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THE successful transplantation of a heart from one human being to another, by Dr. Christian Barnard of South Africa, has occasioned an intense renewal of public interest in organ transplantation. The background of transplantation, and its present status, with a note on certain ethical aspects are reviewed here with the interest of the lay reader in mind.

History of Transplants

Transplantation of tissues was performed over 5000 years ago. Both the Egyptians and Hindus transplanted skin to replace noses destroyed by syphilis. Between 53 B.C. and 210 A.D., both Celsus and Galen carried out successful transplantation of tissues from one part of the body to another. While reports of transplantation of tissues from one person to another were also recorded, accurate documentation of success was not established.

John Hunter, the father of scientific surgery, practiced transplantation experimentally and clinically in the 1760's. Hunter, assisted by a dentist, transplanted teeth for distinguished ladies, usually taking them from their unfortunate maidservants.

Modern methods for the surgical transplantation of skin from one portion of the body to another date back to the late 1800's. At the turn of the 19th century techniques for the transplantation of vessels and organs were developed. The efforts of Alexander Carrel in this field attracted much popular interest; Dr. Charles C. Guthrie, however, should have much of the credit given to his colleague Carrel. Guthrie transplanted a dog's head as early as 1908, and in 1912, published a complete report describing transplantation of the heart, the lungs, the kidneys, the thyroid, and the ovaries. These were, of course, short-term transplants, and the survival of an organ taken from one animal to another for long periods of time was not observed. Although Guthrie made substantial contributions to the development of vascular surgery and organ transplantation, Carrel's charming manner and flair for

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publicity placed him in the limelight. As a result, Carrel was awarded the Nobel Prize for work which might well have been shared with his associate. The first real attempt to preserve organs outside the body came in 1938, when Carrel, in cooperation with Charles Lindberg, developed an extracorporeal pump for human organs.

While World War II dampened the enthusiasm for organ transplantation, it nevertheless provided the setting for studies of the rejection process when transplants were made from one animal to another. Because of the number of individuals suffering extensive injuries and burns, the graft of skin from healthy donors to injured men was seriously entertained. Peter Medawar and Thomas Gibson, at the Glasgow Royal Infirmary, undertook a study of the fate of homografts of skin used in the treatment of burns. Similar studies had been carried out previously, most notably by Dr. Emile Holman, subsequently a Professor of Surgery at the Stanford University Medical School in California. Dr. Holman concluded that homografting was not a feasible means of treating burn patients; he also deduced that the factor that destroyed homografts was specific to the individual from whom the graft was taken. Although the possibility of some type of immune factor was evident, for a variety of reasons it was not pursued at that time. Thus, it was Gibson and Medawar who first noted that when a second set of homografts was transplanted a very rapid dissolution of the second graft took place. Professor Medawar concluded that "the mechanism by which foreign skin is eliminated belongs to the general category of activity acquired immune reactions."

Since World War II a number of investigators have made elaborate studies relative to the nature and prevention of this immune reaction. In 1953, Medawar and two colleagues accomplished a permanent breakdown of the transplant barrier by innoculating cells into a mouse prior to birth. Five years later, Professor F. M. Burnet, of Australia, proposed a theory to explain how a foreign protein causes cells to respond by making antibodies that react with and reject the foreign invader. Certain features of Burnet's theory corresponded with Medawar's earlier findings, and in 1960, they were jointly awarded the Nobel Prize.

The Modern Era

What might be called the modern era of human kidney transplantation was ushered in at Boston's Peter Bent Brigham Hospital in the 1950's. Dr. George Thorn, a professor of medicine, had had a long-standing interest in the possibilities of kidney transplantation. In 1947, Thorn actually initiated an attempt at transplantation which was carried

out by Dr. Charles Hufnagel, presently Professor of Surgery at Georgetown University Medical School. This was a very dramatic case; the transplanted kidney, which was attached to vessels in the arm, functioned sufficiently well to enable a very ill patient to recover from a reversible form of severe kidney failure. Although the kidney was rejected several days after it was transplanted, its function was sufficient to tide the patient over a crisis. The development of the artificial kidney by Professor Kolff of Holland made this particular use of kidney transplantation unnecessary.

In the 1950's, stimulated in part by Professor Thorn, Dr. David Hume, presently Professor of Surgery at the Medical College of Virginia, began a series of carefully studied transplants of human kidneys. In these transplants, no effort was made to alter the immune response. It is of particular significance that in one patient the transplant functioned successfully for nearly six months; the patient died almost as much from severe vascular disease and heart failure as from renal insufficiency. Dr. Hume's work was further developed by Dr. Joseph Murray, a graduate of Holy Cross College and the Harvard Medical School. Dr. Murray performed additional transplants in unprepared recipients; but again no long term success could be claimed.

As the interest in homografting kidneys began to wane, an opportunity occurred to carry out a kidney transplantation between identical twins. In December of 1954, Dr. Murray, jointly with Dr. J. Hartwell Harrison, transplanted a kidney from a healthy twin to his brother who was suffering from advanced kidney disease. The operation was in every respect a complete success, and the patient was discharged from the hospital fully recovered—so healthy that he married one of the nurses who helped care for him. It was now clear that kidney transplantation was feasible and practical; however, a means of suppressing the immune response on the part of the recipient remained to be found.

The story is a long one. Many methods of suppressing the immune response have been and are being tried. Exposure of the whole body to X-rays was dismissed as too dangerous for the patient. In 1959, a very important observation was made by Robert Schwartz and William Dameshek of Tufts; certain drugs were found to have a specific blocking effect upon immunological responses. Dr. Roy F. Calne of England was among the first to recognize the significance of these observations and undertook a practical resolution of the problem in the laboratories of Dr. Joseph Murray at Harvard. Working jointly with Dr. Murray, Dr. Calne demonstrated that successful transplantations of kidneys from one dog to another could be accomplished by

appropriate adjustment of the dose of immunosuppressive drugs. While the exact actions of the drugs are still not fully understood, their suppressive effects upon the immune reaction to transplantation have been confirmed in many laboratories and clinics. Other drugs were later used, such as cortisone, certain antibiotics, and most recently an immune serum that destroys the small cells known to effect rejection.

The next step in the development of organ transplantation was the cautious application of this newly acquired knowledge to man. Once again, the pioneer work was done in Boston by Dr. Murray and his team. The work proceeded carefully and cautiously. Between 1960 and 1963, hardly a dozen operations were performed. Success came slowly, but steadily, and by 1963, it was evident that wider employment of the operation was possible under carefully controlled clinical and laboratory conditions. In a number of institutions, including the University of Colorado and the University of California (Los Angeles and San Francisco), human transplantations of kidneys from one living donor to another were undertaken. A registry of kidney transplantations was established in which more than 2000 such operations have been recorded. Presently, there are about a dozen major centers throughout the world engaged in kidney transplantation, and each year the possibilites for long term, permanent survival of the transplanted kidney are growing.

The Present State of Kidney Transplantation

At the University of California, San Francisco, Dr. John Najarian initiated a clinical study of renal transplantation in January of 1964. Dr. Najarian had previously spent three years in the study of immunology and utilized this background and knowledge to establish a specific pattern for transplantation. His results are typical of the best transplant centers in the world. The operation is done in two stages. The patient is prepared for the first operation by treatments with an artificial kidney until the serious effects of renal failure are corrected. Both kidneys and the spleen (an organ which produces many of the small cells known to participate in organ rejection) are removed during the first operation. After additional treatment on the artificial kidney, a kidney from another person, usually a close relative, is transplanted in a second operation. With modern technique, the new kidney begins to function immediately and early rejection rarely occurs.

The work begun by Dr. Najarian has been continued by Dr. Samuel Kountz and Dr. F. O. Belzer at the University of California, San Francisco. New methods of tissue classification have shown that unrelated people may have kidneys of a similar type, just as unrelated

people have blood groups of a similar type. This chance relationship may account for the rare prolonged survival of kidney transplants to unrelated donors before the use of immunosuppression. Skillful and experienced use of the immunosuppressive drugs and cortisone has almost eliminated the immediate rejection crisis, and recent data from the University of California, San Francisco, promises initial success for as long as one year in 90 percent of all transplants.

Despite initial success, late complications and crises still prevent the widespread adoption of kidney transplantation. Each patient is a special experiment requiring the most minute attention, both during the operation and in immediate and long-term postoperative care. The use of new radio-isotope techniques by Dr. Samuel Kountz at the University of California, San Francisco, promises to detect rejection before overt changes in renal function appear. Such detection will permit changes in immune therapy and help prevent late crises. The specific immune serum mentioned earlier has also been used in human transplantations, notably by Dr. Thomas Starzl at the University of Colorado. While the results are encouraging, the method is extremely painful and not sufficiently established to supplant other measures.

Being a paired organ, the kidney lends itself to donation from one person to another. The transplantation is so safe that no kidney donor has died or suffered any serious consequences. Nevertheless, it is a substantial sacrifice, particularly for parents donating a kidney to one of many children. A mother has obligations not only to the child with renal failure, but to her other healthy children. Although one kidney will sustain life normally and indefinitely, there is the risk that disease or injury will affect the remaining organ. The ethical questions involved in asking a minor to give a kidney to a brother or a cousin have become so complex that it is no longer practiced in most centers.

While there is increasing interest in obtaining kidneys from the dead, securing kidneys from cadavers and performing immediate transplantation is very difficult. The recipient must be adequately prepared and often spends weeks in the hospital awaiting transplantation. At the time of death, it may not be known whether the donor's kidney is transplantable. Studies to determine the transplantability of a kidney may be too dangerous for a patient struggling for life; and in the case of sudden accidental death, there usually is not time for such studies. Consequently, it is often impossible to use what might have been a very satisfactory kidney for transplantation.

The taking of an organ from a dead person has raised a pressing ethical issue: When is the patient dead? It has been proposed that

death be defined as "when the brain appears to be irreversibly damaged, but while the heart is still beating." Such an interpretation would permit the taking of organs which are living, at least as organs. Many surgeons and other authorities object to this interpretation maintaining that a person cannot be pronounced dead until he is "legally dead," namely, no respiration, no heart beat, no eye reflexes, and no electrical activity of the heart and brain. Adhering to these criteria subjects the kidney to a long period without oxygen which often results in damage to the organ. For these reasons, cadaver transplants have not been widely utilized.

The original dream of Alexis Carrel and Charles Lindberg to develop a pump which would keep organs alive outside the body has been pursued by many investigators. Recently, effective short term success has been attained by Dr. F. O. Belzer in the Department of Surgery at the University of California, San Francisco.

The Contribution of Organ Preservation

In 1955, Dr. Stanley Jacob, working with Professor Collins of the Massachusetts Institute of Technology, devised new methods of freezing tissues and organs in the hope of maintaining viability. Their experiments confirmed the observations of others that thin tissues and cells could be frozen to temperatures of -273° centigrade without injury; however, when whole organs were frozen serious damage resulted. Subsequently, at the University of Oregon, Dr. Jacob devised methods of super-cooling without ice formation by placing organs in cold chambers under pressure at temperatures well below freezing. Using this technique, Dr. Jacob kept hearts alive and functional for periods of up to eight hours. While Jacob was experiencing some success with the super-cooling method, another approach was initiated by Drs. Mark Vetto and F. O. Belzer at the University of Oregon. Their method was more akin to the original concepts of Carrel and Lindbergh in that the kidney or liver was perfused with special fluids using different kinds of pumps and oxygenators. Similar experiments were carried out by others; but it was invariably found that after a few hours higher pressures were required to force the fluid through the isolated organ. This resulted in hemorrhage into the organ and progressively increasing injury. This problem plagued all workers in this field, and it was generally concluded that it was not possible to preserve organs by perfusion for more than a few hours. However, Dr. Belzer continued his studies. By eliminating all cells, using only the plasma or fluid part of blood, and utilizing a special method of filtration and a pump which

simulated the action of the heart, Belzer found that the isolated kidney could be perfused experimentally for as long as three days. When the kidney was transplanted back to the same animal, uniformly good function was observed.

Once again, the stage was set for a cautious application of the findings in the experimental laboratory to the treatment of patients. Dr. Belzer worked with a patient suffering from a fatal disease affecting the heart, kidney and other organs. Because correction of the kidney failure restored health for only a short time, such patients were not usually accepted for treatment by the artificial kidney or for transplantation. While the kidney condition made death imminent, the patient's heart function was good. The possibility of receiving a kidney which had been under perfusion for many hours was proposed to the patient and his family, and they avidly accepted. Despite some complications that related to the patient's underlying disease, the kidney functioned immediately after transplantation and continued to do so for many months. This carefully executed experiment clearly established that the human kidney could function after perfusion as well as the animal kidneys in the experimental laboratory.

Since that time, more than 40 human kidneys have been transplanted after perfusions for varying periods of time. One case involved a young child with cancer of both kidneys. Patients with cancer are not acceptable for either transplant or chronic dialysis. The immediate use of a cadaver kidney was not feasible due to the time required to remove the patient's cancerous kidneys before the transplant could be inserted. Once again a cadaver kidney was placed upon the perfusion pump; when the kidney was determined to be functioning properly, the patient was scheduled for operation. After removing the diseased kidneys and spleen from the patient, the transplant was performed with excellent results.

Certain details of isolated organ perfusion are currently being perfected by Dr. Belzer. It will soon be possible to place cadaver kidneys upon a portable pump that can be taken from hospital to hospital. Under these circumstances, cadaver transplants can be performed on a regular schedule, which will eliminate the need to have a surgical team ready to operate upon the death of the donor. Moreover, and perhaps most important, the use of the pump to preserve the kidney before transplantation greatly shortens the period without blood supply and oxygen. Further perfection of this technique will do much to resolve the problems in heart transplantation.

Transplantation of Other Organs

Despite the temporary success of several heart transplants, there are many inherent difficulties in transplanting the heart which demand a cautious approach. In contrast to the kidney, a patient has but one heart, and to remove this heart while still beating raises obvious moral and ethical issues. While the patient with an advanced kidney disease may be effectively prepared for a transplant with the use of an artificial kidney, at the present time there is no such way to prepare a prospective heart recipient. Thus a "good heart" must be taken from a dying or dead person and transplanted to another patient who is also dying. A pump is needed which can adequately prepare the recipient patient for the operation; hearts taken from patients already dead and maintained on pumps of the type developed by Dr. Belzer could then be transplanted. It has been established that hearts can be maintained satisfactorily on such pumps. Under these circumstances, heart transplantation could be accomplished under the same "ideal conditions" now available for kidney transplantation. There is a growing body of opinion that heart transplantation in humans should probably await such developments.

Of all the organs that have been transplanted (or are likely to be transplanted) in man, the liver, a highly complex organ with more important functions than any other organ in the body, is the most difficult to transplant. The liver was transplanted experimentally by Dr. Stuart Welch of the Albany Medical School many years ago; his work has been confirmed and extended by Dr. Thomas Starzl at the University of Colorado and Dr. Francis D. Moore at the Peter Bent Brigham Hospital in Boston. Dr. Starzl has carried out several liver transplants in patients with encouraging results, particularly in children. Although the accomplishments of Dr. Starzl have attracted far less attention than those in heart transplantation, they represent a much greater technical and biological accomplishment; the heart is simply a pump, whereas the liver is an enormously complex metabolic factory which produces sugars, proteins, enzymes, bile, and hormones. There is scarcely a function that the human body performs in which the liver does not participate. Its successful transplantation in the laboratory and in man is the acme of transplantation surgery. Unfortunately, because the liver is a single, complex organ which can only be secured after death, it is unlikely that liver transplantation will become an established operation in man for some time to come; extensive study and occasional transplants in man, however, will be continued by those groups prepared to evaluate every step of the process.

There are diseases, common among children, which seriously cripple the brain and raise the possibility of brain transplantation from children dying from a heart or liver disease. The possibility of a transplant of the brain staggers the imagination; but transplantation of the brain alone is a technical impossibility. Moreover, the brain is the most sensitive of all organs to lack of oxygen. Brain transplantation, therefore, can only be accomplished by transplanting the head of one living animal to another as Guthrie did experimentally many years ago. Even if the brain lives, however, the recipient's spinal cord will be divided creating total paralysis. The spinal cord does not regenerate even in the intact animal, and there is no reason to expect a different result after transplantation. This thought of beheading a person, even a dying one, to transplant his head to another's paralyzed body raises ethical and moral issues which override all other considerations.

Excessive publicity given to heart transplantation obscures the very practical accomplishments of transplantation of many other tissues and organs, particularly within the same patient. The transplantation of skin, bones, tendons, muscles, and arteries is performed every day with restoration of normal function to many parts of the body; and the homotransplantation of skin is also commonly employed in the treatment of burns and large wounds. Transplants of the cornea for blindness are now well established. The transplanting of many structures and organs from one person to another, including portions of the intestinal tract, the spleen and various endocrine glands is almost certain to occur.

The transplantation of organs will soon be a regular clinical accomplishment. This will be beneficial only if employed to restore health and not to maintain life. Serious moral and ethical issues are arising because our hedonistic and materialistic society is changing our concept of death; like Camus we are becoming afraid of it. This fear is reflected in the concern over capital punishment and the obsession with heart transplantation. The heart means life; transplant the heart and we shall live forever. But are we thinking enough about the quality of living? Because of the fear of death, the aged are subjected to the most extraordinary measures to maintain viability. Too many physicians, particularly of the younger generation, cannot let a patient die with dignity.

It is time men took a long hard look at the normality of death. Organic life is a constant cycle of cellular death and renewal. Eventually all men die. Despite the extraordinary advances of scientific medicine, man as a species lives no longer today than he did before.

Many individual men live longer, so the average duration of life has been greatly increased; but very few men live for more than a hundred years, and of those who do, few enjoy it. Modern society seems to have forgotten that under certain circumstances death, far from being a tragedy, may be a comforting release.