Enzyme Replacement for Immunodeficiency

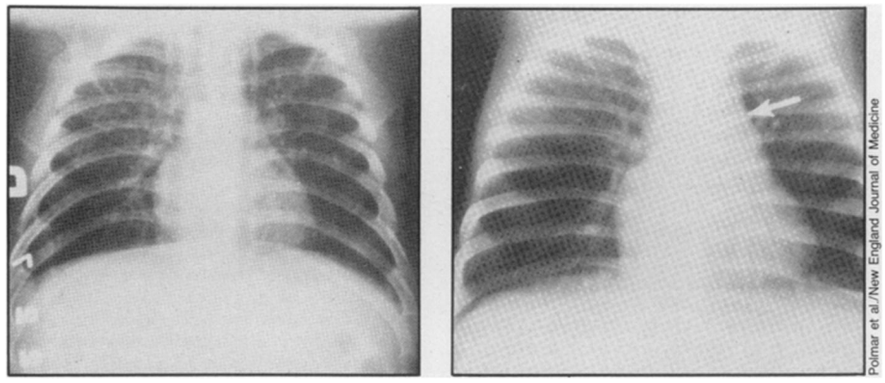
The most devastating of all immunodeficiency diseases is severe combined immunodeficiency disease where an infant lacks both cellular and humoral (antibody) immunity and will rapidly die from infections if its immune system is not reconstituted. Bone marrow transplants can reestablish immunity in such patients, but finding an immunocompatible bone marrow donor is difficult. Transplantation of a fetal thymus has been attempted, but with varying degrees of success. (This gland is essential for the processing of T cells, those lymphocytes that provide cellular immunity.) Patients have also been treated with thymosin, a hormone made by the thymus, or by transfer factor, material that confers cellular immunity. But the results have been equivocal.

Now a promising new treatment looms large for such patients—enzyme replacement therapy. Stephen H. Polmar of Case Western Reserve University School of Medicine and his colleagues have successfully treated one patient with it.

In 1972 Hilaire Meuwissen of the Albany (N.Y.) Medical Center and his colleagues found that a baby who had severe combined immunodeficiency disease also lacked an enzyme in various cells of his body, including those that provide immunity. The enzyme was adenosine deaminase; it catalyzes the breakdown of the nucleoside adenine to inosine. Since then, other patients with severe combined immunodeficiency disease have been found to lack the enzyme. These discoveries suggested that the enzyme deficiency might be intimately involved in the disease and that replacing the enzyme might help correct it (SN: 1/18/75, p. 43).

Subsequently Polmar's group found that putting adenosine deaminase into a test tube with immune cells from a patient afflicted with combined immunodeficiency disease permitted the cells to proliferate and respond to antigenic stimulation. This result further supported the possibility of using the enzyme to treat patients with the disease.

But how should such an enzyme be given? The only clinically successful enzyme therapy to date—enzyme injections into patients with lipid storage diseases—had a serious handicap: The enzymes did not stay long in patients' blood and tissues (SN: 11/23/74, p. 326). So Polmar and his co-workers decided on another treatment that had never been attempted before clinically—injecting enzyme-loaded red blood cells into a patient. Since red cells contain generous amounts of adenosine deaminase and the enzyme is enclosed in cells, they hoped that the enzyme-containing red cells would provide more and longer-lived enzyme material.



X-ray after enzyme therapy (right) shows shadow of thymus where none was before.

They injected red cells with or without blood plasma over four-week intervals into an infant diagnosed for severe combined immunodeficiency disease and lacking adenosine deaminase. His sister had died with the disease at age 13 months. The treatments helped the boy develop a thymus. They increased his T lymphocytes and his B lymphocytes (those immune cells that make antibodies) and improved the lymphocytes' responses to antigens. The treatment also got B lymphocyte synthesis of antibodies underway. The boy is now two years old and has remained well at home for one year in spite of discontinuation of isolation procedures. He continues to receive the transfusion of enzyme-containing red cells at four- to six-week intervals.

How the enzyme restored the patient's immune system is not yet clear. There is reason to believe that the enzyme helped clear immune cells of excessive amounts of the energy molecule adenosine triphosphate (ATP) and, in turn, of excessive amounts of the intracellular messenger, cyclic AMP, since ATP is the substrate for its manufacture. What does appear reasonably clear, however, is that the enzyme cannot get through the membranes of red cells and into cells of the immune system. Instead, adenosine in immune cells migrates into red cells and is catalyzed there by adenosine deaminase.

"Enzyme replacement therapy may provide a way to treat patients with adenosine deaminase deficiency associated with severe combined immunodeficiency disease who do not have histocompatible bone-marrow donors," Polmar and his team conclude in the Dec. 9 NEW ENGLAND JOURNAL OF MEDICINE. They acknowledge that this therapy has some drawbacks. Transfused red cells have a maximum lifespan of only a few months. They are capable of causing hepatitis or an iron overload or of leading to the development of antibodies against themselves since they are foreign to the recipient's body. "Some of these problems," Polmar and his colleagues say, "could be avoided by use of human adenosine deaminase entrapped within the patient's own red cells, provided sufficient quantities of the human enzyme are available and that the half-life of these enzyme-loaded erythrocytes is sufficient to make this mode of therapy practical." □

Rat pancreases survive slow freezing

The biggest obstacle in organ transplants is not the surgery, but rejection of the tissue by the recipient afterward. The surest way to lessen this problem is to transplant organs between persons with similar genetic backgrounds, the best being identical twins. But when someone needs an organ transplant, a genetically similar organ is not often available.

Frozen, genetically-analyzed organs, ready for transplant, would be one solution to this problem. Few cases of successful freezing of mammalian organs, however, have been reported. Now in the November PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES researchers at the Oak Ridge National Laboratory describe a reliable technique for freezing pancreases from rat fetuses. "Hopefully, the approaches used here in freezing pancreases will prove to be useful guides to the successful freezing of other mammalian organs," they say.

To select the conditions for their procedure, Peter Mazur, John A. Kemp and Robert H. Miller relied on recent physical-chemical analyses of cell injury during freezing. After the fetal pancreases were frozen by the chosen technique to either −78° or −196°C for days or weeks and then thawed, the organs successfully synthesized 80 to 100 percent as much protein