Restoring Immunity to Deficient Patients

Immunologists are trying to improve current treatments and devise more effective therapies

by Joan Arehart-Treichel

During 1968, a five-month-old child named David C. was flown from Connecticut to the University of Minnesota. David had virtually no immune system because he lacked the bone marrow stem cells that make the immune system. Like all 12 male children on his mother's side of the family, he was marked for an early death unless something were done, and soon.

At the University of Minnesota, immunology pioneer Robert Good went to work. He and his colleagues found that David and his sister Doreen had identical transplantation antigens on their cells. This discovery suggested that Doreen would be an ideal bone marrow donor for David. Because the bone marrow cells matched, there was little chance that the cells would reject David's body as foreign. So Good and his team took some billion bone marrow cells from Doreen's hip bone. They injected these cells into David's abdomen. They hoped that some of these cells would be the stem cells that David needed in order to develop the immune system he lacked. They kept their fingers crossed that Doreen's bone marrow would not fatally attack David's body.

They won. A new immune system sprang up in David's body. This abundant new supply of immune fighters helped David overcome his many infections. Today David is seven years old and in vigorous health.

The same year, something equally dramatic happened in a nearby state, Wisconsin. A two-year-old boy named David Z. had another serious immune-deficiency disease. This boy had an immune system of sorts, but it had serious defects. His future looked equally grim. Fritz Bach of the University of Wisconsin and Mortimer Bortin of the Mount Sinai Medical Center in Milwaukee attempted to save his life. David Z. was as lucky as David C. One of his two sisters, Barbara, was an ideal bone marrow donor.

David received bone marrow cells from Barbara. David's defective immune system tried to reject the cells. But finally the cells won out. David's body became populated with lymphocytes made by Barbara's cells. With this new immune system, David's infections were overcome. Today he is eight years old and healthy.

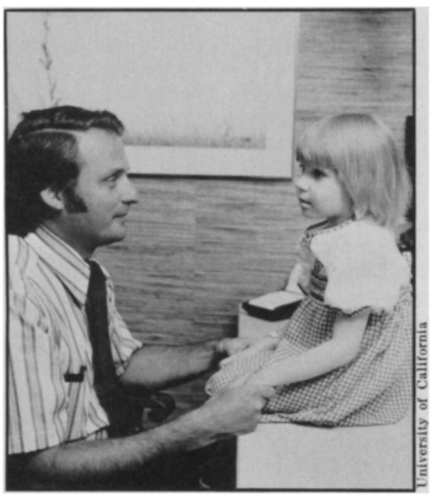
These case histories are gratifying because the lives of two children were saved by the heroic efforts of immunologists. But they are significant for another reason too. They presaged a new era in immunology: restoring immunity to those persons who are immunologically deficient.

Since 1968, immunologists have tried an assortment of treatments for immunodeficient patients. They include bone marrow or fetal liver grafts to restore those stem cells that make the immune system and fetal thymus grafts to restore missing thymuses or missing cellular immunity. Blood fractions that are rich in antibodies are used as treatment in patients who lack sufficient antibodies to fight infections. These treatments have been spectacularly successful in some patients. Yet they have failed in many others. Immunologists are trying to overcome the problems associated with these treatments. They are also trying to better understand the subtle differences between the diseases so they can tailor treatments to these differences.

During the past seven years, for example, 52 attempts to treat immunodeficient patients with bone marrow, fetal liver or fetal thymus, have been reported to the American College of Surgeons/National Institutes of Health Bone Marrow Transplant Registry. Of the 52 patients, only 22 are alive today with functioning grafts. Why did the treatments often fail? One of major reasons was that the implanted tissues and the recipients' bodies did not have the same transplantation antigens. In other words, as in heart and kidney transplants, it was a matter of immunological rejection of incompatible tissues. This is the opinion of Bortin, who is also consultant to the ACS/NIH marrow transplant registry.

Some of these cases of immunological rejection were classical host-versus-graft rejections. In other cases, however, the implanted immunological tissues rejected the patients. This is called graft-versus-host disease. A full-blown graft-versus-host reaction is a frightening thing to observe. It strikes patients in the skin, stomach, liver, lymphoid tissues. It leads swiftly to death unless it is brought under control with drugs.

Immunologists are taking various approaches to solving these two kinds of rejection problems. One approach is to give patients repeated inoculations of small amounts of marrow. The idea here is a sneak-through approach. If



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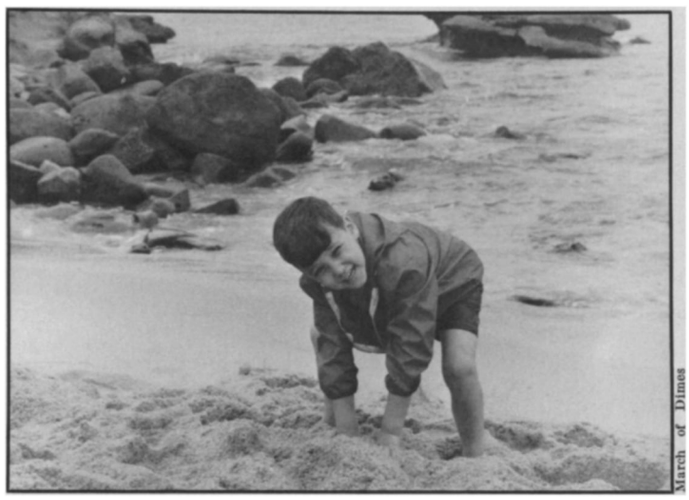
Amman with Heather. Amman and Goldstein gave Heather a thymus hormone, which has enhanced her cellular immunity considerably.



March of Dimes

David C., now in vigorous health, had his life saved by a bone marrow transplant.

marrow is gradually added to a patient's body, then there should be less danger of its rejecting the patient, or of the patient rejecting it. Another approach is to give recipients immunosuppressive drugs until the dangers of rejection are past. But these drugs open patients to the danger of uncontrollable infections.

Joseph Bellanti and his team at Georgetown University Medical School have taken still another approach to minimize the danger of rejection in thymus transplants. They put the thymus into a porous membrane chamber before it is implanted in a patient. The chamber lets substances from T cells escape from the thymus to give the patient cellular immunity. But it also keeps the thymus and T cells from having direct contact with the patient's body and trying to destroy it.

Good, who is now with the Sloan-Kettering Institute in New York City, and his co-workers, are setting up a data bank of potential bone marrow donors for immunodeficient patients. Potential donors are typed for transplantation antigens, and the results are fed into a computer. Then, if a particular patient needs bone marrow, the computer can find a donor with transplantation antigens identical to those of the patient. The chances of finding an ideal donor outside one's immediate family are extremely slim. That is why a large data bank and computer will be so valuable.

The data bank at Sloan-Kettering is being hooked up with others at the University of Minnesota and Duke University and in Holland, Denmark and Sweden. The ultimate aim, says Richard O'Reilly, one of the Sloan-Kettering doctors setting up the bank, "is to get a large cooperative system for potential marrow transplant donors."

Still other approaches, more experimental, are being taken to overcome the rejection problems. A few immunologists, notably Karl A. Dicke of the Radiobiological Institute in Rijswijk, Holland, are trying to separate stem cells from those cells in bone marrow that cause graft-versus-host reactions. They have tried injecting only the stem cells into immunodeficient patients. So far, though, these efforts have not been very successful. Either they have not given patients an immune system, or they have caused a graft-versus-host reaction.

Patricia Bealmear and her colleagues at Baylor College of Medicine in Houston have managed to overcome acute graft-versus-host reactions in animals. They first separate out those fragments of antibodies that attack tissue antigens. They inject the fragments into animals that have received bone marrow fragments. The antibody fragments attach themselves to the bone marrow cells and keep the cells from attacking the animals. However, this approach has not yet worked in preventing long-range graft attacks.

Meanwhile, other immunologists are trying to better understand those diseases for which bone marrow, liver or thymus is given, with an eye toward coming up with more effective treatment. Rebecca Buckley and her colleagues at Duke University have studied 40 patients with combined immunodeficiency disease. They found, contrary to what they expected, that these patients do not lack T and B cells. (B cells are the cells that make antibodies.) Rather, the patients' B and T cells do not function right. Why don't the cells function right? "A defective enzyme may be the key," Buckley suggests.

In 1972, Hilaire Meuwissen of the Albany Medical Center in New York and his colleagues found that one baby who had combined immunodeficiency disease also lacked an enzyme. This enzyme, adenosine deaminase, helps metabolize DNA, the genetic material of cells. Since then, other investigators have found 14 other patients with this disease who also lack the enzyme.

David Z., with his sisters Mimi and Barbara, shortly after Barbara gave him the bone marrow transplant that saved his life. David is now eight years old and healthy (see cover photo).

These discoveries open new treatment possibilities for combined immunodeficiency disease. For instance, malfunctioning B and T cells can now be grown in the laboratory, so it may be possible to find a drug that can correct their defects. Adenosine deaminase therapy might eventually correct the malfunctioning B and T cells. At this time, however, it would be tricky injecting the enzyme into a patient and making sure that the enzyme ends up in the patient's B and T cells, where it is needed.

A treatment that looks promising for defects in cellular immunity is thymus hormone. Alan A. Goldstein of the University of Texas at Galveston and Arthur Amman of the University of California at San Francisco tried this treatment on a frail five-year-old, Heather. Heather had spent most of her young life ill with one disease or another. Her thymus was underdeveloped. Her T cells were not working right. The doctors isolated thymosin, a hormone from the calf thymus. They put this hormone in a test tube with some of Heather's T cells. The hormone imparted cellular immunity to the cells. Then they injected thymosin into Heather for 23 successive days. As they hoped, Heather's T cells started working and fighting off infections in her body. Amman and Goldstein conclude in the Jan. 9 NEW ENGLAND JOURNAL OF MEDICINE that "thymosin probably matures an already existing population of precursor lymphocytes in the patient" resulting in repair of cellular immunity.

Nor are immunologists ignoring antibody deficiencies and ways to help patients with these diseases. Thomas Waldmann and his team at the National Cancer Institute have been studying a disease that causes an underproduction of antibodies. The NCI researchers have found that some patients with this disease have a superabundance of T cells that suppress B cells. As a result, the patients' B cells cannot make all the antibodies that the patients need to fight off infections. "Ultimately we may find drugs to act specifically on these suppressor cells," says Warren Strober, a team member.

The sooner immunologists can advance the treatment of immunodeficient patients, the better. The lives of some little patients are hanging in the balance until that time. A prime example is Baby David of Houston, Texas. For three years now this black-eyed little fellow with a winning smile has lived in a plastic bubble (SN: 5/25/74, p. 335). The bubble protects him against life-threatening infections as he waits for the ideal bone marrow donor to turn up, or for immunologists to find another treatment to counter his immunodeficiencies. □