosclerotic disease are still generally held to be a contraindication to receiving a heart transplant.

f. HLA-A2 compatibility

Although the Stanford University group has suggested that HLA-A2 histocompatibility matching may be important, particularly with regard to avoiding chronic graft rejection, this opinion is not generally shared by other investigators (2). However, Yacoub (12) has suggested that if the MT locus and not just the DR locus is matched, 1 year survival in his series is greater than 90% as compared to approximately 75% when these loci are not matched.

(2) *Aggressive diagnosis and treatment of acute rejection*

Acute rejection of the transplanted heart remains one of the most frequent troublesome complications to beset heart transplantation.

a. Clinical signs and electrocardiographic changes

A diagnosis of acute rejection was initially based on clinical signs and symptoms, or electrocardiographic changes, particularly a decrease in QRS voltage. 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 and may only occur once a considerable amount of myocardium has been irreversibly damaged. In the patient with a heterotopic heart transplant, these findings are of little value since the presence of the patient's own heart will obscure the signs of right sided failure even in advanced rejection (14). Preclinical studies of heart transplantation revealed that rejection was heralded by decreases in QRS voltage (15) and histological findings consisting of myocardial edema and serous infiltration (16). The ECG findings in patients with allograft rejection were studied in the 1960s (17). A decrease in QRS voltage was found to be 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 interrupted and the 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.

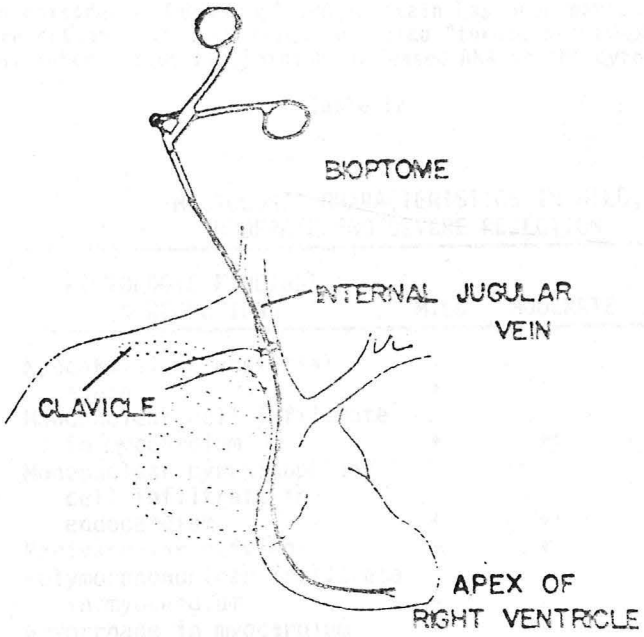
With conventional immunosuppressive therapy, ECG voltage is highly sensitive but not entirely specific for rejection. Technical factors such as lead placement and variability in electrode contact may account for voltage decreases. Changes in thoracic impedance from pneumonia, pneumothorax and pleural 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).

With the advent of cyclosporine-A as the main immunosuppressive agent, the sensitivity of electrocardiographic changes, such as a reduction in QRS voltage, for the detection of transplant rejection, has decreased (18). This is probably because the rejection process that is seen in patients who are receiving cyclosporine-A generally results in much less interstitial edema in the myocardium and hence less change in QRS voltage. Therefore, much less reliance is now being placed on QRS voltage changes for detecting acute rejection.

b. Endomyocardial biopsy

Percutaneous transvenous biopsy of both right and left ventricles with specially designed biopsy forceps was first described by Sakakibara and Konno (19). This technique was modified for use in cardiac transplantation by Caves and Billingham in 1973 (20-22). The technique of endomyocardial biopsy via the right internal jugular vein is illustrated in Figure 5.

Figure 5



Endomyocardial biopsy via the right internal jugular vein. Reference 23

The biopsy procedure takes 10-15 minutes and is performed under local anesthesia in a procedure room with fluoroscopic control. Three to five separate specimens are generally obtained during each procedure. These specimens are 2-3 mm in size and are routinely obtained from several different sites on the septal wall of the right ventricle. In large series of patients, the incidence of significant complications is less than 0.5%. The most frequent complication (0.4%) is pneumothorax (23).

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 and characterize, in a semi-quantitative fashion, the severity of the rejection episode (Table IV) (23). Interstitial graft fibrosis is sometimes seen and may reflect the degree of irreversible damage sustained by the graft during previous rejection episodes. 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.

Table IV

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	-	+	++

Reference 23

Criticism of the biopsy technique has focused primarily on the possibility of sampling error and the subtlety of histologic changes in diagnosing rejection (24). However, Rose et al (25) 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 (22). Since the procedure can be performed percutaneously, rapidly and safely, it can be repeated as often as necessary to assess graft histology serially. 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.

At the present time, most heart transplant centers perform endomyocardial biopsies weekly for the first 3 months, monthly for the next 3-6 months, and yearly after 12 months, or if there is any clinical reason to suspect rejection. With current therapy, including the use of cyclosporine-A, about 3 rejection episodes can be expected during the first 3 post-operative months, and 1 in 10 will experience no rejection. In subsequent months, approximately 1 acute rejection episode per year is expected (26). The use of cyclosporine-A appears to be associated with a reduction in the severity, but not necessarily the frequency, of rejection episodes (18).

c. Immunologic monitoring

The use of a wide variety of immunological monitoring techniques as an alternative to endomyocardial biopsy has enjoyed considerable attention. Clearly, a less invasive procedure that could detect early evidence of graft rejection would have a great deal to recommend it.

Initially, when rabbit anti-thymocyte globulin was introduced as part of the immunosuppressive regimen for heart transplantation, T-cell levels were markedly and uniformly found to be reduced within 5 days post-operatively from 65% to less than 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 was found to correlate closely with, and precede, histologically detectable rejection (27). Unfortunately, this test is of no value after 6 weeks post-operatively since T-cell levels tend to rise toward normal, irrespective of the presence or absence of graft rejection (28). More importantly, monitoring circulating T-cell levels has been found to be of virtually no use even in the early post-operative period in patients treated with cyclosporine-A (18). Therefore, this technique of immunologic monitoring has fallen into disfavor. Other immunologic evaluations, including the phytohemagglutinin blastogenesis test, modified reactive leukocyte blastogenesis test, B cell levels, T-cell reactivity to mitogens, B-cell reactivity to staphylococcal strain, spontaneous lymphocyte blastogenesis, "K"-cell cytotoxicity, and mixed lymphocyte culture have been proposed (23). None of these has yet found widespread favor.

The lack of utility of circulating levels of T-lymphocytes, or subsets of T-lymphocytes, for the detection of graft rejection has resulted in even greater reliance on endomyocardial biopsy as the only certain technique for the early detection of graft rejection, or response to therapy.

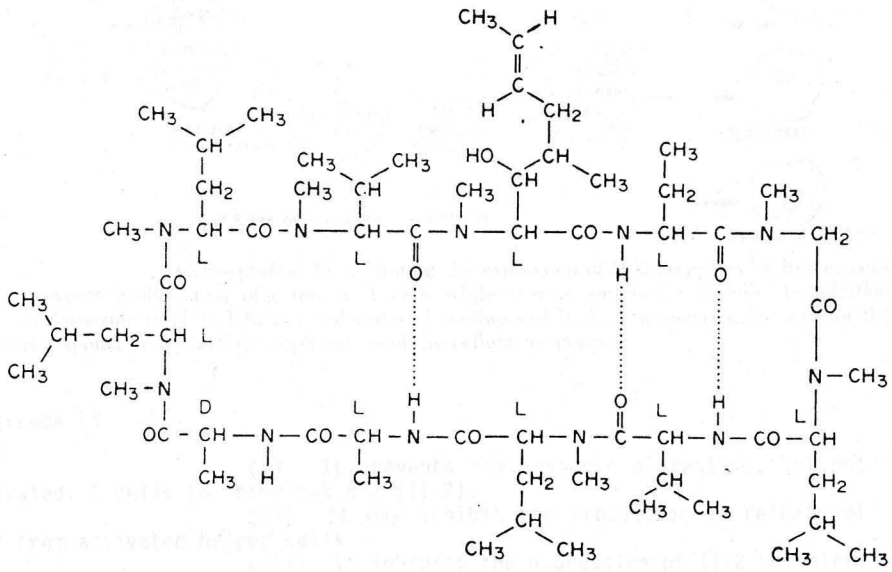
(3) *New immunosuppressive modalities*

During the late 1970s, the conventional mode of therapy for heart transplant recipients developed by the group at Stanford University and the Medical College of Virginia comprised rabbit antithymocyte globulin (RATG), prednisone and azathioprine. With these drugs, both centers ultimately reported graft and patient survival of 50-70 percent at 1 year and 30-50 percent at 5 years (2,29). However, the initial reports of the successful use of cyclosporine-A by Calne (30), Starzl (31) and their associates for renal and hepatic transplantation, and Oyer, et al for heart transplantation (32), suggested that the use of this agent might even further improve the results of transplantation.

a. Structure and function of cyclosporine-A

Cyclosporine-A is a lipophilic, hydrophobic, cyclic endecapeptide which was first developed from crude extracts of two fungi Imperfecti, *Cylindrocarpon lucidum Booth* and *Tolypocladium inflatum Gams* (33) (Figure 6).

Figure 6



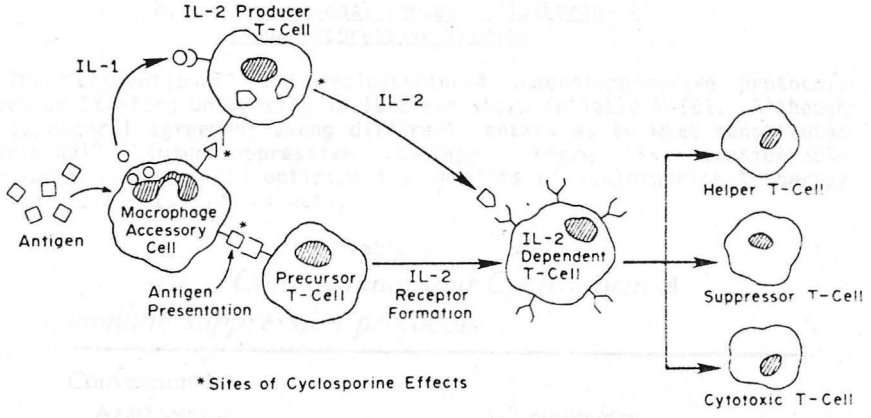
The cyclosporine molecule is a lipophilic cyclic peptide.

Reference 18

The immunosuppressive effects of cyclosporine-A appear to occur at an early stage after the exposure of the host to foreign antigens. It appears to have a selective action on lymphocytes. It is not lymphocytotoxic but affects and regulates T-cell proliferation in a reversible manner. There are two very important advantages to the use of cyclosporine-A. First, it is not myelosuppressive and lessens the potential for anemia, thrombocytopenia, and leukopenia with resultant infection. Second, it enables the transplant recipient to be managed with much lower dosages of corticosteroids. This limits or obviates the steroid-related complications that are only too prevalent in transplant recipients.

The precise mechanism whereby cyclosporine-A is immunosuppressive has been reviewed in the past two years in Grand Rounds by Drs. Hal Helderman (34) and Jennifer Cuthbert (35). I shall therefore only touch on this question briefly. In essence, cyclosporine-A has several major immunosuppressive effects, which are largely mediated by its effects on the lymphokines, interleukin 1+2 (Figure 7):

Figure 7



Cyclosporine, by inhibiting the expression of IL-2 receptors by helper cells, prevents proliferation of cytotoxic T cells while sparing suppressor T cells. In addition, cyclosporine inhibits T-helper-cell–induced synthesis of IL-1 by accessory cells, a factor that is responsible for further amplification of the cellular response.

Reference 18

(i) It prevents the response of resting, but not activated, T cells to interleukin 2 (Il-2).

(ii) It may inhibit the production or release of Il-2 from activated helper cells.

(iii) It inhibits the expression of Il-2 receptors by helper cells thereby preventing proliferation of cytotoxic T cells while

sparing T suppressor cells. This allows selective activation of suppressor T cells.

(iv) It inhibits T-helper-cell synthesis of Il-1 by accessory cells, a factor that is responsible for further amplification of the cellular response.

Cyclosporine-A has no direct action on B cells. It also does not appear to act directly on macrophages and other accessory cells. The clinical correlation of this *in vitro* information is that cyclosporine-A suppresses the response to new antigenic stimuli but is relatively ineffective in suppressing the response of the host previously sensitized to a specific alloantigen. In general, it is not useful for the treatment of early acute rejection, although it has proven useful in some cases (36). The immunosuppressive effects of cyclosporine-A do not seem to be of long duration, since patients cannot be successfully removed from cyclosporine-A immunosuppression without rejection, unless alternative immunosuppressive therapy is commenced. Goldman et al (18) have recently provided an excellent review of the use of cyclosporine-A in heart transplantation that provides additional information on pharmacokinetics, drug interactions, monitoring of drug levels, and the frequency and severity of side-effects.

b. Conventional versus cyclosporine-A immunosuppressive therapy

The "conventional" and cyclosporine-A immunosuppressive protocols employed by Stanford University in 1982 are shown in Table V (8). Although there is general agreement among different centers as to what constitutes "conventional" immunosuppressive therapy, there is considerable disagreement as to how to optimize the benefits of cyclosporine-A therapy while minimizing its side-effects.

Table V

Conventional and Cyclosporin-A immune suppression protocols

Conventional	
Azathioprine	1-2 mg/kg/day
Prednisone	1.5 mg/kg/day (initial)
	1.0 mg/kg/day (2 months)
	0.3 mg/kg/day (1 year)
Antithymocyte globulin	14 day initial course
Cyclosporin-A	
Cyclosporin-A	18 mg/kg/day (initial)
	6-10 mg/kg/day (4-6 months)
Prednisone	1.0 mg/kg/day (initial)
	0.3 mg/kg/day (6 weeks)
	0.2 mg/kg/day (2 months)
Antithymocyte globulin	3-4 day initial course

Reference 8

The group at Stanford University, who have performed well over 300 heart transplants commencing in 1968, are now using lower initial doses of cyclosporine-A, use RATG for the first 7 days, attempt to reduce patients to prednisone 0.2 mg/kg/day earlier, and maintain patients on azathioprine treatment in addition to cyclosporine (13). Dr. Magdi Yacoub's group at Harefield Hospital in England has performed over 220 heart transplants (including 45 heart lung transplants) in just the past 3½ years, with similar, or even better results than the Stanford group using a very different regimen (37). His regimen comprises:

Cyclosporine-A (10mg/kg) Azathioprine (2mg/kg)	A few hours pre-operatively
Methylprednisolone (1gm iv)	Intra-operatively
Cyclosporine-A (5-22mg/kg/day) (depending on blood levels & renal function)	Post-operatively
Azathioprine (0.5-1.5 mg/kg/day) (depending on WBC count)	Post-operatively
Oral acyclovir x 3 months	Post-operatively

Of particular note, is the fact that RATG is not used, long-term steroid therapy is not employed and acyclovir is employed prophylactically in an attempt to eliminate herpes and Ebstein-Barr virus, and possible related malignancies. This is the only major center to have completely eliminated the chronic use of corticosteroid agents. Most other centers in this country are currently using cyclosporine-A in addition to corticosteroids, with or without the use of azathioprine.

c. Treatment of acute rejection episodes

The pervasive use of cyclosporine-A immunosuppression has rendered ECG voltage changes and changes in circulating lymphocyte subpopulations too unreliable for the diagnosis of rejection (38). Therefore, endomyocardial biopsy alone is the only accepted method of assessing rejection in cardiac recipients treated with cyclosporine-A. Dr. Margaret Billingham has developed criteria for the diagnosis of rejection based on the histology of the endomyocardial biopsy specimen in patients treated with cyclosporine-A (39,18) (Table VI). Amounts and types of infiltrating cells and the degree of myocyte necrosis provide a qualitative assessment of the degree of rejection: minimal, mild, moderate, severe, or resolving. In addition, the presence of methyl green-pyronine (MGP)-stained cells, or activated lymphocytes, is indicative of ongoing rejection. In general, minimal or mild rejection shown on a biopsy does not require treatment, but a second biopsy should follow within a week. Severe rejection should be treated. Various regimens are used, but solumedrol 500-1000mg i.v. daily for 3-5 days is a common initial treatment. Subsequent management is illustrated in the schema in Figure 8 (18).

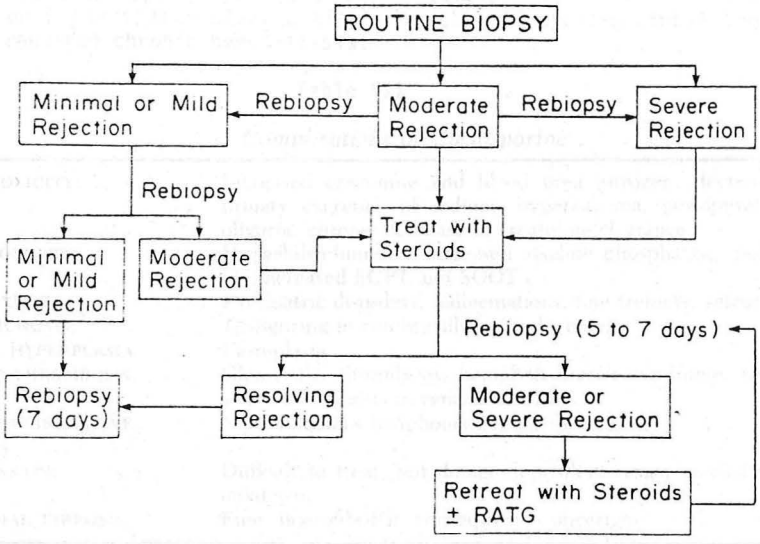
Table VI

Criteria for Diagnosing Acute Cardiac Allograft Rejection in Patients on Cyclosporine

EARLY AND/OR MINIMAL
Endothelial cell swelling
Interstitial edema
MILD
Same as minimal but with the addition of:
Low-density lymphocyte, plasma cell, and/or histiocyte perivascular or endocardial infiltrate*
Myocellular nuclear alteration characterized by nuclear enlargement with wrinkled nuclear membrane
MODERATE
Same as mild but with the addition of:
Moderate-density perivascular, endocardial, or interstitial inflammatory cell infiltrate
Focal myocytolysis
SEVERE
Same as moderate but with the addition of:
Prominent neutrophil and/or lymphoplasmocellular or histiocytic perivascular and interstitial infiltrate
Vascular or myocellular necrosis with interstitial hemorrhage
RESOLVING
Small lymphocytes and plasma cells without the presence of pyroninophilia
Hemosiderin deposition
Active and maturing fibrosis
CYCLOSPORINE EFFECT
Wispy interstitial fibrosis, independent of rejection

Reference 18

Figure 8



Algorithm for the assessment of cardiac biopsies and rejection therapy.

Reference 18

d. Problems associated with cyclosporine-A therapy

It is generally agreed that cyclosporine-A therapy is associated with a shorter in-hospital stay, a reduction in steroid-related side-effects, and possibly an improvement in survival. In addition, the severity of acute rejection episodes, if not their frequency, is reduced. The incidence of early life-threatening bacterial and fungal infections may be less, but viral (especially herpes and cytomegalovirus) and protozoal infections seem to be as frequent, or even increased (18,40-44).

Since cyclosporine-A has major toxic side-effects, it is imperative to monitor blood or serum levels of cyclosporine-A frequently and consider these in association with other laboratory data, particularly those related to renal function. Unfortunately, there is no standardized technique for assaying cyclosporine concentrations. Some laboratories use a radioimmunoassay while others use high pressure liquid chromatography; some report on serum levels while others report whole blood levels. The group at Harefield Hospital (37) use a radioimmunoassay, and aim to keep the serum level of cyclosporine-A at 500-1000ng/ml during the first month, and then try to reduce it to 300ng/ml, or even 150ng/ml. Conversely the group at the University of Pittsburgh also use a radioimmunoassay technique but aim to keep the whole blood cyclosporine level at 1000 ng/ml chronically (45). The precise values used need to be standardized for each laboratory depending on the technique used.

The most troublesome side-effects with cyclosporine-A therapy are detailed on Table VII. Nephrotoxicity is the single biggest concern and has led certain groups to switch some patients back to conventional therapy and discontinue cyclosporine-A therapy. While it is generally held that the nephrotoxic effects are reversible with cessation or reduction of cyclosporine-A therapy (46), Myers et al (47,48) from Stanford recently reported on 3 heart transplant patients on chronic cyclosporine-A therapy who have required chronic hemodialysis.

Table VII

Complications of Cyclosporine

NEPHROTOXICITY:	Increased creatinine and blood urea nitrogen, decreased urinary excretion of sodium, hyperkalemia, postoperative oliguria, chronic decrease in creatinine clearance
HEPATOTOXICITY:	Hyperbilirubinemia, increased alkaline phosphatase, possible increased SGPT and SGOT
NEUROTOXICITY:	Psychiatric disorders, hallucinations, fine tremors, seizures
HYPERTRICHOSIS:	Disfiguring in young children and women
GINGIVAL HYPERPLASIA	Fibroplasia
VASCULAR THROMBOSIS:	Glomerular thrombosis, hemolytic-uremic syndrome, renal artery thrombosis in renal transplants
LYMPHOPROLIFERATIVE DISORDERS:	Non-Hodgkin's lymphomas, Kaposi's sarcoma
HYPERTENSION:	Difficult to treat, not dosage-dependent, exact mechanism unknown
MYOCARDIAL FIBROSIS:	Fine, microfibrillar; consequences uncertain

Hypertension is ubiquitous in patients treated with cyclosporine-A, but may be more common when cyclosporine-A is used in combination with corticosteroids than when it is used alone (12). There is also some concern about the long-term effects of the fine, microfibrillar myocardial fibrosis that may occur in these patients.

Although some groups doubt that cyclosporine-A has led to an improvement in survival (49), the International Society for Heart Transplantation Registry suggests that the use of cyclosporine-A is indeed associated with improved survival in heart transplant recipients (Table VIII) (Figure 9) (4). However, these data are based on historical controls and are, therefore, suspect. There is unfortunately no true randomized comparison of a standardized "conventional" immunosuppressive therapy protocol with a standardized cyclosporine-A immunosuppressive therapy protocol for heart transplant recipients.

Table VIII

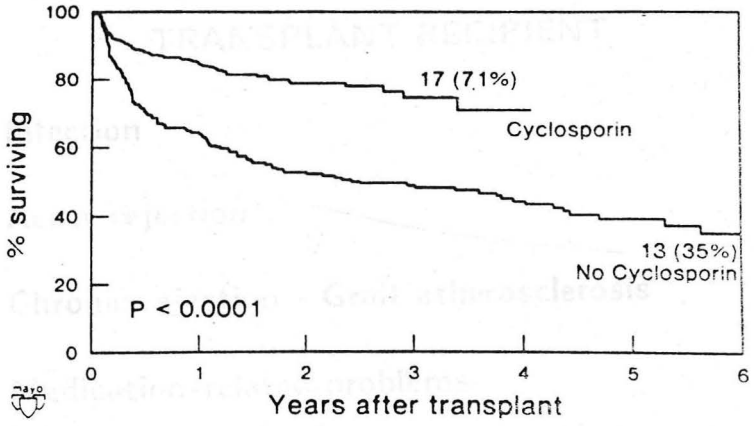
PREDICTORS OF SURVIVAL FOLLOWING HEART TRANSPLANTATION

Variable	Beta	Chi-square	P
Age	0.0244	14.33	0.0002
Sex (1=male) (2=female)	0.1735	1.09	0.2968
Place	0.3581	5.73	0.0167
Cause (0=CAD) (1=Cardiomyopathy)	-0.0491	0.15	0.6997
Transplant Date	-0.0002	9.43	0.0021
Cyclosporine (0=No) (1=Yes)	-0.7601	20.33	<0.0001
Age	0.0241	16.55	<0.0001
Place	0.03778	6.48	0.0109
Transplant Date	-0.0002	10.44	0.0012
Cyclosporine	-0.7529	20.03	<0.0001

International Heart Transplantation Registry (1984)

Reference 4

Figure 9



Six-year survival of heart transplant recipients. Impact of cyclosporine therapy on survival excluding the first 30 day mortality. Transplantations performed during and after 1978 only.

Reference 4

4. Causes of Graft Failure and/or Death Following Heart Transplantation

The most important causes of graft failure and/or death following heart transplantation are infection, acute rejection, graft arteriosclerosis, and malignancy, (Table IX) (8). The cumulative causes of death following cardiac transplantation in 131 patients at Stanford University from 1968-1981 are illustrated in Figure 10, while the linearized rate of life-threatening complications at yearly intervals is shown in Figure 11.

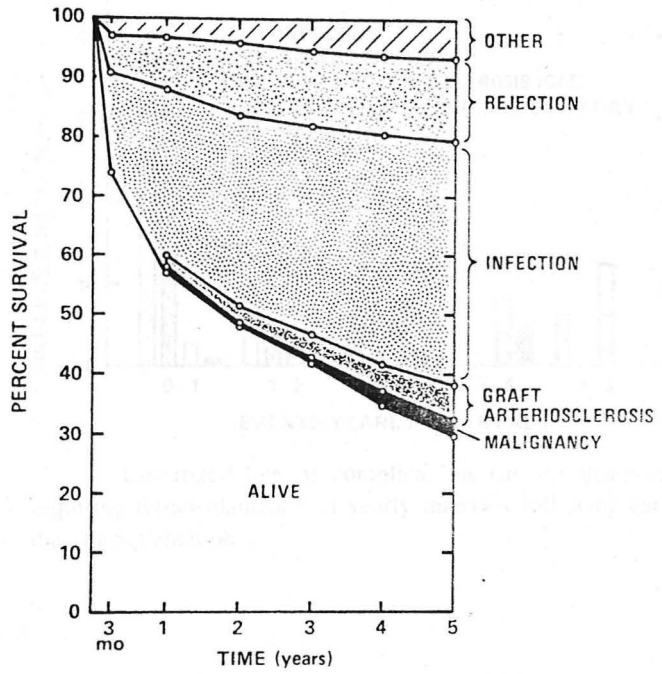
Table IX

MAJOR MEDICAL PROBLEMS IN THE HEART TRANSPLANT RECIPIENT

1. Infection
2. Acute rejection
3. Chronic rejection - Graft atherosclerosis
4. Medication-related problems
5. Malignancy

Graft arteriosclerosis remains an enigma. It may occur in some patients within the first year of life and increases in frequency with time. By 4-5 years after transplantation, the incidence of death, or graft failure necessitating retransplantation due to graft arteriosclerosis approximates 12% per patient-year in the Stanford experience (50,51). The pathological findings are consistent with the concept that immune injury to the coronary artery in time exposes a thrombogenic surface, leading to the aggregation and activation of platelets with release of mitogenic factors that promote proliferation of myointimal cells and migration through the internal elastic lamina. The morphologic result of this initial phase of accelerated graft arteriosclerosis is a thickened intimal layer resulting from cellular proliferation and increased amounts of ground substance. Subsequent lipid deposition ensues, and autopsy findings in patients dying after 2 years from graft arteriosclerosis show lesions morphologically similar to native spontaneously occurring atherosclerosis (52).

Figure 10

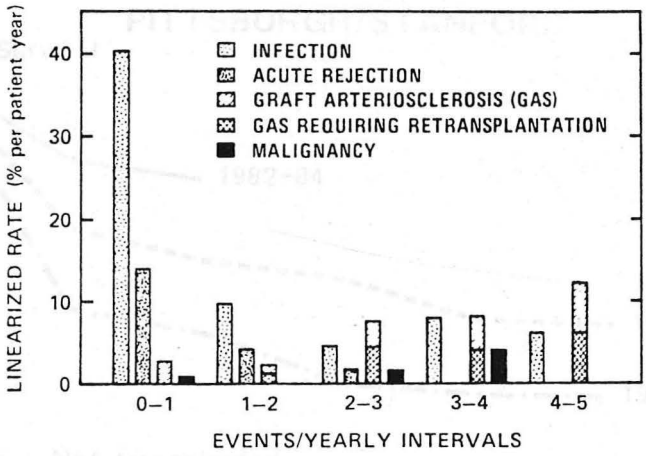


Cumulative causes of death following cardiac transplantation.

Reference 8

The development of graft arteriosclerosis was examined in 85 one-year survivors of heart transplantation at Stanford by annual coronary arteriograms (52). By multivariant analysis, HLA-A2 incompatibility, and serum triglyceride levels greater than 280ng/ml at 1 year post-operatively, were found to be significant independent predictors of late graft arteriosclerosis ($p<0.026$ and $p<0.034$, respectively). These findings have not yet been corroborated by other investigators.

Figure 11



Linearized rate of complications causing death or requiring retransplantation at yearly intervals following cardiac transplantation.

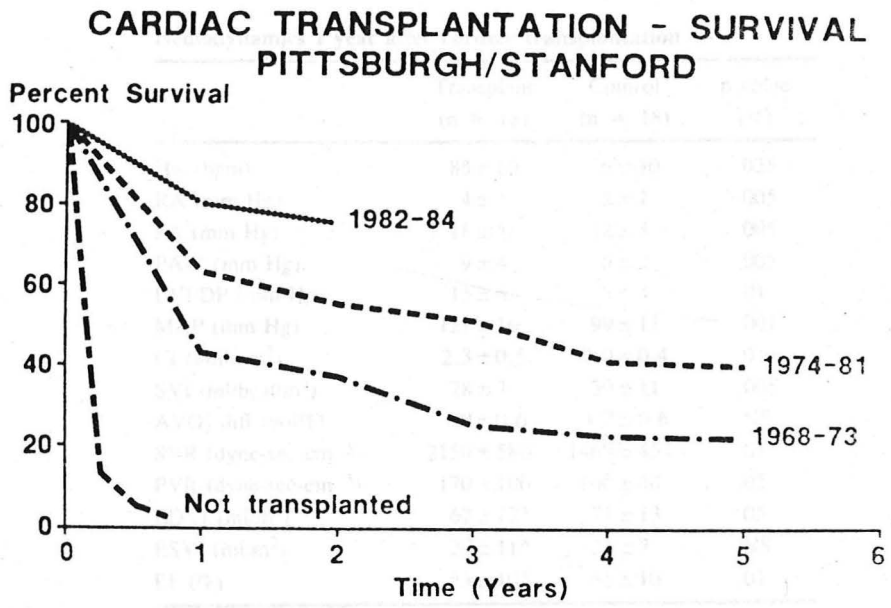
Reference 8

Malignant neoplasms occur with an increased frequency in immunosuppressed patients. While lymphomas are the most common malignancies encountered, squamous cell lesions and adenocarcinomas may also occur (8,53). Although the risk of developing a malignancy is real, the linearized rate of death from this cause is less than 4% per patient year. An increased incidence of lymphoma has been reported in younger transplant recipients, those with a dilated cardiomyopathy rather than coronary artery disease, and patients undergoing retransplantation (8). Initial fears that the use of cyclosporine *per se* increased the incidence of lymphoma, have not been substantiated.

5. Hemodynamic and Functional Results of Heart Transplantation

The potential problems following heart transplantation have been discussed in some detail. Nevertheless, the generally favorable survival rate of greater than 80% at 1 year and greater than 50% at 5 years at the present time, implies that the vast majority of patients do not succumb from these dread complications (Figure 12).

Figure 12



Reference 9

1. *Late hemodynamic sequelae of transplantation*

Greenberg et al (54) evaluated the long-term hemodynamic results in cardiac transplant patients treated with cyclosporine and prednisone 1 year post-operatively. These 18 patients were asymptomatic but had developed post-operative systemic hypertension, which required treatment in 17 patients. These patients were compared with a normotensive group of 18 controls without cardiovascular disease. Significant differences were found in a number of variables, shown in Table X. The most frequent hemodynamic abnormalities included an elevated systemic arterial pressure in 10 patients, (56%), an elevated left ventricular end-diastolic pressure in 6 (33%), and a reduced left ventricular ejection fraction in 5 patients (28%). Hemodynamic abnormalities tended to resolve or improve in the five patients restudied 2 years after heart transplantation (Table XI). There was no significant relationship between fibrosis or inflammation on endomyocardial biopsy and hemodynamic abnormalities. A more detailed, sophisticated study of left ventricular function 1 year following transplantation, at rest and during inotropic stimulation, indicates that left ventricular function, as well as contractile reserve, is generally normal at this time (55).

Table X

Hemodynamics 1 year after cardiac transplantation

	Transplant (n = 18)	Control (n = 18)	p value (<)
HR (bpm)	85 ± 10	76 ± 10	.025
RA (mm Hg)	4 ± 3	2 ± 2	.005
PA (mm Hg)	18 ± 5	12 ± 3	.005
PAW (mm Hg)	9 ± 4	5 ± 2	.005
LVEDP (mm Hg)	13 ± 6	8 ± 4	.01
MAP (mm Hg)	121 ± 16	99 ± 11	.001
CI (l/min/m^2)	2.3 ± 0.5	3.0 ± 0.4	.01
SVI (ml/beat/m^2)	28 ± 7	39 ± 11	.005
AVO_2 diff (vol%)	4.9 ± 0.6	4.7 ± 0.6	NS
SVR (dyne-sec-cm^{-5})	2150 ± 580	1469 ± 454	.01
PVR (dyne-sec-cm^{-5})	170 ± 100	100 ± 40	.05
EDVI (ml/m^2)	62 ± 12^	71 ± 13	.05
ESVI (ml/m^2)	29 ± 11^	25 ± 7	NS
EF (%)	53 ± 10^	65 ± 10	.01

Reference 54

Table XI

Hemodynamics 1 and 2 years after transplantation

	HR (bpm)	RA (mm Hg)	PA (mm Hg)	PAW (mm Hg)	LVEDP (mm Hg)	MAP (mm Hg)	CI (l min m^{-2})	AVO_2 (vol%)	PVR (dyne-sec-cm^{-5})	SVR (dyne-sec-cm^{-5})	EDVI (ml m^{-2})	ESVI (ml m^{-2})	EF (%)
Patient 1													
First year	80	3	14	5	10	122	3.0	4.4	163	2395	70	32	55
Second year	71	2	12	4	6	108	2.2	4.7	139	1843	73	25	65
Patient 2													
First year	94	9	20	12	16	130	2.1	5.0	168	2547	55	21	63
Second year	75	3	11	8	8	112	1.8	5.3	69	2520	60	22	63
Patient 3													
First year	82	0	16	7	9	123	1.7	5.0	261	3562	73	49	34
Second year	100	2	14	6	8	125	2.2	5.3	182	2810	63	31	47
Patient 4													
First year	80	6	27	18	21	110	2.9	4.6	122	1410	65	30	54
Second year	100	3	22	8	15	112	3.6	4.3	143	1111	48	18	62
Patient 5													
First year	80	5	18	8	13	130	2.0	5.4	152	2057	75	39	48
Second year	100	6	20	9	14	105	1.7	5.8	230	2134	50	20	60

Reference 54

2. *Rehabilitation following cardiac transplantation*

The quality of life of 106 heart transplant recipients at Stanford University who survived more than one year was reviewed by Pennock et al (8). As shown in Table XII, 97% had achieved NYHA Class I cardiac disability. This is quite remarkable since virtually all patients had NYHA Class IV clinical status and a predicted survival of less than 6 months before transplantation. Eighty-two percent enjoyed active rehabilitation and 73 percent returned to active employment, activity as homemakers, or continuing education. Similar gratifying functional results have been observed by most other major heart transplant centers.

Table XII

Rehabilitation following cardiac transplantation: One-year survivors (N = 106)

	No.	*Percent*
New York Heart Association functional status		
Class I	103	97
Class II	2	
Class III	1	
Class IV	0	
Rehabilitated		
Yes	87	82
No	19	
Work activity		
Employed full time	45	
Employed part time	14	
Homemaker	8	
Student	10	
	77	73
Retired by choice	19	
Medical disability	10	

Reference 8

II. HEART-LUNG TRANSPLANTATION

Heart transplantation alone, whether orthotopic or heterotopic, is not feasible in patients with severe irreversible pulmonary hypertension. However, such patients may be candidates for combined heart-lung transplantation.

There are two major, different groups of patients, who may benefit from combined heart-lung transplantation:

(i) Patients with advanced pulmonary vascular disease, and associated cardiac failure, either due to congenital heart disease with Eisenmenger Syndrome or due to primary pulmonary hypertension. These patients are generally in their 3rd and 4th decades of life and have marked functional disability.

(ii) Patients with irreversible parenchymal lung disease (e.g. due to chronic obstructive airways disease, pulmonary fibrosis, cystic fibrosis, bronchiectasis) with secondary pulmonary vascular disease and heart failure. In general, these patients are much less suitable for transplantation because of the fear of chronic infection following transplantation in most of these conditions.

1. Current Status of Heart-Lung Transplantation

After nearly 20 years of laboratory experience, the first successful human heart-lung transplantation was performed at Stanford University in 1981 (56). At the present time, several heart transplantation centers are also performing heart-lung transplants. The major heart-lung transplant centers at present include Stanford University, the University of Pittsburgh and Harefield Hospital, England. More than 45 heart-lung transplants have been performed by Dr. Yacoub's group at Harefield Hospital/The National Heart Hospital, London, England, while more than 30 heart-lung transplants have been performed at Stanford University (12,13).

The primary indications for heart-lung transplantation are the presence of severe pulmonary, or combined pulmonary and cardiac disease, in patients who have a low likelihood of surviving 6 months with conventional therapy (57-59). The vast majority of heart-lung transplants have been performed on patients with primary pulmonary hypertension or Eisenmenger Syndrome. Apart from the permissible presence of severe pulmonary hypertension in the recipient, the donor and recipient selection criteria conform in most respects to those previously outlined for heart transplantation. In addition, the donor must have normal pulmonary function. This generally implies a normal chest roentgenogram, an arterial oxygen tension of more than 350 mmHg on an inspired oxygen fraction of 1.0 without positive end-expiratory pressure, peak inspiratory pressures less than 20 cm H_2O at tidal volumes of 15 ml/kg, and normocarbia with these tidal volumes and respiratory rates of 10 to 14 breaths per minute. There are several important considerations that apply to the technical aspects of heart-lung transplantation (60,61). First, the lungs tolerate prolonged ischemia even less well than the heart. While an ischemic time of 5 hours (from explantation to reimplantation) may still be compatible with a good functional heart transplant, successful heart-lung transplants generally necessitate much shorter ischemic times, of the order of two hours or less. In general, this mitigates against distant organ procurement, which

markedly limits the supply of available donors. Second, the transplant procedure is in some respects easier than orthotopic or heterotopic heart transplantation, since the heart and lungs are transferred en bloc. Thus, there are really only three anastomotic sites: the tracheal anastomosis, the right atrial anastomosis, and the ascending aortic anastomosis. Third, since the heart and lungs are transplanted en bloc, a good size match between the donor and recipient is much more critical than with heart transplantation alone. This further limits the available donor pool. Finally, while the merits or demerits of cyclosporine-A for heart transplantation may be debated, its use is imperative if heart-lung transplantation is to be successful (62). Bitter past experience has led many investigators to appreciate that the tracheal anastomosis will not heal when high-dose corticosteroids rather than cyclosporine-A is used.

The patient data on the first 22 heart-lung transplants performed at Stanford are shown in Table XIII. Ten patients carried a diagnosis of primary pulmonary hypertension and 12 had congenital heart disease with severe pulmonary hypertension. The actuarial survival curves for these heart-lung transplant patients and for patients undergoing simple heart transplantation during the same period are shown in Figure 13. Actuarial survival at 1 and 2 years for heart-lung transplants was predicted to be 71±9.9% (SEM) and 57±12%, respectively as compared to 83±3.6% and 76±4.5%, respectively. The preoperative hemodynamic data in 13 of these patients who survived for more than 1 year are shown in Table XIV, while the post-operative hemodynamic data at 1 year in these patients are shown in Table XV (63). There is a striking reduction in mean pulmonary arterial pressure (73±19 to 9±3 mmHg). There is also an increase in mean aortic pressure, which is at least in part due to the use of cyclosporine-A, an increase in cardiac index, and a marked reduction in pulmonary vascular resistance. Five patients were restudied 2 years after transplantation and no significant changes in hemodynamics were noted.

The effects of heart-lung transplantation on the arterial blood gases in these 13 patients are equally interesting (Table XVI) (63). One year following transplantation, arterial pO_2 had increased from a mean of approximately 52 mmHg to 87 mmHg and the pCO_2 had increased from approximately 27 mmHg to 36 mmHg. Although the arterial blood gases were normal 1 year following transplantation, the alveolar-arterial gradient for oxygen was increased to 18±9 mmHg (normal less than 10 mmHg for this age group). Although there is an initial severe restrictive ventilatory defect following transplantation due to a decrease in most lung volumes, lung function tends to improve progressively with the passage of time (64).

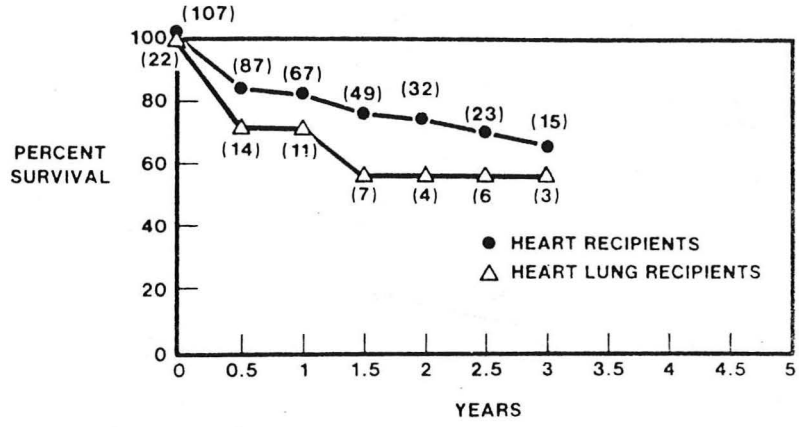
TABLE XIII

Patient data

Patient No.	Age (yr)	Sex	Age of donor (yr)	Diagnosis	Follow-up	Outcome
1	45	F	15	PPH	44	Alive
2	39	M	21 (14)	ASD; VSD (Holt-Oram)	42	Alive (retx 37 months)
3	28	F	22	TGA; ASD; VSD[V]	0	Died 4 days
4	40	M	19	ASD; VSD	37	Alive
5	37	F	30	PPH[II]	35	Alive
6	26	F	15	PPH	0	Died 23 days
7	22	M	27	VSD[V]	0	Died at operation
8	40	M	23	VSD	24	Alive
9	22	M	18	VSD	24	Alive
10	27	M	22	VSD	14	Died 14 months
11	38	M	17	VSD	22	Alive
12	32	M	32	VSD	15	Died 15 months
13	33	M	21	PPH	17	Alive
14	28	F	15	PPH	0	Died 15 days
15	42	M	20	UVH(R); L-TGA; ASD	1	Died 33 days
16	22	M	26	PPH	12	Alive
17	37	M	18	PPH	11	Alive
18	33	F	16	PPH	7	Alive
19	40	M	19	A-P window	6	Alive
20	20	M	21	PPH[II]	4	Alive
21	31	F	25	PPH	3	Alive
22	37	M	20	VSD[IV]	0	Died 17 days

Demographic data on the first 22 heart-lung transplants at Stanford University. Reference 63

Figure 13



Actuarial survival curves for all patients undergoing heart-lung transplantation (△) compared with those for patients undergoing simple heart transplantation during the same period (●).

Reference 63

Table XIV

Patient No.	PAP	PACWP (mean)	Ao	PVR	CO/CI
1	72/38 (50)	5	130/84 (104)	13.8	2.7/1.9
2	94/52 (66)	0	—	13.5	4.9/8.3
4	120/60 (90)	5	140/80 (100)	—	—
5	120/40 (70)	0	—	36.8	1.9/1.3
8	110/55 (73)	—	110/60 (77)	—	—
9	115/60 (82)	6	103/66 (78)	24.1	3.4/1.8
10	120/70 (87)	14	104/70 (80)	15.8	5.5/2.7
11	115/80 (92)	8	125/70 (90)	—	—
12	122/70 (85)	10	120/80 (95)	—	—
13	43/22 (32)	8	—	5.6	5.7/2.8
Total mean	103/55 (73)	6	119/73 (89)	18.3	4.0/3.1

Pre-operative hemodynamic data in 13 heart-lung transplant recipients.
Reference 63

Table XV

Patient No.	PAP	PACWP	LV	Ao	PVR	CO/CI	A-V O_2 difference
1	13/2 (6)	a4 v4 (2)	175/0/4	170/104 (132)	0.9	4.4/3.5	3.6
2	10/3 (6)	a1 v2 (0)	146/0/4	154/105 (124)	0.4	4.5/2.6	4.8
4	14/6 (10)	a5 v5 (3)	140/0/4	140/100 (113)	1.4	4.9/2.5	5.1
5	9/4 (6)	a2 v4 (1)	124/0/2	124/91 (104)	1.5	3.3/2.0	5.2
8	10/4 (6)	a4 v3 (2)	125/0/6	118/88 (103)	0.5	7.6/3.9	3.6
9	12/7 (9)	a5 v1 (2)	169/7/8	169/129 (147)	1.3	5.3/3.8	3.8
10	25/10 (14)	a14 v13 (8)	—	—	0.8	7.3/6.5	3.7
11	13/6 (9)	a6 v7 (5)	164/3/8	164/111 (137)	0.6	6.8/4.0	3.3
12	21/11 (15)	a7 v7 (2)	108/0/0	112/88 (98)	2.2	5.8/3.4	4.2
13	19/10 (12)	a9 v10 (6)	119/2/12	119/91 (105)	0.8	7.1/3.6	4.0
Total mean	15/6 (9)	a6 v6 (3)	141/1/5	141/101 (118)	1.0	5.7/3.6	4.1

Postoperative hemodynamic data in 13 heart-lung transplant recipients at 1 year. Reference 63

Table XVI

Patient	Before surgery		1 yr after surgery		
No.	Pao_2	$Paco_2$	Pao_2	$Paco_2$	A-a
1	79	31	88	40	11.7
2	—	—	81	39	20.0
4	—	—	91	40	8.7
5	61	32	102	32	7.7
8	27	21	76	33	32.4
9	46	27	83	36	21.7
10	45	24	82	39	19.0
11	51	31	97	30	15.2
12	21	31	75	33	33.5
13	89	24	94	34	13.2
Mean	52.4	27.6	86.9	35.6	18.3

Arterial blood gas data pre-operatively and after 1 year in 13 heart-lung transplant recipients. Reference 63

2. Problems with Heart-Lung Transplantation

Patients with heart-lung transplantation are subject to all the same problems as patients with more conventional heart transplants. In addition, there are certain additional problems specific to the lungs that occur in these patients.

(1) *Problems with the tracheal anastomosis*

The healing of the tracheal anastomosis has been the major problem facing heart-lung transplantation until the advent of cyclosporine-A. Unilateral lung transplantation has been plagued by bronchial dehiscence in the past since there is no arterial vascular contribution from the donor side. In contradistinction, with combined heart-lung transplants, coronary-bronchial collaterals can open up to restore vascularity to the vessels previously supplied by the bronchial arteries. Coronary arteriograms done late post-operatively invariably show the development of collaterals to the area of the suture line from the donor left and right coronary arteries (58). Necrosis, rupture or late stenosis at the tracheal anastomosis have not yet been seen in the patients receiving a transplant or in the primate survivors of heart-lung transplantation.

(2) *The implantation response*

The post-operative management of patients with lung transplants is complicated by the development of impaired pulmonary gas exchange and the radiological appearance of interstitial edema about 11 days (range 4-20 days) post implantation (65). The pattern persists for approximately 7 days and then resolves spontaneously. The roentgenographic findings are associated with a reversible defect in pulmonary gas exchange, compliance and vascular resistance. The cause is unknown, but it is likely that surgical trauma, ischemia, denervation, lymphatic interruption and other processes, exclusive of rejection, all contribute. Lymphatics probably regenerate after lung transplantation by the third week, thereby coinciding with the resolution of this process. However, if lymphatic interruption is the cause of this phenomenon, the puzzling aspect is the lag period observed before its onset, since lymphatic interruption is present immediately. This delay might incriminate ischemic changes of the lung as the primary cause, with resolution being aided by lymphatic regeneration. Whatever the precise mechanism of this process, the best method of management according to the Stanford University group is aggressive diuresis, with the aim of achieving a negative weight balance early after operation. However, if such an approach results in oliguria, the hazards of cyclosporine-A are compounded.

(3) *Asynchronous rejection of the heart and lungs*

Conventional wisdom has suggested that rejection of the lung would occur at the same time as rejection of the heart. Therefore, the adequacy of immunosuppressive therapy for the transplanted lung has generally been judged based on the result of endomyocardial biopsy. However, rejection of the lungs may occur in the absence of cardiac rejection (66,67). The group at the University of Pittsburgh suggest that in 6 of their first 10 heart-lung transplants, isolated rejection of the lungs developed in the absence of cardiac rejection. In 3 of these patients, the suspicion of pulmonary

rejection was confirmed by open lung biopsy. In addition, patients responded within 12 to 24 hours to augmented immunosuppression with a dramatic improvement in the abnormal chest radiograph. This has led the group at the University of Pittsburgh to suggest that in the absence of clinical infection, the appearance of a diffuse pulmonary infiltrate after the first post-operative week should be treated with a brief course of intravenous corticosteroids, irrespective of the results of endomyocardial biopsy.

The dispassionate reviewer of the literature on heart-lung transplantation is clearly faced with an unresolved question. In the absence of infection or of evidence of cardiac rejection on endomyocardial biopsy, does a diffuse bilateral infiltrate on chest roentgenogram in the 2nd or 3rd week following transplantation represent isolated asynchronous *rejection* of the lungs and not the heart that should be treated with steroids, or is it an *implantation response* that should be observed and not treated in any specific manner? Since pulmonary histology is available in only a few patients in this situation, it begs the further question whether the concept of a benign "implantation response" is indeed correct or whether all such cases in fact represent pulmonary rejection episodes that may be self-limited? This question is unresolved at present. However, more liberal use of limited open-lung biopsy in this setting in the future will hopefully resolve this question.

(4) *Bronchiolitis obliterans*

Following heart-lung transplantation, an asymptomatic *restrictive* ventilatory defect typically occurs early (68). This improves slowly towards normal at one year. However, in some patients an *obstructive* ventilatory defect is seen with or without a progressive restrictive process. These alterations in lung function are associated histologically with obliterative bronchiolitis. The clinical course of 5 such patients from the Stanford experience has been carefully documented (69). The results of serial pulmonary function tests in these patients are shown in Table XVII and the changes in FEV_1 with time are shown in Figure 14. The features that serve to differentiate this entity from other forms of obstructive lung disease are shown in Table XVIII.

The occurrence of post-transplant obliterative bronchiolitis is worrisome. It seems very possible that this entity is the pulmonary equivalent of late graft arteriosclerosis in the heart. Of the five patients reported above, two patients had died, two were markedly symptomatic but still alive, and one was asymptomatic at the time of writing. It is of particular interest that one of the deaths was due to acute myocardial infarction in the transplanted heart. This adds further credence to the idea that graft arteriosclerosis and bronchiolitis obliterans have a common basis. However, the precise mechanisms, which are almost certainly immunological, need to be elucidated. Once bronchiolitis obliterans develops, there does not seem to be any spontaneous regresssion of the process. Neither the frequency nor the natural history of this condition is well characterized as yet. To what extent bronchiolitis obliterans may be related to prior low grade acute rejection episodes is also unknown.

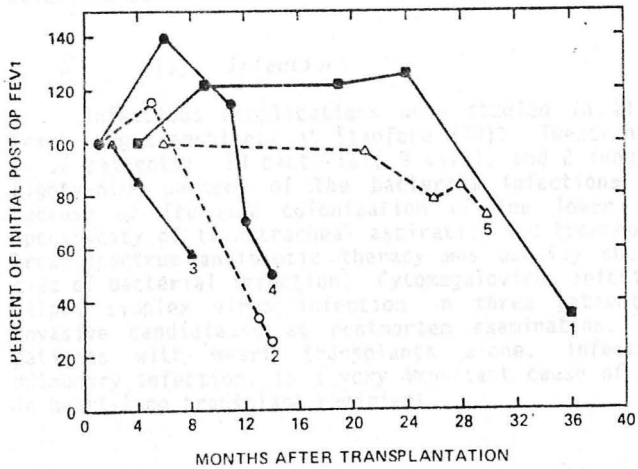
Table XVII

Pulmonary Function Variables in Five Heart-Lung Transplant Recipients

Patient No	Months After Surgery	FEV_1(L)	FVC(L)	FEV_1/ FVC(%)	FEF_{25}/ FVC	FEF_{25-75} (L/s)	RV(L)	TLC(L)	RV/ TLC(%)	Helium Equilibr (Min)	PaO_2/ $PaCO_2$ (mmHg)	Dco
1	4	2.3 (56)	2.6 (50)	89	1.4 (117)	2.9 (66)	0.9 (56)	3.6 (53)	25	3.0	—	(73)
	9	2.8 (68)	3.2 (62)	88	1.2 (100)	3.7 (84)	1.5 (94)	4.8 (71)	31	3.0	—	(73)
	19	2.8 (68)	3.0 (58)	91	1.4 (117)	3.1 (72)	1.0 (63)	4.3 (63)	23	3.0	—	(46)
	24	2.9 (71)	3.3 (63)	87	1.2 (100)	3.5 (81)	1.1 (69)	4.5 (66)	24	3.0	—	(69)
	36	0.8 (20)	1.7 (33)	49	0.2 (17)	0.3 (7)	2.0 (125)	3.8 (56)	53	6.0	—	(44)
2	1	3.2 (71)	3.5 (60)	91	1.5 (125)	4.4 (94)	1.0 (59)	4.6 (62)	22	2.0	82/39	(64)
	5	3.7 (82)	4.4 (77)	85	1.1 (92)	4.2 (91)	1.2 (71)	5.8 (78)	21	3.5	—	(66)
	13	1.1 (24)	1.8 (32)	59	0.3 (25)	0.5 (11)	1.8 (106)	3.7 (50)	49	7.0	58/38	(40)
	14	0.8 (18)	1.4 (25)	56	0.1 (8)	0.4 (9)	2.0 (118)	3.5 (47)	57	7.5	54/42	(45)
3	2	2.6 (60)	3.3 (59)	77	0.8 (67)	2.2 (49)	2.6 (144)	5.9 (80)	44	6.0	75/33	(51)
	4	2.2 (51)	3.2 (57)	69	0.4 (33)	1.4 (31)	2.0 (111)	5.5 (74)	36	6.5	72/32	(97)
	8	1.5 (35)	2.5 (45)	56	0.2 (17)	0.6 (14)	2.0 (111)	4.6 (62)	43	6.0	62/33	(64)
4	1	2.0 (47)	2.1 (40)	95	1.5 (125)	3.0 (64)	3.0 (200)	5.1 (75)	59	6.0	93/36	(75)
	6	3.0 (70)	3.3 (62)	91	1.1 (92)	3.3 (70)	2.0 (133)	4.9 (72)	41	4.5	91/38	(100)
	11	2.3 (53)	2.4 (45)	95	1.6 (133)	3.6 (77)	1.8 (120)	4.1 (60)	44	7.5	90/36	(50)
	12	1.4 (33)	2.1 (40)	68	0.4 (33)	0.9 (19)	2.4 (160)	4.7 (69)	51	6.0	74/32	(49)
	14	1.0 (23)	2.2 (42)	45	0.2 (17)	0.4 (9)	2.5 (167)	4.9 (72)	51	7.0	67/33	(56)
5	6	3.2 (73)	4.1 (69)	80	1.2 (86)	3.8 (90)	1.3 (65)	5.4 (68)	24	4.0	100/33	(64)
	21	3.1 (72)	4.1 (71)	77	1.0 (71)	2.5 (60)	1.6 (80)	5.4 (65)	30	4.0	84/34	(69)
	26	2.5 (58)	3.6 (62)	68	0.4 (29)	1.4 (33)	1.8 (90)	5.3 (67)	34	6.5	73/35	(68)
	28	2.7 (63)	4.1 (71)	67	0.6 (43)	1.6 (39)	1.7 (85)	5.8 (74)	29	6.0	68/34	(73)
	30	2.3 (53)	3.6 (62)	64	0.4 (29)	1.0 (24)	2.3 (115)	5.9 (76)	39	6.0	73/35	(69)

Sequential pulmonary function tests in 5 patients who developed bronchiolitis obliterans. Reference 69

Figure 14



FEV_1 values (expressed as percentage of initial postoperative values) in five patients after combined heart-lung transplantation. Numbers on graph correspond to patient numbers in text. Note that decrease in flow rates occurred between four and 36 months post-transplantation.

Changes in FEV_1 with time in 5 heart-lung transplant recipients who developed bronchiolitis obliterans. Reference 69

Table XVIII

Differential Features of Posttransplantation Obliterative Bronchiolitis Compared with Classic Forms of Chronic Obstructive Lung Disease

Feature	Posttranspl. OB	Non-Infectious Chronic Bronchitis	Obstructive Emphysema	Chronic Bronchial Asthma
Rate of development	Rapid: several months to 1-2 years	Slow many years	Slow many years	Paroxysmal, but usually slow
Clinical features	Bronchitic symptoms followed by early development of dyspnea	Bronchitic symptoms with delayed development of dyspnea	Slow development of dyspnea which antedates bronchitic symptoms	Dyspnea fluctuates as do bronchitic symptoms
Chest x-ray film findings	Distinct infiltrative component	Infiltrative component usually not extensive	No infiltrative component except with infection or heart failure	Infiltrative component only under special circumstance
Mechanical abnormalities	Severe obstructive and restrictive lung disease	Obstructive lung disease	Obstructive lung disease	Obstructive lung disease
Total lung capacity	Decreased	Increased	Increased	Increased
Blood gases	Blue puffers	Blue bloaters	Pink puffers	Depends on severity
Reversibility with bronchodilators	Largely irreversible	Often reversible	Largely irreversible	Frequently reversible
Spontaneous improvement of flow rates with time	None	Occasionally	None	Frequently

Reference 69

(5) *Infections*

Infectious complications were studied in 14 patients who received heart-lung transplants at Stanford (70). Twenty-nine infections occurred in 12 patients: 18 bacterial, 9 viral, and 2 fungal (Tables XIX and XX). Eighty-nine percent of the bacterial infections occurred in the lung. Because of frequent colonization of the lower respiratory tract, the specificity of transtracheal aspiration and bronchoscopy are low. Empiric broad-spectrum antibiotic therapy was usually successful and no patient died of bacterial infection. Cytomegalovirus infection occurred in six and herpes simplex virus infection in three patients. Two patients had invasive candidiasis at postmortem examination. Thus, as is true in patients with heart transplants alone, infection, and particularly pulmonary infection, is a very important cause of morbidity and mortality in heart-lung transplant recipients.

Table XIX

Microbiologically Proved or Clincally Suspected Bacterial Infections in Heart-Lung Transplant Recipients

	Number of Episodes
Pneumonia	
Microbiologically proved	
Bacteroides melaninogenicus*	1
Legionella pneumophila	2
Mixed aerobic/anerobic infection	1
Clinically suspected	
Pseudomonas aeruginosa	1
Serratia marcescens	2
Saphylococcus aureus	2
Hemophilus influenzae	1
Unknown†	6
Acute bronchitis	1
Sinusitis/otitis media	1
Total	18

Reference 70

Table XX

Nonbacterial Infections in Heart-Lung Transplant Recipients

	Number of Patients	Total
Viral		9
Cytomegalovirus		
Asymptomatic shedding	2	
Fever only	2	
Fever and leukopenia	1	
Disseminated*	1	
Total	6	
Herpes simplex virus		
Asymptomatic shedding	1	
Perianal ulceration and hemorrhage	1	
Disseminated*	1	
Total	3	
Varicella-zoster virus	0	
Fungal		2
Candida		
Disseminated*	2	
Pneumocystis		0
Toxoplasma		0
Nocardia		0

Reference 70

III. ARTIFICIAL HEART AND VENTRICULAR ASSIST DEVICES

The most common disorder causing suffering, loss of health and premature death in our society is failure of the heart to function normally. While heart transplantation is showing impressive results, there will always be far more potential recipients (17-35,000 annually) than donors (approximately 1,300-2,000 annually) (71-73). Hence, the enthusiasm for the development of permanent ventricular assist devices. The heart is an organ with a basically mechanical function and is inherently suitable for replacement by a prosthetic mechanical device. Therefore, despite much sensational and often adverse publicity recently, the idea of replacing the failing biological heart with a mechanical pump is in many ways still attractive (74).

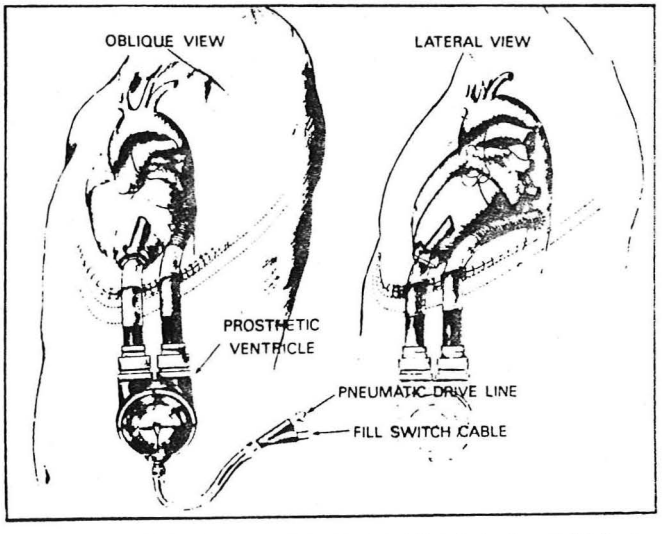
It seems appropriate to review at this time the status of the National Heart, Lung, and Blood Institute (NHLBI) artificial heart program (74). This program has been in existence for 21 years and has consumed some $200 million of public funds. It has concentrated primarily on the development of an implantable left ventricular assist device (LVAD) rather than a total artificial heart. The rationale for this is that many patients may not require replacement of the right side of the heart, which may be functioning normally, and the fewer the components, the smaller the likelihood of mechanical failure. Nevertheless, the expectation is that the principles learned from the left (or right) ventricular assist devices could be rapidly implemented in the development of a total artificial heart. This would merely represent two ventricular assist devices in series.

1. Artificial Heart or Ventricular Assist Devices and Potential Power Supplies

A total power supply of approximately 30 watts is required to drive a total artificial heart. Because of differences in the arterial input impedance facing the left and right sides of the heart, a LVAD would require approximately 90% of this power while a RVAD would require only 10% (75). Since the inception of the NHLBI artificial heart program in 1966, four major sources of power have been considered and/or evaluated, namely pneumatic, nuclear, thermal and electrical. Pneumatic power sources have been used for ventricular assist devices designed by several different groups. Such a device with its coupling to an external pneumatic-power source, is shown in Figure 15. A pneumatic power source has also been used for the Jarvik 7 total artificial heart. The internal design of one of the pumping chambers of the Jarvik 7 is illustrated in Figure 16. In common with many other systems, the blood chamber has an inlet and an outlet valve. Tilting disc valves of the Bjork-Shiley or Medtronic-Hall type are commonly used. The blood chamber is separated from an air chamber by a diaphragm. Blood is moved rhythmically in and out of the blood chamber by the movement of the diaphragm which in turn is regulated by the movement of compressed air from an external source. *Temporary* ventricular assist devices, with an external power source have been used nearly 300 times to wean patients from heart-lung machines and to salvage others in profound cardiogenic shock. In addition, such devices have been used at least 6 times to provide *temporary* support until a suitable heart transplant donor could be found (TABLE XXI). In addition, total artificial hearts with

external power supplies, have been used either as *permanent* devices or as a *bridge to heart transplantation* in at least 9 patients (Table XXII) (77-79). While there is general agreement in the scientific community that *temporary* ventricular assist devices may be of value, the state of the permanent artificial heart, particularly the Jarvik-7 device, is much more controversial because of the complications that have occurred with its use. These will be discussed later. The quality of life enjoyed by the patients in whom these devices were used as a *permanent* implant has been generally unacceptable and the subject of much sensational publicity. There are many problems with an external power source. These include: 1) the need for a transcutaneous pneumatic power line, with its attendant risk of infections; 2) the size and lack of portability of this power source; 3) the noise associated with an air compressor; and 4) the complexity of such a power source. Nuclear energy, using plutonium as the substrate, has been seriously considered. It has recently been abandoned as an alternative because of the radioactive hazard that it might pose if leakage of the required 50 grams of plutonium occurred, for example during an automobile accident. Thermal sources of energy, that depend on the interaction of certain chemical reagents which are stored within the body in a thermal storage unit are under evaluation. This system is thought to afford potential for the most compact system with the longest lifetime, but still needs considerable refinement.

Figure 15



Prosthetic Ventricle Connected from the Left Ventricular Apex and Returning Blood Flow to the Descending Aorta.

Reference 74

Figure 16

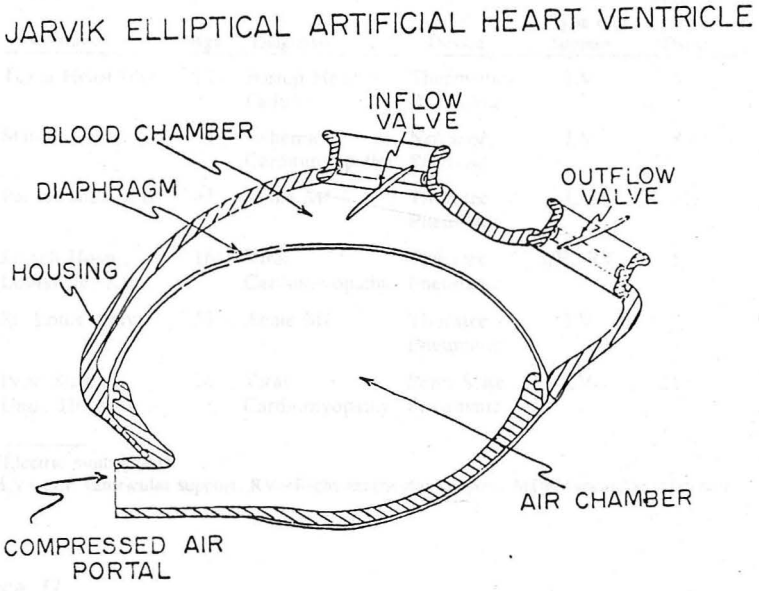

JARVIK ELLIPTICAL ARTIFICIAL HEART VENTRICLE
INFLOW VALVE
BLOOD CHAMBER
DIAPHRAGM
OUTFLOW VALVE
HOUSING
AIR CHAMBER
COMPRESSED AIR PORTAL

Table XXI

Ventricular Assistance As Bridge to Transplantation

Institution	Age	Diagnosis	Device	Type of Support	Support Prior to Transplant (Days)
Texas Heart Inst.	21	Postop Heart Failure	Thermedics Pneumatic	LV	5
Stanford Univ.	51	Ischemic Cardiomyopathy	Novacor[1] Solenoid	LV	8½
Pacific Med. Ctr.	47	Acute MI	Thoratec Pneumatic	LV	2½
Jewish Hosp., Louisville, Ky.	16	Viral Cardiomyopathy	Thoratec Pneumatic	LV, RV	5
St. Louis Univ.	53	Acute MI	Thoratec Pneumatic	LV	2
Penn State Univ. Hosp.	24	Viral Cardiomyopathy	Penn State Pneumatic	LV	21

[1]Electric motor VAD

LV=Left ventricular support, RV=Right ventricular support, MI=Myocardial infarction.

Reference 77

Table XXII

Artificial Heart Implantation

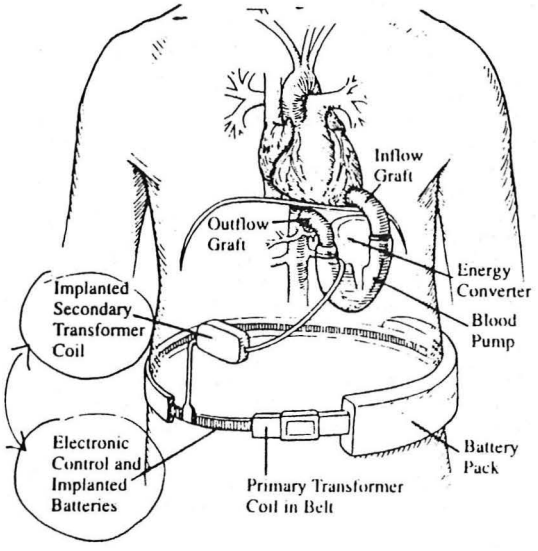
Institution	Age	Diagnosis	Device	Duration	Comments
Texas Heart Inst.	47	Ischemic cardiomyopathy	Liotta/Hall	64 hours	Transplanted. Died 32 hrs. later.
Texas Heart Inst.	36	Postop. MI	Akutsu III	39 hours	Transplanted. Died 8 days later.
Univ. of Utah	61	Idiopathic cardiomyopathy	Jarvik-7	112 days	Permanent implant.
Humana Heart Inst.	52	Ischemic cardiomyopathy	Jarvik-7	Alive 10 months postop.	Permanent implant.
Humana Heart Inst.	58	Idiopathic cardiomyopathy	Jarvik-7	Alive 7 months postop.	Permanent implant.
Univ. of Arizona	33	Ischemic cardiomyopathy	Phoenix heart	12 hours	Transplant. Died 36 hrs. later.
Humana Heart Inst.	62	Ischemic cardiomyopathy	Jarvik-7	10 days	Permanent implant.
Karolinska Inst.	53	N/A	Jarvik-7	Alive	Permanent implant.
Univ. of Arizona	25	Viral cardiomyopathy	Jarvik-7	9 days	Transplanted. Convalescing.

N/A = Not available

Reference 77

At the present time, electrical sources of energy seem to be the most viable possibilities for the development of an implantable ventricular assist device without the need for transcutaneous tubes or wires (75,80). Such an electrically powered system is shown in Figure 17. The left ventricular assist device incorporates an energy converter and is attached to an electronic control and implanted batteries, which in turn are connected to an implanted secondary transformer coil. The primary tranformer coil is external and a battery pack is worn around the waist. The small rechargeable implanted battery will allow 30-45 minutes of pump operation without any external apparatus. The external batteries must be recharged or exchanged for charged batteries every 8-10 hours.

Figure 17



Diagrammatic representation of fully implantable electrically powered left ventricular assist device. Reference 77

2. Tether-free Ventricular Assist Devices

Within the NHLBI program, four electrically-powered, tether-free systems are under development (75). Each has focused in the early stages on a left ventricular assist device with emphasis on miniaturization, integration of the pump with the implantable power source, and the control and reliability of the whole system. Systems under consideration at this time include: 1) the Pierce-Donachie-Thoratec device; 2) the Novacor device; 3) the Nimbus device; and 4) the Thermedics device. The initial development of these devices was funded via NIH grants. At the present time, much of the development is being undertaken by individual investigators in collaboration with industry. Most of these devices are driven by DC brushless motors that provide non-pulsatile flow. Although pulsatile flow is more appealing teleologically, non-pulsatile flows of more than 90 ml/kg per minute have kept animals alive in good physiologic condition for up to 3 months. In addition, these devices are provided with certain feed-back loops so that the output can be varied depending on

filling pressures. Most of these devices would be connected on the inflow end to the apex of the left ventricle and on the outflow end to the descending aorta. The pump itself would be placed either in the thorax or the abdomen. For a typical left ventricular assist device, the components might weigh 1200 gm and occupy 1000 ml. The size and weight of a total artificial heart are likely to be 50% greater.

A 3 year Device Readiness Program was initiated by the NHLBI in 1984 to evaluate the suitability of the electrically-powered untethered left ventricular assist device for clinical investigation in patients. The immediate goal of the NHLBI artificial heart program is validation of a totally implantable electrically powered left ventricular assist device with a 2 year reliability in bench tests. Acceptable reliability has been defined as a less than 20% incidence of "soft failures" i.e. minor aberrations necessitating adjustments to the device, as opposed to potentially life-threatening failures. An interim milestone of this testing is projected 1 year reliability. These devices will then have to demonstrate satisfactory operational characteristics in animals for periods up to 6 months. Once this is achieved, and this may still occur in 1986, investigators may seek FDA approval for clinical investigative use of these devices. They will be used only in patients with end-stage heart disease, and actual long-term reliability will be established through clinical experience. A somewhat more distant goal is development of a compact longer-life (5-10 year) implantable left ventricular assist device.

3. Complications with Ventricular Assist Devices and the Total Artificial Heart

Implantable ventricular assist devices, as well as the total artificial heart, have been beset with a number of problems (75). Most publicized, has been the high incidence of thromboembolic complications, despite anticoagulation. Much attention is currently being given by investigators, including Dr. Bob Eberhart and his associates at this institution, to the development of a non-thrombogenic lining for the ventricular assist devices (80). One system that is being tested at this institution would allow for the deposition of a thin film of a polypeptide polymer which would adsorb a small quantity of albumin from the blood and hence produce a non-thrombogenic surface. Hemolysis remains a problem due to trauma from the prosthetic valves and contact with other moving parts. Tissue ingrowth at the site of the inlet connection has been another major problem which has recently been resolved by certain technical modifications. Failure at anastomotic sites remains a potential problem with any form of vascular surgery. Implantation of a foreign body in the blood stream is likely to pose at least the same risk of infection as is present with prosthetic heart valves. Any system that entails transcutaneous power transmission, such as the current pneumatically powered devices, is subject to an even greater risk of infection. Finally, mechanical failures are inevitable. Expecting any mechanical device to operate continuously without even minor adjustments for a period of at least 2 years is a tall order!

4. NHLBI Working Party Report

A working group appointed by the Director of the National Heart, Lung and Blood Institute (NHLBI) has reviewed the current status of mechanical circulatory support systems (74). It has examined the potential needs for such devices, their cost, and certain societal and ethical issues related to their use. This working party has concluded:

1. Long-term, effective and safe artificial heart and ventricular assist devices are feasible
2. An extended lifetime of acceptable quality is projected
3. Tethered pneumatic activation systems are importantly suboptimal
4. Electrical systems will be fully implantable and will presumably allow relatively normal activity
5. An estimated 17,000 to 35,000 patients below age 70 could benefit annually
6. Actual need will be determined by patient criteria, device effectiveness, safety, acceptance, reliability, availability, entitlement, and reimbursement

The expectations are:

1. Ventricular assist devices will extend life by at least 2 years initially, and ultimately by at least 5 years
2. They will enable the patient to enjoy a generally good quality of life
3. Normal ambulation will be possible
4. Moderate activity will be feasible
5. The power supply will probably need to be recharged 2-3 times per day
6. Long-term anticoagulation will remain essential for the foreseeable future
7. Regular follow-up, and possible minor non-invasive adjustments to the device will be required.

IV. SOCIOECONOMIC AND ETHICAL CONSIDERATIONS

Cost escalation for medical care and the need for cost-containment in medicine are of major concern to physicians, hospital administrators, and legislators alike. It is currently estimated that the spending for health care will rise from 10.8 percent of the gross national product of the US in 1983 to 12 percent in 1990 and to 14 percent in the year 2000. Consequently, the possibility of more extremely expensive technology entering the medical arena sends shock-waves through those sections of the community that are concerned with providing equal access to reasonable medical care (81).

There appear to be certain self-evident truths that are common to heart transplantation, heart-lung transplantation, and untethered mechanical circulatory assist devices (74).

1. They will be very expensive
2. One way or another, people will pay
3. These advances may displace other goods and services
4. They will not displace any procedure currently known to be more efficient in management of end-stage heart disease

5. However, more effective ways may exist to reduce overall cardiovascular mortality and morbidity and improve health in general.

1. Heart Transplantation

The costs associated with heart transplantation, and with transplantation of organs in general, is high. A considerable increase in surgical personnel and ancillary staff is required. The impact of a transplantation program on the central chemistry laboratories alone is formidable and is graphically illustrated by the experience at the University of Pittsburgh (82). In 1979-80, 24 kidney transplants, no liver transplants and no heart transplants were performed; in 1983-84 184 kidney, 138 liver, and 57 heart transplants, or a total of 379 transplants were performed. In 1979-80, about 10,000 transplant-related tests were performed by the chemistry laboratory; by 1983-84, there were about 268,000 transplant-related tests. Today, transplant-related chemistry procedures account for more than 20% of all laboratory procedures performed in their central chemistry laboratories. The costs of transplant-related tests has risen from $46,915 in 1979-80 to $1.25 million in 1983-84. The costs for cyclosporine-A measurements alone account for $295,632 in expenditure. If the number of chemistry tests is divided by the number of livers, hearts, and kidneys transplanted, approximately 1,214 procedures per liver, 664 procedures per heart, and 390 procedures per kidney transplant patient were performed. It behoves any institution contemplating a major transplantation effort to be cognizant of these realities.

Heart transplantation is at present covered by approximately 80% of private insurance carriers. Heart transplantation is also covered by Medicaid in 24 states (not Texas) and the District of Columbia. However, despite the fact that the results of heart transplantation have veen very comparable to those of cadaver kidney transplantation for the past 5 years, Medicare still officially views the procedure as "experimental" (73).

Roger W. Evans, of the Batelle Human Affairs Research Center, who recently headed a four year study on heart transplantation for the Department of Health and Human Services concludes "this procedure has been excluded from Medicare coverage for political and economic - not medical - reasons" (73). He further states that "the argument in favor of Medicare funding for heart transplantation is at least as compelling as that for kidney dialysis, as well as that for the treatment of patients with cancer or AIDS. If we decide we cannot afford a new technology, such as heart transplantation, then we should reconsider coverage of other "accepted" therapies that have lesser or equal benefits". His analysis further suggests that the per procedure, first year cost to Medicare for a heart transplant would be between $57,000 and $80,000. If the lifetime costs likely to be incurred by the heart transplant recipient are included, average Medicare costs per year per patient are estimated to be $23,500. This should be compared with the costs incurred by a patient who dies while awaiting a donor heart - approximately $9,000-12,000 per month-during the waiting or latency period. Transplant candidates who fail to receive a donor heart generally die within 45 days of being selected. Therefore, it is clearly less expensive to permit end-stage cardiac patients to die than to perform a transplant! But is that desireable? The comparative costs of

certain "accepted" therapies on a per case per year basis are shown in Table XXIII. For comparative purposes, it is worth noting that the costs to society of cardiac pacemakers and the current end-stage renal disease program are each about $2 billion per annum (73).

TABLE XXIII

Costs of "accepted" therapies

Total parenteral nutrition	$110,000 per year per case
Maintenance hemodialysis	25,000 per year per case
Treatment of hemophilia	10,000 per year per case
Treatment of cancer	30,000 per year per case
Major adolescent psychiatric disorder	185,000 per case
Treatment of AIDS	40,000–140,000 per case
Bone marrow transplant	100,000 per case
60% burn patient treatment	100,000 per case
Coronary artery bypass graft	25,000 per case
Treatment of variceal bleeding	18,000 per case

At the present time, Medicare benefits are extended only to US citizens 65 years of age or older, or to patients who are disabled or have end-stage renal disease. Because disabled persons represent only 11 percent of Medicare enrollees and because of the medically agreed-upon, 55 year age limit for heart transplants, only between 35 and 85 Medicare beneficiaries per year would qualify for heart transplant under present entitlement rules. However, there is currently a strong move afoot for Medicare entitlement rules to be changed to cover transplantation of organs other than kidneys. A 25 member Federal Task Force on Organ Transplantation appointed by the Department of Health and Human Services in 1985 recently recommended "that private and public health benefit programs, including Medicare and Medicaid, should cover heart and liver transplants, including the costs of outpatient drug therapy to prevent bodily rejection of organs after surgery" (83). The detailed recommendations of this task force are shown in Table XXIV. At the present time, Medicare pays for more than 90 percent of all kidney transplants in this country, but it does not pay for the drugs needed to make the transplants succeed -- approximately $4-5,000 per year.

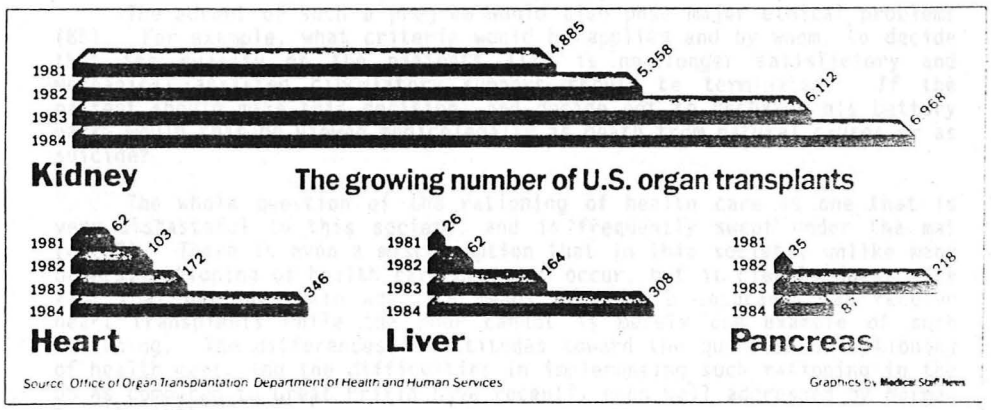
TABLE XXIV
HHS Task Force on Organ Transplantation Recommendations (May, 1986)

1. All hospitals should establish procedures to identify patients near death who might donate organs for possible use in transplants; doctors and nurses should be trained in these procedures.
2. As a condition of participating in Medicare, the Federal health insurance program for the elderly and disabled, hospitals should be required to ask relatives of dying patients whether they would be willing to authorize the donation of organs.
3. Aliens who come to the United States for surgery should receive no more than 10 percent of the kidney transplants at any hospital. Heart and liver transplants should be reserved for American citizens and permanent resident aliens wherever possible. American hospitals should stop soliciting transplant patients in other countries. In 1983 it was reported that nonresident foreigners were receiving about one-third of the kidneys transplanted at several American hospitals, but the overall proportion nationwide is thought to be smaller.
4. The Federal Government should designate hospitals qualified to carry out kidney, heart and liver transplants. To qualify, a hospital would have to perform a certain number of transplants each year (for example, 25 kidney, 12 heart or 14 liver transplants annually within 2 years of inception of the program), with specified survival rates. Hospitals not designated in this manner would not receive payment from the Government.
5. The Government should establish a national network of private nonprofit agencies to obtain and distribute organs among hospitals. Every acute-care hospital should be affiliated with such an agency. Although the 1984 law which called for the establishment of a task force on organ transplantation also directed the Secretary of Health and Human Services to establish such a network, it is not yet in operation.
6. Government agencies, schools and health-care providers should step up efforts to educate the public, especially members of minority groups, about the need to donate organs. The rate of donation is "very low" among blacks, even though many of the patients needing transplants are black.
7. The selection of transplant patients must be based solely on objective medical criteria, such as the patient's need and the probability of a successful transplant. The commercialization of organ transplants, including the export of human kidneys for profit should be condemned and prohibited.

Reference 83

The Batelle Human Affairs Research Centers estimates the actual average first-year costs of a kidney transplant at $35,000, a heart transplant at $95,000 and a liver transplant at $130,000, including drug therapy (73). Figure 18 graphically depicts the increase in the number of kidney, heart, and liver transplants from 1981-4 (84). It is estimated that in 1985, the number of kidney transplants rose to 7800, heart transplants to 719 and liver transplants to 602 (83). The Task Force on Organ Transplantation estimates that their proposed changes in entitlement rules would cost the Government $42-70 million per year. However, it is also recognized that the number of organ transplants would probably double if their recommendations were adopted. Nevertheless, the availability of donor organs (at most 1300-2000 per year) is likely to place a finite constraint on the number of heart transplants that can and will be performed.

Figure 18



Organ transplantation: Comparative numbers of kidney, heart, liver and pancreas transplants performed. Reference 84

Neither the Administration nor the U.S. Congress has yet responded to the recommendations of the Task Force on Organ Transplantation. Whether or not heart transplantation will be undertaken in Parkland Memorial Hospital in the foreseeable future is likely to depend in a major way on the response that ensues.

2. Ventricular Assist Devices and the Total Artificial Heart

The socioeconomic implications relating to the widespread implantation of untethered ventricular assist devices, or a total artificial heart, has some similarities to and some differences from those already outlined for heart transplantation. The similarities are that one is dealing with patients with end-stage heart disease; the differences are that the techique can potentially be applied to a much larger number of patients -- possibly 17,000 to 35,000 per annum. The current estimate for the implantation and maintenance of a total left ventricular assist device for a projected average of 4½ years of survival is approximately $150,000 (in 1983 dollars) (75). The gross annual cost to society could fall in the range of $2.5-5 million i.e. comparable to the costs to Medicare of the present end-stage renal disease or cardiac pacemaker programs, or some 2 orders of magnitude greater than the costs of funding a heart transplant program alone.

The advent of such a program would also pose major ethical problems (85). For example, what criteria would be applied and by whom, to decide that the quality of the patients life is no longer satisfactory and mechanical assisted circulatory support should be terminated? If the patient should make this decision, and decide not to recharge his battery pack, would this be viewed medicolegally as death from natural causes or as suicide?

The whole question of the rationing of health care is one that is very distasteful to this society, and is frequently swept under the mat (86,87). There is even a misconception that in this society, unlike many others, rationing of health care does not occur, but it clearly does. The fact that patients with adequate means or private insurance can receive heart transplants while the poor cannot is merely one example of such rationing. The differences in attitudes toward the question of rationing of health care, and the difficulties in implementing such rationing in the US as compared to Great Britin have recently been well addressed by Norman Daniels (88).

When faced with weighty decisions about how to proceed into the unknown future, it is common to turn to the sages of the past for guidance. Unfortunately, Aristotle did not make any clear statement about the advisability of heart transplantation, the artificial heart or ventricular assist devices. However, he did leave these wise words to posterity:

"The heart alone of all the viscera cannot withstand injury. This is to be expected because when the main source of strength is destroyed, there is no aid that can be brought to the other organs which depend on it".

Aristotle

REFERENCES

1. Barnard CN: A human cardiac transplant: An interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J 41:1271, 1967.
2. Copeland J, Stinson EB: Human heart transplantation. Curr Probl Cardiol 4:4, 1979.
3. Barnard CN, Barnard MS, Cooper DKC, et al: The present status of heterotopic cardiac transplantation. J Thorac Cardiovasc Surg 81:433, 1981.
4. Kaye MP, Elcombe SA, O'Fallon WM: The international heart transplantation registry. The 1984 report. Heart Transplantation 4:290, 1985.
5. Novitzky D, Cooper DKC, Barnard CN: The surgical technique of heterotopic heart transplantation. Ann Thorac Surg 36:476, 1983.
6. Barnard CN, Cooper DKC: Heterotopic versus orthotopic heart transplantation. Transplant Proc 16:886, 1984.
7. Firth BG: Heart Transplantation. Medical Grand Rounds, Southwestern Medical School, July 9, 1981.
8. Pennock JL, Oyer PE, Reitz BA, et al: Cardiac transplantation in perspective for the future. Survival, complications, rehabilitation and cost. J Thorac Cardiovasc Surg 83:168, 1982.
9. Griffith BP, Hardesty RL, Trento A, Bahnson HT: Five years of heart transplantation in Pittsburgh. Heart Transplantation 4:489, 1985.
10. Griffith BP: Personal communication, 1986.
11. Copeland JG: Personal communication, 1986.
12. Yacoub MH: Personal communication, 1986.
13. Schroeder JS: Personal communication, 1986.
14. Wolpowitz A, Barnard CN, Barnard MS: A review of experience with cardiac transplantation. Israel J Med Sci 15:212, 1979.
15. Lower RR, Dong E, Shumway NE: Suppression of rejection crises in the cardiac homograft. Ann Thorac Surg 1:645, 1965.
16. Koser JC, Hurley EJ, Lower RR: Histopathology of orthotopic canine cardiac homografts. Lab Invest 19:97, 1968.
17. Stinson EB, Dong E, Bieber CP, et al: Cardiac transplantation in man: I: Early rejection. JAMA 207:2233, 1969.
18. Goldman MH, Barnhart G, Mohanakumar T, et al: Cyclosporine in cardiac transplantation. Surg Clin N Amer 65:637, 1985.
19. Sakakibara S, Konno S: Endomyocardial biopsy. Jap Hrt J 3:537, 1962.
20. Caves PK, Billingham ME, Schulz WP, et al: Transvenous biopsy from canine orthotopic heart allografts. Am Hrt J 85:525, 1973.
21. Billingham ME, Caves PK, Dong E, Shumway NE: The diagnosis of canine orthotopic cardiac allograft rejection by transvenous endomyocardial biopsy. Transplant Proc 5:741, 1973.
22. Caves PK, Billingham ME, Stinson EB, Shumway NE: Serial transvenous biopsy of the transplanted human heart. Improved management of acute rejection episodes. Lancet 1:821, 1974.
23. Baumgartner WA, Reitz BA, Oyer PE, et al: Cardiac homotransplantation. Curr Probl Surg 16:3, 1979.
24. Thomas FT, Lower RR: Heart Transplantation - 1978. Surg Clin N Amer 58:335, 1978.

25. Rose AG, Uys CJ, Losman JG, Barnard CN: Evaluation of endomyocardial biopsy in the diagnosis of cardiac rejection: A study using bioptome samples of formalin fixed tissue. Transplantation 26:10, 1978.
26. Baumgartner WA, Reitz BA, Bieber CP, et al: Current expectations in cardiac transplantation. J Thorac Cardiovasc Surg 75:525, 1978.
27. Bieber CP, Griepp RB, Oyer PE, et al: Relationship of rabbit ATG serum clearance rate to circulating T-cell level, rejection onset, and survival in cardiac transplantation. Transplant Proc 9:1031, 1977.
28. Oyer PE, Stinson EB, Bieber CP, et al: Diagnosis and treatment of acute cardiac allograft rejection. Transplant Proc 11:296, 1979.
29. Hastillo A, Hess ML, Richardson DW, Lower RR: Cardiac transplantation - 1980. The Medical College of Virginia Program. South Med J 73:909, 1980.
30. Calne RY, Rolles K, White DJG, et al: Cyclosporine-A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases and 2 livers. Lancet 2:1033, 1979.
31. Starzl TE, Weil R, Iwatsuki JT, et al: The use of cyclosporine-A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 151:17, 1980.
32. Oyer PE, Stinson EB, Jamieson SW, et al: Cyclosporine in cardiac transplantation: a 2½ year follow-up. Transplant Proc 15:2546, 1983.
33. Borel JF: The history of cyclosporine-A and its significance. In: White DJG (ed): Cyclosporine-A: Proceedings of an International Conference on Cyclosporine-A. Amsterdam. Elsevier Biomedical Press 1982, pp. 5-17.
34. Helderman JH: Renal transplantation 1984. In celebration of 20 years of transplantation at PMH-SWMS. Medical Grand Rounds, Southwestern Medical School, October 25, 1984.
35. Cuthbert J: Liver Transplantation. Medical Grand Rounds, Southwestern Medical School, October 31, 1985.
36. Novitzky D, Cooper DKC, Barnard CN: Reversal of acute rejection by cyclosporine in a heterotopic heart transplant. Heart Transplantation 3:177, 1984.
37. Yacoub MH, Alivizatos PA, Khagani A, Mitchell A: The use of cyclosporine-A, azathioprine and ATG with no or low dose steroids for immunosuppression of cardiac transplant patients. Transplant Proc 17:221, 1985.
38. Kawaguchi A, Goldman MH, Hoshinaga K, et al: Monitoring of lymphocyte subpopulations in cyclosporine (CYA) and azathioprine (AZA) treated cardiac allograft recipients. Transplant Proc 16:1542, 1984.
39. Billingham ME: Some recent advances in cardiac pathology. Human Pathol 10:367, 1979.
40. Dummer SJ, Hardy A, Poorsattar A, Ho M: Early infections in kidney, heart and liver transplant recipients on cyclosporine. Transplantation 36:259, 1983.
41. Dummer JS, Bahnson HT, Griffith BP, et al: Infections in patients on cyclosporine and prednisone following cardiac transplantation. Transplant Proc 15:2779, 1983.
42. Mammana RB, Petersen EA, Fuller JK, et al: Pulmonary infections in cardiac transplant patients: Modes of diagnosis, complications, and effectiveness of therapy. Ann Thorac Surg 36:700, 1983.

43. Fuller J, Levinson MM, Kline JR, Copeland J: Legionnaire's disease after heart transplantation. Ann Thorac Surg 39:308, 1985.
44. Cooper DKC, Lanza RP, Oliver S, et al: Infectious complications after heart transplantation. Thorax 38:822, 1983.
45. Griffith BP, Hardesty RL, Trento A, et al: Targeted blood levels of cyclosporine for cardiac transplantation. J Thorac Cardiovasc Surg 88:952, 1984.
46. Griffith BP, Hardesty RL, Lee A, et al: Management of cyclosporine toxicity by reduced dosage and azathioprine. Heart Transplantation 4:410, 1985.
47. Myers BD, Ross J, Newton L, et al: Cyclosporine-associated chronic nephropathy. N Engl J Med 311:699, 1984.
48. Moran M, Tomlanovich S, Myers BD: Cyclosporine-induced chronic nephropathy in human recipients of cardiac allografts. Transplant Proc 17(Suppl I):185, 1985.
49. Copeland JG, Emery RW, Levinson MM, et al: Cyclosporine: An immunosuppressive panacea? J Thorac Cardiovasc Surg 91:26, 1986.
50. Griepp RA, Stinson EB, Bieber CP, et al: Control of graft arteriosclerosis in human heart transplant recipients. Surg 81:262. 1977.
51. Bieber CP, Hunt SA, Schwin DA, et al: Complications in long-term survivors of cardiac transplantation. Transplant Proc 13:207, 1981.
52. Uys CJ, Rose AG: Pathologic findings in long-term cardiac transplants. Arch Pathol Lab Med 108:112, 1984.
53. Cleary ML, Sklar J: Lymphoproliferative disorders in cardiac transplant recipients are multiclonal lymphomas. Lancet 3:489, 1984.
54. Greenberg ML, Uretsky BF, Reddy PS, et al: Long-term hemodynamic follow-up of cardiac transplant patients treated with cyclosporine and prednisone. Circulation 71:487, 1985.
55. Borow KM, Neumann A, Arensman FW, Yacoub MH: Left ventricular contractility and contractile reserve in humans after cardiac transplantation. Circulation 71:866, 1985.
56. Reitz BA, Wallwork JL, Hunt SA, et al: Heart-lung transplantation: Successful therapy for patients with pulmonary vascular disease. N Engl J Med 306:557, 1982.
57. Dawkins KD, Jamieson SW: The current status of heart-lung transplantation. Int J Cardiol 5:406, 1984.
58. Jamieson SW, Stinson EB, Oyer PE, et al: Heart-lung transplantation for irreversible pulmonary hypertension. Ann Thorac Surg 38:554, 1984.
59. Jamieson SW, Reitz BA, Oyer PE, et al: Combined heart and lung transplantation. Lancet 1:1130, 1983.
60. Hardesty RL, Griffith BP: Procurement for combined heart-lung transplantation. J Thorac Cardiovasc Surg 89:705, 1985.
61. Jamieson SW, Stinson EB, Oyer PE, et al: Operative technique for heart-lung transplantation. J Thorac Cardiovasc Surg 87:930, 1984.
62. Modry DL, Oyer PE, Jamieson SW, et al: Cyclosporine in heart and heart-lung transplantation. Can J Surg 28:3, 1985.
63. Dawkins KD, Jamieson SW, Hunt SA, et al: Long-term results, hemodynamics, and complications after combined heart and lung transplantation. Circulation 71:919, 1985.
64. Theodore J, Jamieson SW, Burke CM, et al: Physiologic aspects of human heart-lung transplantation. Pulmonary function status of the post-transplanted lung. Chest 86:349, 1984.

65. Chiles C, Guthaner DF, Jamieson SW, et al: Heart-lung transplantation: the post-operative chest radiograph. Radiology 154:299, 1985.
66. Griffith BP, Hardesty RL, Trento A, Bahnson HT: Asynchronous rejection of heart and lungs following cardiopulmonary transplantation. Ann Thorac Surg 40:488, 1985.
67. McGregor CGA, Jamieson SW, Billingham ME, et al: Isolated pulmonary rejection after combined heart-lung transplantation. J Thorac Cardiovasc Surg 90:623, 1985.
68. Mancini MC, Borovetz HS, Griffith BP, Hardesty RL: Changes in lung vascular permeability after heart-lung transplantation. J Surg Res 39:305, 1985.
69. Burke CM, Theodore J, Dawkins KD, et al: Post-transplant obliterative bronchiolitis and other late lung sequelae in human heart-lung transplantation. Chest 86:824, 1984.
70. Brooks RG, Hofflin JM, Jamieson SW, et al: Infectious complications in heart-lung transplant recipients. Am J Med 79:412, 1985.
71. Evans RW: Economic and social costs of heart transplantation. Heart Transplant 1:243, 1982.
72. Evans RW: The socioeconomics of organ transplantation. Transplant Proc 17:129, 1985.
73. Evans RW: The heart transplant dilemma. Issues in Science and Technology, p. 91-101, Spring, 1986.
74. Van Citters RL, Bauer CB, Christopherson LK, et al: Artificial heart and assist devices: Directions, needs, costs, societal and ethical issues. Artificial Organs 9(4):375, 1985.
75. Kolff J, Deeb GM: Artificial heart and left ventricular assist devices. Surg Clin N Amer 65:661, 1985.
76. Relman AS: Artificial hearts-permanent and temporary. N Engl J Med 314:644, 1986.
77. Richenbacher WE, Peirce WS: Clinical spectrum of mechanical circulatory assistance. Heart Transplant 4:481, 1985.
78. DeVries WC, Anderson JL, Joyce LD, et al: Clinical use of the total artificial heart. N Engl J Med 310:273, 1984.
79. Hill JD, Farrar DJ, Hershon JJ, et al: Use of a prosthetic ventricle as a bridge to cardiac transplantation for post infarction cardiogenic shock. N Engl J Med 314:626, 1986.
80. Eberhart RC: Personal communication, 1986.
81. McGoon DC: Cardiac surgery in perspective. Chest 89:737, 1986.
82. Sanghvi A: Impact of organ transplant program on the clinical chemistry laboratory at the University of Pittsburgh. Arch Pathol Lab Med 110:95, 1986.
83. Pear R: Federal payment for transplants for poor studied. Panel on organ donations to propose wider access to them for US citizens. New York Times, May 18, 1986
84. Dreuth M: Physicians seek help in assessing organ donor laws. Med Staff News, May 1986, p. 9.
85. Fletcher JC: Cardiac transplants and the artificial heart: ethical considerations. Circulation 68:1339, 1983.
86. Iglehart JK: Transplantation: the problem of limited resources. N Engl J Med 309:125, 1983.
87. Knox RA: Heart transplants: to pay or not to pay. Science 2:570, 1980.

88. Daniels N: Why saying no to patients in the United States is to hard. Cost containment, justice, and provider autonomy. N Engl J Med 314:1380, 1986.