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Recent activity by others in heart transplantation makes this review of some 60 years of scientific experiment of timely interest. Present obstacles and future goals are cited.—Ed.

Homotransplantation of the Heart: A Synopsis

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An obituary in the Argentine newspaper, *La Nacion* (February 5, 1968), recently recorded the death of Ana Carrel in the province of Cordoba, at the age of 91. Ana Carrel was the widow of Alexis Carrel — one of the great medical innovators of this century, particularly in the field of organ transplantation. In 1905, while this unusual man was working at the University of Chicago, he reported the homotransplantation of a dog's heart.[1] He also successfully performed vascular homografts and even transplanted the head, kidney and hind limb of one animal to another. The recipient of his canine heart graft lived but two hours. However, this visionary accomplishment assumes added importance when considered in respect to the period in which it was performed. The transplant was accomplished in the same year the Wright brothers were making their epochal flight! Carrel received a Nobel prize for his efforts. Fifty-five years later, the second Nobel prize to be awarded to medical scientists was given to Medawar[2] and Burnet[3] for their contribution describing the mechanism of homograft tolerance and rejection. Their work was made possible, of course, by the 1862 studies of an Austrian monk, Gregor Mendel, who developed the theory of inheritance by crossing various strains of peas.

Without surveying the previously reported work in the field of experimental heart homografting, the recent dramatic clinical transplants may appear, at first consideration, to have a limited scientific background. Actually, large numbers of competent investigators and clinicians have worked toward the goal of replacing the irreparably damaged human heart with a healthy donor organ.

In 1905, when Carrel performed the first experimental cardiac transplant, he anastomosed the vessels of a puppy's heart to the cervical vessels of another dog — an allograft. Arterial blood from the proximal carotid artery of the recipient perfused the right heart, and blood from the distal carotid artery of the recipient traversed the left heart (Fig.1).

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In 1933, 28 years later, Mann of the Mayo Clinic[4] modified this procedure so that the donor heart coronary arteries were perfused at systemic arterial pressure, and the heart continued to beat for eight days. At this early date he recognized that immunologic rejection was the cause of death in his transplants.

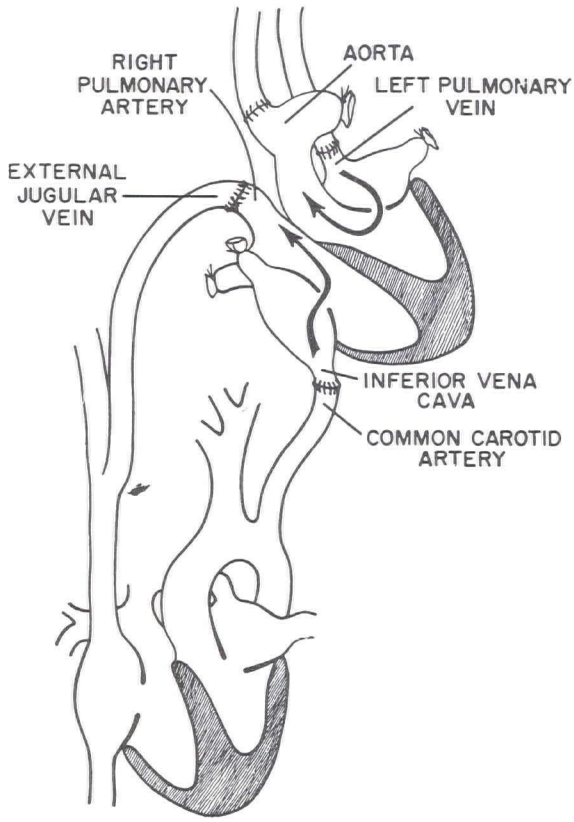

Figure 1

The experimental model used by Carrel in 1905 for the first heart homotransplant. A donor puppy heart was anastomosed to the cervical vessels of the recipient dog. The ends of the divided recipient carotid artery and jugular vein were anastomosed to the inferior vena cava, pulmonary artery, aortic arch and a pulmonary vein of the donor organ.

By permission of P. Hairston and the *Journal of Thoracic and Cardivascular Surgery* (50:1, 1965).

Marcus, in 1933,[5] further modified the experimental model of Carrel to utilize the principle of requiring the heart to perform a work load instead of remaining in a parasitic manner. Survival of the transplants was improved. This investigator also described transplantation of the heart and lungs of one dog to the abdominal aortic and vena caval position of another where they formed an auxiliary organ system.[5]

A Russian, Demichov,[6] utilized the same transplantation procedure again in 1959 and achieved survival of a dog for 32 days. This feat held the world record for several years.

Deep hypothermia at 20°C was used by Neptune and Bailey[7] in 1953 to accomplish experimental transplantation of donor heart and lungs to the normal intrathoracic or orthotopic position; however, the animal lived only six hours.

Experimental transplantation of the heart alone into the orthotopic position of the recipient, that is, replacing the heart as used clinically, should be credited to Goldberg[8] who performed it in 1958 but was unable to obtain a surviving dog.

A genuine technical breakthrough occurred in 1960 when Lower and Shumway[9] of the Stanford Medical Center at Palo Alto were able to report orthotopic heart transplantation in dogs with survival for up to 21 days. They described an operative method in which the posterior portions of the atria containing the pulmonary vein orifices and vena cavas were left intact in the recipient. This procedure greatly simplified the anastomoses by eliminating the need for individual suturing of the pulmonary veins and vena cavas (Fig. 2). Barnard[10] modified this anastamotic method so as to avoid injury to the sinus node area at the superior vena caval-right atrial junction, thereby preserving a normal sinus rhythm in the donor organ.

Autotransplantation, a procedure in which the heart of an experimental animal is completely divided from its connections and resutured in place, has been used for physiological study of the denervated heart graft and as an exercise in operative technique for surgeons. Survival of these animals beyond 18 months has been attained by two groups of investigators.[11,12] Surprisingly, cardiac output measurements and metabolic studies in these 18-month survivors revealed all of the physiologic signs of nerve regeneration.[13] Several of the animals had a normal sinus rhythm and there was a physiological response to exercise and pharmacologic stimulation with adrenalin.

Organ Storage

Since it would indeed be uncommon that the death of a satisfactory heart donor would occur at the proper moment for tranplantation into a patient, there is a need for storage methods which will allow short-term organ preservation without loss of transplantability. Satisfactory organ storage becomes even more desirable as means for tissue typing are developed which require a brief period for matching procedures to be performed. A variety of storage methods have been suggested and tested experimentally. As a reference point, experiments by Wuerflein and Shumway[14] demonstrated that leaving the donor heart in a canine cadaver at room temperature for more than 1 to 1½

hours resulted in sufficient anoxic damage to the myocardium so that only a few of the hearts could be successfully transplanted. Organ storage techniques and time limits of the various methods have been reported as follows:

Hypothermia at 4°C — 12 hours[15]

Hypothermia and hyperbaric 0_2 (2 atmospheres) — 24 hours[16]

Hypothermia and hyperbaric 0_2 (8 atmospheres) — 48 hours[17]

Intermediate host — 24 hours[18]

Biologic heart-lung storage — 24 hours[19]

Pump oxygenator perfusion and hypothermia (kidney) — 72 hours[20]

Other more imaginative ideas have been suggested for organ storage which may become feasible with continued progress in the area of immunosuppression. It has been postulated that a baboon colony might be conditioned immunologically to act as an organ donor farm and the ape family has also been suggested as an intermediate host in which a human donor heart could be kept functioning and viable until needed. Both of these

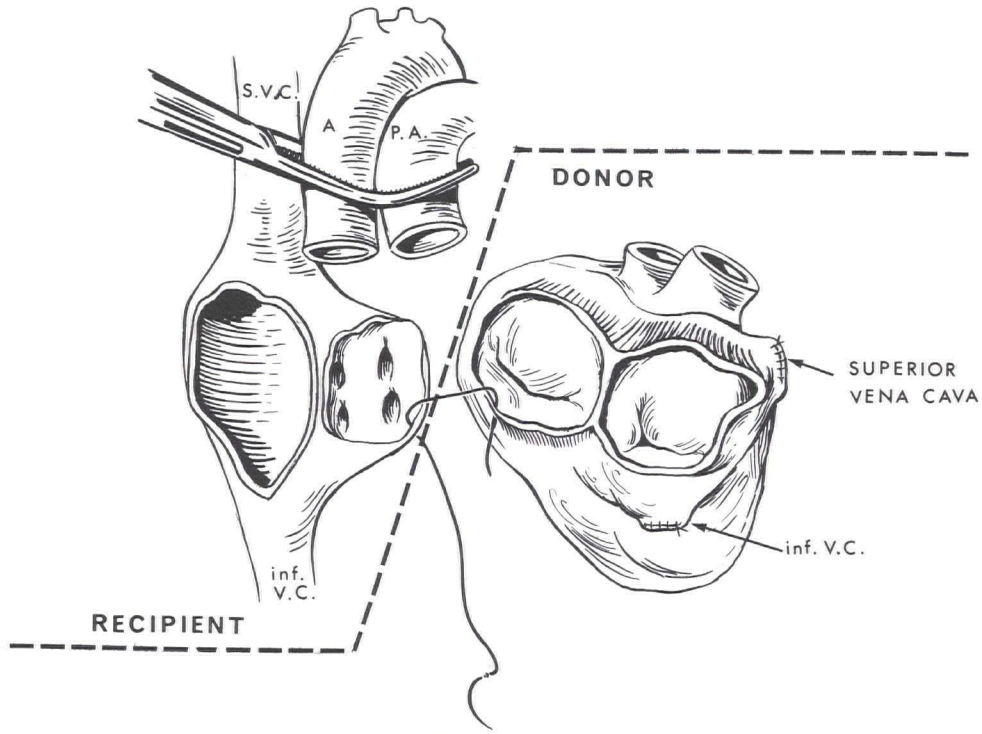

Figure 2

Operative procedure for transplantation of the heart based on the method of Lower and Shumway.[27] The artial anastomosis is first completed by approximation of the adjacent portions of donor and recipient tissue with a continuous suture. The posterior walls of the donor heart atria have been excised and tailored to match the recipient heart remnant.

In order to preserve the sinoatrial node and maintain a normal sinus rhythm in the donor organ, the superior vena caval — right atrial junction area is left intact as advised by Barnard.[10] Enlargement of the donor right atrial opening is gained by extending the incision into the atrial appendage. The procedure is completed by suture anastomosis of the pulmonary artery and ascending aorta.

proposals require attenuation of the rejection phenomenon beyond that available at this time. In this area of clinical investigation, the unsuccessful 1964 chimpanzee-to-man cardiac transplantation at the University of Mississippi by Hardy [21] has almost been forgotten. Another novel approach to organ storage was suggested by recently reported experimental work indicating that intra-arterial hydrogen peroxide (0.2%) furnished the same degree of protection against anoxia as that of hyperbaric storage at two atmospheres pressure of oxygen.[22]

The clinical heart transplants performed in Capetown and Palo Alto have utilized external cardiac compression or femoral artery to femoral vein perfusion with a pump oxygenator to preserve the donor organ in the cadaver, while preparations were made for the transplantation. This application of existing pump oxygenator equipment will prevent anoxic damage to the tissues at the cost of a reasonable amount of blood trauma for two to three hours. San Francisco workers have devised a modification of a membrane pump oxygenator system for perfusion storage of organs which extended the preservation period to 72 hours for renal homografts.[20]

Immunology

Inability to suppress the transplant rejection reaction without serious or fatal side effects is undoubtedly the greatest barrier to more widespread and successful organ transplantation. An indication of the slow progress in this field to date is apparent when one recalls that with the exceptions of tissue typing and antilymphocyte serum, the rejection minimizing measures used in the cardiac transplants thus far in 1968 were essentially the same as those employed by Merrill [23] at the time of his first cadaver kidney transplant in 1962. Prednisone, and usually cortisone, have been routinely employed in most treatment protocols, supplemented by one of the nuclear DNA metabolic inhibitors such as 6-mercaptopurine, azathioprine or methotrexate. Whether the latter drugs actually act specifically in an immunosuppressive manner, or are only anti-inflammatory agents, remains to be proven. Whole body irradiation of the recipient — to suppress immunologic activity in the bone marrow and reticuloendothelial system — has been largely discarded because of inability to avoid a lethal degree of suppression in these vital areas. Irradiation of the donor organ to suppress antigenic activity, however, is receiving considerable attention and has been used for human cardiac and renal transplants. Continued interest is also being maintained in depleting the body of immune-active lymphocytes and subcellular elements by producing a chronic fistula of the thoracic duct. To date, there has been no reported application to cardiac transplantation of the principle of chronic local infusion of immunosuppressive agents through an indwelling intra-arterial cannula in the organ, such as has been applied to renal homografts. Such a regional approach to immunosuppressive therapy might be possible in cardiac transplants through use of a small catheter in the aortic root near the coronary ostia.

There is, of course, no need for immunosuppression in a patient receiving an isograft, the donor organ coming from a genetically (monozygotic) identical twin, such as is possible with paired organs. Blood group matching between recipient and donor has been found helpful in minimizing the rejection reaction in renal transplants and pre-

sumably would be of value with cardiac grafts. For instance, the second Palo Alto heart transplant donor was a patient with the universal donor blood group — type O. Pretransplant tissue typing with various antigens and the detection of cytotoxic antibodies will apparently play an increasingly important role in the matching of donor organs and recipients. An extensive project has been funded through the National Institutes of Health to set up regional laboratories for this purpose. Antilymphocyte serum or globulin is a similarly selective approach to ameliorating the rejection reaction in distinction to the administration of pharmacologic immunosuppressive agents which indiscriminately suppress immunologic activity. To make antilymphocyte globulin (ALG), a homologous blood cell or tissue antigen is used to produce a hyperimmune serum in the horse. The serum may be administered pre- and postoperatively to the patient for suppressing the activity of antibody forming lymphocytes, possibly without producing a lymphopenia. Starzl[24] has used ALG extensively in renal homotransplants from both related and unrelated donors. His results suggest that it improves renal transplant survival. Unfortunately, as presently carried out, harvesting and purification of the serum is time-consuming and costly. Interestingly, the second Capetown heart transplant patient did not receive antilymphocytic serum but tissue typing was employed. When these types of selective immunosuppression are more highly refined, it will be logical to direct more attention toward the use of cardiac heterografts — donor organs obtained from species other than man. That immunologic problem possibly will be more easily solved with the experience gained in managing homograft rejection.

Pathologic Considerations

The pathologic findings in homograft rejection have been extensively investigated by Drs. Chiba and Bing[25] of Wayne State University. Their studies were made using the experimental model of cervical homotransplantation of the heart in dogs similar to that originated by Carrel. They were able to demonstrate to their satisfaction that the homograft rejection reaction is mediated in part through circulating antibodies in the gamma globulin fraction of the blood and that it involves both cellular and subcellular elements. They were able to show that the earliest local tissue alteration, after homotransplantation, was accompanied by increased vascular permeability in the graft as measured by the injection of radio-iodinated albumin.[26] They postulated that it was mediated through release of histamine from mast cells in the donor organ. Altered vascular permeability occurred within one hour of transplantation and preceded perivascular round cell infiltration which became apparent at three hours. Following this stage, there was evidence through histological staining techniques of increased RNA content in the perivascular plasma cell infiltrate which was thought to be a sign of protein antibody synthesis. By 19 hours post-transplant, Aschoff-type giant cells appeared in the cellular infiltrate and within a few days, a vasculonecrotic reaction was evident. Following this, a granulomatous myocarditis with necrosis appeared, resulting in death of the untreated transplant in six to eight days. Bing and associates also studied the metabolism of heart grafts and showed that glucose was utilized with the production of pyruvate and lactic acid. Their investigation[25] indicated that hypoxia was not present, as manifested by a positive redox potential across the transplant (difference between pyruvate and lactate levels in arterial and coronary sinus blood).

Homotransplantation of the Heart: A Synopsis

In order to evaluate the propriety of human cardiac transplantation at this time, a review of the published survival record of experimental homografts is in order. Five-day survival of untreated combined heart-lung transplants was reported as early as 1961.[27] This was followed shortly by 21-day survival of an untreated orthotopic heart homograft.[9] The longest survival of an untreated orthotopic cardiac transplant thus far reported was 313 days. Kantrowitz and associates,[28] who performed the procedure under deep hypothermia at 16°C without a pump oxygenator, reported that the animal died of an obstruction at the atrial suture line, and that the heart failed to show pathological evidence of rejection. Most of the animals in his series, however, succumbed in the shorter period of 21 to 57 days. Orthotopic heart transplants treated with methotrexate (.1mgm/kg every other day) have survived 42 days and Blumenstock,[29] who reported this work, stated that most of the animals died of drug toxicity rather than myocardial necrosis. The most encouraging evidence for long-term survival of organ transplants is that which has been obtained with renal homotransplants from related donors, some of which are now surviving up to five years. Most of these patients continue to receive intermittent immunosuppressive medication.

The administration of antirejection therapy, according to need rather than on a daily basis, constitutes a significant recent advance in the field. Shumway[30] has been able to maintain orthotopic cardiac homotransplants in the dog for three months to one year with this type of program. The one-year survival, however, incurred permanent bone marrow damage due to the immunosuppressive therapy which necessitated frequent whole blood transfusions.

Periodic biopsy of the kidney transplant has been helpful in directing the administration of antirejection medication on an intermittent or demand basis but this is impractical in heart grafts. With cardiac transplants, both experimental and in the recent clinical cases, alterations in the EKG have proved to be the most valuable indicator of the rejection activity level. Shumway has described these findings, the most important of which consists of a reduction in the "R" wave voltage.[30] Although progression of the EKG changes reliably predicts death due to necrosing myocarditis within 18 to 24 hours, most investigators have noted a remarkable preservation of cardiac function until immediately before death. Serum enzyme determinations, such as the lactic acid dehydrogenase (LDH) and serum glutamic oxaloacetic transaminase (SGOT), have been of little demonstrated value in predicting rejection activity.[30]

Clinical Heart Transplantation

Since the giant step into the era of clinical heart transplantation by Barnard of Capetown on December 2, 1967, a total of 14 have been carried out up to the time of this writing (May 20, 1968). With the exception of the infant patient of Kantrowitz's with tricuspid atresia and one of Cooley's patients with triple valve disease, the indications for transplantation have been progressive and intractable heart failure or other complications of ischemic coronary artery disease. Now that the longest survivor, 58-year-old dentist Phillip Blaiberg of Capetown, is apparently progressing satisfactorily five

months post-transplant, patients with other forms of heart disease should be considered as candidates for cardiac replacement. These might include patients with rhabdomyosarcoma of the heart and those with progressive myocardopathies as well as some uncommon congenital lesions not amenable to currently employed surgical procedures.

Nonmedical Considerations

There are, of course, myriad unsolved problems in the exciting field of organ transplantation. Even the most skeptical must soon admit, however, that a more pertinent question than "Was clinical heart transplantation premature?" would be "How long will it be before the procedure is more widely and successfully practiced?" Some members of the medical profession claim privately and in the public communications media that the problems of "What is death?" and "When does it occur in an organ donor?" are formidable barriers, the solutions of which should involve clergymen, lawyers, philosophers and administrators, as well as government representatives. Unfortunately, with this approach, the most knowledgeable workers in the field of transplantation — the clinicians — are greatly outnumbered by well-meaning, but poorly informed, advisors. Undoubtedly, more accurate criteria to establish the time of irreversible antemortem brain damage in a potenial heart donor — the accepted yardstick of inevitable death — will be forthcoming, now that the need is apparent. At present, it would seem appropriate that this determination should be left to the most informed and experienced, ie, the neurosurgeon. Undoubtedly a degree of objectivity will be added to this evaluation by requiring that the EEG show an absence of electrical activity for a specified period.

Medical spokesmen for the National Science Foundation have recently stated that human cardiac transplantation is justifiable on an investigational basis. Also, it should be done by those with a background in appropriate experimental work along with the availability of necessary ancillary personnel experienced in managing the problems peculiar to the transplantation field.

In order to estimate the number of potential heart transplantation procedures which might be required in a medical center, such as the Henry Ford Hospital, the autopsy records for a one-year period were studied. During 1961, there were 780 autopsies, and 48 of these deaths occurred in patients who might be considered potential donors. They involved patients under 50 years of age without clinically significant infection or heart disease. Twenty-eight of the 48 potential heart transplant donors were patients with fatal central nervous system or kidney disease. Six were children under five years of age. Concerning potential recipients, there were 55 autopsies during the year in patients under 65 years of age in which the cardiac pathology was not a type amenable to currently practiced surgical procedures, such as valve replacement. Twelve of the 55 potential transplant recipients were under five years of age. It was surprising to note this approximate balance between potential recipients and donors.

Although investigation in the field of cardiac transplantation has been undertaken sporadically throughout a 60-year period, the important advances have been forthcoming

in the last seven years. It seems reasonable to speculate that a continuation of the present level of progress will shortly place clinical cardiac transplantation on a sound footing, resulting in as yet untold benefits for patients with otherwise incurable heart disease.

Addendum:

A review of the clinical heart transplants described in current magazines and the public press as of August 2, 1968, indicates that a total of 26 human transplants have been performed by 18 different teams. Seven survivors were recorded with the Capetown second patient now eight months post-transplant.

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