AN INTRODUCTION TO CLINICAL TRANSPLANTATION

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In introducing clinical transplantation, it will be worth focusing upon certain phenomena which have been seen after whole organ transplantation under immunosuppression, which form the basis for the clinical discipline of transplantation, but which have not yet been precisely and satisfactorily explained.

Major progress toward the objective of tissue transplantation has been achieved only in the past few years. Before then, an almost total ignorance of the barriers which would be encountered after transplantation precluded the development of appropriate methods of therapy. Definition of the fundamental biologic problem came about 30 years ago from the studies of Sir Peter Medawar and his colleagues in England.

MEDAWAR'S CONCLUSIONS

Medawar's investigations were carried out with rabbits in which the genetic homogeneity of the donor and recipient animals was sufficient to permit a reasonable reproducibility of results. The conclusions were precise.

First, skin grafts were rejected in about 10 days. Second, 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 skin graft from the original rabbit 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 pertained to all tissues subsequently transplanted from the donor. The sensitization was specific inasmuch as grafts from other donor strains were not usually rejected in

an accelerated manner. The initial delay between the actual transplantation and the subsequent development of active immunity prompted comparison between these events and the delayed hypersensitivity which permits immunity to develop to diseases like tuberculosis.

NOMENCLATURE

The terminology used in transplantation is based upon genetic and phylogenetic relationships which, in turn, roughly determine the hostility with which a graft is viewed by its recipient. When tissue is transplanted from one location to another place on the same host (an autograft), it is identified as "self" (Fig. 1) and does not, therefore, evoke a defensive 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. Similarly, tissues exchanged between identical twins (isografts) are not recognized as foreign inasmuch as there is total genetic identity of such twin donors and recipients. This was first proved in man by Dr. J. B. Brown of St. Louis with skin transplantation experiments and later by the transplantation of kidneys (J. E. Murray) and bone marrow between identical twins.

Tissue transplanted from non-identical members of the same species (Fig. 1) are called homografts (or allografts). The host response (rejection) has an intensity which is roughly determined by the degree of genetic dissimilarity between donor and recipient. The genetic factors of transplantation, often referred to as Snell's Laws (after Dr. George

Snell) were precisely worked out in inbred rodent experiments. Unfortunately, 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. These techniques are referred to as _tissue typing_, a subject to which we will return later and which will also be covered by Doctors van Rood and Dausset.

If transplantation is from a donor belonging to a different but similar species, the tissue is called a _heterograft_ and on the average the rapidity and intensity of rejection are even greater than with homografts. However, studies with chimpanzee to human renal heterografts pioneered by Dr. Keith Reemtsma have shown that such transplants can sometimes be tolerated for long periods in patients who are receiving immunosuppressive therapy (maximum patient survival, 10 months).

Tissues or organs transferred between widely divergent species (as, for example, between pigs and dogs) are called _xenografts_. In most instances, xenografts are destroyed within a few hours by a kind of hyperacute rejection which is apparently subserved by preformed heterospecific humoral antibodies.

MECHANISMS OF REJECTION

Cell-mediated Immunity

There is abundant evidence that lymphocytes participate in the rejection process in an important way as was illustrated by experiments of the late

Dr. Glenn Algire, using millipore chambers. He transplanted free fragments
of tissue which were shielded by a mesh barrier of appropriate size inter-
stices to exclude lymphocytes and other mononuclear cells but which were
exposed to nutrient fluid and even red cells (Fig. 2). Survival of the
grafts was longer than with tissue that was not thus protected.

The participation if not the precise action of mononuclear cells in
the unmodified (or ineffectively modified) rejection of tissues and organs
can be appreciated in a more direct way by histopathologic studies which
reveal massive infiltration by lymphocytes and plasma cells. Coinciden-
tally, the blood supply to whole organ grafts is diminished and later all
but cut off so that more or less complete ischemic necrosis is the ultimate
fate of the transplant if the recipient animal lives long enough for this
stage to be reached. The various hallmarks of classical unmodified cellular
rejection are much the same in all acutely rejecting organs, whether these
be liver, kidney, heart, or skin.

Humoral Antibodies

The cellular immune response is not the only means by which delayed
homograft rejection can occur. In the serum of patients undergoing acute
rejection, cytotoxic or other kinds of antibodies have been described.
Even in the serum of patients who have tolerated renal homografts for
years, there are often circulating antigraft antibodies, but in these
cases apparently with a low capacity to cause transplant injury. Neverthe-
less, homografts in such recipients commonly contain deposits of gamma
globulin, as well as host complement.

Antibody deposition has been very well documented after transplantation

of human kidneys, livers, hearts and lungs. The patterns of the immuno-globulin binding are particularly interesting in renal grafts since they resemble those of two major kinds of experimental glomerulonephritis, namely Masugi nephritis caused by anti-GBM antibody and the kind of nephritis caused by the filtration by the kidney of soluble antigen-antibody complexes. In many cases, the glomerulonephritis in these trans-plants has been similar or identical to that which destroyed the native kidneys, indicating a recapitulation of the original disease. However, it may also be said that glomerulonephritis can be one manifestation of humoral homograft rejection. This position has received support from the fact that "glomerulonephritis" has been observed in homografts transplanted to recipients whose renal failure was due to polycystic kidney disease, cystinosis, pyelonephritis or other disorders not suspected to be of autoimmune etiology.

In other organs, such as the liver, immunoglobulin deposits have been somewhat less extensive than in renal homografts and they have tended to be unevenly distributed throughout the vasculature.

Presensitization States

Second Set Rejection --- In Medawar's original experiments, skin trans-planted to rabbits that had been sensitized by one exposure to donor tissue were rejected in an accelerated, or second set, fashion. Instead of being repudiated after an average of 10 days, this time was shortened to 6 days. The assumption was (and still is) that lymphoid tissue or other contributors to cell-mediated immunity were mobilized more quickly than normal because of

prior antidonor instruction. An additional role of circulating humoral antibodies may also be important.

After whole organ transplantation under immunosuppression, there have been numerous reports of accelerated rejection apparently comparable to that in Medawar's rabbit system. It has been speculated that the advance sensitization in these humans could have been induced by antigens also found in donor tissues during the course of pregnancies, by the previous administration of white cells or platelets in multiple blood transfusions or by other means including prior renal homotransplantation. In such patients, rejection occurs earlier and often more vigorously than expected but it does not necessarily proceed to immediate destruction of the graft. Reversal of this kind of uncomplicated accelerated rejection has often been observed (Fig. 3).

Preformed Antibodies and Hyperacute Homograft Rejection --- The first clear examples of hyperacute rejection of renal homografts were in patients who received kidneys from ABO blood group incompatible donors. An effective blood flow to some of these transplants was not restored when the vascular anastomoses were opened. The small vessels of the excised kidneys were demonstrated by angiography to be closed and, histopathologically, the arterioles and capillaries were plugged with formed blood elements, particularly erythrocytes (Fig. 4). A rational although partial immunologic explanation was available since the blood group substances which allow red cells to be typed had been shown by Högman and Szulman to also be found in other tissues including the kidneys. Consequently, if the kidney of

an A, B, or AB donor were placed in a patient whose serum contained naturally occurring anti-A and/or anti-B isoagglutinins (an example would be a recipient with O blood type who would have both kinds of iso-agglutinins), these antibodies might be predicted to bind with the renal red cell antigens. Serologic studies in some of our cases showed that falls in systemic isoagglutinin titers did, in fact occur. The rules of red cell compatibility as they apply to whole organ transplantation are summarized in Table I.

Hyperacute kidney rejection in the presence of <u>red cell group compati-bility</u> has been seen with increasing frequency and, in fact, this kind of rejection has become the chief cause of acute homograft loss in most major transplantation centers. The first case was described by Dr. Paul Terasaki of Los Angeles in a patient whose serum contained lymphocytotoxic anti-bodies that killed donor cells. Terasaki theorized that, in the course of being transfused prior to operation, the recipient had been immunized (probably on multiple occasions) to white cells that shared histocompati-bility antigens with the eventual renal donor. Since then, no one has seriously challenged this general hypothesis of presensitization. The concept has been indirectly supported by the high rate of hyperacute rejec-tion with retransplantation in patients whose first homografts were rejected and who were thereby presumably immunized to some antigens also present in the second graft.

Subsequently, many other authors have confirmed the adverse implications of preformed antidonor antibodies as detected with several techniques. The

most commonly employed methods have measured lymphocytotoxins and leuko-agglutinins but the most sensitive examination has been said by G. M. Williams and Felix Milgrom to be the mixed agglutination test.

While certain tests may be more sensitive than others for the detection of the preimmunized state, it does not seem likely that a single antibody will be found to have unique predictive significance. In our laboratories, deliberate sensitization of dogs by repeated skin grafts led to the formation of a variety of antiwhite cell and antired cell antibodies, with antidonor reactivity. However, the titer of these antibodies is not well correlated with the rapidity of rejection of a kidney from the skin donor. Moreover, it has been emphasized in reports of clinical cases that hyperacute rejection which is presumably due to presensitization may occur even though antidonor antibodies cannot be found with any currently available technique including the mixed agglutination method. Under these latter circumstances it has been necessary to assume that an immediate, albeit undiscernible, immunologic reaction is the initiating event in the destructive process that follows. With or without demonstrable antibodies in the recipient serum, the immunoglobulin deposition in the transplants may be in such small quantities that their specificity as judged by strictly morphologic criteria in immunofluorescence studies could be open to question even though on other grounds it is reasonable to believe they are significant.

One view of hyperacute rejection might be that the antidonor antibodies discussed in the preceding section were destructive of renal homografts by their direct nephrotoxicity. The observations already cited in the ABO

incompatible cases were not consistent with such a conclusion since the most obvious lesion in the rapidly repudiated kidneys was occlusion of their blood supply by clot and mechanical debris including formed blood elements.

In cases with hyperacute rejection despite red cell compatibility, there has also been evidence of interference with the blood supply. In hyperacutely rejected kidneys, the glomerular capillaries and the arterioles are full of microthrombi making the morphologic features indistinguishable from those of a generalized Shwartzman reaction. The consequence is devascularization of the kidney and cortical necrosis.

The explanation for hyperacute rejection that has evolved in the past 3 or 4 years is based upon interlocking relationships between several triggering and effector mechanisms, all conspiring to destroy or occlude the graft blood supply. In sensitized recipients, it is clear that a transplanted kidney almost immediately becomes a trap for antidonor antibodies, formed blood elements and·clotting factors. The removal of these various substances occurs almost simultaneously. Nevertheless, it must be assumed that an antigen-antibody reaction induces the clotting process, presumably with the collaboration of polymorphonuclear leukocytes.

An understanding of the pathogenesis of hyperacute rejection may help in the development of methods of therapy. Although clotting is prominent in this vicious kind of rejection, the use of potent anticoagulants, including heparin and cobra snake venom, have not provided effective prophylaxis. In contrast, the intra-arterial infusion of either citrate or ethylenediamine tetracetic acid (EDTA) is of great benefit, apparently secondary to

calcium binding. Calcium has an essential role in the clotting process, but it is also vital to the activation of complement. Since citrate and EDTA therapy impose predictably high risks under the laboratory conditions tested so far, these drugs have not yet been used clinically.

Within the last few months, Kobayashi of Boston has reported some potentially practical experiments in which organ pretreatment was carried out prior to transplantation. Monkey kidneys were perfused with pepsin digested $F(ab)_2$ fragments made from the serum of an animal specifically sensitized against the organ donor. The non-complement binding immuno-globulin fragments prevented the subsequent hyperacute rejection of these organs after transplantation to the sensitized original serum donors.

Hyperacute Xenograft Rejection --- In recent years, it has been thought on the basis of indirect evidence that the violent rejection occurring after xenotransplantation between divergent species was initiated by the action of preformed heterospecific antibodies. Support for the hypothesis included the fact that antidonor antibodies of several kinds were often demonstrable by preoperative in vitro testing of the recipient animal's serum, that such antibodies were cleared by organs transplanted from this donor, that the vascularization of successive kidneys from the same donor (or donors of the same species) usually prolonged the function of the last organ presumably by antibody depletion, and that physiochemical removal of immuno-globulins or the inactivation of complement in the recipient sometimes increased heterograft survival.

It has been of considerable interest to compare the events of hyper-acute xenograft rejection to those which abruptly lead by unquestionably immunologic mechanisms to the destruction of homografts that are placed into recipients deliberately sensitized to donor tissue (see preceding section). The observations have been so similar in each circumstance that progress in ameliorating hyperacute rejection would be expected to be applicable to both situations. This prediction has been strikingly ful-filled in that both the citrate and EDTA therapy described in the preced-ing section can prevent the rejection of porcine to canine renal grafts for as long as a half day. If untreated, such kidneys fail within 2 to 10 minutes.

IMMUNOSUPPRESSION

For a number of years after the features of cell-mediated rejection were defined, the not unreasonable assumption was made that this process was one of nature's most powerful and perservering reactions which could be prevented only by relatively complete crippling of the host's natural defenses. Such fears of lethal immunologic invalidism appeared fully justified by the consequences of total body irradiation. In order to be effective, this kind of recipient modification required doses sufficient to cause bone marrow depression. There was a consequent acute mortality which was so excessive that clinical organ transplantation proved to have little chance of success from the years 1957 to 1962 during which total body irradiation was given a number of clinical trials. Nevertheless,

there were two patients treated before 1962, who survived more than a decade after renal transplantation under irradiation, one from Boston and the other from Paris. Both of these recipients were given kidneys by fraternal (non-identical) twins.

Clinically Important Drugs

Azathioprine --- A highly significant subsequent advance was the development of azathioprine, a potentially radiomimetic drug with the predominant effect of inhibiting DNA synthesis. 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.

Cyclophosphamide --- Almost a decade ago, cyclophosphamide was given a very brief clinical trial for renal homotransplantation, but was promptly abandoned because of its toxicity. Within the past year, cyclophosphamide was reintroduced at our institution as a substitute for azathioprine in a triple drug combination that also included heterologous antilymphocyte globulin (ALG) and prednisone. More than 100 human recipients of livers, kidneys, and hearts have been treated with this regimen. The conclusion from these studies has been that cyclophosphamide is equivalent to azathioprine as a component of this kind of drug combination. As an interesting footnote, it may be noted that cyclophosphamide does not mitigate renal homograft rejection in dogs although it is a very potent immunosuppressant

in rodents or in humans. Lack of success in the canine model probably greatly inhibited and delayed the widespread clinical use of this important drug.

Adrenal Corticosteroids --- Cortisone, the first major immunosuppressant to be discovered, was described by Billingham, Krohn, and Medawar in 1951 to delay the rejection of first set skin grafts in rodents. Krohn demonstrated in 1954 that cortisone could partially abolish a pre-existing state of delayed hypersensitivity in rabbits. The crucial role of prednisone for the control and reversal of the rejection process has been unequivocally established in cases of clinical whole organ transplantation under conditions to be described later.

Heterologous Antilymphocyte Serum --- Since 1965, heterologous antilymphocyte serum (ALS) and its globulin derivative (ALG) have received an enormous amount of attention and since 1966 ALG has been used clinically with increasing frequency. The ALS is obtained from animals (such as the horse) previously immunized against the lymphoid tissue of the species which is eventually to be treated (Fig. 5). For example, horses can be inoculated with human lymphocytes obtained from spleens, lymph nodes, thymuses, thoracic duct lymph, or tissue culture. 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 spectacular heights; antiwhite cell titers of 1:16,000 are not at all unusual.

The serum collected from an immunized animal is a powerful immuno-suppressive agent when given by a variety of routes to members of the lymphoid donor species. In patients, ALG is usually given intramuscularly in combination with azathioprine (or cyclophosphamide) and prednisone and its use is limited to the first few postoperative months. By administering ALG within these guidelines, the risks of foreign protein sensitization and anaphylaxis are minimized.

Drug Synergism

In dogs, and probably in humans as well, consistent survival after renal homotransplantation is not obtainable by treating solely with any one of the four immunosuppressive agents described above. Consequently, the clinical application of organ transplantation has been based upon the combined use of immunosuppressive measures. The first combination which was widely exploited was azathioprine plus prednisone, hereafter referred to as the "double drug" regimen (Fig. 6). In 1966, heterologous ALG was added to make the "triple drug" regimen (Fig. 7), that has become increasingly widely used. Finally a triple drug program has received an extensive

used

clinical trial in the last year in which cyclophosphamide has been/in place of azathioprine (Fig. 8).

CHANGING HOST-GRAFT RELATIONSHIPS

There has been for some time an impressive body of information indicating that whole organ homotransplantation with the immunosuppressants described above can eventually lead to selective abrogation of the host rejection

response, that the success with which this can be done is related amongst other things to histocompatibility factors, and that the degree to which it is achieved is the most important determinant of prognosis in any given case. Appreciation that the immunologic relation of the graft to the host is a fluid rather than a fixed one adds an important dimension to the consideration of any kind of immunosuppression.

Rejection and its Remission

There are two clinically identifiable phases in the chain of events under discussion. The first consists of an attack by the host's immune defenses upon the new organ, usually within a few days or weeks after its transplantation. The vigor of the process is highly variable, as judged by the magnitude of the changes caused in the morphology and function of the homograft.

The remission of rejection was not convincingly demonstrated in animals until it had been seen following clinical renal homotransplantation. The first indications that rejection was a highly controllable and regularly reversible phenomenon, and that it was often followed by a state of relative "host-graft nonreactivity," came from observations of a number of patients who had clear-cut rejections commencing from a few days to several weeks after operation. The process was regularly reversed by the addition of massive doses of prednisone to the pre-existing therapy with azathioprine (Fig. 6). Then, within a surprisingly short time it became possible to drastically reduce the steroids that initially had been necessary to rescue the grafts (Figs. 6, 9). In several instances the patients were soon returned

to treatment only with azathioprine, the agent which at the beginning had
not been capable of preventing an acute rejection crisis (Fig. 9). Many
of these patients are still alive 9 or 10 years later.

There is no point in commenting further about the fully accepted fact
that kidney rejection can undergo remission beyond noting that such an
occurrence is uncommon in dogs and probably also in humans if immunosuppression
is not increased with steroids playing the central role in the intensification
of therapy.

In laboratory animals, there have been histopathologic studies which
support the idea that an initial forceful host attack can subsequently tend
to exhaust itself or at best to become less effective. Initially, the homo-
grafts become invaded with mononuclear cells, even in some animals which
are not undergoing biochemical and clinical signs of rejection. In surviv-
ing animals, the infiltrate in various kinds of grafts may decrease in
density or disappear. Subsequently, the predominant morphologic changes
usually become those of repair and/or regeneration.

<center>Mechanisms of Graft Acceptance</center>

Although it has been well established that a homograft may come to be
more or less tolerated in its new host, the explanation for the privileged
status is not accepted with any more unanimity today than it was five years
ago. Probably, more than one immunologic pathway may be involved.

Specific Immunologic Tolerance --- It is almost certain that the con-
tinuous presence of a transplanted organ in a host being treated with immuno-
suppressive therapy often leads to a selective loss of responsiveness to the

antigens of the homograft (tolerance). The evidence that chemotherapy

can be used for the induction of narrow range tolerance is unequivocal.

The literature on this subject will not be reviewed here since it has

been well summarized by Dr. Robert Schwartz, who was the first to call

attention to this possibility. Suffice it to say that azathioprine, 6-

mercaptopurine, amethopterin, cyclophosphamide, and even total body irradia-

tion can be used to promote specific tolerance, providing the antigen in

question is administered in an appropriate dose and in close temporal ap-

proximation to the immunosuppressive treatment.

One of the theories to explain the specific effect of chemotherapy

under these circumstances is depicted in Fig. 10. The illustration suggests

that a clone of lymphocytes which presumably have an active metabolism as

the result of stimulation by antigen should be differentially susceptible

to antimetabolites. This concept of "clone stripping" is consistent with the

cyclic phenomena which actually do occur characteristically after whole organ

transplantation both in treated animals and man in that the first evidence

of graft "acceptance" is often coincident with or just after reversal of a

rejection.

Enhancement --- If specific immunologic tolerance were the sole explana-

tion for graft "acceptance" it should be possible to then successfully

transplant other tissues from the same donor. This later step is often not

possible in carefully controlled animal experiments, suggesting instead

some change in the primary graft which gives it a privileged status. Many

years ago, it was shown by Kaliss in tumor systems that homografts may be

protected by the presence of certain kinds of antigraft antibodies (enhancement). It is conceivable by a feedback mechanism that the same thing occurs under the conditions of whole organ transplantation. The process could be envisioned as shown in Fig. 10, whereby immunoglobulins synthesized by the activated clone return to the target tissue and coat or protect it in some way. The means by which this might occur are obscure since by and large the finding of host immunoglobulins in a homograft by immunofluorescence techniques does not connote a favorable prognostic sign but rather the converse.

Recently, Hellstrom and Hellstrom of Seattle have published with Pierce and Marchioro some observations that may be related to enhancement. They showed that the serum of patients with well accepted renal homografts contain antibodies that are capable of "blocking" the cytotoxic action of recipient lymphocytes upon donor tissues. Further characterization of these blocking antibodies and their biologic significance is one of the most active areas of applied immunologic research.

Failure of Antigen Processing --- There is the added possibility that a defect in antigen processing by the reticuloendothelial system could be responsible for graft acceptance, a concept for which there is not yet any firm evidence. However, it is known that antisera can under certain circumstances markedly and specifically inhibit for long periods the responsiveness to   antigen recognition. The way in which an analogous sequence of events could be hypothetically injected into the picture after organ transplantation is shown in Fig. 10.

THE PRACTICALITY OF CLINICAL RENAL TRANSPLANTATION

Although the primary purpose of this article is not to present clinical data, a brief statement is in order about what has been achieved so far with transplantation of the kidney. The modern era of renal transplantation began in late 1962 and early 1963, from which period there are still about two dozen patients living who have had continuous subsequent function of their grafts. Subsequently, thousands of patients have benefited from renal homotransplantation and have thereafter undergone relatively complete social and vocational rehabilitation. This has been particularly true in recipients of consanguineous grafts who now can expect to survive the first post-transplantation year at the rate of approximately 90% (Fig. 11). It is less true of recipients of unrelated (cadaveric) transplants in whom only 60 to 80% of grafts function for as long as a year (Fig. 12).

In successfully treated patients there has not been the theoretical impasse referred to earlier of having an unacceptable susceptibility to infection. These patients have not required a controlled bacteriologic environment after discharge from the hospitals. All that is necessary is that they seek prompt medical attention if they develop any kind of infectious disease. Then they can usually be treated successfully with antibiotics or other standard measures. The reason why this kind of happy outcome is so often possible is that complete host crippling is not required to achieve "graft acceptance," as was explained in an earlier section.

Thus, although there is always an increased risk of infection, this is not so grave as to vitiate the value of the procedures.

The other highly identifiable risk of chronic immunosuppression is an increased incidence of de novo malignancy. From the premises of Burnet and Thomas about the immunologic control of malignancy (surveillance hypothesis) it could have been predicted, and was, that an increased incidence of de novo tumors would develop in people with naturally occurring immunologic deficiency diseases or in patients whose immune reactivity was deliberately depressed in order to permit their acceptance of organ homografts. The hazard of malignancy consequent to spontaneous immunologic deficiency is so well known from Dr. Robert Good's surveys that it will not be reviewed here.

Analogous data in iatrogenically immunosuppressed transplant recipients was not publicized until the spring of 1968. Since then, more than 60 examples of new malignancy in transplant recipients have been recorded in an informal registry maintained at the University of Colorado. More than a third of these neoplasms have been of the lymphoreticular system. The main practical consequence of this information is that chronically immunosuppressed patients should be watched closely for any evidence of new growth. Early diagnosis is especially important since many recipients with this complication have now been cured with standard means of treatment including excision, irradiation, and even chemotherapy--especially if this therapy is combined with a lightening of immunosuppression.

TISSUE TYPING PROCEDURES

It would be superfluous as well as presumptuous in this discussion to do more than briefly allude to the role of tissue typing in clinical transplantation since the subject will be so thoroughly covered by at least two and possibly all of our distinguished colleagues on this symposium. In our center, all donors and recipients are typed prior to operation for the HL-A antigens by the serologic techniques of Dr. Paul Terasaki. From a practical point of view the most important test is a direct cross match between donor cells and the recipient serum to rule out the presence in the recipient of antidonor cytotoxic antibodies. If such antibodies are present a hyperacute (or at least an accelerated) rejection is apt to follow, for which reason it is now recognized to be a culpable act to proceed under these adverse conditions if there is any prospect of avoiding them.

Except to predict hyperacute rejection, tissue typing has not played a major role in our own transplantation practices. The reason is that a strong correlation between a good serologic "tissue match" and the clinical outcome has not been evident except in a few special cases of sibling transplantations. Consequently, we do not place reliance upon tissue typing as a means of matching up donors and recipients. It is particularly important to realize this in cadaveric cases in which a recipient could be given an unwarranted good prognosis on the basis of good tissue match, or, alternatively, could be denied a cadaveric kidney on the grounds that it could not succeed because of the presence of a bad match.

It should be emphasized that methods of tissue matching are available in addition to the serologic ones just alluded to. Mixed lymphocyte culture techniques (MLC) should be much more discriminating, but these require the better part of a week to be completed, a time that is much too long to permit practical application in most cadaveric cases.

TRANSPLANTATION OF EXTRARENAL ORGANS

Transplantation of extrarenal organs has not yet become practical to an extent comparable to the kidney in spite of the fact that the feasibility stage of liver, cardiac and lung transplantation has already been passed. There are a number of reasons for the high failure rate after transplantation of the extrarenal organs, but for the most part these reasons are non-immunologic. They include greater technical difficulties; the lack of artificial organs comparable to renal dialysis which could tide the hepatic, cardiac, or pulmonary patient over transient periods of poor function; and even the lack of discriminating techniques to diagnose rejection in its early and most reversible phases.

ILLUSTRATIONS

FIG. 1 --- Fundamental difference between autografts (left) and homografts (right). Tissues transferred between identical twins behave as autografts. They are termed isografts and are not rejected. (From Surg. Clin. N. A. 42:55, 1962; by permission of W. B. Saunders Co.).

FIG. 2 --- Diffusion chamber experiment, after Algire. The enclosed homograft which is protected from physical contact with lymphocytes can survive for protracted periods. (From Surg. Clin. N. A. 42:55, 1962; by permission of W. B. Saunders Co.).

FIG. 3 --- Development of a rejection crisis less than 36 hours post-transplantation. Although transient anuria resulted, the process was reversed after the addition of high dose prednisone therapy. Note that a dialysis (D) was required before adequate function returned. Each arrow is 200 μg Actinomycin C intravenously. This patient, whose transplantation was on July 8, 1963, still has excellent function of the same homograft almost 8 1/2 years later. It is probable that presensitization had occurred in this case and that the violent and early crisis was a second set or accelerated rejection. (By permission of Surg. Gynec. Obstet. 118:819, 1964).

FIG. 4 --- A homograft removed a few hours after revascularization. The recipient was O+ blood type and the donor was A+. After releasing the vascular clamps, the kidney became pink for a few seconds, then deeply cyanotic. Upper --- note the cortical devascularization and dye staining at the cortical-medullary junction. Lower --- In the histopathologic

section, note the occlusion of small arteries and glomerular capillaries. (H and E,X32) (By permission of Surg. Gynec. Obstet. 118:819, 1964).

FIG. 5 --- The preparation in the horse of heterologous antilymphocyte globulin for use in patients. (By permission of W. B. Saunders Co., 1968).

FIG. 6 --- Classical rejection crisis in a patient treated with azathioprine (Imuran) to which prednisone was added. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection were present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. Acti C --- Actinomycin C; LN --- Left nephrectomy at time of transplantation; RN --- Right nephrectomy. (By permission of Surg. Gynec. Obstet. 117:385, 1963).

FIG. 7 --- The course of a patient who received antilymphocyte globulin (ALG) before and for the first four months after renal homotransplantation. The donor was an older brother. There was no early rejection. Prednisone therapy was started 40 days postoperatively because of the high rises in the serologic titers which indicated a host response against the injected foreign protein and which warned against a possible anaphylactic reaction. Note the insidious onset of late rejection after cessation of globulin therapy. This was treated by increasing the maintenance dose of steroids. (By permission of Surg. Gynec. Obstet. 126:1023, 1968).

FIG. 8 --- The first 60 days after the transplantation of a kidney from a mother to her daughter. Although the rejection crisis after a week was a

severe one, it was easily and completely reversed. Note that leukopenia was never produced by the daily doses of cyclophosphamide that were usually between 0.5 to 1.0 mg per kg/day. ALG --- horse antilymphocyte globulin; BUN --- blood urea nitrogen; CCr --- creatinine clearance; WBC --- white blood cell count; ARROW --- 625 mg methyl prednisolone intravenously. (By permission of Surg. Gynec. Obstet. 133:981, 1971).

FIG. 9 --- The first two postoperative years of the same patient whose early course is displayed in Fig. 6. Note that the steroid therapy was discontinued after 5 months, and that eventually the maintenance azathioprine treatment was about half the daily dosage which at the outset did not prevent the onset of a moderately severe rejection. (By permission of Ann. Surg. 162:749, 1965).

FIG. 10 --- Hypothetical mechanisms by which non-specific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone and, hence, tolerance. Since maintenance of such cell lines even in adult life is apparently thymic dependent in experimental animals, thymectomy would be expected to aid the process; this appears to be true in rodents, but such an effect of thymus removal has not been detected in dogs or humans. A possible protective role is also shown of immunoglobulins elaborated by the replicating cells. Conceivably the antibodies could act either at the site of the antigen (enhancement) or by affecting the macrophage processing of the antigen. (From Experience in Hepatic Transplantation; by permission of W. B. Saunders Co., 1969).

FIG. 11 --- Life survival curves of 3 groups of recipients of consan-
quineous kidneys. The patients in Series I were treated with the double
drug program of azathioprine and prednisone from 1962 to March, 1964 and,
consequently, have potential follow-ups of 8 to 9 1/2 years. The patients
of Series II were treated from October, 1964 to April 1966 and, consequently,
have potential follow-ups of 6 to 7 1/2 years. They received the same
drug therapy as in Series I and, in addition, an attempt was made at donor
selection by HL-A matching. Note that the tissue typing did not influence
the survival curve. The recipients of Series III were treated with the
triple drug program of azathioprine, prednisone, and ALG between June,
1966 and April, 1968; they have potential follow-ups of 4 to almost 6 years.
In all 3 series, the denominator indicates the surviving patients whereas
the numerator tells the number of originally transplanted kidneys that are
still functioning in those survivors.

FIG. 12 --- The results after the transplantation of non-related kidneys.
The conditions of treatment, and follow-ups and the meaning of the figures in
the parenthesis are the same as in Fig. 11. Note that the results with
non-related kidneys have been inferior to those with related grafts at
all levels of our experience.

TABLE I.   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.

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