

Historical Milestones

Human Cardiac Transplantation

An Evaluation of the First Two Operations Performed at the Groote Schuur Hospital, Cape Town*

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ON DECEMBER 3, 1967, the heart of a girl who died from brain injury was transplanted to a patient suffering from heart disease that, until then, had proved untreatable. This operation, as might be expected, met with reactions ranging from acclaim to condemnation. Of the various criticisms one above all others merits the most careful consideration: the objection that heart transplantation in man is premature.

To refute this criticism, three basic questions need to be considered. First, is there any need for this type of surgery—have we patients who can benefit by this new technic? Second, have we developed this technic sufficiently to use it without undue risk in the treatment of human beings? Third, are we able to detect the complications that may follow this type of procedure, and can we effectively control them when they arise?

I should like to answer these questions in the light of our experience with the first two human heart transplantations we have performed.

THE SCOPE OF CARDIAC TRANSPLANTATION

Major heart surgery has been practiced in Cape Town for approximately 15 years. The diseases we have been able to treat mostly involve the pericardium, the valves of the heart and congenital conditions. Apart from attempts to revascularize the myocardium and to

employ procedures for excising small pieces of the heart, we have been unable to help patients with myocardial damage so extensive that the heart was failing in its prime duty as a competent pump. Up to this time we have found that the condition of such patients gradually deteriorates, and they die. There are two ways in which we can assist these patients: (1) by some mechanical means, or by an auxiliary transplant procedure, to support the failing heart in its function, or (2) by replacing the failing heart completely, either by transplanting a normal heart (human or animal) or by introducing a mechanical device to maintain the patient's circulation after excision of the diseased heart. In Cape Town we elected to study the approach of excision of the diseased heart and transplantation of a normal heart.

CLINICAL PRESENTATIONS

THE FIRST PATIENT

The first man whom we treated in this way is representative of the type of patient we thought would benefit by this operation. He was a 54 year old Caucasian groceries dealer with known diabetes since 1955. In 1959, 1960 and 1965 he had documented episodes of myocardial infarction. Following the last attack myocardial insufficiency gradually developed with symptoms and signs of right- and left-sided heart failure. In addition to measures for control of his diabetes he received the usual treat-

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ment—diuretics, digitalis, aminophylline and long-term anticoagulants. Despite this, his condition deteriorated.

In February 1967 he was admitted to the hospital for careful study. At that time, approximately 10 months before the transplant operation, there were, owing to treatment, no signs of systemic venous congestion; the heart was greatly enlarged, the apex beat was in the sixth left intercostal space and a palpable third heart sound was present. On auscultation the first heart sound was barely audible; the second sound was widely split as a result of right bundle branch block; and there was a loud third heart sound. The rhythm was irregular as a result of partial heart block of the Wenckebach type attributed to digitalis. The electrocardiogram showed diaphragmatic and anterolateral infarction and right bundle branch block. Radiography at this stage showed a massively enlarged heart with pulmonary venous congestion. On fluoroscopy there was poor contraction of the ventricles, with paradoxical movement at the apex indicative of a ventricular aneurysm.

Intracardiac pressures and related catheterization data (Table 1) confirmed the presence and extent of circulatory impairment. On selective cineangiography it was seen that the right coronary artery was partially occluded 2 cm. from its origin and thereafter was so beaded and progressively narrowed that it prematurely disappeared. The left coronary artery showed complete obstruction of the circumflex

TABLE I
Patient 1. Cardiac Catheterization Data
(February 14, 1967)

	Pressures (mm. Hg)	Blood Oxygen— Satura- tion (%)	Content (ml./L.)
Right atrium	<i>a</i> = 17 <i>x</i> = 6 (10) <i>v</i> = 10 <i>y</i> = 8.5		
Right ventricle	85/15-9		
Pulmonary artery	75/38 (54)	58	117
Right brachial artery	130/75 (90)	96.5	198
Pulmonary wedge	<i>a</i> = 40 <i>x</i> = 32 (35) <i>v</i> = 36 <i>y</i> = 29		
Left ventricle	125/25-30		

Body surface area = 0.95 M.²; hemoglobin = 15.3 gm./100 ml.; O₂ capacity = 205 ml./L.; O₂ uptake = 192 ml./min.; cardiac output = 2.36 L./min.; cardiac index = 2.43 L./min./M.²; systemic vascular resistance = 35 units; pulmonary vascular resistance = 11.5 units.

Figures in parentheses indicate mean pressures.

branch and partial obstruction of the anterior descending artery.

It was decided that myocardial damage was so extensive that no further medical treatment could avail the patient, and he was therefore discharged.

He was readmitted in August 1967 in severe congestive heart failure with marked edema; he had orthopnea and paroxysmal nocturnal dyspnea. Vigorous medical treatment was reinstated, but it was found impossible to control his heart failure with digitalis, prednisone, or diuretics. Eventually we resorted to Southey's tubes and, with the combined treatment, were able to reduce his weight from 183 to 130 lb. (indicating a loss of approximately 53 lb. of edema fluid). Despite this, the patient's condition did not improve; he could hardly move in bed, he was nauseated and could not eat, and there was evidence of increasing renal as well as hepatic derangement. The severity of the patient's incapacity was reflected later in the morbid anatomic appearance of his excised heart (Fig. 1).

There was no reasonable doubt that this man was inexorably dying from heart disease for which we could do nothing. We therefore presented the facts to him and asked whether he would agree to undergo cardiac transplantation. All the dangers and uncertainties of this procedure were explained to the patient and his relatives, but it took him, and them, very little time to agree to the operation.

THE SECOND PATIENT

A white male dental surgeon of 57 had documented cardiac infarction in June 1955 at the age of 46, presenting with the classic severe chest pain of sudden onset. He was treated with bed rest and administered anticoagulants, the latter administered orally on

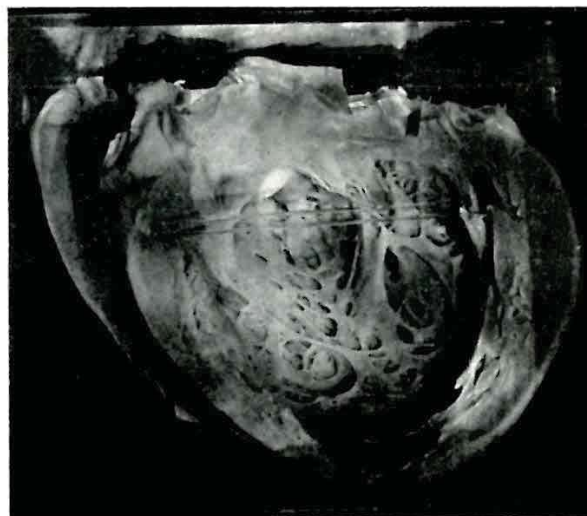


Figure 1. Case 1. Photograph of the left ventricular cavity showing the extensive fibrous replacement of the muscle wall which extends from the apex to about 1 inch from the atrioventricular border. At the apex there is a small aneurysm with a blood clot.

a permanent basis. As soon as he became ambulant he began to experience angina after moderate exertion, and five months after the initial episode he had a paroxysm of atrial fibrillation which precipitated acute left heart failure. This responded to digitalization with digitalis folia, and sinus rhythm was restored.

He was referred to the Cardiac Clinic in April 1956 and attended regularly thereafter. On examination during this period there were no abnormal clinical findings apart from mild systemic hypertension, but the electrocardiogram showed extensive anterolateral infarction. On fluoroscopy moderate cardiomegaly was observed, with abnormal pulsation of the apex of the left ventricle, regarded as due to a cardiac aneurysm.

Two attempts were made at discontinuing digitalis, the first in 1960 and the second in 1963, but each time the drug had to be recommenced because of the development of acute left heart failure. In 1960 symptoms of gout (mild in nature) developed, for which he received colchicine. Transient glycosuria was noted in 1960, but the glucose tolerance curve was normal.

By 1963 he began to notice diminution of effort tolerance manifested by dyspnea and some reduction in his feeling of well-being. At the same time the angina disappeared. His condition remained stationary, however, until March 1967, when he suddenly became short of breath on the slightest effort and attacks of pulmonary edema developed, for which he was admitted to Groote Schuur Hospital. The sudden deterioration in his condition was attributed to the development of atrial fibrillation. Recurrence of cardiac infarction could not be substantiated by electrocardiogram or by enzyme studies, but a silent infarct seemed to be the most probable explanation. Diuretic therapy with Furosemide® was commenced with good effect, but while he was in the hospital acute urinary retention developed. The latter required catheterization and was associated with prostatitis and with urinary infection, which responded to chloramphenicol.

Examination during this admission showed transient basal crepitations, normal blood pressure and enlarged heart, but no systemic congestion. X-ray examination confirmed the cardiomegaly, and on fluoroscopy the apical aneurysm of the left ventricle was once more noted. Despite quinidine medication and electrical cardioversion on two occasions, it was not possible to maintain the sinus rhythm. Thereafter his course progressively deteriorated, his symptoms being mainly those of left heart failure with progressively increasing effort dyspnea, orthopnea and paroxysmal nocturnal dyspnea. Furosemide therapy was continued and gradually increased to 200 mg. daily; aminophylline suppositories and digoxin were also administered.

Cardiac catheterization (Dr. W. Beck) was performed on April 18, 1967. Moderate pulmonary hypertension (54/25 mm. Hg) due to left heart

failure was found; mean pulmonary wedge pressure was 26 mm. Hg and left ventricular pressure, 125/15 to 25 mm. Hg. The cardiac index was reduced to below 2 L./min./M.² Cineangiography revealed a large myocardial aneurysm involving the apex of the left ventricle. Coronary angiography revealed a well opacified dominant right coronary artery with multiple insignificant narrowings. The right atrial branch was large and formed a collateral that filled the distal and descending branch of the left coronary artery distal to the obstruction. The ostium of the left coronary artery was 90 per cent narrowed just distal to its origin. The left anterior descending artery filled for a short distance and was narrow. The question of aneurysmectomy was raised, but the patient was thought to be unsuitable for this procedure. This view was supported by members of the Cleveland Clinic, who independently scrutinized the cine films.

The patient's condition continued to deteriorate until he was completely incapacitated. By the time he was readmitted he could not brush his teeth, wash his face, or blow his nose. A recovery period of up to an hour was needed after use of a bedpan. He was so weak that he could not hold a newspaper and did not have the necessary concentration to absorb what he read. He would stop three times before he could shave himself. He could not complete a sentence in one breath, and the least bit of effort, such as turning in bed, was soon beyond him. He now manifested the signs of combined right- and left-sided heart failure. The jugular venous pressure was above 15 cm. and hepatomegaly of 4 fingerbreadths was present. Anticoagulant therapy was discontinued in anticipation of operation. He was admitted to the Intensive Coronary Unit for preoperative care, being treated with large doses of Furosemide orally and intravenously, isoprenaline and aminophylline intravenously, mercurials intramuscularly, oxygen therapy, and the like. A sudden further deterioration in his condition and sudden collapse with a transiently unrecordable blood pressure was followed by the typical cough and hemoptysis of pulmonary infarction associated with clinical and radiologic signs of this condition. With death imminent, in a semimoribund condition, the patient was transferred for heart transplantation, which was performed on January 2, 1968.

There can be little dispute about the first of the three introductory questions—there is undoubtedly need for a procedure, be it only palliative, to treat this category of patients, and their number is substantial.

THE OPERATION

The second question concerns the adequacy of our surgical technic in terms of an "acceptable" operative risk. I will briefly describe the technic used in the first two heart transplant procedures.

PREOPERATIVE PREPARATION

The First Patient: The patient was prepared as for any major heart operation. The only additional investigations were, first, the study of the patient's bacterial flora (nose, throat, ears, perineum and rectum and urinary system), including their antibiotic sensitivities on culture. Second, white cell-typing studies were performed to determine the patient's leucocyte antigens. We use the Van Rood technic and, in the first case (for those who are familiar with these studies), the results were 4a, 4b, 6b, 7c and 8a. Our policy has been not to use a donor for organ transplantation if there is more than one incompatibility in any of the major antigens.

The patient was then prepared for the heart transplant. We decided that we would use as donor a young patient, under the age of 30 years, with a normal heart and in whom the cause of death would probably be a brain injury or brain hemorrhage.

On December 2 at 4 P.M. a young woman and her mother were crossing a main road about a mile from the hospital when they were hit by an automobile. The mother was killed immediately, and the girl received fatal injuries to the brain. She was admitted to the hospital five minutes after the accident and was attended by the neurosurgeons and neurologists. They examined and treated her and only at 11 o'clock that evening was the cardiac patient notified that a donor for a heart transplantation had possibly become available. At that stage the young woman had no reflexes present whatsoever, and no spontaneous respiration; she was being maintained by an artificial respirator. Her blood pressure had dropped to 60/0 mm. Hg, and severe metabolic acidosis was present. We first determined that the red cell group was compatible with the patient's, and we then approached her father, obtaining permission for the heart to be removed after her death, for transplantation.

The remaining studies then performed had the following objectives: (1) to ensure that the donor had no disease that could be transferred by transplanting the organ; (2) to satisfy ourselves that the donor had a normal heart; and (3) to study antigens in the white cells of the donor. These were found to be 4a, 4b, 6a, 7b, 7c and 8a, showing that there was incompatibility at the 6a antigen (a medium-strength antigen which the recipient lacked), and "reverse" incompatibility at the 6b. The data met our agreed criteria for a satisfactory donor for transplantation.

The Second Patient: The patient's leucoagglutination tests were positive for 4b, 6a, 7a and 7b and the donor for 4a, 4b, 6a, 6b, 7a and 7b. There was, thus, incompatibility at 4a and 6b. The 4a being a strong antigen and the 6b of medium strength, the donor was accepted.

SURGICAL TECHNIC

On completion of the necessary preparations and with the donor's death imminent, both the

donor and recipient were taken to the operating rooms. After the death of the donor, the heart was removed and transplanted in the following way.

The Donor: Two adjoining operating rooms, each with a pump oxygenator, were used. The death of the donor was determined by the absence of reflexes, of spontaneous respiration and of electrical activity on the electrocardiogram for five minutes. After death had been ascertained, the donor's chest was opened by means of a median sternotomy. She was connected to a heart-lung machine primed with Ringer's lactate solution (Fig. 2).

A single catheter was placed in the right atrium and connected to the venous line of the oxygenator. A vent was placed in the left ventricle to decompress this chamber since the heart was flabby and atonic, and another catheter was placed in the ascending aorta and connected to the arterial line of the oxygenator. At that stage the donor was heparinized, and total body perfusion was started. We used total body perfusion and cooling because a kidney was required for another transplantation procedure. When the body temperature had reached 25° C. perfusion was discontinued. The catheter in the left ventricle was disconnected from the heart-lung machine but left in place; the catheter in the right

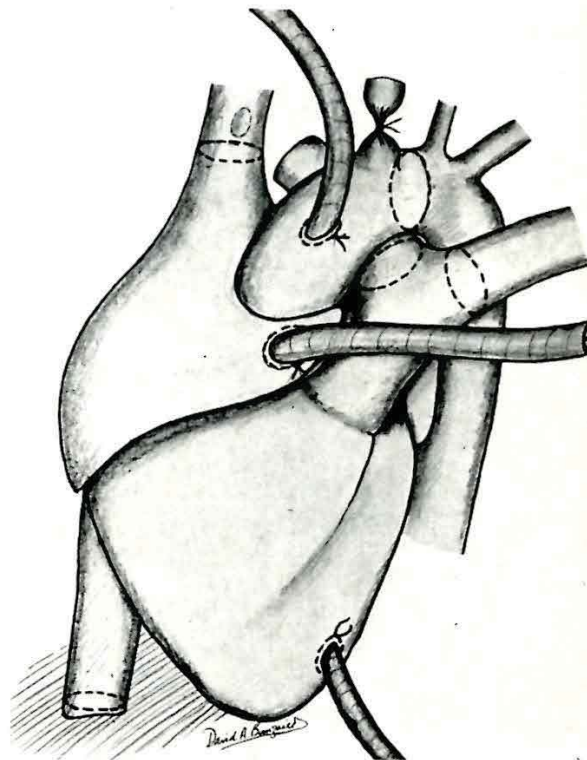


Figure 2. Diagram showing the venous arterial connection of the donor heart to the heart-lung machine, with a left ventricular vent in position for decompression of the left heart. The levels at which the venae cavae, pulmonary arteries and aorta are divided are also shown.

atrium was removed. The catheter in the ascending aorta was also disconnected from the pump but left in place. The heart was then excised as follows: The superior vena cava was divided high up near the azygos vein, and the inferior vena cava cut at the diaphragm. The aorta was severed distal to the innominate artery, and the right and left pulmonary arteries were divided. In addition the four pulmonary veins were divided. The heart was removed with portions of the venae cavae, the entrances of the pulmonary veins, the pulmonary artery bifurcation and a portion of the aorta. It was taken, immersed in Ringer's lactate at 10° C., to the other operating room, where the patient had already been connected to the heart-lung machine.

The Recipient: One catheter was placed in each of the patient's caval veins through the right atrial appendix; these were connected to the venous line of the oxygenator (Fig. 3). Because of severe atherosclerosis of the right common femoral artery, the arterial blood had to be returned through a catheter placed in the ascending aorta. The patient's temperature was lowered to 32° C. and, at that stage, the patient's heart was excised. The atria were detached from the ventricles as near as possible to the atrioventricular groove. The aorta was divided on the coronary ostia and the pulmonary artery on the pulmonary valves, leaving the aorta, the pulmonary artery with its bifurcation, the right atrium carrying the superior and inferior venae cavae, and

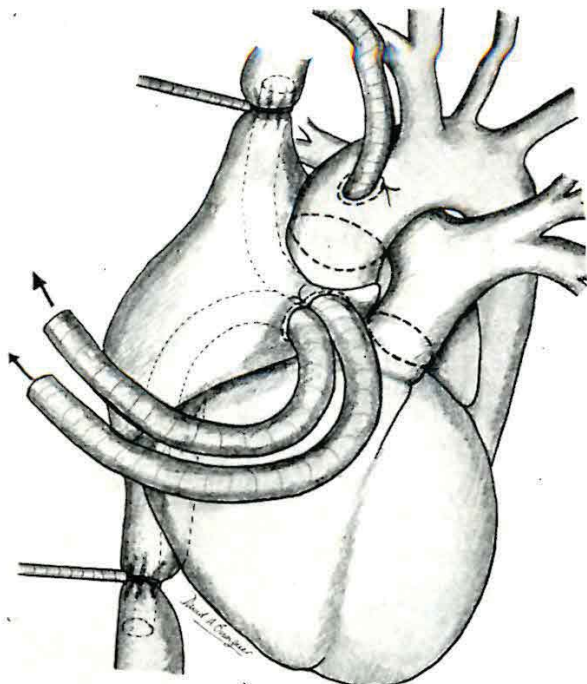


Figure 3. Diagram illustrating the connection of the recipient to the heart-lung machine, with two venous catheters into the superior and inferior venae cavae and an arterial return into the ascending aorta. The levels at which the aorta and pulmonary artery are divided are also illustrated.

the left atrium with the four pulmonary veins (Fig. 4). The donor heart was now connected to the patient's heart-lung machine. The catheter in the ascending aorta was connected to the coronary pump, allowing blood to well up in the aorta, and as soon as this had displaced all air, the aorta was cross-clamped. The coronary arteries were therefore perfused through the aortic catheter, at the rate of about 350 ml./min. The vent in the left ventricle was again connected to suction so as to allow decompression of the heart. The donor heart was then prepared for anastomosis.

The Anastomosis: The back wall of the left atrium at the entrance of the four pulmonary veins was excised. In the first patient we opened the back of the right atrium from inferior vena cava to superior vena cava (Fig. 5). This procedure, however, may conceivably injure the sinoatrial node, and in the second patient the superior vena cava was accordingly avoided by making the incision away from it and to one side; the vein itself was ligated just above its entry into the atrium (Fig. 6). The openings in the posterior walls of the left and right atria were then anastomosed, with the use of double layers of continuous 4-0 silk, to the remnants of the left and right atria of the patient (Fig. 7). By joining the posterior wall of the right and the left atria to the corresponding margins of the recipient's remnant chambers, sutures do not pass through the intra-atrial septum of the

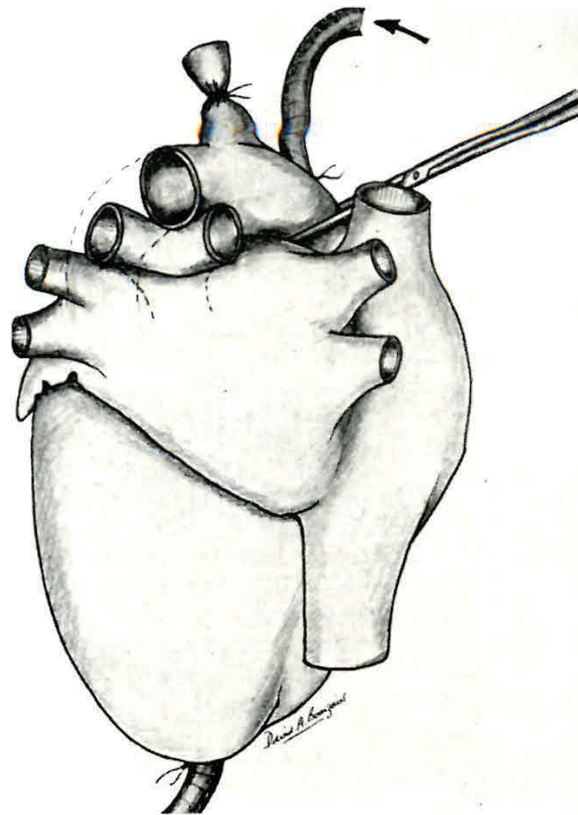


Figure 4. Diagram illustrating the extent to which the donor heart is excised and the way in which it is continually perfused from the patient's heart-lung machine. Note that the whole of the right and left atria are removed.

donor heart. In this respect the technic we used differs from that of Shumway.¹

The pulmonary artery was next anastomosed, followed by the aorta, and rewarming the patient was then finally instituted (Fig. 8). To restart the heartbeat in the first patient, direct application of a 35 joule shock from a D.C. defibrillator was used; the heart in the second patient started beating spontaneously.

The technical adequacy of the operative procedure was substantiated both by the immediate events and those following. In neither patient were there any postoperative complications attributable to the surgical technic as such; both hearts took over function immediately and maintained it with complete adequacy, as described later. There was no excessive postoperative bleeding. The first patient died 18 days after operation, and the second patient is still alive after six months. Thus, the technic evolved has so far carried a direct mortality of zero.

POSTOPERATIVE COURSE AND MANAGEMENT

The third and last of the introductory questions is: Are we capable of detecting the com-

plications which may follow this operation, and of dealing with them when they occur?

What complications may be expected? They fall into two main groups. The first includes those that may arise after any major heart operation, namely, failure of the heart, development of acidosis and electrolyte imbalance. Technics for their avoidance or prompt correction are by now familiar to all experienced cardiac surgeons, and the same principles of management afforded successful control after both these operations.

The second group of complications is peculiar to this operation, and mainly concerns the body's tolerance of the transplanted heart. Can one detect and control rejection in the transplanted heart? The following schedule of observations was undertaken in order to recognize possible graft rejection in the transplanted heart:

1. Studies of the functional efficiency of the

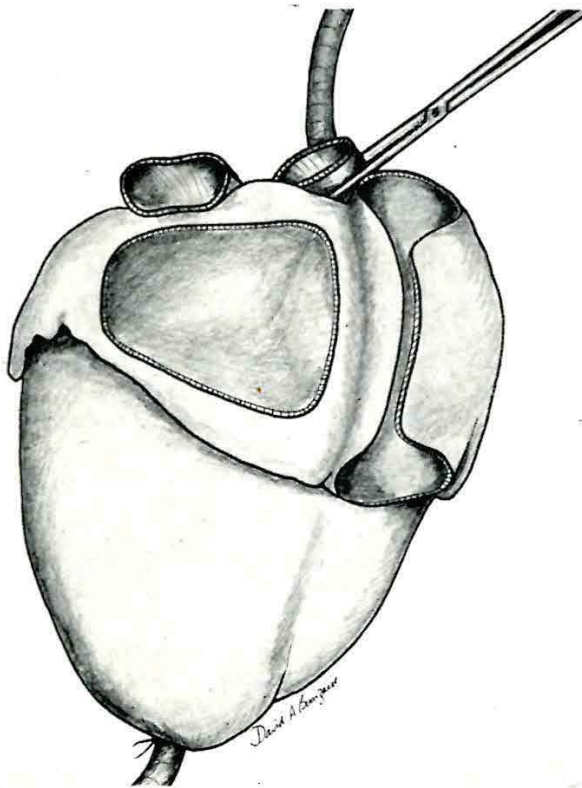


Figure 5. Case 1. Diagram illustrating the openings made in the left and right atria of the donor heart for anastomosis to the remnants of the left and right atria. Note that the right atrium was opened from the inferior vena caval orifice to the superior vena caval orifice.

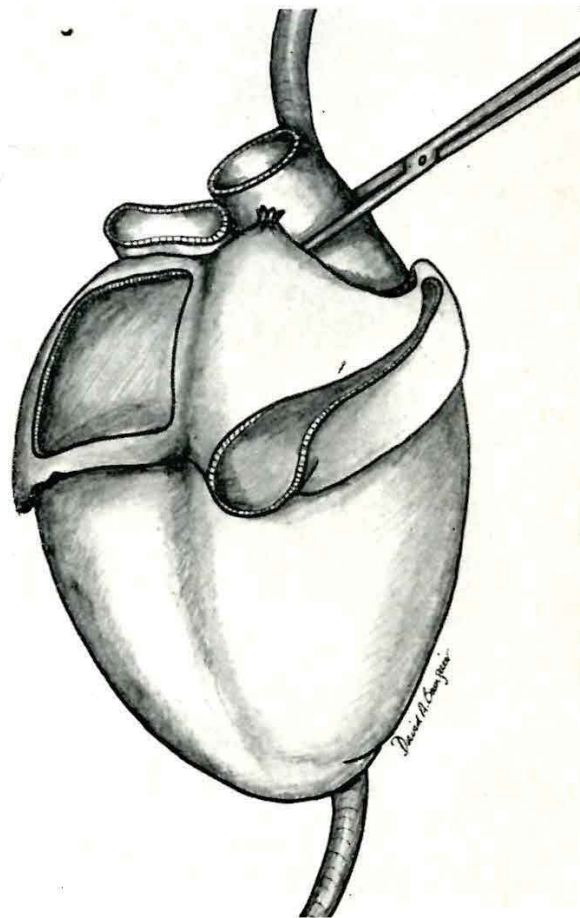


Figure 6. Case 2. Diagram illustrating the change in technic in the opening of the right atrium. The superior vena cava was ligated and the incision in the back of the right atrium was made from the inferior vena caval orifice laterally toward the atrial appendage, thus avoiding any possibility of damaging the sinoatrial node.

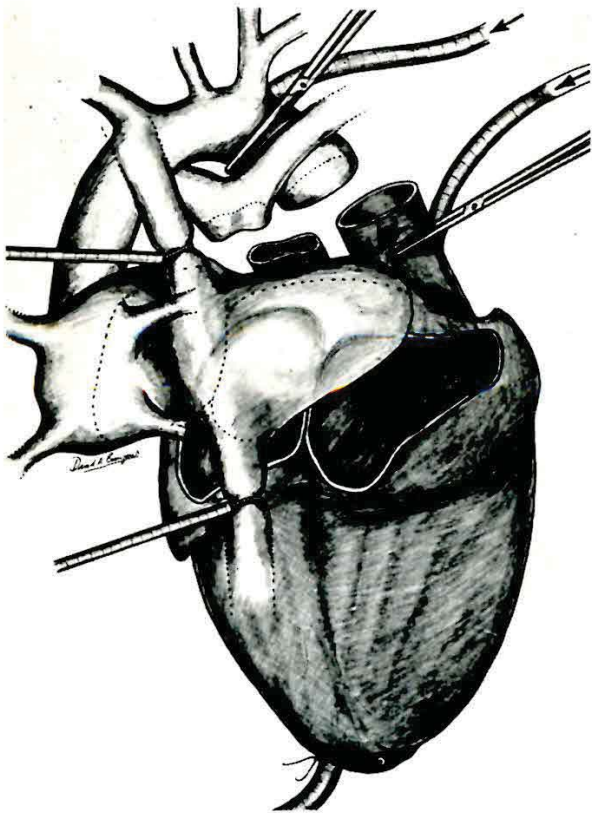


Figure 7. Diagram illustrating the donor heart (in heavy stipple) and the remnants of the recipient's heart (in light stipple.) Both the recipient's and the donor's hearts are perfused at this stage and the transplant is commenced by first anastomosing the left border of the left atrium.

transplanted heart, bearing in mind the deterioration characterizing the rejection of kidney grafts. Cardiac function was evaluated both by meticulous clinical examination for evidence of heart failure and by close attention to the electrocardiogram.

2. Careful radiographic observation of heart size for any signs of enlargement.

3. Biochemical estimations of various blood enzyme levels that might reflect myocardial injury, and frequent hematologic and serologic tests for abnormal immunity responses.

THE FIRST PATIENT

Immunosuppressive Measures: Anticipated rejection was treated by the use of corticosteroids, commencing on the day of operation with hydrocortisone, 500 mg., administered intravenously over 24 hours; in addition, prednisone, 60 mg., was administered orally. The hydrocortisone dosage was gradually reduced by 100 mg. daily, whereas the prednisone dosage was maintained at 60 mg. daily. The heart was irradiated locally, using a 1 curie source of cobalt⁶⁰, starting with a dose of 100 rads on day 3, then 85 rads on day 4 and 200 rads on days 5, 7 and 9, given in the Radiotherapy Department.

Initially, 150 mg. azathioprine was administered

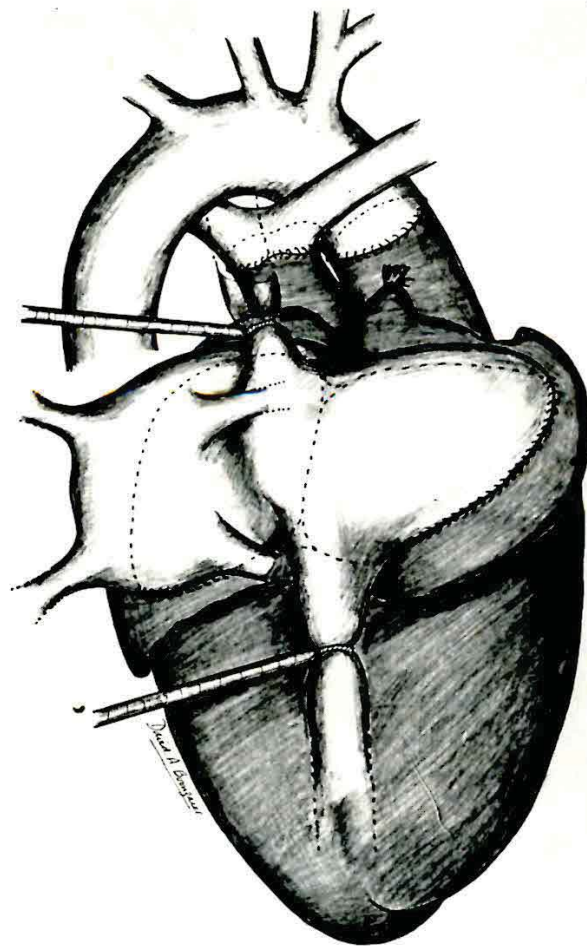


Figure 8. Completion of transplant indicating the various suture lines. Donor tissues in heavy stipple and recipient's in light stipple.

daily through a nasogastric tube; as soon as urinary function improved, the dose was increased to 200 mg. daily.

Threatened rejection was treated by administration of prednisone, 200 mg., and actinomycin-C, 200 μ g., daily for 3 days. The dosage of prednisone was then gradually reduced.

Clinical Progress: Temperature, pulse rate and respiration are charted in Figure 9. Early post-operative tachycardia due to atrial flutter-fibrillation was slowed with digitalis, and the heart rate increased again only in the last five days with the onset of pneumonic pyrexia. Central venous pressure remained normal after a slight rise during the first two days. Arterial blood pressure caused no concern after the patient left the operating theater.

The electrocardiogram showed the continued sinus rhythm of the patient's atrial remnants, and the f waves of atrial flutter-fibrillation in the donor heart (Fig. 10).

Organ functions previously impaired by cardiac failure were relieved by the new heart (Fig. 11). In addition to a pronounced early diuresis, followed

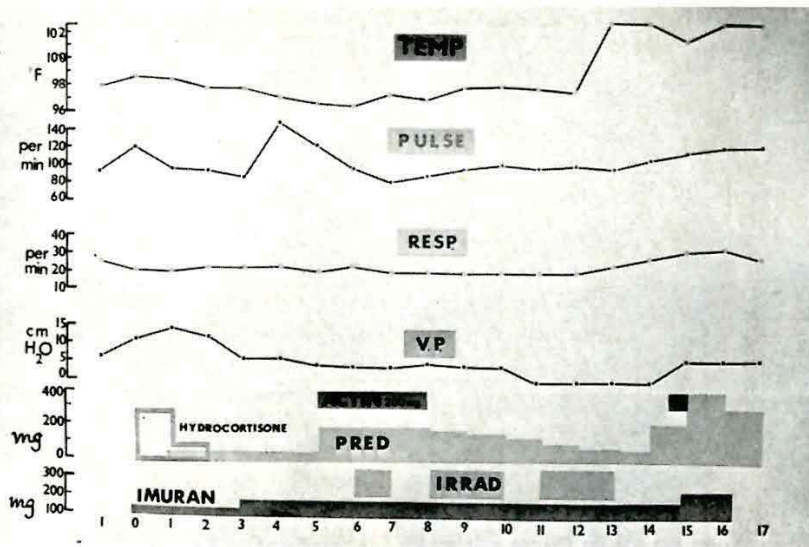


Figure 9. Case 1. Chart of temperature, pulse rate, respiratory rate, venous pressure and immunosuppression, indicating a relatively stable course until the twelfth day, when pneumonia set in.

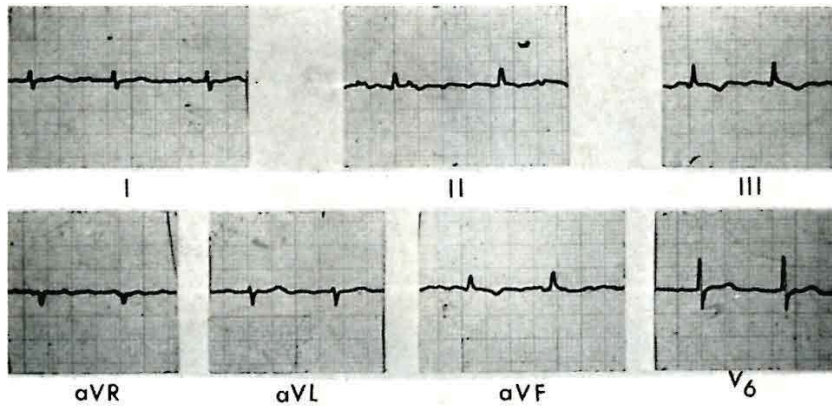


Figure 10. Case 1. Electrocardiogram clearly illustrating the P wave activity of the recipient's old atria and the atrial flutter waves of the donor's atria.

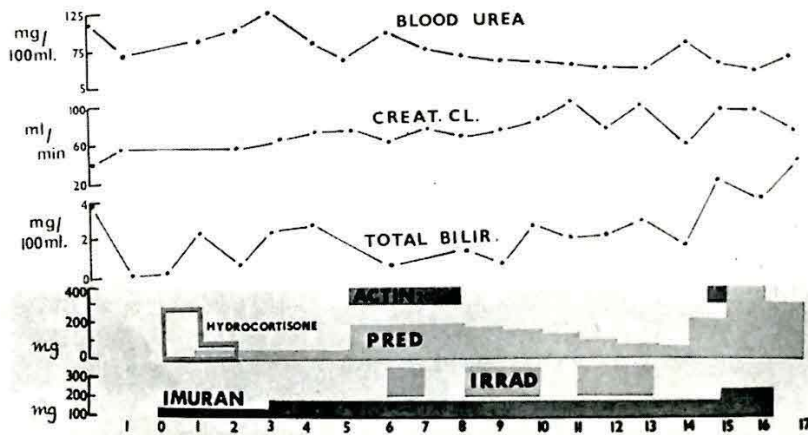
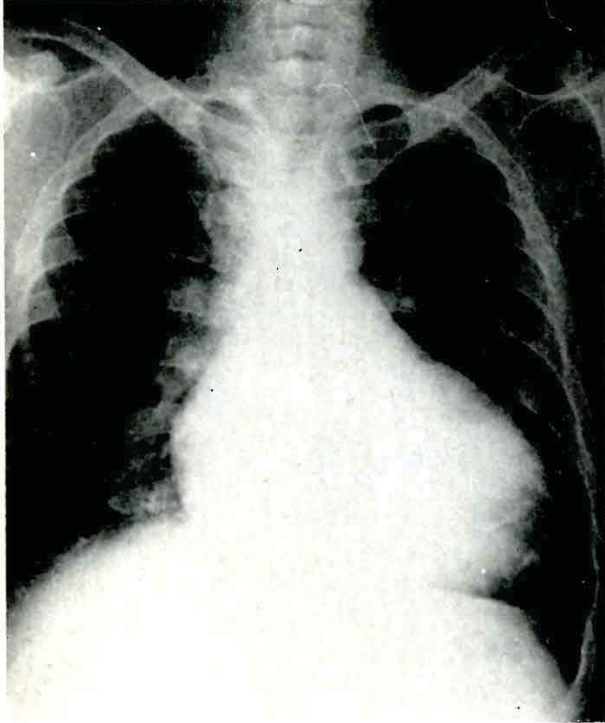
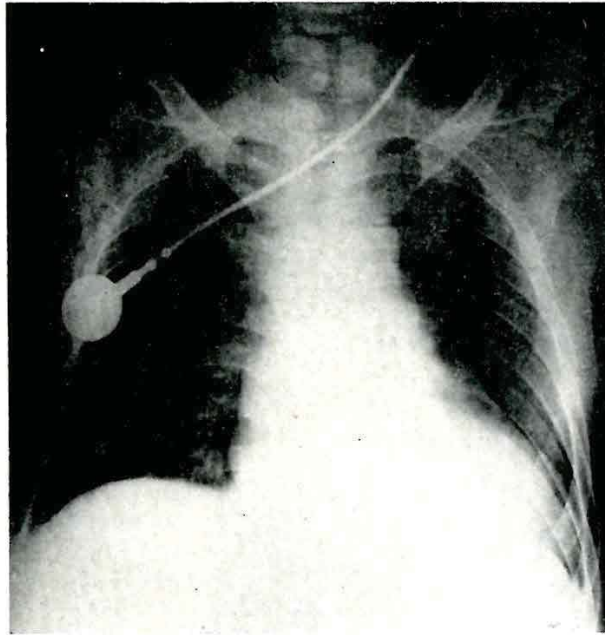


Figure 11. Case 1. Graph illustrating the changes in blood urea, creatinine clearance and total bilirubin, demonstrating the improvement in function of the kidneys and liver after transplantation. This improvement continued until complications set in.

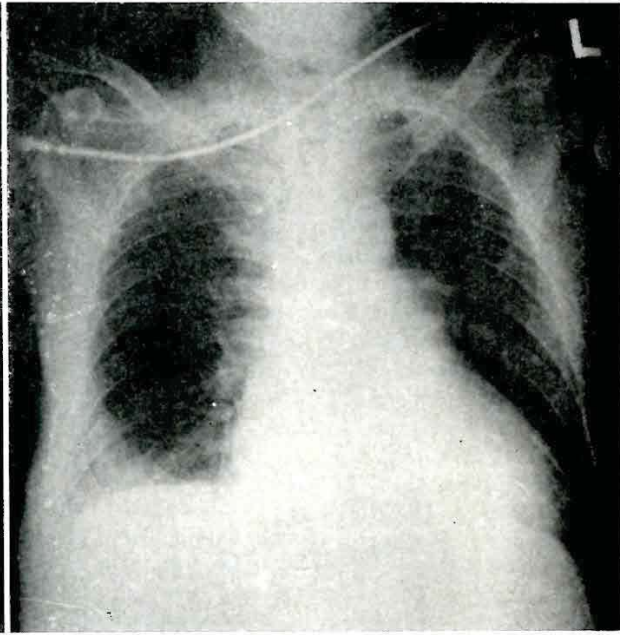
by a normal urine output until just before death, the preoperative blood urea of 179 mg./100 ml. dropped after perfusion, rose again for a few days, and then fell to normal levels and stayed there. Creatinine clearance, previously 29 ml./min., slowly approached normal values; then with some preterminal fluctuation, it fell shortly before death.



A



B



C

Figure 12. Case 1. *Chest roentgenograms.* **A**, before surgery, indicating the cardiac enlargement and pulmonary venous congestion. **B**, immediately after transplantation, still showing enlargement of the cardiac silhouette due to enlarged pericardial sac. **C**, five days after operation, showing a further increase in the cardiac silhouette, probably due to an immunologic attack on the transplanted heart.

The preoperative level of total serum bilirubin was 4.5 mg./100 ml.; two days postoperatively it was normal, and it rose again significantly only on the last two days of illness. The conjugated bilirubin also stayed down until near the end. These observations indicate that the transplanted heart substantially overcame the renal and hepatic impairment which were a feature of the patient's preoperative heart failure; adequate function was maintained until fatal complications ensued.

Cardiac Size: Immediately after the operation radiography of the chest revealed the heart shadow to be still enlarged (Fig. 12), probably due to the unaltered pericardial sac. In the future, silver clips will be put on the edges of the heart to facilitate subsequent assessment of its size. One week after operation the transplanted heart showed enlargement.

Laboratory Data: Daily basic hematologic, serum enzyme and electrocardiographic studies were performed, but as the patient lived only 18 days definite conclusions could not be drawn.

Fatal Pulmonary Infection: Five days after excision and replacement of his diseased heart, the patient was manifestly transformed from being an ill person in constant orthopneic distress to one who could breathe normally lying flat and showed no signs of heart failure. On the twelfth day he was well enough to be allowed out of bed; but the same evening signs of pulmonary infection became evident. Radiography showed no change in heart size, but there was a small area of pulmonary consolidation. On the thirteenth day the area of consolidation had

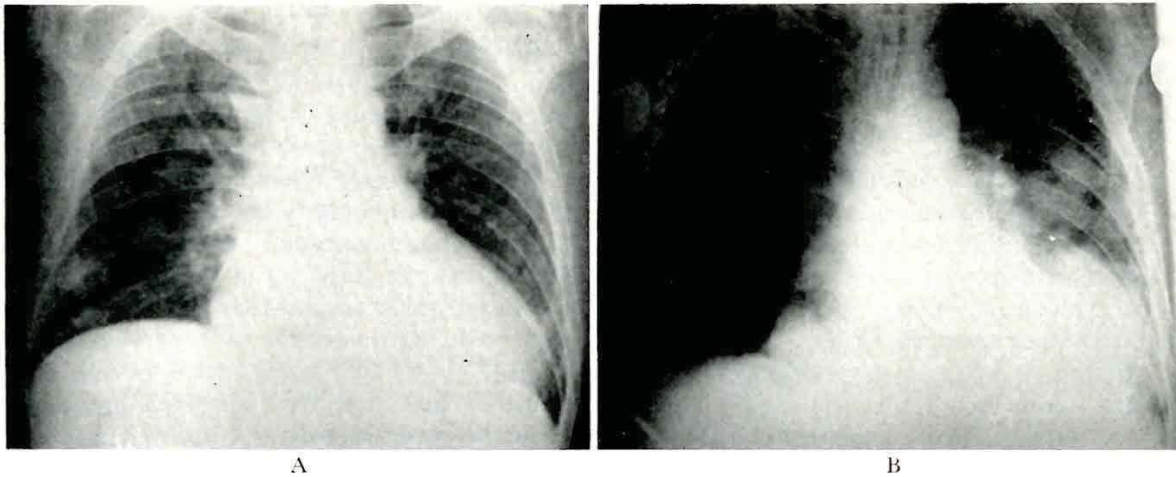


Figure 13. Case 1. *Chest roentgenograms.* **A**, 12 days after surgery, illustrating a small round opacity in the base of the right lung, the beginning of the pneumonic process. **B**, 24 hours before death showing the extensive involvement of both lungs by pseudomonas and klebsiella infection.

become bigger (Fig. 13A), and other areas soon developed. The clinical diagnosis was pneumonia, but a casual organism could not be isolated from the sputum specimens, although some 50 cultures were performed. (The isolation of *Diplococcus pneumoniae* and its abolition by intravenously administered penicillin G did not improve the clinical or radiographic signs.) Accordingly, carbenicillin, cephaloridin and gentamycin were vigorously administered, together with nystatin, given orally.

The lung state steadily deteriorated, contrasting sadly with the unaltered size and sustained function of the transplanted heart (Fig. 13B). On the eighteenth day the patient died from apparently overwhelming clinical pneumonia and hypoxia; blood pressure and other parameters of circulatory function were unimpaired until relatively close to death.

Autopsy Findings: Examination of the heart showed no enlargement (Fig. 14). The suture lines were intact, there was no thrombosis, and the ventricles appeared normal. The clinical evidence that death was due to overwhelming bilateral pneumonia, and not to rejection of the transplanted heart, was fully corroborated. There were only 50 ml. of fluid in the pericardial sac, and the heart was not enlarged. The myocardium, endocardium and valve cusps were normal in color and texture. The coronary vessels were normal on macroscopic examination.

Extensive bilateral pneumonic consolidation was present, verging on pulmonary gangrene. On bacteriologic culture, klebsiella organisms and *Pseudomonas aeruginosa* were isolated from the lungs.

Histologically, it is interesting to note that the patient's own atrial remnant had degenerated, presumably from lack of blood supply; the only fibers surviving were those under the pericardium and on the endocardial surfaces. There was no cell infiltration of the recipient's residual atria. The donor's atria showed perivascular round cell in-

filtration by lymphocytes, plasma cells, Anitschkow myocytes and fibroblast-like cells; the muscle fibers were normal. The ventricles showed much less cell infiltration around the blood vessels, with a few fibroblasts and occasional tissue mast cells; lympho-

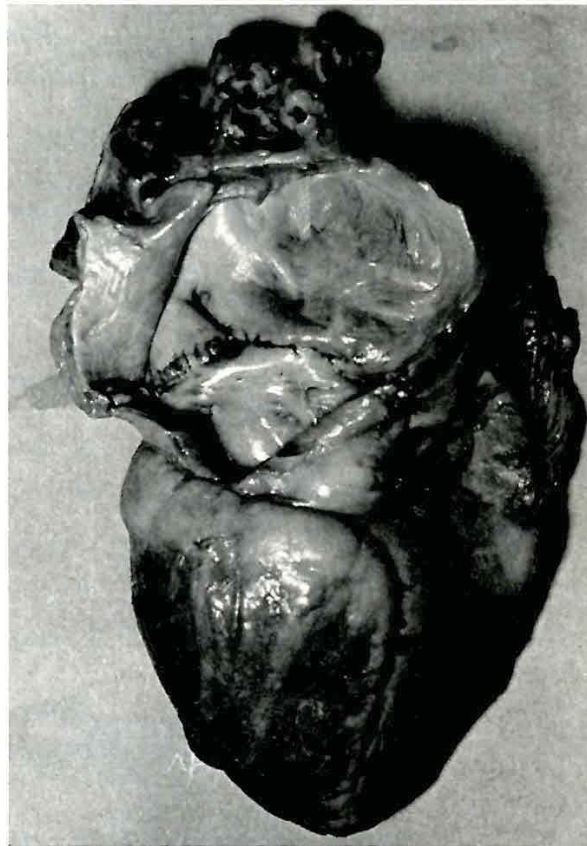


Figure 14. Case 1. *Photograph of the transplanted heart* showing the anastomotic line between the left and right atria. Note that there is no evidence of rejection on the endothelial surface of the donor's atria, no thrombosis and no macroscopic evidence of rejection.

cytes and plasma cells were present singly and in small groups. There were traces of edema, and some ventricular fibers showed indistinct striations and loss of nuclear structure. There were foci of fibrinoid necrosis in small arteries of both ventricles.

Although preterminal anoxic damage, and possibly even local irradiation, may account for some of these features, there is little doubt that the histologic heart changes are consistent with a degree of immunologic rejection. At the present time such changes may be expected with any allograft between two persons, and the problem is whether or not the rejection tendency can be controlled. Neither clinically nor histologically was there any evidence that the first transplant failed because of an unrestrained immune reaction.

THE SECOND PATIENT

Immunosuppressive Measures: The immunosuppressive regimen in the second patient was essentially the same as in the first, except that local irradiation was omitted.

During the longer observation period in the second patient, it became clear (1) that, as in the first patient, organs deranged by the congestive heart failure returned to normal after the heart was transplanted, and (2) that rejection could be diagnosed by observation of the clinical course and some laboratory investigations. When detected, the rejection episode could be reversed with the immunosuppressive agents available. The urinary output, initially low, improved and then ranged between 4 and 5 liters per day. After an initial rise in the blood

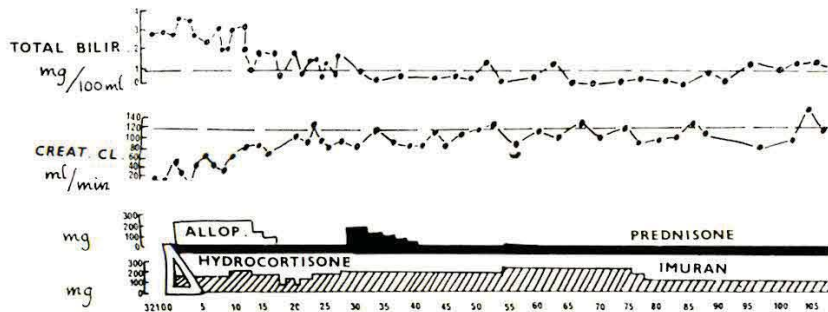


Figure 15. Case 2. Graph showing the changes in total bilirubin and creatinine clearance with the immunosuppression. Note that Allopurinol[®] was used for the first 17 days as the patient suffered from gout. As observed in Case 1, there was a rapid improvement in kidney and liver function.

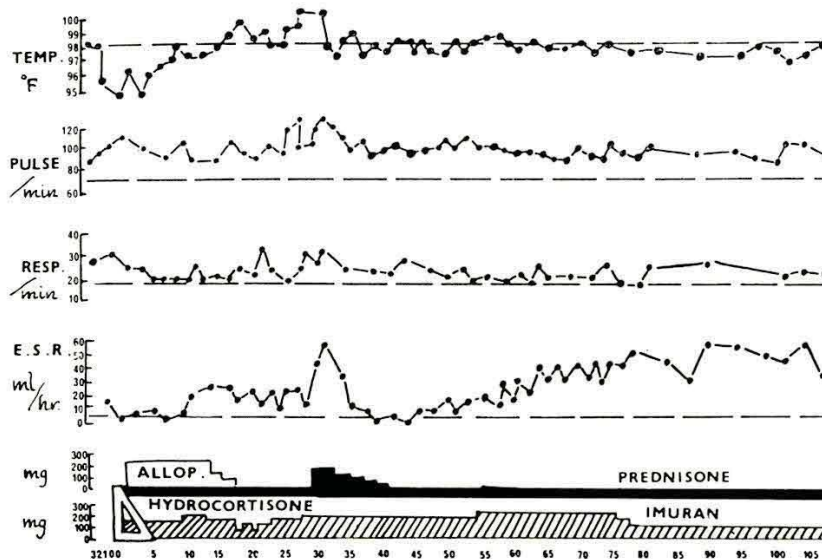


Figure 16. Case 2. Graph showing temperature, pulse rate, respiratory rate, red cell sedimentation rate with the immunosuppression. On the twenty-fifth day there was systemic evidence of rejection, as illustrated by a rise in these parameters. There was a prompt return to normal when the prednisone dosage was increased. The subsequent rise of the sedimentation rate was unexplained, as during this period there was no evidence of any deterioration in the function of the transplanted heart.

urea, there was a fall, and the level then remained more or less normal. The creatinine clearance rose to 154 ml./min. and then remained in the region of 120 to 150 ml./min. The serum bilirubin, high to start with, also fell to normal, as did its conjugated fraction (Fig. 15). As surmised, therefore, threatened rejection can be detected by (1) systemic evidence of immunologic activity; (2) enlargement of the transplanted organ; and (3) derangement in its function.

Systemic evidence of rejection can be clearly observed in Figure 16; toward the twenty-fifth day, there was a rise in temperature, pulse rate and sedimentation rate. At the same time, there was enlargement in the cardiac silhouette. It was difficult to determine whether this increase in size of the cardiac silhouette was a result of dilatation of the heart, a pericardial effusion, or both, since the heart was situated in the old, enlarged pericardial sac. The sac was therefore explored, and 400 ml. of fluid was aspirated. However, roentgen studies revealed that the heart size was larger than immediately after operation, and therefore rejection probably had caused both pericardial effusion and dilatation of the heart (Fig. 17). During this period there was also evidence of a deterioration in cardiac function: the exercise tolerance which had rapidly improved after the transplantation, showed a distinct deterioration. There was also a slight rise in systemic venous pressure and a fall in the voltage of the electrocardiogram (Fig. 18). Studies of the serum levels of serum

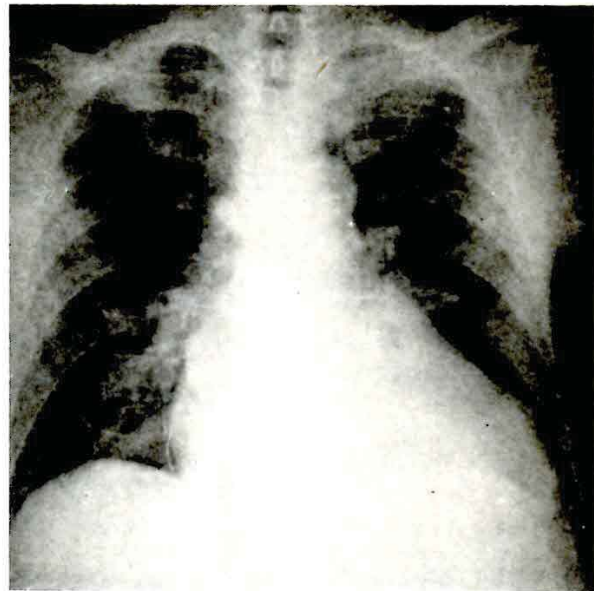


Figure 17. Case 2. Roentgenogram of the chest during the period of rejection, showing enlargement of the cardiac silhouette, which was due to both pericardial effusion and dilatation of the heart.

glutamic oxalacetic acid transaminase, lactic dehydrogenase, alpha hydroxybutyrate dehydrogenase and creatinine phosphokinase, which may be liberated as a result of damage to the myocardium, did not indicate a significant change during this period (Fig. 19).

It was encouraging for us to find that the various parameters mentioned returned to normal levels as soon as the dose of immunosuppressive drugs was increased and the attack on the transplanted heart was reversed.

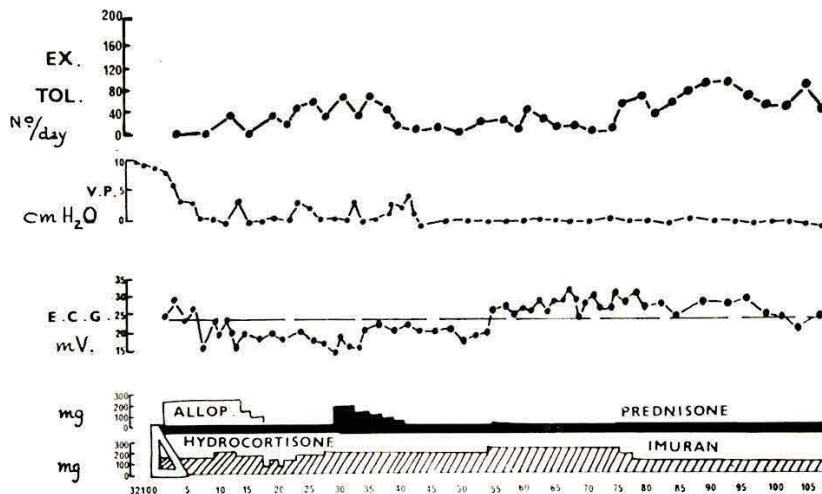


Figure 18. Case 2. Chart showing the exercise tolerance, venous pressure and electrocardiogram voltage, with the immunosuppression. After a steady improvement in exercise tolerance, there was a sudden drop at the time of rejection, with a steady fall in electrocardiogram voltage and a slight rise in venous pressure, all these parameters indicating a change in cardiac function at the time of rejection. There was rapid improvement when the prednisone dosage was increased.

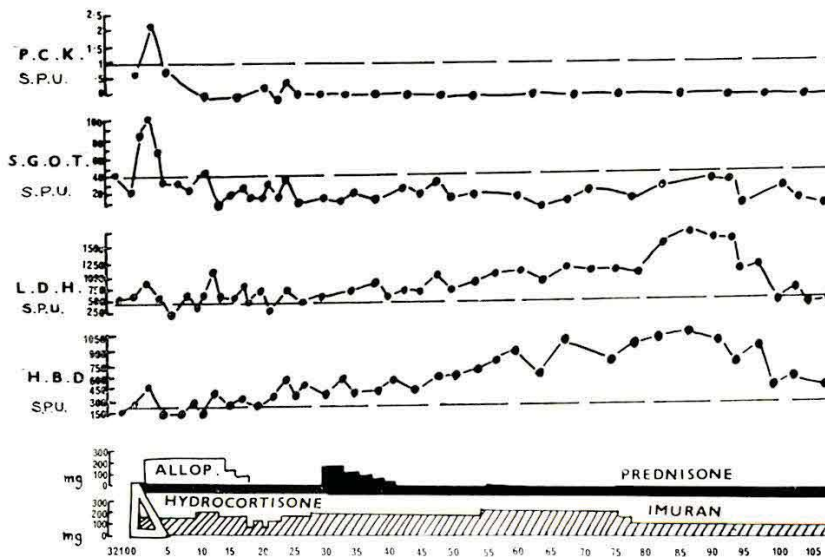


Figure 19. Case 2. *Graphic illustration of changes in creatinine phosphokinase, serum glutamic oxaloacetic acid transaminase, lactic dehydrogenase and alpha hydroxybutyrate dehydrogenase.* The levels of these enzymes do not appear to be altered significantly during periods of rejection. The steady rise in the lactic dehydrogenase and alpha hydroxybutyrate probably relates to increased immunosuppression since these enzymes returned to more or less normal levels as soon as the immunosuppressive dosage was reduced.

CONCLUSION

We have shown this operation of human heart transplantation to be eminently feasible, and in these 2 cases it carried no direct surgical mortality. We are also able to detect and treat possible complications with a high incidence of success, but it is clear that here still lie the major risks and challenges to enduring success.

The World Medical Association has decided that the use of tissues and organs for transplantation should be governed by certain rules. Among the suggestions they have made are the following: in the treatment of a sick person, the physician must be free to use the new therapeutic measure if, in his judgment, it offers hope of saving life, restoring health, or alleviating suffering. I think we alleviated the suffering of our first patient although we did not save his life. It is not quite certain yet for how long we have saved the second patient's life, but I have no doubt that we have alleviated his suffering.

In conclusion, I believe that we have dealt with all three questions relating to whether clinical cardiac transplantation in the human is premature. Final judgment of this issue will rest with a growing number of gravely ill patients who are salvaged, and with the testimony of time.

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