Chapter 38

TRANSPLANTATION OF TISSUES AND ORGANS

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INTRODUCTION

Although the prospect of replacing defective organs has intrigued physicians and surgeons since antiquity, there was little evidence until the last few years that this was a realizable objective. Before then, an almost total ignorance of the biologic problems which would be encountered precluded the development of appropriate methods of therapy. As recently as 1940, there was still a widespread belief that application of tissue transplantation needed only the refinement of better surgical techniques, despite the slow accumulation of evidence that this was not the case.

Early in this century, Carrel had appreciated that the fate of transplanted canine kidneys was different when the organs were obtained from another animal than when they were transferred from one location to another in the same dog. Jensen had noted that the behavior of transplanted tumors was markedly influenced by a host reaction against the inoculated neoplasms. He believed that the same phenomenon applied to normal tissues. Loeb explained the nonacceptance of alien tissue by a somewhat confusing hypothesis that all organisms are born with an "individuality differential" present in both cells and body fluids.

The shrewd clinical observations of Holman came close to the truth. He placed small skin grafts upon the granulating wounds of several patients. Permanent takes were obtained when the patients provided their own grafts from other portions of the body. Skin from other donors was ultimately rejected, but the period of viability was longer for those transplants obtained from family members than for those taken from genetically nonrelated sources. Holman observed that a second graft from the same donor was rejected more quickly than the first, leading him to suggest that a state of specific sensitization had developed as a consequence of the initial exposure. At the time, these findings attracted

little attention, and the situation remained obscure for almost another 20 years until the appearance of the first of the studies by Medawar and his colleagues.

Medawar's investigations were conceived and executed under trying circumstances. Questions concerning skin replacement had become more urgent than ever because of the need to treat mass wartime casualties. The answers were provided on the basis of investigations with inbred rodents in which the genetic homogeneity of the donor and recipient animals permitted a high degree of reproducibility of results. The conclusions were precise.

First, skin grafts were rejected after an interval which was essentially invariable for given donor-recipient strain combinations. There was evidence that the repudiation was due to an immunologic reaction of the host to the foreign tissue. The key observation in support of this concept was the fact that a second homograft from the original donor was destroyed in an accelerated fashion, suggesting the acquisition of immunity by the host. The immunity, conferred by contact with the first graft, was permanent or of long duration, and applied to all tissues subsequently transplanted from the same donor. The sensitization was specific inasmuch as grafts from other donor strains were not usually rejected in an accelerated manner. The initial delay before the first set rejection, and the subsequent development of active immunity prompted comparison between these events and those of delayed tuberculin type hypersensitivity.

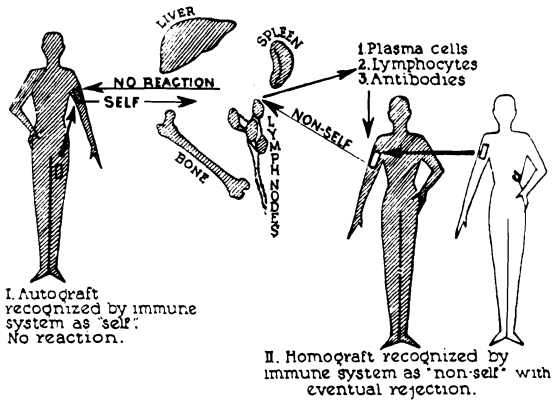

Figure 1. Response of the immune mechanism to autografts (I) and homografts (II). When tissues from one homozygous twin are transplanted to the identical sibling, the situation is analogous to autotransplantation in that there is no rejection.

GENERAL PRINCIPLES

REJECTION. The control problem of transplantation is summarized in Figure 1. Tissue which is transplanted from one location to another on the same person is termed an *autograft*. It is not identified as "non-self" and does not, therefore, evoke a hostile host reaction. The success or failure of the graft is exclusively dependent upon the technical adequacy of the procedure and upon other well-accepted principles of surgical care.

The same applies when tissues or organs are exchanged between identical twins (*isografts*). Because there is total genetic identity of the donor and recipient, the graft is not recognized as foreign and can be expected to have the same life expectancy as that of the host. This was first proved in man by Brown with skin transplantation experiments, and later applied by Murray and Merrill to the inter-twin transplantation of kidneys.

Tissues transplanted from nonidentical members of the same species are called *homografts* or *allografts*. A host response follows which is termed rejection. The intensity of the reaction is roughly related to the degree of genetic dissimilarity between donor and recipient, as defined by Snell in inbred rodents. In the outbred canine and human populations, there is a tremendous and as yet unpredictable variability in the vigor of the attack which a homograft will elicit. These observations have led to an intensive search for methods which would allow identification of a favorable donor-recipient combination in advance of clinical transplantation.

When transplantation is from another species, the tissue is called a *heterograft* and the rapidity and magnitude of rejection are even greater than with homografts. However, Reemtsma's studies with chimpanzee to human heterografts have suggested that such transplants can sometimes be tolerated for long periods in recipients who are receiving immunosuppressive therapy.

The mechanism by which homografts or heterografts are rejected is poorly understood. There is abundant evidence that lymphocytes participate in the process in an important way. This can be illustrated by experiments using millipore chambers, in which enclosed fragments of tissue are shielded by a mesh barrier of appropriate size to exclude lymphocytes but through which nutrient fluid can pass. Survival of the trans-

plants is longer than with tissue that is not thus protected. Corneal homografts, which have been used clinically for many years, presumably escape rejection for similar reasons; their nutrition is from a cell-free fluid. If a corneal graft becomes revascularized, it usually fails.

Unfortunately, the way in which lymphocytes contribute to rejection, or to a variety of delayed hypersensitivity reactions, is not known. Presumably, the antigen is brought to lymphoid centers, possibly after an intermediary stage in phagocytosis. Subsequently, there is rapid multiplication of other lymphocytes which are now specifically sensitized against and capable of reacting with the original antigen. The fraction of lymphocytes which undergo this change is probably small, totaling no more than 5 to 10 per cent.

There is reason to believe that the cellular immune response is not the only means by which homograft rejection can occur. In millipore chamber experiments, grafts are quickly destroyed if they are placed in animals previously sensitized to tissue from the same donor, apparently as the result of attack by humoral antibodies. In a small number of well-documented renal homotransplantations, preformed humoral antibodies which were demonstrated in the recipient prior to operation have caused immediate destruction of renal homografts by almost instantly binding to the revascularized kidney tissue. In the serum of patients who have tolerated renal homografts for years, there are often circulating antibodies which can be demonstrated by absorption techniques to react against tissues of the original donor or against the transplanted kidney. Finally, such homografts commonly contain deposits of gamma G, gamma M, and gamma A globulin as well as host complement, suggesting an antigen-antibody reaction with the alien tissue.

Recently, an additional possible mechanism of injury termed allogeneic inhibition was described by Hellström and Hellström and by Möller and Möller. This phenomenon is not dependent upon a classic antigen-antibody reaction, but it is due to differences in the antigenic structure of surface cell membranes. When certain dissimilar cells are contiguously placed in cell cultures, one can destroy the other even if the first has been previously rendered nonviable by irradiation. The significance of this observation in transplantation remains to be clarified.

MANIFESTATIONS OF UNMODIFIED REJECTION. Although a precise explanation of rejection is not available, the effects of this process upon various tissues and organs have been thoroughly studied. In the untreated recipient, the end point for each is necrosis but the preceding stages are of interest because changes observed during this time may also be seen despite the provision of host immunosuppression.

After transplantation of a whole organ in which revascularization is established by direct vascular anastomosis, the homograft usually functions well for several days. In dogs whose livers are removed and replaced with those from other animals, there is prompt arousal from anesthesia. The animals may resume a diet. They often appear to be quite normal. After three to four days, however, function begins to deteriorate. There is progressive jaundice as well as changes in serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase which are indicative of hepatic necrosis. At about this time, there is an abrupt fall in total blood flow to the homograft. Death almost always occurs within three or four days. The same events follow renal homotransplantation and can be monitored with appropriate tests of kidney function such as blood urea nitrogen, plasma creatinine and creatinine clearance. For other organs, characteristic syndromes can be defined based upon tests of function of the grafts.

Histologic changes in the various homografts are minimal or absent during the first few postoperative days (Fig. 2). Then, immature and metabolically active mononuclear cells appear at the same time that similar cells begin to be seen in large numbers in host lymphoid organs. Within the graft, these tend to be concentrated around small vessels. In both rejecting renal and hepatic grafts, fusion of these immunoblasts has been noted to the endothelial cells of small vessels.

The number of infiltrating mononuclear cells increases until the entire organ is eventually riddled. In time, their character begins to change; there are increasing numbers of mature lymphocytes and plasma cells and finally, neutrophils. Large areas of parenchymal necrosis develop, which are usually most extensive around the blood vessels: finally extensive destruction occurs (Fig. 2). If the graft is a life-sustaining organ such as the kidney, liver, or heart, the unmodified canine recipient usually dies within seven to 14 days. However, longer survival is occasionally obtained.

These events in the liver and kidney per-

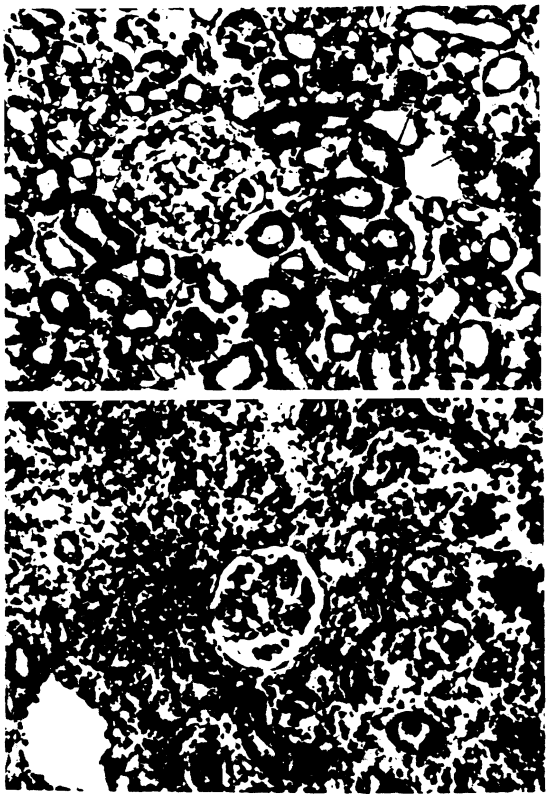

Figure 2. Progressive abnormalities of a canine renal homograft in an untreated recipient. The graft repudiation was less rapid than usual in this dog, apparently because of an accidental good histocompatibility match between the donor and recipient but the ultimate pathologic findings were typical of acute rejection. *Upper*, Biopsy after three days. There is swelling of the endothelial cells lining the arterioles and small arteries (arrows). Otherwise the kidney is relatively normal. *Lower*, The same homograft after 18 days. There is marked cellular infiltration, edema and tubular damage. (H & E × 250.)

tain in a general way to rejection of all organs. There is a delay before host defenses are brought to bear upon the homografts, but following this, the anatomic features of the tissue are distorted, and its blood supply is choked off at the microcirculatory level.

HISTOCOMPATIBILITY. The magnitude of rejection in healthy inbred strains of experimental animals can be more or less well correlated with the degree of genetic dissimilarity between the donor and the recipient. In this kind of investigation, variables other than the genetic differences can be largely eliminated, making it possible to use the homograft reaction itself as the means of classifying those genetic factors which are important in directing the intensity of this process.

In mice, at least 15 histocompatibility loci are known to exist. The gene determinants of several of these are associated together from generation to generation on specific non-sex chromosomes. There is also a weak histocompatibility antigen on the Y chromosome which can be responsible for what is called the Eichwald-Silmser effect, an indolent kind of rejection after placement of male to female skin isografts. In the mouse, the strongest transplantation antigen is found at what is designated as the H-2 locus. The H-2 system involves at least 20 alleles. Its antigens are not only involved in transplantation immunity but also in the elicitation of humoral antibodies such as hemagglutinins and cytotoxins.

In outbred groups including the canine or human populations, it is impossible to categorize antigens on the basis of such genetically controlled experiments. Nevertheless, there is hope that individual specific human antigens can be classified. When this is accomplished, it will be possible to identify in advance of operation the histocompatibility differences between donors and recipients. If the number of distinctive transplantation antigens in man is relatively limited, as now seems likely, some donors could be found who would be superior to others on the basis of their not possessing antigens which are absent in the proposed recipient. Statistically, the chances of meeting this objective would be better by intrafamilial transplantation. However, even with people who have no blood relationship it would also be possible to exclude donor-recipient pairs in which there was incompatibility of strong or multiple transplantation antigens.

The principal hope that this kind of matching will become feasible comes from current studies of human isoimmune antisera. These antisera are obtained from patients who have been accidentally or deliberately sensitized to cell membrane antigens. Typical examples are women who have had several pregnancies, patients who have had multiple blood transfusions, or volunteers who have received skin or lymphoid tissue homografts. The sera from such donors contain antibodies which can be used to determine the antigenic structure of nucleated cells in other people.

For example, the agglutination or cytolysis of test lymphocytes by a given antiserum indicates that the lymphocytes possess the same or similar antigens as those which originally sensitized the serum donor. Failure of the reaction implies the absence of the antigen in the lymphocytes. In various centers in Europe and the United States, large numbers of sensitized donors have been identified and the

activity of their sera has been determined against panels of human lymphocytes collected from normal people. The results have been pooled in recent scientific workshops. The conclusions were, first, that the available antisera could identify approximately a dozen different white cell antigens; second, that these antigens by and large were the same as those in other tissues including the kidney; and finally, that an antigenic profile which might be useful for tissue typing could be established for each human.

However, the application of these techniques to tissue typing was not yet assured, because there was as yet no real evidence that the antigens being catalogued were in any way associated with histocompatability. Subsequently, observations in humans after test skin grafting, or therapeutic renal homotransplantation, have provided such evidence. In untreated patients who received skin homografts, the interval before rejection was longest when the donors were shown to have the best antigen match. In the patients who were treated with immunosuppression after receipt of renal homografts, the kidneys were biopsied after two postoperative years. The quality of histologic preservation in these renal homografts was strongly, although not absolutely, correlated with the degree of antigenic compatibility between the donors and their recipients.

These findings, as well as others too numerous to cite, provide reason to believe that a tissue typing method will be part of the future in organ transplantation. The system which evolves will probably be somewhat more complicated than that necessary to type blood. At the moment, it seems unlikely that any single histocompatibility factor will be found in man that has the overriding importance of the H-2 antigen in mice. There will probably be two or three strong antigens and a number of moderate or weak ones. It is highly unlikely that any single histocompatibility antigen will preclude successful clinical transplantation if adequate immunosuppression is used.

MEASURES TO PREVENT REJECTION. For a number of years after the features of rejection had been defined, the not unreasonable assumption was made that this process was one of nature's most powerful and persevering reactions which could be prevented only by relatively complete crippling of the host's immune potential. In view of the evident connection between the capacity to mount an effective rejection and to react forcibly against a variety of other inimical environmental antigens, including those of pathogenic microorganisms, the possibility of achieving chronic graft survival without killing the host was seriously questioned.

The first clue that this might after all be realizable came from the observation that permanent acceptance of adult donor tissue could be induced in fetuses or newborn animals. The initial disclosure was made by Owen, who noted that dizygotic calf siblings, whose circulation in utero communicated freely, had each others' formed blood elements which persisted indefinitely (Fig. 3).

On the basis of this, Burnet suggested that exposure of the fetus to donor tissue might similarly confer protection persisting after birth to subsequent grafts from the same donor but not to those from other donors. The hypothesis was confirmed by Billingham, Brent, and Medawar in rats and later extended to other species. It was soon found that the use of immunologically competent lymphoid tissue for inoculation caused a serious and often fatal disease, termed the "runt syndrome," which was caused by an attack of the mature homograft cells upon the defenseless recipient. In contrast, the transplantation of skin, kidney and liver did not have this complication.

These remarkable events appeared to be the result of exposing the host to donor antigens at a time when its immune mechanism was too rudimentary to recognize the graft tissue as foreign. After maturation of the immune mechanism, neither the graft nor other tissues from the same donor were identified any

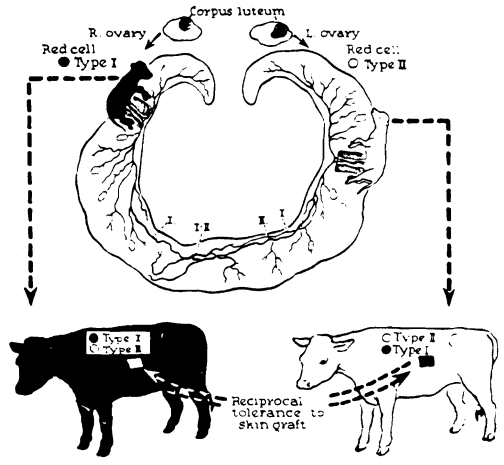

Figure 3. Chimerism in cattle siblings. There is cross tolerance to formed blood elements and to subsequently placed homografts as the result of intrauterine circulatory communication.

longer as alien. Although of no immediate clinical value, the studies were of great importance. They indicated the feasibility of inducing acquired tolerance, and thereby stimulated the search for immunosuppressive agents with which it was hoped that a similar sequence of events could be duplicated in adult recipients. Those agents which have since been effectively used to abrogate rejection do not act by this mechanism of inducing tolerance, but the stimulus that this possibility provided was an important factor in subsequent research efforts.

Total body irradiation was the first kind of therapy which was demonstrated to prolong the life of homografts in adult animals. However, the treatment was dangerous, requiring doses sufficient to cause bone marrow depression. There was a consequent excessive acute mortality. Nevertheless, the two first long-term survivors after clinical renal homotransplantation were treated primarily by this means. These patients, who were at the Peter Bent Brigham Hospital in Boston and the Necker Hospital in Paris respectively, both received kidneys from their fraternal twins more than seven years ago. They are still alive.

For a time, it was hoped that the risks of irradiation therapy could be reduced by transplanting to recipients either lymphoid tissue or bone marrow from the same donor as that from which kidneys, livers or other organs were obtained. The resultant composite subject, termed an *irradiation chimera,* could then have function of the desired organ as well as an endowed means of defense which would not identify the presence of the homograft as abnormal. Unfortunately the irradiation chimera is an unstable preparation in which re-colonization by host elements usually eventually eliminates the lymphoid or hematopoietic graft. Even if this does not occur, the immunologic reactivity is directed by the donor tissues. If these remain in ascendancy, antigens from the defenseless host may provoke an attack by the graft with a consequent graft versus host reaction. This complication, which is comparable to the runt syndrome, has been called secondary homologous disease.

A highly significant subsequent advance was the development of azathioprine, a potentially radiomimetic drug which is a ribonucleic acid inhibitor and possibly a desoxyribonucleic acid inhibitor as well. With this drug, chronic homograft function could often be obtained without the need for doses large enough to cause leukopenia. For the first time, whole organ grafts could successfully be performed in dogs in a standard laboratory environment in which no extraordinary infectious precautions were taken. However, the number of really long-term survivors after homotransplantation of vital organs was still small, because no more than one-fifth of the animals lived for as long as six months.

Similarly, there is at present no single immunosuppressive agent reliable enough to be used as the sole treatment for patients who receive homografts. Fortunately, there are adjuvant measures which can be taken, including the administration of azaserine or intravenous actinomycin C, and the use of local homograft irradiation. With these methods the desired effect upon rejection is relatively feeble and transient.

In contrast, the action of adrenal corticosteroids is a powerful one, and the use of one of the steroid analogues, prednisone, has been a decisive factor in the development of clinical transplantation. Prednisone has a synergistic effect with either total body irradiation or azathioprine. It can either reverse a rejection which has developed in spite of prior therapy with either total body irradiation or azathioprine or, alternatively, it can reduce the incidence of rejection if it is used from the time of transplantation with one of the aforementioned agents.

In the past several years, another immunosuppressive agent, heterologous antilymphocyte serum has received increasing attention. The serum is obtained from animals previously immunized against the lymphoid tissue of the species which is eventually to be treated. For example, horses can be inoculated with human lymphocytes obtained from spleens, lymph nodes, or thymuses (Fig. 4). The resulting antibody response of the horse can be measured by determining the ability of the serum to agglutinate or to lyse human white cells in vitro. After intensive immunization the equine titers may rise to as high as 1:32,000.

The serum collected from an immunized animal is a powerful immunosuppressive agent when given by a variety of routes to members of the lymphoid donor species. Previously established delayed hypersensitivity reactions become negative within a few days. Skin or whole organ grafts have a prolonged functional survival.

Unfortunately, there are certain risks with the administration of foreign protein. In dogs

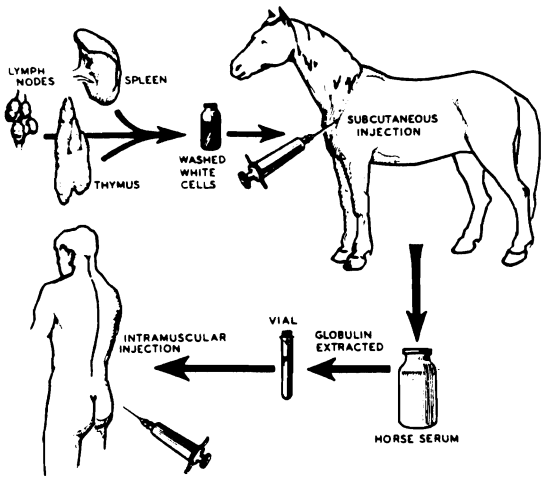

Figure 4. The preparation in the horse of heterologous antilymphocyte globulin for use in patients.

treated chronically with heterologous anticanine antisera raised in the horse, there are occasional anaphylactic reactions. Furthermore, a significant number of the treated animals develop renal lesions.

The latter complication is a form of serum sickness nephritis which is due, first, to an antibody reaction of the treated animal to the foreign protein; then, to the formation of soluble antigen-antibody complexes by their interreaction; and, finally to the mechanical entrapment of these complexes in the microcirculation of the kidney. There, the complexes evoke a secondary inflammatory reaction.

The undesirable reactions are related in part to the amount of animal protein injected. One way of reducing the dose is to remove and use only the active antibody fractions. This can be done by several biochemical methods. The product obtained is a globulin, which can be sufficiently concentrated to permit intramuscular injections in dogs or humans of volumes as small as 1 to 4 ml. Despite this improvement, renal lesions can still be produced in some dogs treated with the refined horse globulin.

The potential threat of serum sickness nephritis has influenced the way in which derivatives of antilymphocyte serum have been tested clinically. Thus far, they have been used only as adjuvant agents, added to therapy with reduced quantities of azathioprine and prednisone, and with limitation of their administration to the first few postoperative months. The patients who have been so treated appear to have benefited.

ADAPTATION. Because successful clinical organ transplantation cannot usually be done with a single immunosuppressive agent, various combinations of drugs have been used to prevent loss of the homografts. Azathioprine and prednisone have most often been used together. It was soon learned that the most intensive therapy was required during the early postoperative weeks or months. This was fortunate, for it is highly unlikely that chronic survival could be achieved in any but the rare instance, if the stringency of such early therapy had to be maintained for long periods. The fact that the degree of immunosuppression can often be subsequently relaxed is apparently due to some alteration in the host-graft relationship which transpires during residence of the foreign tissue in its new environment.

This change was called "adaptation" by Woodruff. He originally studied small thyroid homografts which were transplanted to the anterior chamber of the eye in unaltered guinea pigs. In this location, normal rejection does not occur, because the transplants are not revascularized and receive nutrition by diffusion. This favored site is not unlike that which can be artifically created in other locations by the use of millipore chambers.

Woodruff later removed the tissues from the eye, and transferred them to other portions of the body where they were promptly revascularized. Surprisingly, they did not undergo rejection. In contrast, other grafts from the same donor which were then placed in comparable recipient beds were promptly repudiated. Woodruff predicted that an essential goal of clinical therapy would be to prevent destruction of the homograft until there had been time for the adaptation to take place. It was upon this foundation that many advances in clinical transplantation were later based.

The nature of the change in graft-host reactivity is not understood, but much evidence is consistent with the hypothesis that it is the graft which undergoes the most important metamorphosis, as shown by the fact that other subsequently transplanted tissues from the same donor enjoy no special advantage. The alteration is apparently not one of basic genetic structure, because accepted grafts can be later transferred back into the original donor without eliciting any reaction. It is possible that the adaptation is due to some kind of coating of the cells with nonlethal host antibodies and that utilization of available binding sites in this way is itself a long-term protective device.

Whatever its explanation, the importance of changes in the graft-host relationship can be appreciated in almost every successful instance of either experimental or clinical organ transplantation. This is exemplified by the clinical course of a patient who received a kidney homograft from his younger brother. Initial therapy was solely with azathioprine. There was an immediate diuresis and continued excellent renal function which lasted for more than two weeks. During this time, the pre-existing metabolic defects of uremia were completely corrected and the patient felt better than he had for years.

After 17 days, however, the smooth convalescence was interrupted by a rather sudden deterioration of homograft function. The blood urea nitrogen began to increase secondarily. Urine volume diminished. The creatinine clearance fell and protein appeared in the urine in increased quantities. The blood pressure rose, requiring treatment with antihypertensive drugs. There was leukocytosis, and a rise of rectal temperature to almost 40° C. It was a classic rejection crisis which consisted of manifold evidence of homograft failure, plus the manifestations of a systemic immunologic disease.

At this critical time, many of the events which can be documented are identical to those in the nontreated recipient. There is a reduction in organ blood flow. Biopsies from the homografts may be full of mononuclear immunoblasts, and focal areas of necrosis may be present. However, these morphologic changes and the consequent adverse effects are more or less reversible.

Complete functional reversal was almost immediately achieved with the addition of large quantities of prednisone. Later, it became possible to attenuate rapidly the steroid doses, and after five months to discontinue them altogether. Thereafter, the patient had stable renal function while being treated only with azathioprine which at the beginning had been incapable of preventing a moderately serious rejection. A biopsy of the kidney after two years was normal. The patient is in good health after more than four postoperative years.

After all organ transplantations in which survival of more than a few weeks is attained, it is probable that adaptation occurs to some degree. The extent to which it happens determines the subsequent outlook. If it is relatively complete, the ultimate maintenance doses of prednisone may be very small or may not be required at all, in which circumstances the patient can be expected to live for years. If the adaptation is minor, the recipient is usually committed to long-term therapy with unacceptably large quantities of steroids and his morbidity both from sepsis and from unstable homograft function is apt to be great.

There is now evidence that the development of adaptation is relatively rapid, and that it is in fact already occurring even during a rejection crisis. In a number of dogs, it has been possible, as early as four months after transplantation of either kidneys or livers, to stop all immunosuppression. Between a third and a half of these animals have then survived for several years. The unpredictability of the outcome after such a drastic step has precluded this practice in patients.

Animal experiments have clarified other features of rejection, its reversal, and the events of adaptation. The value of steroids in reversing rejection is indisputable. However, it has been noted in canine experiments that rejection can sometimes recede without the addition of any additional therapeutic agent.

A dog treated before and for only three weeks after removal of his liver and its replacement with a homograft, had an early rejection as indicated by the appearance of jaundice. This reversed and he has had more than a year of relatively good health, during which he has received no therapy whatever. This kind of observation has led to the conclusion that rejection is not only a phenomenon which can be reversed, particularly with steroids, but also one which tends to be spontaneously reversible.

These observations indicate that the effective control of rejection is not simply a matter of poisoning the host to the extent that he cannot respond to foreign antigens. Instead, an important contributing factor is the development of a dynamic biologic alteration which occurs rather quickly and which is probably not dependent upon any peculiar quality of the immunosuppressive agent being used.

INITIAL HOST REACTIVITY. Some degree of therapeutic specificity is eventually possible even when techniques are used which cause nonspecific depression of immunologic reactivity. A system can ultimately be established in many patients in which the effectiveness of host responsiveness against the antigens of the homograft is selectively attenuated.

The ease with which this can be achieved is influenced by several factors of which the degree of histocompatibility is perhaps the

most important. Another critical variable is the capacity for immunologic response with which the host is originally endowed. In uremia, for example, many but not all patients have a reduced ability to mount either a cellular or humoral response to a variety of antigens. The need for heavy iatrogenic immunosuppression is probably thereby correspondingly decreased. Other disease states such as Hodgkin's disease, agammaglobulinemia, thymic aplasia and terminal liver failure are other well-documented illustrations of diseases which are accompanied by immunologic depression.

In patients who have received renal homografts, certain surgical procedures, including excision of the thymus gland and the spleen, have been used with the objective of similarly reducing the intrinsic level of host immunologic competence. The effectiveness of this approach, as an aid to homotransplantation in man, has not been proved. For splenectomy, the rationale is based upon animal experiments which suggest that the immediate responses to intravenous antigens may be partially spleen dependent. However, there is no clear evidence that patients subjected to this procedure have fared better after transplantation than those in which the spleen was not disturbed.

An effect of thymectomy upon the outcome after human renal homotransplantation has also never been demonstrated, despite the strong evidence in animals that this could be anticipated. The role of the thymus in the development of immune competence was first clarified by the studies carried out in rodents by Miller, Good and their associates. They and subsequent workers showed that the presence of this gland was essential for normal maturation of lymphoid tissue throughout the body, probably as the result of the elaboration and release of a thymic humoral substance (Fig. 5). Loss of this influence as the consequence of thymectomy of fetuses or newborn animals resulted in immunologically crippled offspring which had generalized lymphoid hypoplasia, retarded physical development, and a reduced ability to reject skin homografts.

In adult rodents, continuing function of the thymus can also be demonstrated under specific experimental conditions. If mature inbred rats are subjected to sublethal total body irradiation, the degree to which reactivity to skin homografts is eventually restored can be sharply reduced by thymectomy. The same has been reported to be true after therapy

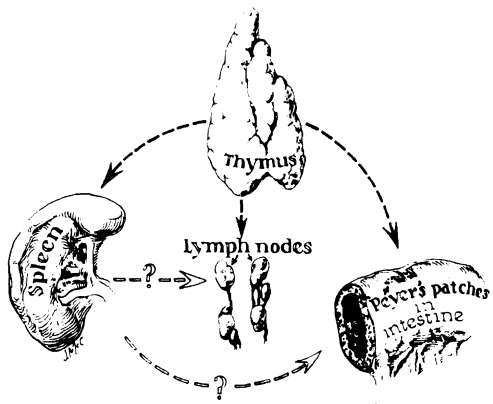

Figure 5. Theoretical considerations in the use of adjuvant thymectomy and splenectomy for the conditioning of recipient patients. The concept of organizer function of the thymus in establishing fetal and neonatal immunologic reactivity is based largely on the work of Miller and Good, and may have no relevance in the adult human. The role of the spleen in controlling response to antigenic stimuli in adult life is suggested by the work of Wissler and his colleagues. The contribution of these ancillary procedures to homograft survival in humans is highly speculative at present. (By permission of Surgery 56:296, 1964.)

with heterologous antilymphocyte serum. More recently, evidence has been reported that a gradual loss of immunologic reactivity follows adult thymectomy in rodents, although at a very slow rate.

The conclusion seems justified that the thymus retains its monitor role in adult life, usually in a relatively unimportant way, but that this function could become highly significant during recovery from a state of immunologic depression such as that induced by iatrogenic immunosuppression. In clinical transplantation, however, it has not yet been possible to detect any difference in the course of patients treated with immunosuppression who have, versus those who have not had, either pre- or post-transplantation thymectomy.

RENAL HOMOTRANSPLANTATION

The application of these concepts to the treatment of human disease has unfolded one of the most fascinating and potentially rewarding chapters in medicine. It has now been possible on several hundred occasions to restore patients to vigorous health who had previously been crippled by the complications of terminal renal failure.

The swiftness with which rehabilitation could be expected was demonstrated by the early experience of Murray and Merrill with

identical twin transplants. In most of these patients, good graft function was immediately obtained. There was a brisk or even massive postoperative diuresis, disappearance of anasarca, resolution of heart failure, and rapid return of serum chemistries to normal. Frequently, the recipient patients recovered more quickly than their donors. Most of these same benefits can be expected after homotransplantation, but the course is complicated by the need for constant immunosuppression.

SELECTION OF RECIPIENTS. The initial screening of candidates for homotransplantation is by ordinary medical criteria. The patient should have irreversible renal disease from which life expectancy without definitive therapy is limited to a few weeks.

A highly desirable condition is that he not have major disease of other organ systems. The original disease may itself be responsible for a number of extrarenal complications including neurologic disorders, muscle wasting, pancreatitis, gastrointestinal ulceration, or heart disease. In older patients who have had chronic uremia, it is particularly important to look for evidence of generalized atherosclerosis. A 40-year-old man with a 15-year history of chronic glomerulonephritis may have the blood vessels of a septuagenarian. His chances of dying from a myocardial infarction or a stroke will not be eliminated by a successful renal homotransplantation. In general, the operation is offered only to patients who are less than 45 years old.

A crucial criterion is that the patient be free of all sepsis before immunosuppressive therapy is started. Occasionally, it will be possible to convert an unacceptable candidate to one who is suitable. An example would be a patient with an intractable upper urinary tract infection who could have preliminary nephrectomies.

Providing active infection is not a factor, and if a normal lower urinary tract is present through which to provide drainage, the original cause of the recipient's uremia is usually not an important consideration. The results have been similar in treating patients with chronic glomerulonephritis, burned out pyelonephritis, and polycystic kidney disease. There are exceptions, however. Homografts in patients with congenital oxaluria or certain other inborn errors of metabolism are subject to the same complications which destroyed their own kidneys. The serum of patients with acute glomerulonephritis may contain antiglomerular antibodies which can damage a homograft. In such patients, preliminary removal of the diseased kidneys may be mandatory before transplantation can even be considered.

THE DONOR PROBLEM. A decision for or against transplantation is inevitably influenced by donor availability. There are three sources: the healthy volunteer who is willing to submit to an elective nephrectomy, the patient who is having a normal kidney excised for some surgical indication, and the recently deceased cadaver. In the first two instances, there is time for complete assessment of the health of the person who is to give, as well as of the kidney which is to be removed. With cadavers, there is a need for haste and such careful evaluation may not be possible.

In any case, it is essential to know the blood types of both donor and recipient. If these are not the same, a judgment must be made concerning the advisability of using the donor-recipient blood group combination which is available. The rules upon which the decision is made are simple (Table 1), and are the same as those which govern transfusion of other than matched blood. They are designed to avoid exposing the red cell antigens, which are the same in the renal tissue as in the red cells of the donor, to circulating hemagglutinins which may be in the plasma of a prospective recipient.

For example, a person with AB blood type does not have circulating anti-A and anti-B hemagglutinins. He could, therefore, receive a kidney from a donor of any blood group. He is a universal recipient. However, because his kidney cells contain both A and B antigen, he could only give to another patient of AB type.

In contrast, the plasma of a patient with O blood type contains both anti-A and anti-B hemagglutinins. Such a person could receive a kidney only from another O patient, but be-

*Table 1. Direction of Acceptable Mismatched Tissue Transfer**

O to non O	Safe
Rh− to Rh+	Safe
Rh+ to Rh−	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*O is universal donor. AB is universal recipient.

cause his renal tissue has no A and B antigens, he could serve as a universal donor.

Having determined the acceptability of a donor's blood type, further information is sought. In potential living donors, a complete physical examination is done and a chest x-ray is obtained as well as an electrocardiogram and a glucose tolerance test. Detailed studies of renal function are made, including a blood urea nitrogen and creatinine, inulin, and para-aminohippurate clearances. Multiple urine cultures are mandatory, as are careful urinalyses. An intravenous pyelogram and an aortogram complete the workup. Generally speaking, kidneys are not removed which are shown by aortography to have a multiple arterial supply.

Another factor enters into selection of the donor. There has been an increasing confidence in antigen typing techniques. Although these are imperfect, they do appear to be able to discriminate both very bad and very good histocompatibility combinations. Consequently, matching is probably an important step to take, even in the present state of our knowledge, particularly when several otherwise equally good volunteers are available.

There are a number of volatile social and ethical issues concerned with donor procurement from either living volunteer or cadaveric donors.

PREOPERATIVE PREPARATION OF THE RECIPIENT. Renal homotransplantation is never an emergency. Usually, the condition of the uremic patient is initially too poor to permit a major surgical operation. Very effective resuscitative measures can be instituted.

The most useful of these is renal dialysis. This can either be done with peritoneal lavage or, preferably, by hemodialysis on one of several kinds of artificial kidney. To obtain a substantial improvement in the patient's condition, it is usually necessary to have intensive therapy with dialyses at least two or three times a week for two or more weeks. Excess fluid can be removed, electrolyte abnormalities can be restored toward normal, the bleeding tendency of uremia can be partially corrected, and the patient can be placed back on an adequate diet.

Because a single hemodialysis is almost never adequate, all such patients should be initially managed as if they were entering a chronic dialysis program. Rather than sacrificing peripheral vessels for single hemodialyses, a Scribner-type shunt should be placed either in the upper or lower extremity (Fig. 6).

This provides a high flow arteriovenous connection. At the time of hemodialysis, the shunt can be taken apart and the two ends attached to the inlet and outflow of the artificial kidney. Between treatments the arms of the shunt are reconnected. After transplantation, the prosthesis is removed as soon as it is evident that good homograft function has been obtained. If this objective is not immediately achieved, as is often the case after cadaveric transplantation, the shunt is retained and used for postoperative treatment for as long as is necessary.

The ability to maintain patients on intermittent renal dialysis for months or even years has been a critical factor in the development of renal homotransplantation for reasons other than just resuscitation. It has provided the necessary time to obtain the requisite medical information alluded to earlier concerning blood groups, the etiology of the uremia, histocompatibility data, and the state of the recipient's lower urinary tract. Furthermore, it has allowed patients who did not have volunteer living donors to be kept alive until suitable cadaveric organs could be found.

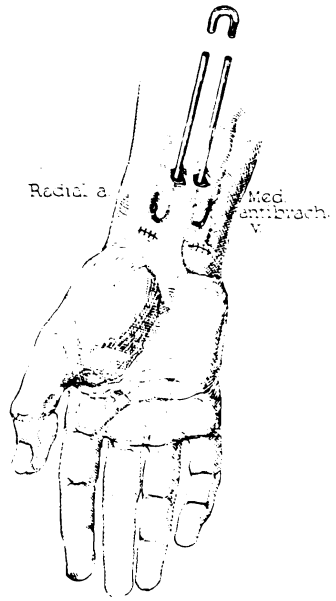

Figure 6. External arteriovenous shunt used for chronic hemodialysis. For attachment to the artificial kidney, the connection between the arterial and venous sides is removed. At all other times these two limbs communicate. The high flow through the prosthetic fistula is a crucial factor in the prevention of clotting.

TECHNICAL CONSIDERATIONS. Donor nephrectomy must be performed with attention to important details. The requirements are to avoid trauma to the kidney itself, to obtain adequate lengths of the renal vessels for subsequent anastomosis, and to protect the blood supply of the pelvis as well as a long segment of ureter. To accomplish these things, it is necessary to perform the dissection as far away from the hilum as possible. In some cases, the ureteropelvic blood supply comes from a fine spray of arteries which originate from the main renal artery. These filamentous structures must be preserved.

After its removal, the homograft is without a blood supply for whatever period is required to re-establish its vascular channels in the recipient. Significant protection of the kidney from ischemic injury can be obtained by quickly cooling it. The most efficient method is to perfuse the organ through the renal artery with a cold fluid. If procaine is not added to the solution, afferent arteriolar constriction may occur, making the perfusion difficult. Heparin is used to prevent intraparenchymal clotting during the avascular interval.

Ordinarily the excised donor kidney is transplanted to the contralateral iliac fossa of the recipient, in an extraperitoneal location (Fig. 7). This reverses the normal anteroposterior relationship of the hilar structures. The pelvis and ureter are now in front, the renal arteries intermediate, and the renal vein posterior. The arterial and venous anastomoses are usually made to the hypogastric artery and the external iliac vein respectively.

However, the exact technique of establishing the vascular connections is not important and can be adjusted to meet the requirements imposed by many situations. For example, the presence of atherosclerosis in the lower pelvic arteries may make it necessary to implant the kidney into the common iliac artery or even the aorta. In very small children, the attachment of the renal vessels at this more superior site is usually necessary when adult kidneys are to be placed. Under these circumstances, the operation is done through an intraperitoneal incision.

The rapidity with which the cooled renal homograft can be transferred has an important bearing upon its immediate function. When this can be done with an ischemic interval of 40 minutes or less, excellent urine excretion is almost always observed within two hours. With longer times, good early

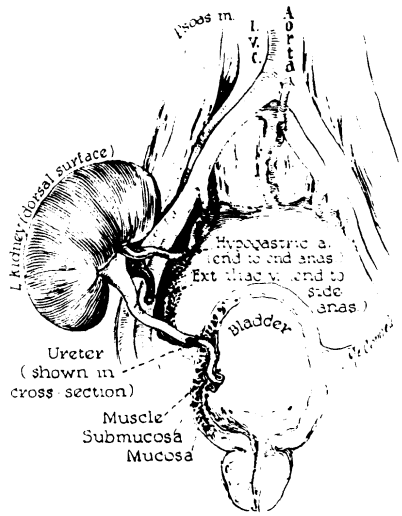

Figure 7. Usual method of renal transplantation. The operation is performed in the extraperitoneal space through an oblique lower abdominal incision. This is a useful technique but there are several alternative ways of revascularizing the organ or of establishing urinary drainage. (By permission of J.A.M.A. *187*:734, 1964.)

function can also often be obtained, but its predictability is progressively diminished with each further increment of time. If kidneys are to be stored for one or more hours, refinements in preservation techniques are necessary.

The methods of restoring a blood supply to the homograft kidney are quite satisfactory. The chief risk of technical complications is from reconstruction of the channels for urinary drainage. This can be done by implanting the homograft ureter directly into the bladder, passing it through a submucosal tunnel in order to duplicate the valve action of the normal ureterovesical junction. With this method, postoperative urinary fistulas are rare, but there is approximately a 10 per cent incidence of late anastomotic stricture.

Alternatively, the homograft ureter may be anastomosed to the distal portion of the recipient ureter, following ipsilateral nephrectomy. This method has important advantages. The ureterovesical junction is, of course, normal. It is not necessary to enter the bladder. Late anastomotic strictures almost never occur. However, the incidence of postoperative urinary fistula is between 5 and 10 per cent and in an occasional patient such a complication eventually leads to death or to loss of the homograft.

PROBLEMS AND COMPLICATIONS OF POSTOPERATIVE CARE. If a technically satisfactory operation has been performed, the im-

mediate beneficial effects can be expected which follow identical twin transplantation. However, continuation of function depends in every instance upon a greater or lesser reduction of the host immune potential. This fact influences almost every decision concerning postoperative management. For one thing, cystostomy drainage is avoided, and when bladder catheters are used they are removed within a day after operation. Usually drains are not employed. These measures are designed to prevent contamination of either the wound or the urinary tract.

At frequent intervals cultures are made of the patient's wounds, skin, urine, sputum, and feces. At the first sign of significant growth of pathogenic bacteria, specific antibiotic therapy is instituted. These antimicrobial measures are far more important than aseptic isolation of the patient. It has been learned that most postoperative infectious complications are due to endogenous pathogenic organisms harbored by the patient himself, and that prophylactic measures are best applied to eradication of these microorganisms rather than to strict avoidance of those in the general hospital environment.

In the long run, however, precautions to prevent sepsis are doomed to failure if excessive immunosuppression is given either by accident, or by the necessity imposed by an uncontrolled rejection. When azathioprine and prednisone were first used together, there were many deaths from bone marrow depression. Most of these tragedies were attributable to the azathioprine. A common sequence of events is shown in Figure 8. The patient received azathioprine both before and for some days after operation. Early renal function was excellent, but a severe rejection crisis developed after ten days, resulting in complete anuria. Following the addition of high dose steroid therapy, urine excretion eventually returned. Just when it appeared that the rejection was reversing, pancytopenia developed, and the patient died of a mixed fungal and bacterial blood infection.

Subsequently, the role of rejection itself in fostering this lethal chain of events has become appreciated. Azathioprine has an important renal pathway of detoxification in that significant quantities of the drug or its breakdown products, including 6-mercaptopurine, are cleared through the kidney. In the event of a severe rejection crisis, this avenue is lost, and the same quantities of azathioprine may have a far more profound effect. It is important to reduce drastically the dose under these circumstances.

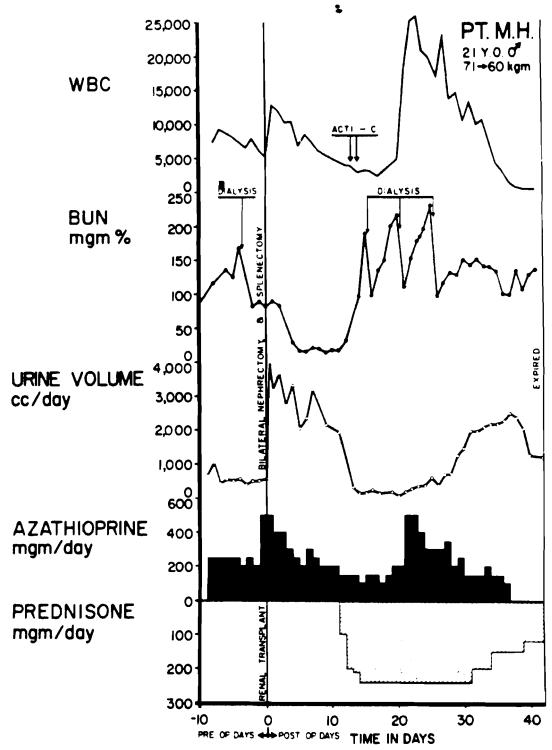

Figure 8. Typical unsuccessfully treated case. The donor and recipient were brothers, both of A+ blood type. A violent rejection crisis followed good early function, and anuria developed which lasted two weeks. Although the rejection was reversed and a secondary diuresis began, the patient died from drug toxicity, leukopenia and septicemia. Acti C – Each arrow is 200 μg. intravenous actinomycin C. (By permission of Surgery 56:296, 1964.)

The same principle applies if early renal function is defective for other reasons. Cadaveric homografts often must pass through a period of acute tubular necrosis caused by ischemia before they begin to function. During such times of poor or absent urine excretion, the amounts of azathioprine should be correspondingly reduced.

As increased experience with azathioprine was accumulated, the deaths during the first few postoperative weeks from acute bone marrow depression were largely eliminated. Remaining, however, were problems with a more insidious and indolent kind of drug toxicity in which prednisone, not azathioprine, appeared to play the dominant role.

The setting in which the resulting complications developed was almost always the same. It was seen in patients who, after passing through a rejection crisis, were not able to maintain good renal function without chronic administration of high doses of steroids. The quantities required many months after operation were as much as 0.5 to 1.0 mg. per kg. per day or even more.

Eventually, often after an interval of many

months, such patients develop a very evident predisposition to infection despite maintenance of a perfectly normal white count. If the responsible bacteria are of the ordinary pyogenic variety, they can be effectively treated with specific antibiotics. Very often, however, the infecting microorganisms are funguses, viruses, or bacteria which ordinarily have a low virulence. Frequently, specific antibiotic therapy is not available and the patients follow a slow but inexorable downhill course.

The most common location for these ultimately lethal infections is the lungs. Collectively, the resulting infections have been termed transplantation pneumonias. They are caused by a wide variety of opportunistic organisms. However, there is one kind of pneumonitis which has had such a consistent clinical course and typical appearance on chest x-rays that it has been accorded a special position in the transplantation literature. Within the lungs is found *Pneumocystis carinii*, a protozoan which ordinarily causes pneumonitis only in debilitated infants, in patients with naturally occurring immunologic deficiency states, or in patients being treated with cytotoxic drugs. Often there is coexistent infestation of the pulmonary tissue with a cytomegalic inclusion virus.

The clinical syndrome which results usually has a slow onset with the insidious development of progressive pulmonary alveolar capillary block. Cyanosis may become intense, often without any change in blood carbon dioxide. Chest x-rays reveal a quite homogeneous infiltrate involving the middle and lower lung fields. There is no good specific therapy. However, somewhat more than half of the patients recover spontaneously. The prognosis is thus better than with any of the fungus pneumonitides which are almost invariably fatal.

Whatever their bacteriologic etiology, it is tempting to ascribe the various delayed infections simply to the necessity of maintaining heavy immunosuppression with multiple drugs for long periods of time. There may, however, be another important factor. Host reactivity to continuously present renal antigens often is eventually reduced. It is conceivable that a similar specific loss of responsiveness to bacterial antigens could also ultimately occur (Fig. 9).

Renal function is often adequate, although reduced until the time of death. One patient had excellent renal function for the first nine postoperative months. Then a late rejection developed. After this, stable renal function

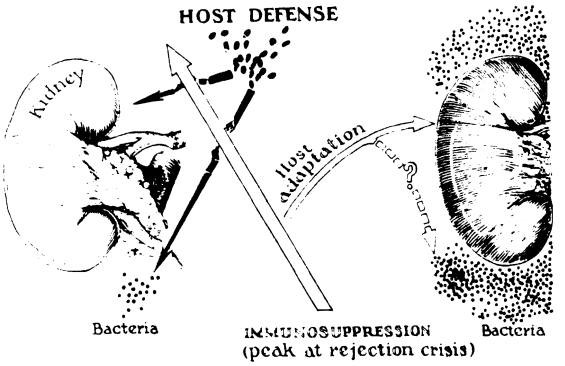

Figure 9. Possible mechanism of simultaneous loss of host reactivity to specific strains of endogenous bacteria, as well as to the alien renal tissue. (By permission of Surgery 56:296, 1964.)

could not be maintained without prednisone doses of 40 to 100 mg. per day. Two months before death, the patient developed a pulmonary infiltrate and eventually died of respiratory insufficiency. At autopsy, the consolidated lungs were diffusely infected by *Pneumocystis carinii*. There were also several necrotic foci filled with colonies of *Aspergillus fumigatus*.

Although infection is the most serious complication of steroid therapy, particularly when it is used in combination with cytotoxic agents such as azathioprine, prednisone in large quantities causes a number of other side effects. These include cosmetic deformity, arrest of normal growth in children, bone demineralization, polyphagia and consequent obesity, hypertension, steroid diabetes, fatty infiltration of the liver, pancreatitis, and endogenous fat embolization.

THE INFLUENCES OF ANTILYMPHOCYTE GLOBULIN UPON MORBIDITY. Many observers have concluded that azathioprine, when it can be used alone and is not given in excessive quantities, is a relatively safe agent. However, it has also become evident that if the other indispensable drug, prednisone, is required in high doses for long periods, the morbidity is predictably unacceptable. Consequently the use of antilymphocyte globulin as a steroid-sparing device has had unusual appeal.

The guidelines provided by animal experimentation have been incorporated into the therapeutic regimen used for patients. The immune horse globulin was used as an adjuvant agent added to therapy with azathioprine and prednisone. It was started intramuscularly five to six days in advance of surgery, continued daily for ten to 14 days afterward, then every other day for two

weeks, two times a week for two months, and once a week for a final month.

The effect of antilymphocyte globulin therapy upon the peripheral white cells was unpredictable during the period of preoperative treatment when only this immunosuppressive agent was being used. The production of lymphopenia was irregular. Nevertheless, a profound effect upon immunologic reactivity was evident. A number of patients previously had positive skin tests to *Candida albicans*, tuberculin, mumps, histoplasmin, and Trichophyton. In each instance, the skin test became negative when redetermined after three or four days of antilymphocyte globulin therapy. Thus, antilymphocyte globulin promptly prevented the expression of preexisting delayed hypersensitivity.

In these patients, the amount of azathioprine given was less than in any previous series of comparable patients. More important was the fact that the amount of prednisone required was sharply reduced during the critical first four months of convalescence. The reduction in dose of the standard immunosuppressive agents was not paid for by the sacrifice of renal function. The blood urea nitrogens and creatinine clearances were better than in any of the earlier series of patients.

Most important, the incidence of septic complications was strikingly reduced. Seemingly, it has thus been possible with the aid of antilymphocyte globulin to improve the protection afforded the homografts and at the same time to less seriously hamper the host's ability to deal effectively with dangerous environmental antigens.

Thus far, there have not appeared to be prohibitively serious toxic reactions with the use of antilymphocyte globulin. The injections are often painful and cause fever. A few relatively minor anaphylactic reactions have occurred but in some patients these have not even necessitated discontinuance of the globulin. The first eight patients treated with globulin therapy had biopsy of their homografts after approximately four months of therapy. In none was there any evidence of serum sickness nephritis.

RESULTS AFTER RENAL HOMOTRANSPLANTATION. Until now, primary attention has been focused upon the problems caused by the slender margin between that therapy which is ineffective and that which is overzealous. Appreciation of these limitations, particularly as they applied in the earlier days of transplantation, should not obscure the fact that many patients have been rewarded with relatively complete social and medical rehabilitation.

A total of 117 patients have been treated from March 1962 to April 1966, three with kidneys from identical twins, nine with cadaveric homografts, and 105 with homografts from volunteer donors. With the exception of the identical twin recipients, these patients were all provided with various combinations of azathioprine and prednisone, to which irregular administration of intravenous actinomycin C and local homograft irradiation were added. Subsequently, from June to December 1966, 20 more patients were treated, with the addition of antilymphocyte globulin to azathioprine and prednisone. Sequential division of the results from this experience illustrate the influence of several factors upon survival, including various adjustments in therapy and changes in policies of donor and recipient selection.

Identical twin cases. Three patients were 27, 20, and 54 years old when their operations were performed 72, 56, and 23 months ago. All three had glomerulonephritis. They now have normal renal function. Their courses have been completely satisfactory.

First living donor series. These 64 consecutively treated patients were treated from 48 to 64 months ago. Forty-six received kidneys from family members (20 parents, 23 siblings, and three aunts, uncles, or cousins); the other 18 donors were nonrelated. No other effort was made to match biologically donor and recipient pairs other than to ensure against ABO blood group incompatibilities.

Life survival curves of the patients are shown in Figure 10. Thirty-seven lived for one year, 34 for two years, and 32 for three years. Thirty (47 per cent) are still alive. The difference in long-term survival was striking in the recipients of homografts from related as compared to nonrelated donors. In the former subdivision, 28 of 46 (61 per cent) are still alive from more than four to five and one-half years. In the latter group, only two of 18 patients survive to date, one by virtue of a second homograft placed after two and one-half years.

Another important point can be made from this early series, aside from the proof it provides that many patients can be expected to live for a long time after homotransplantation. The disparity in results with essentially randomly selected donors is evident when the

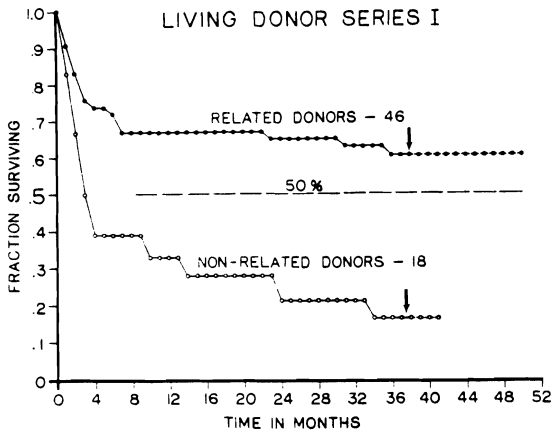

Figure 10. Survival curves of a consecutive series of 64 patients treated with renal homotransplantation from 38 to 55 months ago. Note that the long-term results with the use of kidneys from blood relatives are far superior to those which followed transplantation of genetically nonrelated kidneys. The arrows show the minimal postoperative follow-up for the most recently operated upon of these patients.

outcome is compared with the use of homografts from intrafamilial and nonrelated donors.

Second living donor series. The antigens detected with human isoimmune sera have a significant relationship to histocompatibility. Such methods might have a clinical application even though they are admittedly still imperfect. The second series was, therefore, undertaken with an attempt at prospective antigen matching. Whenever more than one donor was available, the antigen profile of each, as well as that of the recipient, was determined and the most compatible volunteer was accepted. There were 42 recipients who received homografts from 23 to 41 months ago.

In 25 patients, the donors were blood relatives (15 parents, nine siblings, one uncle). Because the selectivity within most families was limited, the quality of matching was only slightly, and not significantly, better than could have been achieved with random intrafamilial pairing. Of these 25 patients, 14 (56 per cent) are still alive (Fig. 11). The survival of 64 per cent after one year was not significantly different than in the previous series in which selection was not attempted on the basis of antigen matching.

For the nonrelated patients, the use of a donor pool, which at times offered as many as 100 possible selections, permitted a very substantial upgrading of donor-recipient antigen matching, as compared to that which would be expected on a chance basis. Of 17 recipients of these kidneys, nine lived for at least one year and six are still alive from 28 to 40 months after operation.

It was discouraging to note that the use of prospective antigen matching for donor selection did not have more influence upon prognosis. This was not surprising in the consanguineous transplantations because of the

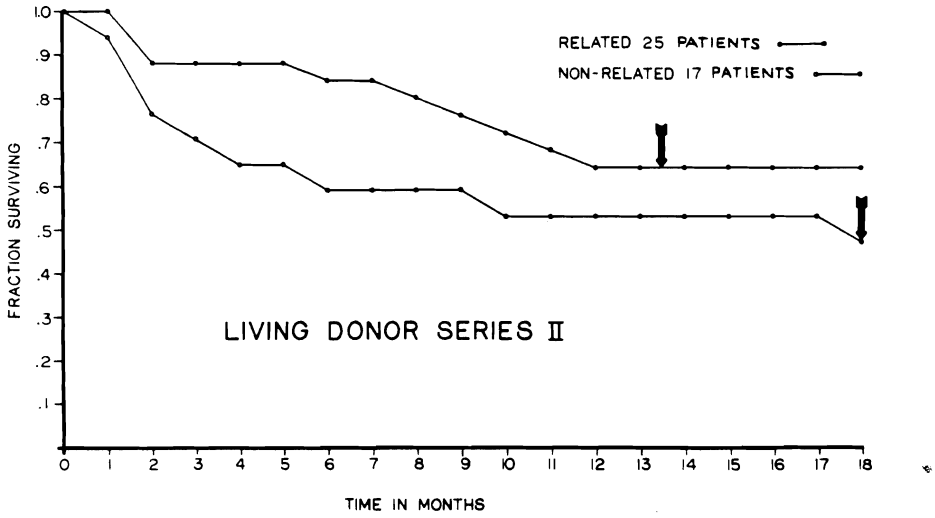

Figure 11. The outcome in 42 patients with renal homotransplantation in which operation was performed from 13 to 31 months ago. The minimal follow-up is indicated by vertical arrows. In this series, an attempt was made to select donors on the basis of the best possible donor-recipient antigen compatibility. In the consanguineous homotransplantations, the results were not improved over those previously obtained with random intrafamilial pairing. However, an improvement was found in the nonrelated patients.

inability to improve selection. For the nonrelated patients, in which the situation was different, survival was increased but only to the still unacceptable one-year level of 53 per cent.

This did not imply that the use of tissue-typing techniques would play an insignificant role in the transplantation practices of the future. Instead, it suggested that antigen matching could not receive a fair trial with the treatment programs being used widely unless transplantation was performed only between almost perfectly matched donor-recipient pairs. Such an approach would limit consideration to all but a very small number of patients who needed this kind of therapy. Consequently, the alternative approach of using new and hopefully better immunosuppressive regimens was evaluated.

Antilymphocyte globulin series. Twenty patients were operated upon. Kidneys were donated to 19 of the recipients by blood relatives on an essentially random selection basis—parents in five instances, siblings in 13, and a maternal uncle in the other. The twentieth patient received a cadaveric homograft from a donor who was shown to have an extremely poor antigen compatibility with the recipient.

Because of the preponderance of related patients, the mortality was compared to that of three consecutive past series of consanguineous transplantations in which therapy had consisted of azathioprine and prednisone. In the globulin-treated patients, there has only been one death (Fig. 12), the fourteenth patient in the group. The failure was caused by complications stemming directly from a technical accident.

The favorable slope of the survival curve in these patients is evident from Figure 12. These findings indicate that at least the early outlook after renal homotransplantation has been improved by the addition of adjuvant globulin therapy.

Cadaveric transplantations. Ten patients were treated with cadaveric transplantation prior to December 1966. Three of these recipients who received cadaveric homografts in 1963 died after four to 39 days with unrelieved uremia and sepsis. In 1965 and 1966, seven more attempts were made, including one patient who was treated with antilymphocyte globulin. All the kidneys functioned following delays of ten minutes to 23 days after revascularization. Four of the recipients died after three, eight, ten and 12½ months with failing homografts and with sepsis. Three are still alive, one after placement of a second homograft.

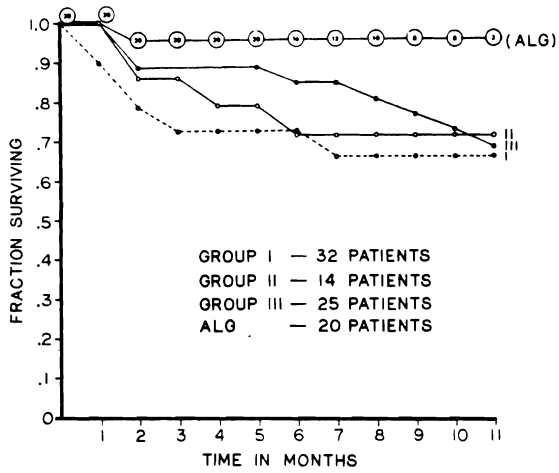

Figure 12. Early mortality in 20 patients treated with adjuvant antilymphocyte globulin (ALG). The number of patients available at each month of follow-up in this series is indicated. For comparison, the death rate is charted for each of three previous consecutive groups of patients in whom transplantation was from genetically related donors.

The future of transplantation is clearly dependent upon the exploitation of cadaveric organs. In the past, the high incidence of both early and gradual late failure has prevented this objective to more than a very limited degree. Nevertheless, the improvements in immunosuppression and antigen typing, as well as research in organ preservation, should make it possible eventually to limit organ procurement to cadaveric sources.

LIFE EXPECTANCY OF TOLERATED RENAL HOMOGRAFTS. The number of chronically functioning and life-sustaining homografts has been exponentially increasing since 1962. There have been 46, 34, and five patients who have lived for at least three, four, and five years respectively with the aid of a single homotransplanted kidney in our group of patients. Nevertheless, the ultimate functional interval of these organs can only be speculated upon.

Actuarial studies have been published based upon projections from follow-ups that are already available. These suggest that the outlook of a typical recipient of a related homograft is quite good for a number of years, if he reaches the sixth postoperative month without significant complications. The prognosis of homografts from nonrelated donors is far less certain. Whereas few kidneys in the former group have failed in the second and third postoperative years, the attrition in the latter group has continued at a moderately high rate.

Although the functional life of either type of homograft is not accurately known, there is reason to believe that it will not be normal. Many patients have had biopsies of their more or less well tolerated homografts two years or longer after operation. In only a small number were the tissues completely preserved. There was a high incidence of vascular lesions which caused obliterative changes in small, medium, and especially in large vessels (Fig. 13).

In addition, a common finding was the presence of interstitial fibrosis, which could have resulted from healing of an earlier rejection or alternatively from a diminished renal circulation caused by the vascular lesions. Many such homografts contained focal collections of mononuclear cells which were morphologically indistinguishable from the immunoblasts characteristically found in acutely rejecting homografts.

When the spectrum of histologic abnormalities in late homografts was first described more than three and one-half years ago, it was feared that many of these kidneys would begin to fail in a relatively short time. The view has proved to be overly pessimistic, because during the ensuing three and one-half years there has not been a further loss of function in the majority of patients insofar as could be detected by detailed testing.

At the moment, it must be conceded that the future is uncertain for any patient after renal homotransplantation, even for those who have had normal function for years. This fact has led to the point of view that such therapy should be considered a useful and increasingly effective form of palliation. Any conclusion that transplantation is a curative procedure will have to await a much longer period of observation.

Figure 13. Vascular lesions in a homograft from a patient who died ten months after operation. The donor was nonrelated. *A*, There is fibrinoid necrosis (arrows) of part of the wall of an afferent arteriole with extension of the process into the glomerular tuft capillaries. The tubules are atrophic and the interstitium shows some fibrosis and edema (H & E × 350). *B*, An arcuate artery which has marked fibrous intimal thickening (elastic–van Gieson × 200). (By permission of Ann. Int. Med. *61*:470, 1964.)

TRANSPLANTATION OF OTHER ORGANS

Efforts have already been made in man to transplant the liver, lung, pancreas, and heart. The possibility has never seemed brighter of treating patients who are dying from isolated failure of these organs, because the advances made with the simpler problem of renal homotransplantation can probably be generally applied.

In the summer of 1967, the first successful orthotopic liver transplantation was performed. The patient is still alive nine months later. In principle, the feasibility of this undertaking had been proved long before because several dogs have now survived for as long as four years after complete excision of their own livers and placement of a homograft in the normal anatomic position (*orthotopic transplantation*). Except for a few details, the techniques of orthotopic liver transplantation in man (Fig. 14) and dogs are comparable in that all major structures entering and leaving the liver are reanastomosed.

Prior to 1967, eight clinical attempts had been made at orthotopic homotransplantation of the liver, in Denver, in Boston, and in Paris. Six of the patients survived the operation, but died from six to 23 days later. The causes of death were similar. Sepsis invariably developed. Gastrointestinal ulceration with hemorrhage, poor early liver function due to ischemic injury to the homograft, and intra- and postoperative abnormalities of blood coagulation were common. In addition, several of the earlier patients had pulmonary emboli which originated from the lower vena cava or

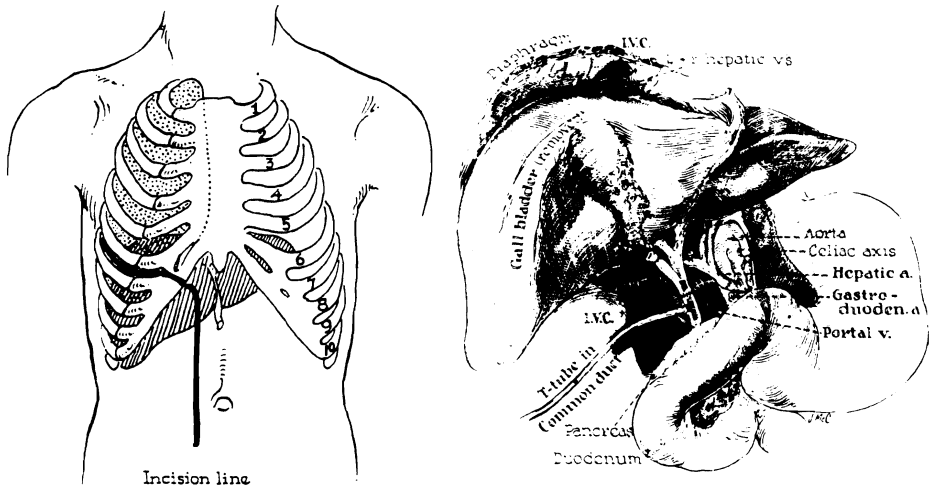

Figure 14. Human orthotopic transplantation of the liver. The diseased liver is removed and replaced with a cadaveric homograft which is revascularized in a normal way. Biliary drainage can be provided for with a choledocho-choledochostomy as shown, or by a cholecystenterostomy. (By permission of Surg. Gyn. & Obst. *117*:659, 1963.)

iliac veins. The complexity of these findings suggested that changes of several kinds would be required before further trials would have a reasonable chance of success. The most evident requisites were to improve both the techniques of immunosuppression, and the means of preserving postmortem homografts. Both objectives were at least partially met, thereby explaining the more encouraging recent results.

With orthotopic transplantation of the liver, immediate life-sustaining function of the homograft is an absolute necessity because there is no instrument analogous to an artificial kidney with which to tide the patient over a recovery period. Consequently, an appealing alternative possibility, particularly for the treatment of nonmalignant disease, would be to transplant an auxiliary liver to some abnormal location without disturbing the patient's own liver. For example, the homograft could be revascularized in the pelvis, the paravertebral gutter, or the splenic fossa.

The latter approach has the important advantage of not eliminating the residual function of the diseased liver, but it also introduces serious problems. The addition of a large extra organ to the abdominal contents may create serious mechanical difficulties. In one such patient, it is known that excision of the autologous liver was ultimately necessary before the incisions could be closed. In addition, it has been established that optimal performance of the homograft can be expected only if its portal venous inflow is derived from the venous effluent of the nonhepatic splanchnic bed. The technical difficulty of connecting the portal vein of a heterotopically placed homograft to the recipient's distal portal bed has led to the evolution of several useful compromise methods in which the venous inflow to the liver is derived from systemic veins. Nevertheless, the results in the laboratory with auxiliary transplantation have been distinctly inferior to those with the orthotopic operation.

Successful orthotopic transplantation of the heart has also been carried out in dogs but with a less consistent success rate. The most useful method is that shown in Figure 15. The recipient heart is removed during circulatory support by a heart-lung apparatus. A cuff of autologous left and right atrium is retained and this is used to suture to the atria and the atrial septum of the homograft. The pulmonary artery and aorta are reconstructed with end-to-end anastomoses.

The clinical application of orthotopic cardiac transplantation will depend upon some very difficult problems of supply. It will be necessary to have an organ which is not badly damaged in the process of donor death, to preserve it for a substantial period, and to have it resume effective pump action quickly after its revascularization.

In addition, this procedure has its own specific complications. The homografted heart does not beat with a normal sinus rhythm. Postoperatively, the impulse initiation is often in the less reliable atrioventricular node. A common cause of death in dogs after

heart transplantation is cardiac arrest owing either to asystole or to the development of fatal arrhythmias. When such operations are employed clinically, it will probably be necessary to provide means to control these complications by electrical stimulation during the postoperative period. That such problems do not preclude at least temporary success has been illustrated by the report of a recent patient with a cardiac transplant who has lived more than five months at this writing.

Orthotopic transplantation of the whole lung is a relatively easy procedure which can be done in several ways (Fig. 16). Technically, it is easiest to transfer a piece of donor atrium into which all the pulmonary veins enter. Homografts of lobes can also be readily transplanted by anastomosis of the major lobar structures.

If entire lungs are transplanted in experimental animals, there are problems caused by the necessity for denervation which in turn result in the loss of certain respiratory reflexes. Equally limiting, when either whole lungs or lobes are used, is the fact that only the pulmonary arterial component of the normally double blood supply can be easily reconstructed; the bronchial arteries are too small to permit their successful anastomosis.

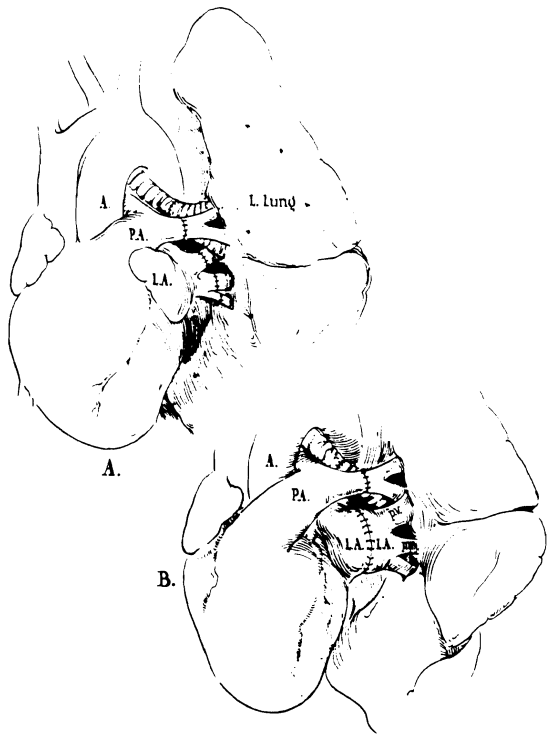

Figure 16. Two techniques for orthotopic homotransplantation of the left lung. In *A*, the pulmonary veins are individually anastomosed. Alternatively (*B*), an atrial cuff with the homograft can be sutured to the left atrium of the recipient. Neither method provides for reconstitution of the bronchial artery supply.

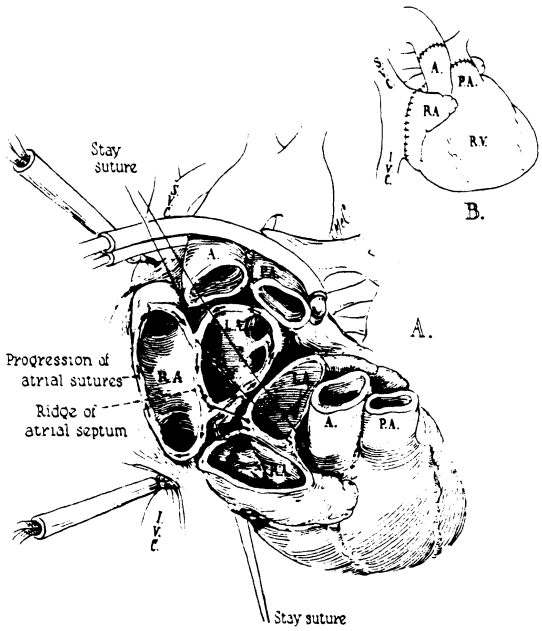

Figure 15. Orthotopic homotransplantation of the dog heart as developed by Shumway and Lower. Note that the atria and interatrial septum of the donor and recipient are sutured. This method makes it unnecessary to anastomose separately the venae cavae and the pulmonary veins.

Consequently, the homograft bronchus which must be sutured has subnormal perfusion. This has caused a high incidence of bronchostenosis or anastomotic disruption in animal experiments, particularly in dogs. There is some evidence that this may present less of a hazard in subhuman primates or in man.

Other tissues and organs have been transplanted in humans, including skin lymphoid tissues of various kinds, various endocrine organs, limbs, and living cartilage, to mention only a few.

ORGAN PRESERVATION

With all living grafts, a crucial technical problem is to restore nutrition within the permissible time limits of ischemia. Although the ability to recover from an avascular interval varies with different tissues, the necessity for prompt transfer imposes sharp limitations on all grafting procedures. Several methods can be used either alone or in combination to prolong the viability of extirpated tissues and organs.

Inhibition of Metabolism

Hypothermia. Hypothermia refers to a reduction in temperature which is not below 0° C. It offers perhaps the simplest and most practical method for short-term preservation. Cooling can be accomplished quickly by the intravascular perfusion of excised organs with chilled electrolyte solutions. Within limits, the magnitude of the protection obtained is more or less directly related to the degree of cooling. This is not difficult to understand because it is known that for each 10° C. decrease in temperature, oxidative metabolism is reduced by one-half. At 2° C., it is less than 5 per cent of that at 37° C., and with supercooling it is possible to bring the oxygen requirement to zero. However, this does not necessarily ensure long-term viability because activity of certain enzyme systems cannot be arrested even with temperatures as low as −80° C. In time, these are responsible for cell death by causing autolysis and by other, poorly understood mechanisms.

The usefulness of hypothermia varies with the metabolic characteristics of individual tissues. Those which are ordinarily resistant to anoxia, such as skin, bone, cartilage, and cornea, can be preserved for several weeks in a cooled state. Complex and metabolically active organs, such as the kidney, liver, heart, and lung, all can be kept in a potentially functional state by this means for only a few hours.

Supercooling. With these techniques, the temperature is reduced to lower than 0° C. Supercooling offers important possibilities for storage sufficiently prolonged to permit establishment of organ banks, because it is probable that all metabolic activity can be arrested at temperatures below −100° C. Organ storage by this means is not yet a practical objective because of damage which occurs as the result of freezing and thawing.

The cause of cellular injury with freezing is still not completely understood. Until relatively recently, it was thought to have a mechanical etiology by which intracellular formation of ice spicules caused perforation of the cell membranes. To some extent this may be true, but it can be avoided by very rapid cooling which promotes the formation of small and nondisruptive ice fragments. Furthermore, it has since been learned that a critical element of the injury is a biochemical one. Ice which is formed, whether it be within or outside the cell, contains little or no solute, and as a consequence the fluid which is left becomes hyperosmolar. It is thought by most authorities that the resulting excessive electrolyte concentrations are responsible for irreversible damage.

Significant protection from these adverse effects of supercooling can be obtained by exposure of some tissues to 10 to 30 per cent glycerol, propylene glycol, or dimethyl sulfoxide. Such substances, which collectively are termed endocellular cryophylactic agents, have in common the ability to freely permeate cell membranes and presumably to bond with water, preventing its crystallization. The use of these agents to preserve red cells, spermatozoa, and bacteria has been spectacularly successful. However, attempts to use them for the conservation of whole organs have not been effective enough to warrant clinical application.

One of the most intriguing possibilities for future investigation is to cool so rapidly that water is frozen into an amorphous glass rather than into crystals. To be able to do this, water must be cooled in one second to at least −130° C. Theoretically, such vitrified water could enter the solid phase without deadly effect.

Chemical protection. Several agents have been described which, when perfused into the vascular system of excised organs, appear to prolong the acceptable limits of ischemia. These include magnesium sulfate, sodium fluoride, and adrenochrome. The reason for the beneficial effect has not been completely explained because aerobic and anaerobic metabolism continue, although at reduced rates.

It is conceivable that these chemicals have some other unrecognized means of protection such as stabilization of cell membranes. During the past few years the role of intracellular enzyme release in determining the irreversibility of anoxic injury has been discussed. It is known, for example, that the escape of lysosomes from their intracellular envelopes is a lethal development. Both adrenal cortical steroids and chlorpromazine are thought to delay this event. In the future, these and other agents with a similar effect may be of adjuvant value in preservation techniques.

Hyperbaric Oxygenation

There have been numerous reports of the benefits of storing organs in chambers containing oxygen under 2 to 15 atmospheres of

pressure. The validity of these claims has been challenged, inasmuch as penetration of the oxygen, even under high pressure, can be demonstrated to be relatively limited in tissue slices. At 7 atmospheres with a temperature of 37°, the distance that oxygen can diffuse in heart muscle is only 2 mm.; at 5° C. it is increased to only 6 or 7 mm. Thus, the effect should only be at the surface of kidneys, livers or other bulky organs. Champions of hyperbaric techniques have pointed out that the pessimistic data from tissue slice experiments may not be directly relevant to preservation of whole organs which are immersed in fluid, and which are kept at very cold temperatures under high compression.

Combined Techniques

The limitations of each of the individual methods of organ conservation can often be partially circumvented by using two or more techniques together. An effective method for protecting several organs in the same cadaveric donor is to institute artificial perfusion of all or part of the body with a heart lung machine (Fig. 17). By incorporating a heat exchanger in the circuit, rapid core cooling can be accomplished at the same time as the perfusion. In dogs, immediately functioning renal homografts can always be obtained with this method when they are removed and transplanted 12 hours after the sacrifice of the donor animal.

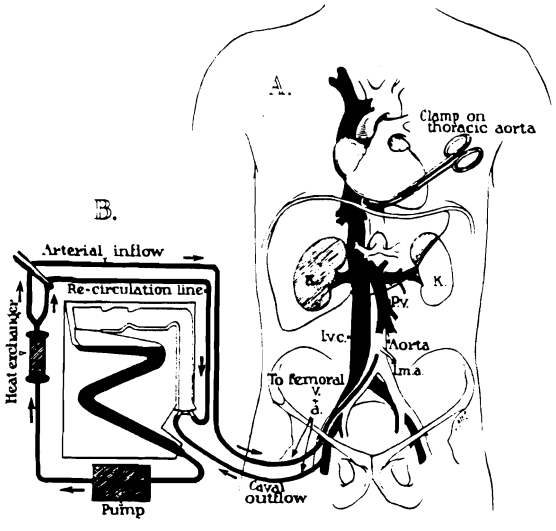

Figure 17. Technique of extracorporeal cadaver perfusion. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with heparinized glucose or electrolyte solution to which procaine is added. The cadaver is anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger.

Some of the combinations are favored by well-accepted physical laws. For example, the inherent value of hypothermia for extending the viability of nonvascularized tissue is not the only advantage of cold. If perfusion at reduced temperatures is carried out with a non-hemoglobin-containing solution, oxygen can be dissolved more readily in the perfusate; furthermore, the rate of flow can be markedly reduced without incurring a metabolic deficit. Similarly the gaseous diffusion through tissues is promoted in hyperbaric oxygen chambers in relation to the degree that the temperature is lowered. With several combinations of these methods, kidneys, hearts, and intestinal segments have been successfully preserved for two to three days.

Premortem Influences upon Cadaveric Homografts

Virtually all research on organ preservation is carried out under ideal circumstances in which a normal circulation of the donor is maintained until the time of homograft removal. When human homografts are obtained from cadavers, these conditions are never duplicated and they are not even closely simulated except for the rare instance in which a patient is rushed to the hospital and dies a few minutes after massive craniocerebral trauma.

For most patients who are considered as potential candidates for cadaveric donation, the events leading to death are less acute and there is a variable terminal period of inadequate tissue perfusion. During this time organs may be damaged, often to an unpredictable degree. In animals, the adverse effects of slow death can partly be circumvented by various measures such as the administration of heparin or large doses of steroids, or by the induction of hypothermia. In humans, the propriety of such actions which are not designed primarily for the treatment of the dying patient has been seriously questioned.

ETHICAL RESTRAINTS IN TRANSPLANTATION

Developments during the past few decades have caused increased and often unwanted

attention to be focused upon the medical profession. The public has begun to appreciate the immense power which is potentially in the hands of physicians and surgeons. For example, it has already become perfectly practical to control population growth. Now, there are authorities who believe that more discriminating efforts should be made at genetic control in an effort to improve the future quality of the human race.

It is important to define the distinction between the noble aims of these society-oriented proposals and the humbler but by no means ignoble objectives of the vast majority of practicing physicians and surgeons whose efforts sometimes seem almost to tend in the opposite direction. It is doubtful if many physicians or surgeons who actually care for the sick and the infirm plan their actions on the basis of the predicted effect upon society. Instead, the dominant tradition is for the doctor to provide the best care of which he is capable for those who either seek his services or who are assigned to his responsibility. By and large this is done without regard for the conceivably broader issue of whether or not treatment is justifiable on social grounds. His reasons may include pride, altruism, compassion, curiosity, a spirit of competition, even avarice, or a combination of all these things. Whatever the motives, the reflexes which follow are sure, and respond similarly to the needs of the productive members of the community, the insane and feeble-minded, children with incurable birth defects, condemned criminals, or even soldiers who moments before were members of a hostile army.

The foregoing viewpoint is a narrow one, but there is no reason to believe that it should be abandoned in the face of advancing technocracy. It has shielded the ill from the caprices and the moral judgments of other men through centuries of evolving philosophical, religious, and legal doctrines. It has placed the concept of the sanctity of human life on a practical foundation, because the responsibility of one person for another could not be more clearly defined than through the doctor-patient relationship, irrespective of the reasons for the contract entered into between the two involved parties.

Has this ancient creed of medicine been ravaged by the scientific explosion in which we are now involved? Examination of this question as it applies to organ transplantation is inevitable, first, because of the widespread lay publicity which has accompanied such efforts and, second, because the harsh term "purely experimental" has consistently been applied to these procedures by virtually all workers in the field as well as by interested observers.

The designation of experimental is perfectly correct. Few endeavors have ever yielded such a rich and diversified harvest of both fundamental and practical information, so united basic and clinical scientists in the pursuit of a common goal, and defined and stimulated such large areas of potentially fruitful new research. Nevertheless, the primary purpose in these patients was therapeutic and it is important to realize the degree to which this objective has already been met. Almost from the beginning of combination therapy with azathioprine and prednisone, it was evident that many patients could profit from homotransplantation, at least of the kidney. Unfortunately, it also quickly became clear that an impasse had been reached beyond which further reductions in mortality could not be expected without new immunosuppressive techniques.

This conclusion raised two important philosophical issues. The first concerned the advisability of continuing to provide a standard form of therapy which carried a high and by now relatively predictable failure rate. The corollary question was whether new, clinically untried, and potentially dangerous immunosuppressive measures should be incorporated in the therapeutic regimen. The gain might be a substantial improvement in patient care. The loss in the event of unexpected complications could be the injury or death of patients who might otherwise have had an untroubled postoperative convalescence had it been realized in advance that they were unusually favorable candidates. Eventually, the change in therapy involving the addition of antilymphocyte globulin was instituted.

The growing field of transplantation can be used to illustrate some principles to which most involved investigators have adhered. First, the clinical trial of new therapeutic methods is based more firmly than ever on prior animal experimentation. Virtually all practices in cardiac as well as in transplantation surgery have been transferred, almost without change, from the laboratory to the clinical ward or operating room.

Not infrequently, the transition has been made with haste and with an air of urgency which was fed by the needs and wishes of

desperate patients who had the misfortune of not becoming ill at a later and more convenient time. Historically, the decisions to proceed have often been wrong. Nevertheless, they have almost invariably been based on the hope, however fleeting or erroneously conceived, of potential benefit to the individual patient.

Right or wrong, the actions are eventually subjected to implacable scrutiny, principally by other members of the scientific community but also by intelligent and informed outsiders. Inaccuracies in reporting, claims that cannot be reproduced, and procedures which neither relieve suffering nor prolong life are rapidly identified. Harmful practices are snuffed out quickly; homeopathic ones may suffer a lingering death but they also ultimately disappear from the scene. The system is ruthless and impiteous and demands a policy of nonconcealment from those who would innovate in medicine. It is not sufficient to report only successes. Failures must also be fully documented, no matter how painful and humiliating these may be, in order to prevent repetition by others of the same mistakes. In general, such openness has characterized efforts in the field of transplantation.

Until now, some problems of transplantation have been discussed only as they apply to the recipients of potentially life-sustaining organs. The thoughtful trial of a variety of therapeutic variables, in which the risk of adverse effects was borne by the persons who had the most to gain, seems highly defensible both in prospect and retrospect. The involvement in such ventures of persons who may be harmed or who do not stand to derive any direct benefit is not such a simple matter. This practice, as epitomized by the testing of new drugs or procedures in human volunteers, is defined in the Helsinki Declaration (1964) as "clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research." It adds that the subject must "be in such a mental, physical, and legal state as to be able to exercise fully his power of choice." Because the propriety or even the legality of such experimentation has been questioned, it may now be well to examine in this context the problem of organ donation.

No easy answers are available. When intrafamilial homotransplantation is performed under the proper circumstances, it cannot be reasonably said that there is no value to the donor who usually has been the first to suggest this possibility. His willingness may be based on the extent to which the fullness of his inner life is involved with and dependent upon that of the recipient or because of a variety of other acceptable reasons; to our knowledge, the objective is never the acquisition of scientific data. Progress in medicine confronts him with a decision which may be difficult but which is consonant with the dignity and responsibility of free life.

Quite another situation exists, of course, with the reluctant donor who by arbitration has been selected by the family on the basis of his or her presumed expendability. It is ordinarily not difficult to detect this kind of coercion, particularly if trouble is taken to make the appropriate specific inquiries. The potential victim is excused from further workup on the grounds of some medical diagnosis which will protect him from guilt feelings and from the ostracism of those who were so anxious to volunteer his services.

In a recent symposium on ethics in medical practice, the previously cited matter of free choice as it affected all kinds of clinical investigation became one of the dominant themes of the conference. The ability of minors, prisoners, and even medical students to "fully exercise their power of choice" was seriously questioned and discussed at some length because transplantation donors had already been employed from the first two of these classes of captive populations.

The transplantations from minors had been done in other institutions under exceptionally favorable psychological and medical circumstances involving identical twins. Nevertheless, it was challenged that these accidents of birth should have set the well twins apart, in the eyes of the law, from other minors who would automatically have been disqualified.

The penal volunteers were accepted under conditions which it was thought would fully ensure the protection of their individual rights and permit their complete freedom of choice, objectives which in principle may have been even less realistic than with the identical twin minors. In any event, there is every reason to believe that this practice, however equitably handled in a local situation, would inevitably lead to abuse if accepted as a reasonable precedent and applied broadly. For these reasons, and because the donor motivation which characterizes proper intrafamilial transplantation could not be

said to exist except in the most idealized and universal sense, the acceptance of criminal volunteers was permanently discontinued at the University of Colorado two and a half years ago.

The question of organ procurement from living volunteers is perhaps the most sensitive and limiting issue in clinical transplantation. The best prognosis today can be offered to the recipient only with the use of such donors, particularly when these are from within the family. In the future, it is hoped that the need for living donors will be made obsolete by improvements in immunosuppression, antigen typing, and tissue preservation. Then, organs obtained solely from cadavers could be used with a high expectation of long-term survival.

Unfortunately, success will not imply that an ethical panacea will have been found, primarily because the terminal events in a prospective cadaveric donor are of such importance in determining the quality of a subsequently transplanted organ. It is conceivable that this fact could lead to subtle or even major adjustments in care which would be designed for the protection of the organ to be removed rather than for the benefit of its donor.

Examples can be cited. In several centers outside the United States, conventional death has been re-defined, in some patients in the presence of a continuing heart beat, in terms of objective evidence of irreversible injury to the central nervous system. The judgment that death was imminent and unavoidable was made by a panel of expert referees who were not members of the transplantation team, although the need for their mediation was clearly the consequence of the requirements for fresh and uninjured organs. One or both kidneys were then removed from these "living cadavers," with apparent benefit to the recipients; the incidence of immediate urine excretion was very high. That a high degree of social conscience dictated these actions is beyond dispute. What could be questioned is the concept of imposing further trauma upon a dying patient, however apparently hopeless his condition, at a moment when he is the epitome of mental incompetence. The act itself could be construed as an erosion of the historic medical creed of responsibility to the individual patient, at least as this applies to the donor, and the timing as a violation of the principle of free choice.

Perhaps it is not inaccurate to say that the important features of the selection and management of homograft recipients or their donors illustrate some problems of day to day ethics which apply in principle to other forms of clinical investigation and in fact to traditional medical practice. No effort has been made to say that errors have not been made in the development of clinical transplantation nor to imply that new mistakes can be completely prevented from this day forward. It has, however, been suggested that progress in this and other new fields of medicine has been made in a sturdy framework which is ethical, practical, and efficiently policed. There are few surgeons who believe that the traditional responsibility of the doctor for the welfare of his patient has been, or that it should be, lessened by the emergence of new forms of therapy which of necessity must at some time be tried for the first time in man.

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