Enzyme Replacement for Immunodeficiency

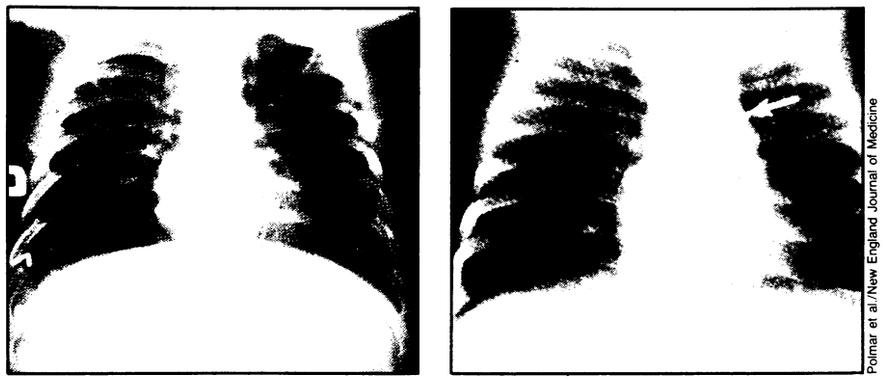
The most devastating of all immunodeficiency diseases is severe combined immunodeficiency disease where an infant lacks both cellular and humoral (antibody) immunity and will rapidly die from infections if its immune system is not reconstituted. Bone marrow transplants can reestablish immunity in such 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

as did fresh, unfrozen organs. Further work with Yoko Mullen, William Clark and Josiah Brown showed that when the thawed pancreases were transplanted into adult rats, they produced insulin and were able to reverse experimentally induced diabetes. Injecting pancreas cells into human patients has already met with some success in treating diabetes (SN: 9/4/76, p. 150).

The most important factor in freezing pancreases, the researchers say, is the slow rate of cooling. Maximum survival of organs occurred when the temperature had been decreased 0.28° per minute, taking more than four hours for the specimens to reach −78°C.

"The best cooling rates to study cell structure may be rapid," Mazur says. "But organ survival is better with slow freezing. The cells dehydrate as they freeze and ice doesn't form inside them. So there is no danger of damage during thawing."

Mazur and co-workers also found that survival of the pancreases required a high concentration of a protective additive, dimethylsulfoxide. As water in a cell freezes, the ions normally present concentrate in the smaller and smaller amount of liquid. High concentrations of salt damage cells, so dimethylsulfoxide may work because it dilutes the ions during freezing.

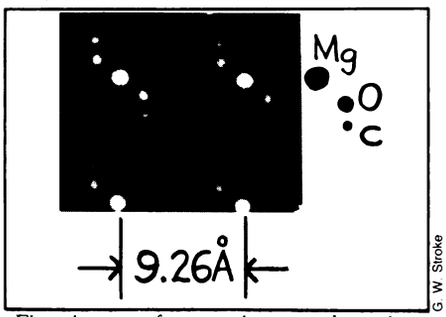
The researchers hope their techniques will lead to future organ banks, storing thousands of genetically classified specimens of essential organs, similar to the banks of frozen blood already common in hospitals around the world. □

Seeing atoms in a crystal

Little by little the once invisible atom is becoming visible—or at least capable of being imaged more or less photographically, generally by highly sophisticated techniques. The latest of such techniques can make images of atoms in a cross section of a crystal. It was developed at the State University of New York at Stony Brook by a group led by George W. Stroke and including M. Halioua, V. Srinivasan and R. Sarma. According to an announcement by the National Science Foundation, the new technique is considered "a major advance in the field of crystallography."

The method combines the oldest probe of crystal structure, X-rays, with optical computation and holography, to produce an image of the locations and relative sizes of the atoms in a crystal. The X-rays yield information in digital form about the locations and sizes of the atoms. This is turned into a visible image by a computer that processes the data and then "writes" a hologram based on the information obtained by the X-rays. This computer-processed hologram can then be treated like an ordinary photographic hologram. Illuminated by laser light of the proper frequency, it will produce the sort of three-dimensional image that holograms are famous for, and the image represents the location of the atoms in the crystal. The NSF says the new method could replace the older method of determining atomic locations by making maps of the electron density in crystals.

One of the first examples is the enlarged image of a magnesium bromide tetrahydrofuran complex. The magnesium atoms show up largest. The smaller pairs on either side of each magnesium are oxygen atoms, and the two smallest and outermost images are carbon. Two full unit cells of the crystal and parts of two others are shown. The actual space between two magnesiums in the crystal is 9.26 angstroms.



G. W. Stroke

First image of atoms in crystal section.

Possible applications of the new method cover the whole range of crystallography, from geology and materials sciences to medicine and molecular biology. Stroke places particular emphasis on the biological aspects of crystallography, saying that the method "provides the scientist with a new tool to help unlock the mysteries of chemical and biological functions of molecules, for example, the functions of antibiotics and the body's natural immunological defenses." □

Seafarer: Cautious approval by NAS

When the Navy announced that it wanted to build the world's largest radio antenna—covering thousands of square miles with a grid of buried cable—environmentalists and others complained that electric and magnetic radiation from the huge project might harm people or animals in the area. After six years of preliminary work and more than 40 separate studies, the issue is still in doubt. Now a committee of the National Academy of Sciences has added its weight to the argument that biological or ecological damage should be minimal.

Called project Seafarer (in an earlier incarnation known as Sanguine), the antenna is designed to improve communication with submarines, which must now slow down and come close to the surface to receive messages. The fear is that within a few years such action would expose them to unacceptable risk of detection, as enemy tracking technology becomes more sophisticated.

Radio signals of much longer wavelengths than those now used would permit contact with a submarine hundreds of feet below the surface, going full speed. But these low frequency waves must be broadcast by proportionally larger antennas.

Three sites are now under consideration for Seafarer: Nevada, New Mexico and the peninsula of northern Michigan. Taking the Michigan proposal as an example, one can begin to comprehend the size of the effort. A cross-hatched grid of two-inch cables, each 30 to 80 miles long, and spaced three to five miles apart, would be spread out across parts of seven counties. A total of 2,400 miles of cable would be required in Michigan and an even larger amount at one of the western sites. Depending on which one site is finally chosen, the entire system would cover between 3,000 and 4,000 square miles.

Those concerned with possible environmental effects of the project cite recent studies that indicate many animals rely on electromagnetic fields for their livelihood. Some birds apparently use the earth's magnetic field as an aid to navigation and some species of fish use weak electric fields to detect and capture prey.

Along most of the cables, the ground-level radiation would be quite small—an electric field only one-third as large as that near an electric light bulb and a magnetic field intensity less than that of the earth's in the region. Near the ground terminals, however, the electric field might be large enough to produce biological effects.

In its preliminary statement based on the study of this data, the NAS committee concludes that "the evidence evaluated so far indicates that at Seafarer frequencies such weak-field effects should not be cause for concern." It did recommend, however, that "additional study of available options with respect to ground terminal design specifications" be considered. A final NAS report will follow later, and the Navy's own environmental impact statement is expected in a few months.

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Another possible application of long-wavelength radio for military communications is also under consideration, but is not being so openly discussed. The scheme would involve a vertical antenna hanging in a roughly 10-kilometer-deep hole. This would set up waves that would be transmitted inside the earth, rather than bouncing off the ionosphere. In principle, rock layers of the earth's crust should act as a waveguide to conduct such waves and they would be practically impossible to jam. Details on how far plans for such a project have gone remain classified. □