

Human Cardiac Transplantation

In December 1967 Christiaan Barnard amazed the world with the first successful human cardiac transplantation. This brilliant surgical triumph actually culminated years of laboratory experience by numerous investigators. The first major contribution to the field of transplantation was made by Alexis Carrell in the early 1900's. Carrel recognized that a major obstacle to transplantation was the lack of a method for rapidly reestablishing normal blood circulation to an organ removed from its natural vascular supply. He soon devised a surgical technique for suturing small blood vessels, thus permitting organ transplantation to be carried out successfully.

Much of the credit for the recent advance in heart transplantation rests with the experimental work of Shumway and Lower. During a decade of experimentation on dogs these investigators perfected the surgical techniques by which a transplanted heart could be affixed to the pulmonary and systemic circulations in a manner that would sustain the host's circulatory system. They also demonstrated that impending rejection in a transplanted heart was signaled by alterations of R wave magnitude in the ECG and that immunosuppressive drugs could assist in preventing myocardial rejection.

The actual transplantation of a heart is no longer a problem from the standpoint of surgical technique. Successful human cardiac transplantation now depends upon the ability to control the rejection response. Graft destruction is an immunological reaction (Fig. 1). The body cells in the host launch a highly specific attack on genetically

determined foreign antigens located in the donor's graft, causing these antigens to be released into the bloodstream of the host.

The immunological mechanism of the host thereupon triggers the release of lymphocytes into the bloodstream. The lymphocytes cause formation of antibodies which ultimately destroy the graft. These genetically determined antigens are specific for each individual.

The specific chromosomal sites that control the transplant antigen are called histocompatibility loci. These loci may produce weak or strong antigens. If there is a difference between donor and recipient at a single weak locus, rejection is slow and much easier to overcome with immunosuppressive drugs. Rejection would be vigorous if several weak loci are incompatible or if incompatibility exists at a single locus. In man the single strong histocompatibility locus has recently been identified and is referred to as the HL-A locus of the leukocyte antigen.

The most effective way of controlling rejection is through tissue typing and through the use of immunosuppressive drugs and antilymphocytic serum. To reduce the factor of incompatibility of donor cells and host cells, tissues are analyzed and typed according to major histocompatible genes. Lymphocytes from the potential donor and recipient are exposed to antisera and the degree of cytotoxic reaction is noted.

The best results are obtained when donor lymphocytes behave most like those of the recipient. People in the same blood group are more likely to

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have histocompatible genes. The immunosuppressive drugs that have been used most frequently in experimental heart transplantation are Immuran and prednisone. Their mechanism of action is unknown, but it is thought that steroids suppress hypersensitivity and impair antibody formation.

This combination of drugs is very effective, but the incidence of complication from their continuous usage is high, especially because they reduce the patient's general ability to resist infection. Antilymphocytic serum prepared in horses may be useful as an adjunct to immunosuppressive therapy, thereby reducing the dosage of these agents and reducing the evidence of complications.

CLINICAL EXPERIENCE

Three human heart transplant operations have been performed at the University of Michigan Medical Center. The patients underwent their operations in September 1968, December 1968, and March 1969. All were men, aged 50, 39, and 43, respectively, and at present all are alive and well.

Figure I
NATURE REJECTION
PHENOMENON

Antigens
Donor Organ
Reticuloendothelial
System
Destroy
Lymphocytes
+
Antibody

These patients were suffering from idiopathic myocardial disease. In each patient the disease was in the end stages and no longer responded to medical management. The patients all were limited physically to the point that none could walk more than a few steps and all were so ill that they could not be discharged safely from the hospital even for short periods.

Cardiac catheterization confirmed the clinical impression of severe congestive heart failure with significantly increased pressures in all chambers. Left ventricular cineangiograms showed a generalized, poorly contracting left ventricle. Because of the far advanced nature of their myocardial disease, no cardiac surgery other than transplantation was available to these patients.

OPERATIVE TECHNIQUE

The recipient patient is placed on cardiopulmonary bypass. The heart is excised so that most of the recipient's atria are left in place. The aorta and pulmonary artery are divided. The donor heart is excised in total and perfused with oxygenated blood through the aorta. The donor heart is then sutured to the recipient heart remnant by anastomosing the atrial septum, the left and right atria, the pulmonary artery and aorta. The sino-atrial node of the donor heart is thus left undamaged.

IMMUNOSUPPRESSION

Immunosuppression was achieved by thymectomy and by chemotherapy with Immuran, prednisone, and anticoagulants. Thymectomy was carried out at the time of transplantation. Experience with animal studies has shown that survival time is greatly increased when this procedure is combined with other types of immunosuppressive therapy.

Figure II
IMMUNO-SUPPRESSIVE
THERAPY

Thymectomy at time of transplant
Azathioprine
Prednisone
200 mg/day—2 months
150 mg/day—thereafter.
150 mg/day—3 weeks postoperative
75 mg/day—4 weeks postoperative
40 mg/day—3 months postoperative
30 mg/day—6 months postoperative

Immunosuppressive therapy was started 12 hours preoperatively at a daily level of 200 mg. of Immuran and 150 mg. of prednisone and was continued at these doses for three weeks after the operation. Thereafter the dosage of prednisone was gradually decreased until a maintenance level of 30 mg. per day was reached. Immuran was decreased to 150 to 175 mg. per day after two months and was maintained at that level (Fig. II).

To prevent small-vessel thrombosis and to help maintain a more normal coronary blood flow the patients were placed on anticoagulant therapy postoperatively. Administration of heparin was started on the fourth postoperative day and continued for six weeks. At that time, anticoagulation was maintained with coumadin.

POSTOPERATIVE PROBLEMS

Experience with laboratory animals has indicated that isoproterenol is needed after cardiac transplantation, and it appears that this drug should be given prophylactically to any patient undergoing transplantation. Isoproterenol was not given to our first patient, and it became necessary to perform open cardiac massage when sinus arrest occurred two hours postoperatively. This patient subsequently developed a pseudomonas infection involving the right pleura, mediastinum, and right lower lobe. Treatment for this involved tube drainage of the chest, appropriate antibiotic therapy, and administration of pseudomonas-immune globulin. Immunosuppressive therapy was not interrupted and the infection cleared within three months.

Preoperatively, hypervolemia was present in all three patients, secondary to their severe congestive heart failure.

Immediately after each of the three operations, it became apparent that a large amount of the patient's blood had remained in the pump oxygenator. Since the patient no longer needed this large volume of blood after myocardial function had been restored, the postoperative blood volume was lowered by a considerable amount—2,000 cc. in the first patient; 3,500 cc. in the second patient; and 5,000 cc. in the third patient. Any attempt to restore the preoperative blood volume postoperatively would have resulted in congestive heart failure.

Cardiac output in all three patients preoperatively was less than one liter per minute. Postoperatively all have a normal restoring cardiac output. One patient has been studied by graded exercise tests at three and six months after operation. On both occasions his cardiac output was over six liters per minute at rest, and with exercise, it rose to over nine liters per minute.

Only one patient has experienced a rejection episode. Three months postoperatively after an uncomplicated convalescence, this patient developed signs and symptoms of congestive heart failure. Coincident with this, his electrocardiographic voltage dropped and his platelet count acutely decreased to 80,000. The patient's regular immunosuppressive therapy was supplemented by 1 gm. per day of antilymphocytic globulin and intravenous administration of heparin for four days. On this regimen, there was amelioration of his congestive heart failure, his electrocardiographic voltage rose, and his platelet count returned to normal. He has had no further episodes of rejection.

SUMMARY

Three patients with end stage myocardial disease have undergone heart transplantation at the University of Michigan Medical Center. Immunosuppression was achieved by thymectomy and chemotherapy with Immuran, prednisone and anticoagulant therapy. Only one patient had an acute rejection episode, three months after transplant. This was reversed by antilymphocytic globulin and intravenous heparin. At present all have had an excellent result with marked improvement in their general well-being.