Surgical Physiology of the Transplantation of Tissues and Organs*

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SINCE 1900, prodigious effort has been expended on the problems of tissue and organ transplantation. Initially, progress was slowed by failure to differentiate the behavior of autografts from that of homografts or heterografts. Holman,[13] Loeb,[17] Guthrie[11] and others had pointed out that homografts initially behaved no differently than autografts but that in a short time they were repudiated by the host organism. However, even at the beginning of the Second World War, many people still believed that homograft failures were primarily due to technical inadequacies.

Failure to recognize the scope of the problem was partly due to lack of a precise explanation for homograft or heterograft incompatibility. Since 1940, invaluable information has become available which has not only allowed quantitation of the details of rejection of foreign tissue, but which has also provided a rational explanation for this incompatibility. In addition, technical advances in tissue transfer and increased knowledge of organ storage have expedited both research and clinical use of grafting procedures. The application of these physiologic principles, insofar as they govern the use, success and failure of various kinds of grafts, is the subject of this report. Emphasis will be placed on the transplantation of living tissue rather than on nonviable grafts which act as prostheses.

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PROBLEMS INHERENT IN TRANSFER OF TISSUE AND ORGANS

Certain problems are common to all living grafts whether they be from the same individual (autograft), from a different individual of the same species (homograft), or from a different species (heterograft). Some grafts serve as scaffolding (bone, cartilage) or as conduits (blood vessels) and are eventually buttressed or replaced by host tissue. Here, it is immaterial whether the tissues are dead or alive.

Problems of Ischemia

If tissue viability of the graft is essential, the most critical of the requirements is to prevent lethal ischemia and necrosis of the tissue during transfer and revascularization. The necessity for prompt restoration of nutrition varies according to the resistance of the tissues to ischemia and the bulk of the graft. Cornea, connective tissue, cartilage and skin are grafted without immediate restitution of the blood supply. The mass or thickness of tissue is usually not great, but in addition, these tissues are resistant to anoxia. After graft placement, the revascularization of skin occurs from the graft bed in a few days. With cornea and cartilage, particularly the former, metabolic requirements may be permanently met by diffusion, and ingrowth of blood vessels may never occur.

In contrast, complex or bulky tissues, especially whole organs, require prompt re-anastomosis of the major vessels. When free transplantation of such tissue is attempted, a few peripheral cells may survive, but the entire central mass undergoes necrosis.[17] The duration of permissible ischemia is measured in minutes or hours. The liver, kidney, heart and hollow viscera are among the most sensitive organs, while endocrine glands and lung are somewhat more resistant. Reduction of metabolism of grafts by cooling increases resistance to ischemia, and will be discussed under the section on procurement and storage.

Problems of Innervation and Lymphatic Drainage

In grafts that are completely removed from continuity at the donor site and transferred, all lymphatic and neural connections are severed. Free grafts, such as skin, have progressive re-establishment of lymph channels and incomplete and disorganized ingrowth of nerve fibers. Organ grafts, in which vascular continuity is restored by anastomoses, have functioned well for long periods despite these deficits. Lymphatic drainage of whole organs may be served by regeneration of lymph channels[16] or by lymphatico-venous connections such as those described by Blalock.[5] In the actual transplantation of very large homografts, the state of denervation and consequent loss of vascular tone may be responsible for the sequestration of large quantities of blood in the graft, leading to congestion and immediate technical failure.[80]

The Function of Living Grafts

The functional capacity of grafted tissue has been of great interest. This is often difficult to measure, especially in its subtler aspects. The kidney, because its excretory products can be accurately evaluated, has provided some of the most precise information on graft function and can be used as a prototype. The bulk of evidence indicates that renal autografts, transferred with good technique, perform as well as normal kidneys.[31] In contrast, renal homografts which are transferred by the same techniques to unaltered recipients initially display good gross function, but in general lose the capacity for completely normal electrolyte manipulation, and never function as well as autotransplants.[34] When the recipient subject is successfully altered to prevent a rejection response, the homograft probably functions as well as an autograft.

TISSUE COMPATIBILITY

Technically, it is possible to transfer virtually all tissues or organs from one site to another in the same or another subject. The central problem in success or failure is whether or not the grafted tissue is biologically compatible with its host. With autografts, in which the transplant is made to a new location in the same individual, permanent graft survival is the rule. This fact has allowed wide clinical use of autografts with skin, cartilage, fat, muscle, bone, tendon, fascia, nerve, blood vessels, bone marrow, endocrine tissue and intestinal segments. In the case of identical twins (monozygotic), tissue can be permanently grafted from one twin to the other (isologous graft). From a biological point of view, this is a special form of autograft, since the two subjects are genetically identical.

The Rejection Phenomenon

When a graft is transferred to a site in a different subject of the same (homograft) or a different (heterograft) species, it is in time destroyed and sloughed by the host. For a few days, the alien graft acts in a manner indistinguishable from an autograft, both anatomically and with respect to gross function. After three to five days, mononuclear cells, chiefly plasma cells and lymphocytes, infiltrate the graft (Fig. 1, *A*). Engorgement, rupture or thrombosis of small vessels may be prominent. These vascular changes are not prevented by anticoagulant therapy. The graft becomes enlarged and firm, and the quantity of blood transmitted by the organ is reduced. Function ceases a few hours or days later. The histologic character of the graft is distorted, and eventually destroyed (Fig. 1, *B*). With free grafts, the regional lymph nodes are enlarged and packed with large lymphoid, reticulum and plasma cells,[28] while a similar inflammatory reaction is seen in the subjacent graft bed. In organ

Fig. 1. Stages in the rejection of a canine liver homograft. *A*, Early stage, after 5 days, with intact architecture but with diffuse and focal mononuclear cell infiltrate. *B*, Late stage, after 13 days, with disorganized parenchymal pattern and massive cellular infiltrate.

grafts attached by vascular anastomoses, no consistent host changes may be found, although in large grafts, widespread round cell infiltration and proliferative changes have been noted in the host reticuloendothelial system.[29] The rapidity of rejection is related to the degree of genetic difference between graft and host. Thus, heterografts are rejected more violently than homografts. Similarly, homografts do not last as long when transferred between unrelated subjects as they do with inbred strains.

The Explanation of Rejection

In 1944 and 1945, Medawar[20, 21] published the first of a series of articles which provided strong evidence that the rejection phenomenon was due to an immunologic reaction of the host to the foreign tissue (Fig. 2). The key observation in support of this concept was the fact that once a homograft had been placed, a second graft from the same donor was destroyed in an accelerated fashion (second set reaction), suggesting the acquisition of immunity. 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 homografts from other donors were not usually rejected in an accelerated manner. A feeble quantitative effect was noted by Medawar, with more rapid rejection of larger than smaller grafts.

The delay between exposure to a foreign graft and rejection has prompted comparisons between homograft immunity and the delayed tuberculin type sensitivity. However, the details of homograft and heterograft immunity are not known. The nature and location of the antigen and of the resultant antibodies are matters on which there are conflicting opinions. There is abundant evidence that the reticuloendothelial system plays an important role in rejection (Fig. 2). The relation of the graft to cellular activity in the regional lymph nodes has already been alluded to. All vascularized homo- and heterografts are invaded by lymphocytes and plasma cells during their rejection. Work by Algire[1] points to the small lymphocyte as the cellular agent of destruction. Finally, paralysis of the host reticuloendothelial system by irradiation

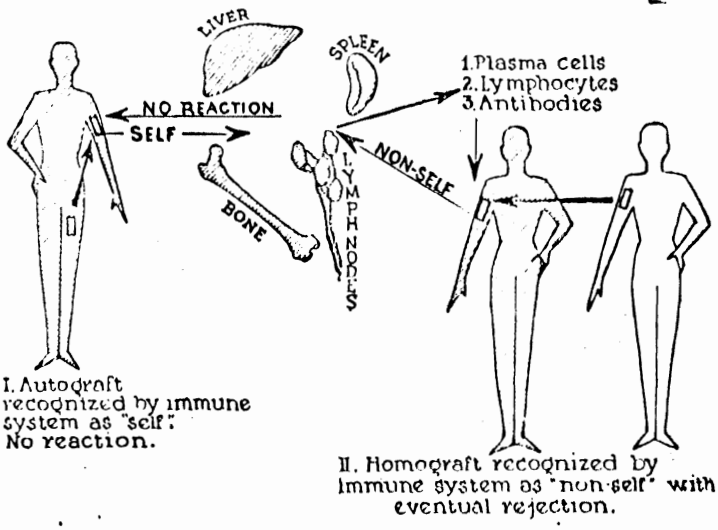

Fig. 2. Response of the immune mechanism to autografts (I) and homografts (II).

or cytotoxic drugs is the most effective method currently available to potentiate homograft survival in adult subjects.

Attenuation or Paralysis of the Rejection Response

Use of ionizing irradiation to reduce or abolish the immunologic competence of the host is the subject of a vast literature, and is the method for abrogation of the host versus graft reaction that has received the greatest clinical and experimental study. Unfortunately, the dose of irradiation upon which graft survival depends causes the lethal combination of general immunologic paralysis and bone marrow suppression.

To avoid this, the irradiated host can be provided with new reticuloendothelial and blood-forming systems by means of a free hematopoietic[18] and/or spleen[7] graft. At a subsequent time, a kidney or other tissues from the same donor can be grafted with permanent or prolonged survival.[14] The resultant composite subject is termed an irradiation chimera. As Burnet[9] has pointed out, the chimera is an unstable preparation in which the immunologic reactivity is directed by the donor tissues. Eventually, the remaining host reticuloendothelial cells, which have survived irradiation, may recolonize the lymphoid tissue and tolerance to the graft is lost. If the graft cells remain in ascendency, then ntigens of the defenseless host may provoke an antibody response from the graft with a consequent graft versus host reaction.

The importance of the latter possibility will be discussed subsequently, but for the moment, the most encouraging indication that this quandary may not be insoluble was provided by Woodruff[35] and Hume.[14] Hume has shown that prolonged survival of an irradiation chimera is possible. Woodruff has presented evidence that if a homograft can be maintained for a certain critical period, mutual adaptation and eventual success can be achieved even in the absence of histocompatibility between graft and host.

In clinical practice, employment of x-irradiation to contravert the immune response has allowed limited use of bone marrow and renal

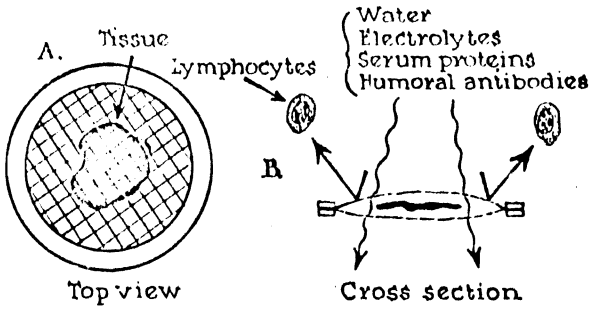

Fig. 3. Schematic representation of diffusion chamber used in homograft studies. Cells cannot penetrate millipores (±0.45 microns) but nutrients and humoral antibodies can.

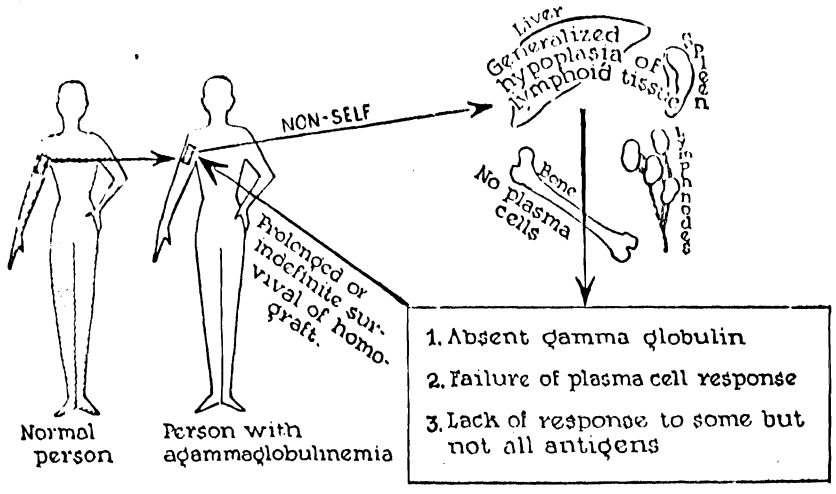

Fig. 4. Findings in patients with agammaglobulinemia.

homografts. Most experience has been acquired with renal homografts used in conjunction with hematopoietic grafts and, in at least one case, a renal homograft has sustained life for more than a year.[23] Hematopoietic grafts alone in the treatment of irradiation disease and of leukemia have had limited clinical trial.

Under certain other specific circumstances, there is abrogation of the host versus graft response with the use of homografts. If free grafts are encased in millipore chambers through which fluids, but not cells, can pass (Fig. 3), rejection does not occur.[1] Homograft viability under these conditions may be analogous to corneal and to a lesser extent cartilage homografts and to various grafts to the anterior chamber of the eye, whose survival continues only as long as they are not vascularized from the host. Millipore chambers encasing endocrine tissue have had a limited clinical trial but without notable success.[31]

Constitutional disorders of the host can also lead to prolonged survival of homografts. This has been noted in patients with uremia[9] or Hodgkin's disease.[15] It is thought that the potentiation of graft survival is due to deterioration of the host immune mechanism and reticuloendothelial system. In cases of agammaglobulinemia and hypogammaglobulinemia,[10] homografts of skin have lived for more than a year. These patients have, in addition to reduced or absent gamma globulin, lymphoid hypoplasia and inability to develop plasma cells (Fig. 4). Capacity to react to some but not all other antigens is similarly reduced (Fig. 4).

Homograft Tolerance After Inoculation of Neonates and Embryos

Despite progress with methods of altering the host response, there are at present no means of consistently assuring persistent viability of homografts in the adult subject. It has been found in various species,

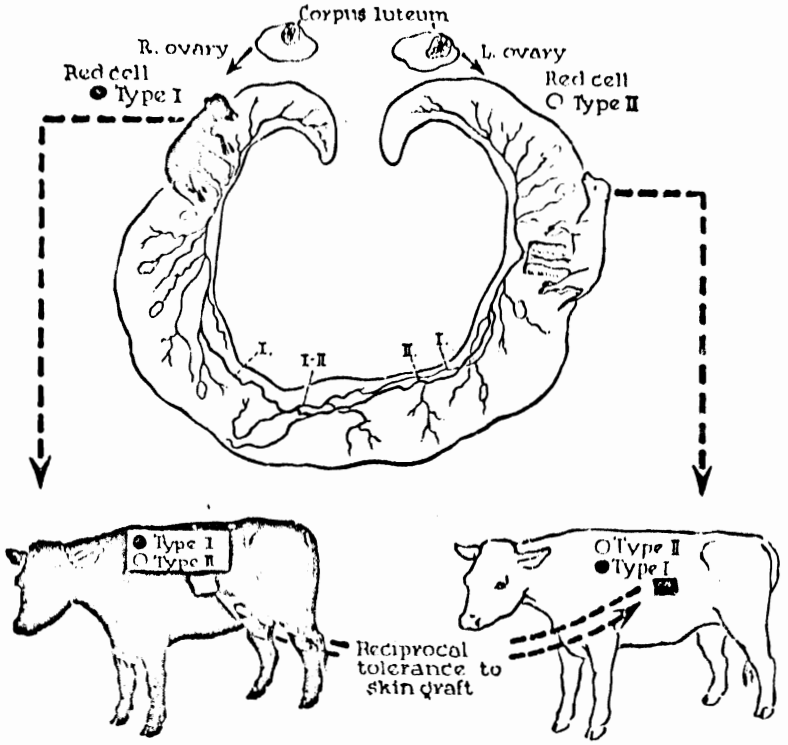

Fig. 5. Erythrocyte chimerism in cattle twins. Cross tolerance to formed blood elements and other subsequent grafts following intrauterine circulatory exchange in dizygotic twins.

however, that permanent immunity to tissues of an adult donor can be obtained by exposure of the fetus or newborn to donor cells. The initial observation in this development was made by Owen[24] who noted that dizygotic calf twins, whose circulation in utero communicated freely, had each other's formed blood elements which persisted indefinitely (Fig. 5). On the basis of this, Burnet[7] suggested that exposure of the fetus to donor tissue might confer immunity persisting after birth to subsequent grafts from the same donor. The hypothesis was confirmed by Billingham, Brent and Medawar[4] in rats and has subsequently been extended to other species.

The explanation for this acquired tolerance appears to be related to exposure of the host to donor antigens at a time when its immune mechanism is incapable of recognizing the graft tissue as foreign. With maturation of the immune processes, the graft is not recognized as alien, nor are other tissues from the same donor. While of no immediate clinical value, these disclosures are of great biological importance. They have strengthened the hypothesis of acquired immunity since similar fetal exposure to other known antigens, such as foreign proteins, has resulted in immunologic tolerance to these substances.

The Graft-Versus-Host Reaction

One result of this type of experiment has been to reawaken interest in the question of what the graft reaction is against the host. In 1957, Billingham and Brent[3] described abnormalities in the development of mice which had been inoculated in utero or at birth with lymphoid tissue from an adult donor and termed these events the "runt syndrome." The mortality rate of the mice was high and those that lived often did not develop, had diarrhea, were subject to infection, and often had hypoplasia of the lymphoid system. A similar adverse effect on adult animals subjected to massive irradiation and given hematopoietic homografts has been observed by Trentin[33] and termed "secondary homologous disease." In both circumstances, it has been suggested that the injurious effects are due to action of the graft antibodies on the defenseless host.

The potential clinical importance of the graft versus host reaction is great since most clinically oriented routes of research today are directed at rendering the host incapable of immunologic response to the graft. The successful transplantation of a vital graft would be of little value if its unopposed antibodies were to visit a debilitating illness or death upon the host. The seriousness of this problem has yet to be clarified, but the findings of Hume[14] in the dog and Murray[23] in man suggest that successful renal and hematopoietic grafts may be tolerated for very long periods without harm to the host.

PROBLEMS OF ORGAN PROCUREMENT AND STORAGE

With all viable grafts, a crucial technical problem is to restore nutritional exchange within the permissible time limits of ischemia. Although the response to ischemia varies with different tissues, the necessity for prompt transfer imposes sharp limitations on all grafting procedures. Efforts to render grafts more tolerant to removal, or to allow their storage in tissue or organ banks, have followed several avenues of research.

Cooling of Grafts

Some of the simpler methods involve lowering the graft temperature with a consequent reduction in its metabolic activity. As an average, the oxygen uptake of tissues falls exponentially with reductions in temperature so that at 15° C. it would be reduced to roughly 12 per cent.[12] Cooling without freezing protects all tissues, and extends the viable interval many times. It has been used clinically for the preservation of skin grafts, bone, cartilage, kidney, endocrine organs, and cornea amongst others. With tissues like skin, cooling allows survival for several weeks. With complex experimental grafts such as liver and bowel, the permissible

ischemia is extended to several hours. The details of refrigeration range from total body cooling of the living or dead donor to regional surface cooling of the prospective graft, to perfusion of the graft with cold solutions. The disadvantage of this type of refrigeration is that the protection afforded is of such limited degree and duration that it does not permit the establishment of organ banks.

Freezing of Grafts

Freezing techniques to temperatures of −10 to −200° C. offer more promise of long-term tissue preservation since metabolic requirements could be reduced to near zero. However, numerous difficulties presently preclude more than limited applicability of these methods. For one thing, freezing causes a variable injury to tissue and the exact mechanism of this effect is not known. A traditional view is that slow freezing causes ice crystal formation within the cells, with consequent rupture of the cell membranes. Recent evidence, however, suggests that the ice crystal formation with the usual freezing techniques is exclusively extracellular, and that intracellular crystallization occurs only with rapid freezing.[22] An alternative explanation is that the cellular injury after freezing is due to altered concentration of electrolytes and other substances within the cells or in the extracellular space due to rapid removal of water in the form of ice crystals.[19] Clarification of these issues will undoubtedly promote more effective freezing techniques. At present, even the proper rates of freezing and thawing are matters of dispute, although the preponderance of evidence favors slow cooling with rapid thawing.

Of great interest is the disclosure of Rolge, Smith and Parkes[25] that exposure of tissue to 10 to 20 per cent glycerol before or during freezing protected the cells from damage. The mechanism of this protection appears to be imbibition of water by glycerol with consequent reductions in the amount of water available for crystallization and in the degree of dehydration.[22] This technique has been successfully applied to the preservation of animal sperm, bacteria and hematopoietic grafts. Results with complex grafts have been less encouraging, although autologous parathyroid tissue has been preserved in the frozen state for as long as 78 days with unquestionable viability after insertion as a free graft.[26] To day, freezing with various techniques has been most applicable to cells or to small bits of tissue. With bulkier preparations, homogeneous preservation is difficult to achieve particularly in the control part of the specimen.

Tissue Culture

Methods other than refrigeration have been used for long-term preservation of viable tissue. Tissue culture, in which the graft is placed into a nutrient medium and intermittently harvested, has allowed main-

tenance of life for years. The method is limited, not only because of its complexity, but because only cells or tiny fragments of tissue can meet their nutritional requirements by the diffusion upon which the method depends.

Organ Perfusion

The perfusion of organs through their vascular pedicles may have great future use. This method was first investigated by Carrel and Lindbergh,[8] and some of its inherent problems are still unsolved even with modern pump oxygenators and the availability of anticoagulants. With present methods, perfusion for a number of hours results in edema, progressive blood entrapment, and eventual architectural damage. Eventually, pump oxygenators in conjunction with hypothermia may allow longer preservation. Perfusion with substances other than blood may also eventually be of use. In this connection, Blalock and his associates[27, 32] have demonstrated that perfusion with oxygen alone could sustain life in whole organ kidney and heart grafts for several hours.

SUMMARY

The surgical and physiologic principles involved in the transplantation of living tissues and organs has been reviewed. Many of the problems encountered are common to autografts, homografts or heterografts. These include surgical techniques, avoidance of irreparable ischemia, and storage.

The greatest deterrent to further development in tissue and organ grafting is the problem of tissue incompatibility. Natural donors whose tissues can be permanently accepted by other individuals of the same species do not exist, unless the donor and recipient are identical twins. Natural recipients are exceedingly rare, and achieve this state only by constitutional disease such as agammaglobulinemia, or by prior fetal or neonatal exposure to the donor's tissues.

The probable reason for homograft and heterograft rejection is the development of a delayed immunity by the host which is provoked by the graft antigens and served by the host reticuloendothelial system. The abolition or mitigation of the host immune response with ionizing irradiation or cytotoxins has permitted limited, and for the most part unsuccessful, exploration with the clinical use of homografts.

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