Current Survey

FUNDAMENTALS IN HOMOTRANSPLANTATION

CHARLES MARKS, M.D., M.S., M.R.C.P., F.R.C.S.

*Professor of Surgery, Marquette University School of Medicine,
and Attending Surgeon, Milwaukee County General Hospital and Marquette Affiliated Hospitals, Wisconsin, U.S.A.*

IN THE past decade rapid strides have undeniably been made in the development of transplantation of tissues and organs. It is, however, true to say that there still exists great ignorance regarding many aspects of the immune responses by recipients of such transplants, as well as regarding methods of suppression of these immune responses. Vigorous and energetic clinical and laboratory investigation will undoubtedly solve these problems.

The Homograft Reaction

The work of Medawar (1944) has thrown a good deal of light on the biological basis of the homograft reaction:

- (1) *The first-set reaction:* The experimental transplantation of skin from one rabbit to another results in apparent primary acceptance of the graft itself. But between the 4th and 15th day after grafting, cellular aggregation develops at the host-graft site with local accumulation of lymphocytes, plasma cells and occasional eosinophils. This is followed by local circulatory stagnation with the formation of microthrombi and cessation of capillary circulation leading to death of the graft and its subsequent rejection.
- (2) *The second-set reaction:* If after the primary rejection described above, a second graft is fashioned between the same host and donor, rejection of the graft is markedly accelerated and occurs within 3-6 days, and this rejection is associated with a more intense local inflammatory reaction. The graft, in fact, shows no signs of healing and is referred to as the "white-graft" type of second-set reaction.
- (3) *Recipient Sensitization:* Rejection of one tissue homograft by a recipient will lead to an accelerated second-set reaction if a later graft of a different tissue is applied. Sensitization is, therefore, not organ specific, but is, in fact, species specific.
- (4) *Primary graft acceptance:* It has been noted that the anterior chamber of the eye, and the cerebral hemispheres do not demonstrate these rejection phenomena, the common denominator in these sites being the lack of a lymphatic drainage emphasizing the role of the reticulo-endothelial system in graft rejection.

Mechanisms of Immune Response

It has been noted that there exists a latent period of 4-15 days before the development of the first-set reaction, and that prior sensitization of the host by previous exposure to donor tissue results in an accelerated second-set reaction.

Mitchinson (1953) has demonstrated that this sensitivity, though species specific could be transferred from one host to another by transplanting lymph node cells, indicating the role of the reticulo-endothelial system in the development of the immune response, which further reflects a reaction between an antigen and an immunologically competent cell.

This immune response is undoubtedly the result of interaction of an antigen and an immunologically competent cell, and the apparatus for the development of this reaction is established late in embryogenesis. Although a host does not usually develop an immune response to his own cells, occasionally a host may react to his own antigens with the development of an auto-immune reaction, this mechanism currently explaining such disease syndromes as Hashimoto's disease, (it has also been invoked as a possible mechanism in the development of ulcerative colitis).

The transplanted antigen makes its way via lymph channels to the regional lymphatics where differentiation occurs into cells which mediate in the production of the immune response, antigenic propensities in the meanwhile being passed on to other adjacent cells. Characteristically identified with the immune response is the large lymphocyte and the plasma cell, and the appropriate nodes increase in size, demonstrating reticular hyperplasia with engorgement of the medullary sinuses by lymphocytes, histiocytes and plasma cells. It is conjectured that the increased nodal activity is probably related to an increase in ribonucleic acid and deoxoribonucleic acid.

For cells separated from such lymph nodes will continue to evoke immune responses when transferred to another host of the same species, continuing to produce antibodies and participating in the delayed hypersensitivity reaction. The basis of the immune response may thus be said to have two components:

- (1) *The Humoral Response:* The immune reaction is transferable to another host by injecting serum from the immunized host into the second host; this results in the presence of demonstrable antibodies in the serum of the second host that produce an immediate immune reaction.
- (2) *The Cellular Response:* This is responsible for the delayed hyper-sensitivity reaction with the absence of an immediate reaction and the development of an indurated erythematous reaction in 12-24 hours. This is associated only with protein antigenic stimulation.

Suppression of Immune Response

As surgical techniques for transplantation of tissues and organs have developed to a high degree of perfection, further advance in this field will depend upon the adequate suppression of the immune response to permit acceptance by the recipient of the graft without the rejection phenomena.

Several mechanisms exist at present for inducing suppression of the immune response and in clinical practice they depend upon the summated effect of Azothioprine, Actinomycin C., prednisone, and the use of irradiation. At the experimental level, however, many other mechanisms have been utilized.

- (1) *Immune Paralysis*: Felton (1949) has observed that mice immunized with large amounts of pneumococcal polysaccharide fail to develop serum antibodies to the polysaccharide, and application of these findings to the field of organ transplantation is tempered by the observation that in animals the immune reaction may be paralysed by large antigen excesses resulting in the development of immunity to the antigen after long periods.
- (2) *Body Irradiation*: The destructive effect of irradiation on lymphoid tissue will result in inhibition of induction with appropriate expression of the immune reactions, and irradiation may also be directed towards destruction of the effector cells.
- (3) *Alkylating Agents*:
 - (a) Imuran or Azothioprine is the most useful agent in this regard.
 - (b) 6-Mercaptopurine: This acts by the competitive inhibition of ribonucleic-acid synthesis in lymphoid tissue.
 - (c) Actinomycin C.
- (4) *Steroids*: By inhibiting the inflammatory effector cells, steroids, particularly prednisone, inhibit the development of the primary immune reaction.
- (5) *Surgical removal of reticulo-endothelial activity*:
 - (a) Thymectomy: This removes the regulatory centre for the development and differentiation of the immune apparatus.
 - (b) Thoracic duct drainage: This has been performed experimentally on the basis that it will deplete lymphoid cells.
 - (c) Reticulo-endothelial blockade: The administration of trypan blue or Thorotrast is exerted in order to engage the phagocytic capacity limiting its immunologic function.
 - (d) Administration of alpha globulin is based on the premise that it will provide a coating on the target cells and limit its reactivity, related to the known fact that agammaglobulinaemia results in a failure to make antibody.

Clinical Implications

A new terminology has developed in relation to the science of homotransplantation and it is necessary to appreciate the semantics of the situation.

Types of Graft

- (1) *Autograft*: This is a graft in which the donor is also his own recipient.
- (2) *Isograft*: This is a graft between individuals who are identical in antigenic histocompatibility and is particularly evident in twins.

(3) *Homograft or Allograft*: This is a graft between genetically dis-similar members of the same species.

(4) *Heterograft or Xenograft*: This is a graft between different species of the animal kingdom.

The allograft or homograft reflects the main source of clinical challenge and the tissues concerned fall into two broad categories:

- a. *Allostatic grafts* which do not depend on continued cellular multiplication to provide clinical function, e.g. cornea, bone, cartilage, blood vessels and dura mater.
- b. *Allovidual grafts* whose cells need to grow and reproduce in order for the graft to be functionally effective.
 - (i) Major vascular reconstruction is necessary, e.g. transplantation of kidney, lung, liver, spleen and heart.
 - (ii) No major vascular reconstruction is necessary, e.g. skin, bone marrow, thyroid, parathyroid, adrenal, and ovary.

Organ Transplantation

The greatest clinical experience in this field exists in regard to kidney transplantation. At this time, there are 342 recorded kidney transplants between other than monozygotic twins, and of these cases 35% are alive and 65% are dead. Few of the survivors have lived more than 2 years after their renal transplantation so that only patients with fatal irreversible bilateral renal disease should be considered for this type of transplantation, the usual underlying disease being chronic glomerulonephritis and pyelonephritis. In contrast to this, 75% of cases whose donor kidney came from a monozygotic twin are alive and well.

The transplanted kidney is placed in the retro-peritoneal position in such a way that a left donor kidney is placed in the right iliac fossa so that the end-to-end arterial anastomosis between the renal artery and the proximal end of the divided hypogastric artery is situated anteriorly, and the end-to-side anastomosis between the renal vein and external iliac vein is posterior in position, the ureter being tunnelled through the bladder wall and a mucosa-to-mucosa anastomosis fashioned.

The donor's diseased kidneys are removed to prevent nephrogenic hypertension or infection as well as to reduce the chance of development of the original host's renal disease in the donor kidney.

Although only four human liver transplants have been recorded for such diverse conditions as congenital biliary atresia, cirrhosis and hepatoma, no survivals have occurred, but in the animal laboratory one-stage hepatectomy and canine homograft transplantation is today standard procedure well described by Starzl and Kaupp (1960) and Moore and colleagues (1960) and in my own practice, but its translation into clinical practice still requires the solution of many immunologic and haemostatic problems which are currently outstanding.

To date, human lung transplantation has been performed on two occasions without success, while transplantation of a chimpanzee heart to man was equally unsuccessful.

Splenic allografts have been used in children on two occasions for agammaglobulinaemia without obvious benefit while skin allografts have been used as a temporary dressing for patients with extensive skin loss owing to burns; survival of such cases being prolonged only on patients having agammaglobulinaemia or hypoglobulinaemia.

Bone marrow allogenic transplantations have been used after total body irradiation in leukaemia as well as a mechanism to prevent graft rejection, but at the time of writing does not have a great place in clinical medicine.

Endocrine grafts of thyroid, parathyroid, and adrenal gland as tissue slices, culture tissue, and vascular pedicle grafts to date provide no clinical scope of any importance.

In selecting a donor for histocompatibility in those cases where organ transplantation is indicated certain tests are necessary, and these include:

- (1) A normal lymphocyte transfer test: A monitor is provided as to whether lymphoid cells from the recipient will react against the tissues of the prospective donor when injected intradermally.
- (2) In vitro lymphocyte interaction tests which provide a complementary laboratory test for the transfer test.
- (3) Serologic typing of leukocytes: This provides a test for typing similar to typing of red cells and is at present the basis of a great deal of experimentation in the laboratory.

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