# Laboratory and Clinical Studies of Cardiac Transplantation*

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Cardiac transplantation was carried out on four patients at the Medical College of Virginia between May and October of 1968, in an effort to salvage them from the terminal stages of otherwise uncorrectable heart disease. Despite a strikingly good early recovery from operation in each case, three of the patients died of acute homograft rejection in one to three weeks; our second case is living and well, ten months after operation, and is at this writing the world's third longest survivor. The world experience to June of 1969 includes about 130 cardiac transplants. Of the first 100 patients operated on over six months ago, 20 are surviving, and the majority of these have returned to a productive existence, demonstrating the feasibility of complete rehabilitation of at least some terminal patients after cardiac transplantation. The high mortality rate—significantly higher than was anticipated—has resulted from acute and chronic homograft rejection and from the equally difficult problem of infection. Certain lessons have been learned from our own experience and from the world experience with this procedure, and these will be reviewed in an attempt to establish the current status and future potential of cardiac transplantation.

## Background: Animal Experimentation

The information gained from ten years of our laboratory experience in part set the stage for the clinical trials of cardiac transplantation initiated by Barnard in December of 1967. These investigations were begun first in the laboratories of Dr. Norman E. Shumway of Stanford University and later continued at the Medical College of Virginia. The feasibility of the procedure was first established in December of 1959 when dogs were shown to recover completely after orthotopic homotransplantation of the heart (Lower and Shumway, 1960; Lower, Stofer and Shumway, 1961). The animals lived from 4 to 21 days without immunosuppressive therapy and exhibited remarkably normal activity until death from rejection supervened, providing convincing evidence that the transplanted heart could recover excellent function despite the interruption of nerves and lymphatics. In a subsequent study two dogs recovered after transplantation of the heart and both lungs (Lower et al., 1961). The animals died after five days, but showed normal ventilation and gas exchange prior to the onset of rejection.

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Further laboratory studies (Lower, Dong and Shumway, 1965a,b; Lower, Dong and Glazener, 1966) revealed that the most sensitive and reliable test for impending cardiac rejection was a fall in the QRS voltage on the electrocardiogram, often with the additional finding of abnormal intraventricular conduction. With the advent of immunosuppressive drugs, specifically azathioprine and methylprednisolone, survival of animals was prolonged by treating each recognized rejection crisis with transiently high doses of the drugs which were then tapered to lower maintenance doses in an attempt to diminish the high incidence of toxicity and infection. A few animals survived more than a year and provided a significant stimulus to the subsequent clinical application of cardiac transplantation. Extensive physiologic tests of the transplanted heart revealed that, although function was often depressed for the first 24 to 48 hours, thereafter cardiac output, even in response to stress, was remarkably adequate (Dong et al., 1965). In some animals made to breathe 7% oxygen, cardiac outputs could be markedly increased (Kontos and Lower, 1969).

Evidence of autonomic reinnervation was seen in the majority of transplants within a few months after operation and was confirmed by appropriate immediate responses to direct electrical stimulation of vagal and sympathetic nerves (H. A. Kontos, M. D. Thames and R. R. Lower, unpublished data). The return of sinus arrhythmia was also seen as a useful indicator of vagal reinnervation (Thames, Kontos and Lower, 1969), and the ability of the heart to respond reflexly to peripheral hypertension also reappeared (H. A. Kontos et al., unpublished data). Recently, fluorescent staining of sympathetic fibers has confirmed their regeneration within the graft after several months.‡

Although these observations fostered considerable enthusiasm concerning the application of cardiac transplantation to human disease, this enthusiasm was tempered by certain additional observations. In about 25% to 30% of acute rejection crises, it was difficult or impossible to control the rejection process with drugs. Where continuous or high dose immunosuppression was needed, infection was often inevitable. Moreover, on histologic examination of animals surviving over three months, all showed some evidence of compromise of coronary arterial lumens by thickening of the intimal layer. In some of the longest surviving cases a few of the coronary arteries were nearly occluded. These findings were presented in 1967 (Lower and Cleveland, 1968), but it was our hope that improved methods of histocompatibility matching along with better drugs for immunosuppression, such as antilymphocyte globulin, might make cardiac transplantation in man less susceptible to both acute and chronic rejection. Unfortunately these aims have not been entirely realized.

## Selection of Recipients and Donors

The selection of patients for cardiac transplantation has generally been reserved for those in the terminal stage of their illness with no alternative hope for recovery. This policy is attested to by the large numbers of patients who have died in our hospital and elsewhere while awaiting a suitable heart donor. In the Stanford series, for example, the mean survival of patients accepted for transplantation, but for whom no suitable donor could be obtained, has been four weeks, with a maximal survival of 12 weeks (N. E. Shumway, personal communication).

Two of our patients had sustained multiple myocardial infarctions with the subsequent development of refractory heart failure. The other two patients had cardiomyopathy of undetermined etiology with severe biventricular failure. Cardiac catheterization in each case revealed pulmonary hypertension, elevation of the left ventricular end diastolic pressure, low cardiac output and extremely poor contractility of the left ventricle. The patients were all considered to have no alternative hope for recovery from their cardiac disease and were, therefore, accepted for cardiac transplantation.

The selection of donors required the establishment of irretrievable brain death by an independent team of neurosurgeons and neurologists. Brain death in these cases was caused by extensive intracerebral hemorrhage or by massive brain trauma. The criteria included no pupillary reaction, absence of spontaneous respiration or movements, absence of reflexes and an isoelectric electroencephalogram. The heart in the donor invariably required vasopressors for support and had usually sustained one or more episodes of arrest. It is of interest that, despite its failing status in the donor, the heart in each case adequately supported the circulation in the recipient as soon as coronary blood flow was reestablished.

Prospective histocompatibility typing by the microlymphocytotoxicity techniques of Terasaki was carried out in each case. However, despite an excellent match with no demonstrable major incompatibility in the first case, the patient died of acute fulminating rejection at one week and was the first patient in the world experience to die from this cause. The course in this patient illustrated that typing, as currently practised, does not in fact detect, with sufficient sensitivity, all forms of incompatibility. The second patient, however, was also an excellent match; and, although

‡ Studies performed by Dr. John E. Norvell, Department of Anatomy, Medical College of Virginia.

he has sustained three rejection episodes, each one responded well to a temporary increase in immunosuppressive therapy, and he remains well.

The third patient in this series demonstrated a principle which may continue to receive increased attention in the preoperative matchings of potential recipients. Despite the absence of preformed antibodies detected by the routine preoperative serum-lymphocyte cross match, retrospective studies of the patient's serum by the technique of immune adherence established that some degree of prior sensitization did exist, as antibodies were present against cultured kidney cells from the same donor. The patient's clinical course was characterized by a fulminating rejection episode at one week which was unresponsive to massive immunosuppressive therapy. The fourth patient, mismatched for histocompatibility antigen HLA-3, initially responded to therapy for a rejection episode at one week, but subsequently became refractory to treatment and died of rejection at 18 days. Antibody was eluted from the heart postmortem in each of the three fatal cases. The possible role of antibody in acute cardiac rejection has been discussed further in another report (G. M. Williams et al., unpublished data).

## Surgical Technique

The basic surgical technique which proved successful in animal transplantation (Lower et al., 1961) was employed in our own cases and has been generally utilized by other transplant surgeons with few modifications. The posterior atrial wall, containing the openings of the vena cavae and pulmonary veins, is retained in the recipient to facilitate anastomosis of the donor heart. Anastomosis of the aorta and pulmonary artery in the supravalvular region completes the procedure. Surgeons have varied most in their management of the donor heart. In our own cases the donor heart was cooled by immersion in saline at 8 to 10 C to afford the myocardium protection during the 60 to 90 minutes that coronary circulation was interrupted and no coronary perfusion was used.

## Postoperative Management

Postoperative management of the recipient has varied little from the care of the routine cardiac surgery patient with the exceptions that immunosuppressive therapy is administered in an effort to prevent rejection, and monitoring efforts are directed toward the early detection of a rejection crisis (Lower et al., 1968; Sewell, Kemp and Lower, 1969). It now seems apparent that the cardiac transplant recipient has an immunologic capability that is less impaired than the chronically uremic renal transplant patient, and the cardiac patient, therefore, requires more intensive immunosuppression, at least in the initial weeks, to control rejection. This was not appreciated early in our experience but has evolved as the world results have been discussed. The current recommendations which have received widest acceptance are that the recipient be given azathioprine in the largest dose tolerated, usually 3 to 4 mg/kg, and prednisone in a dose of 200 mg/day during the initial two to three weeks. Drugs are later tapered to a lower maintenance dose to decrease the risk of infection and the other side effects of steroid administration.

The role of antilymphocyte globulin is less clearly established. Some patients have been managed successfully without it; others have developed fatal, acute or chronic rejection despite its use. The optimal preparation, route of administration and dose have not been agreed upon. Some patients reportedly have rapidly developed antibodies against the horse globulin with evidence that its immunologic effectiveness is rapidly dissipated (Butler et al., 1969). A few investigators have therefore considered it most useful in the treatment of a difficult rejection crisis or where there are wide histocompatibility differences.

## Early Detection of Rejection

The early detection of a rejection crisis requires close monitoring of the electrocardiogram on at least a daily basis for the first few months. The primary signs of impending rejection are a decrease in the QRS voltage, a rightward shift in the frontal plane axis, delayed intraventricular conduction and atrial or nodal arrhythmias. Rejection is characterized clinically by the insidious onset of right heart failure as evidenced by weight gain, edema, venous distention with increased pulsations, right ventricular gallop, and, eventually, the development of murmurs of relative tricuspid or mitral insufficiency. Early in the course of rejection the lung fields appear radiographically clear and even oligemic, in reflecting the predominant right heart failure. Thus, it is suggested that digitalis preparations and diuretics be discontinued as soon as is practical after operation to avoid masking this important collateral evidence of impending rejection.

While serum enzyme abnormalities do occur with some rejection episodes (particularly elevation of the lactic dehydrogenase isozymes I and II and the creatine phosphokinase), these abnormalities occur as a late manifestation of rejection and indicate a more severe degree of myocardial injury. It is apparent from our own observations and the experience of others that a typical rejection crisis can occur and be diagnosed by other clinical and ECG criteria without detectable abnormalities in the serum enzymes. However, enzyme levels were markedly elevated in the terminal stages of each of the fatal rejection episodes in our patients.

The other nonspecific signs and symptoms occurring in conjunction with rejection, such as pericardial

friction rub, fever, leukocytosis and malaise, can all occur with other postoperative complications, e.g., infection, embolism or the various post-perfusion syndromes, and are thus of limited value in the diagnosis of impending rejection.

## Treatment of Acute Rejection

The successful treatment of a rejection crisis requires the immediate administration of prednisone in transiently high doses of 1,000 mg daily until the clinical and cardiographic signs of rejection improve with subsequent tapering to maintenance levels. In addition, local graft irradiation, actinomycin and antilymphocyte globulin may be used. Recent laboratory studies in dogs with cardiac transplants have established by serial myocardial biopsies the effectiveness of these measures in the treatment of the rejection crisis (Graham et al., 1969). It would appear from the recently discussed world experience that about 70% of rejection crises can be successfully managed in this way.

Yet even with successful control of the acute rejection problem, a process which has been termed chronic rejection may develop in the graft, consisting of irregular thickening of the intimal layer of the coronary arteries identical to that which was seen in the transplanted dog hearts (Lower and Cleveland, 1968) and in other organ homografts. It is presumed that antigen-antibody complexes injure the endothelium of the vessels and cause agglutination and adherence of platelets at areas of maximum injury with subsequent organization of thrombi. Unfortunately, the development of such lesions cannot be easily detected clinically, except perhaps by arteriography; and if the process goes unchecked, serious compromise of cardiac function will inevitably result. Whether prophylactic antithrombotic measures can forestall the process until eventually the donor endothelium is repopulated by host cells has yet to be established. More precise histocompatibility matching and more effective immunosuppression would at the moment seem to offer the best insurance against loss of the graft due to chronic rejection.

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