Introduction to the Problems of Tissue Homografts In Man

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In the life of every physician, there comes a time when he sees a patient die of a diseased organ and, at the same time, sees the same healthy organs of other deceased individuals follow them to the grave. This seeming waste of life, has for years occasioned much wistful dreaming and extensive research.

The techniques of autografting are well known and in general are successful. Homografting has been without success except in the case of corneal tissue and cartilage, which are biologically relatively inert, and in the case of homografts between identical twins.

The following terms should first be defined:

Autografts: An exchange of tissue from one region to another site on the same individual.

Chimera: An individual symbiotically harboring the tissues of another.

Homograft: Exchange of tissues between members of the same species.

Implantation: Grafting of the tissue without operative re-establishment of the blood supply.

Isograft: Exchange of tissues between individuals of a highly inbred strain of a species.

Transplantation: Grafting of tissue with operative re-establishment of the blood supply.

THE PROBLEM

The body will react to most foreign material by altering itself in such a manner that it is capable of destroying or neutralizing the invading materials, if the contact is sufficiently prolonged, or at the next encounter. This, of course, is known as active immunity.

In homoplastic skin grafts, if the proper conditions of vascularization are met, the implant for a time remains healthy. Soon, however, this homograft becomes inflamed, leukocytic (particularly plasma cell) infiltration takes place and the vessels are thrombosed, causing the graft to become a necrotic slough. Moreover, if any tissue of the same donor is again grafted into the recipient the graft will slough in an appreciably shorter length of time—and without evidence of having established vascular connections with the host. Apparently, the recipient has in some manner become immune to the donor's tissues.

The mechanism of this immunity is interesting. No serum antibodies have been found which can account for the phenomenon. Berrian and Brent postulate that the antibodies are "cell-bound" and resident in the lymphoid tissues, which experimentally retain their ability to react with the donor's tissues in vitro. The presence of plasma cells and possible serum antibodies would appear to be necessary in the immune mechanism. Patients with agamma-globulinaemia, hereditary or acquired, have a remarkable lack of plasma cells as well. In some of these patients successful homografts have been reported. In Hodgkin's disease and other lymphomas, the development of delay hypersensitivity is defective and prolonged survival of homografts has been noted. This phenomenon has also been noted in patients who are debilitated by such conditions as uraemia. The sequence of events in the immune mechanism is brought to proceed in this manner: Following a graft of foreign tissue, substances diffusing from the graft percolate to the reticulo-endothelial tissues of the body where in some manner they elicit a change in the cells which enables them to migrate to, invade and destroy the graft. It has been further shown that these antigens stimulate the regional lymphoid tissues more than those in more distant sites.

The antigenic structure of the tissue of an individual is genetically determined. It would then seem reasonable that individuals with identical genetic structure, as in the case of monozygotic twins, would freely be able to exchange tissue. Clinically this is the case. In experiments on inbred strains of mice, isografts are permanently successful. The antigenic structure of tissue in mice is determined by at least 15 genetic loci, all dominant, and apparently with multiple alleles. To illustrate this, if we mate two inbred strains, A and B, the progeny will be hybrid, AB. This hybrid will be able to accept from either parent since such a graft will contain no antigens foreign to it. Neither parent can accept a graft from the hybrid, such a graft being sloughed as would tissue exchange between the parents. If the parents were not inbred the experiment would fail. Since the histocompatibility genes are all apparently dominant, and since there are multiple alleles on each locus, the chances of any of the progeny receiving the same genetic makeup as the parent are infinitely small.

An interesting sidelight of this work is the knowledge that not only may the host react against and destroy the graft, but the graft may also harm the host. If we again mate the two strains carrying A and B to produce the hybrid AB, we

see that the graft from parent to progeny can and does react to the foreign antigens found in the host. Experimentally this has produced a picture of a progressive wasting disease which is termed "runt disease" by Billingham.

Fetal tissue, experiments show, are more tolerant of foreign material and apparently are better tolerated by a host.

THE SEARCH FOR A SOLUTION

Since it is not the fate of every man to have an identical twin to supply his spare part, the solution lies in the circumvention of the immune mechanism. Several procedures have been attempted.

In patients with leukemias, destruction of the reticuloendothelial tissues, usually by total body irradiation, and subsequent replacement of these tissues by marrow transfusion from a donor has been tried. Despite the opinion of the lay literature, this procedure has met with no success, and the number of dismal failures is great. Chimeras created in this manner, very often die of a wasting "secondary disease" which is very similar to the "runt disease". It has therefore been suggested that the use of fetal tissues as the replacement infusion might help eliminate this problem. The determination and administration of the proper sublethal dose of radiation is a problem yet to be solved.

Using the same procedure as above, some have attempted kidney transplants as well as bone marrow infusions from the same donor. The problem is compounded and again failure has been the usual outcome.

Endocrine tissues, usually fetal in source, have been used for grafts. These show signs of being successful, though some cast doubt on the survival of such grafts, maintaining that the patients have become adapted to the deficiency and the grafts have in reality died. Experimentally, survival of such grafts has been noted in laboratory animals.

Of the other measures attempted, the use of corticosteroids has been the most frequent, again with little success in humans.

SUMMARY

There is a powerful immune mechanism preventing the acceptance of homografts. The attempts to circumvent this immunity have thus far been on the whole disappointing. The principal hope would appear to lie in the plasticity of fetal tissue.

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