Think

Schematic of antibody molecule shows antigen (striped), combining sites (black), and four protein sub-units.

DOUBLE-EDGED KNIFE

Rejection/Infection

Long before they operated, the surgeons who have performed heart transplants knew that the actual surgery, though tedious and difficult, would be the easy part. What they most feared was the double-edged threat of rejection and infection. These are the two sides of the coin of immune response, the central problem of transplant surgery which is almost as knotty now as when transplants were first thought of.

The body's first and most effective line of defense against invasions of bacteria and other disease-producing organisms and substances consists of the skin and the mucous membranes, which physically block out trouble. Behind the skin lie a variety of bloodborne defense mechanisms the actions of which are more or less immediate. Among these are phagocytic cells, which ingest foreign organisms and then destroy them with enzymes. Other defenses include bloodstream enzymes which destroy certain bacteria, and substances released from some cells which induce fever and thereby make conditions unfavorable for the multiplication of certain viruses.

The defense mechanism next in line is the antibody response. The definition of an antibody is rather circular and vague. It is a protein whose production by the body is initiated by the introduction of an antigen. An antigen, in turn, is identified as the macromolecule which when introduced into the body stimulates the formation of an antibody. Antibodies are synthesized to order for each antigen by white blood cells called lymphocytes. Because they have to be made to order, antibodies appear some time after the introduction of antigens.

There is still much uncertainty surrounding the mechanics of antibody response. It appears that it works as follows: An antigen, be it bacterium, foreign tissue cell, virus, enzyme, or whatever, appears in the bloodstream. There it may be ingested by a phagocyte. If it is, and if it is totally destroyed by the phagocyte's enzymes, that is the end of it. But it may be only modified by the phagocyte, or it may miss being ingested altogether. In the latter two events the antigen floats around in the blood until it runs into a lymphocyte of a certain type.

The lymphocyte that can make the recognition is stimulated thereby into beginning rapid cell division. As division proceeds, the descendant cells' cytoplasm is modified so that the cells can begin antibody synthesis. After eight or ten generations the cells derived from the one that recognized the antigen start producing antibody molecules at the rate of 200 a second. It may take two or three days after exposure to an antigen before an antibody can be detected in the blood.

The antibody, dispersed in the bloodstream, then reacts with the antigen and inhibits or neutralizes its biologic activity. Antibodies are specific to the particular antigen because one portion of the antibody molecule fits a certain site on the antigen molecule like a template or a plug.

Antibodies can also "plug into" molecules in the cell wall of a bacterium or foreign tissue cell. Properly speaking it is this cell-wall constituent that is the primary antigen, rather than the whole cell. When a number of antibody molecules attack a cell in such a way they can set off a complex complementary reaction which destroys first the cell wall and then the cell.

This lysis of foreign cell walls may be the villain in transplant surgery. Most authorities believe that the lymphocytes are responsible for graft deaths, either through producing antibodies or more directly. It has been observed, for example, that these white cells leave the blood vessels and infiltrate the graft in large numbers. Sensitized lymphocytes have been shown in vitro to be cytocidal, destroying cells near them in the culture. It has still to be shown whether this cytocidal ability is due to antibody action or the production of some substance analagous to histamine, or both, or something else altogether.

Dr. Charles A. Hufnagel of Georgetown University Hospital has worked extensively with kidney transplants and now envisions the possibility of transplanting the hearts of specially treated calves into humans. Such a procedure would avoid the ethical and procurement problems of using a human organ, and would eliminate the necessity of doing crash operations: The donor heart could be taken at a time convenient to recipent and surgeons. But if the immunological problems are great in transplanting organs among members of the same species, they double going from one species to another.

Current approaches to the double-edged immune response problem include immunosuppressive drugs, tissue typing and a pair of newcomers:

- Selective suppression of lymphocytes. Lymphocytes appear to exert their greatest influence on foreign tissues, and have been identified as the cells primarily involved in rejection. Granulocytes on the other hand are more involved with fighting infection. One way to suppress lymphocytes selectively is to inject some of the patient's lymphocytes into a horse. The horse develops an antibody against these cells, and horse serum bearing this antibody is then injected into the patient to kill the patient's lymphocytes. Another selective method would be to withdraw lymphatic fluid from the patient's thoracic duct, irradiate it with X-rays, then pump it back into a vein.
- Ribonucleic acid. A new and little understood treatment (SN: 00/00 p. 00) involves bathing the organ to be transplanted with RNA.

Tested only in animals, the treatment has been credited with slowing rejection or preventing it altogether.

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