Transplants treat genetic disorders

Surgical approaches have long tempted physicians dealing with genetic disorders. If only the cells, tissue or organs that carry out the flawed genetic program could be replaced with the normal components, an inborn error of metabolism would be effectively bypassed. Applications of this approach have been limited by the dangers of transplant surgery, especially the problems of graft rejection. Now researchers are optimistic that new methods of preventing immune system attack will allow for amelioration of genetic effects surgically.

Many inborn errors of metabolism should be correctable by transplanting a liver containing normal enzymes, Thomas E. Starzl of the University of Pittsburgh says. He considers the transplants as a form of enzyme replacement therapy. "This concept is so tremendously simple," he says, but its execution has been controversial. Starzl was among a number of researchers speaking in Monterey, Calif., at the Arnold O. Beckman Conference on Genetic Disease.

Liver transplants, although dangerous, have been performed occasionally for more than 10 years (SN: 11/16/74, p. 314). Six inborn errors of metabolism have been treated successfully, if only briefly, with liver transplants, reports Starzl. In the most successful cases, a patient with Wilson's disease has now survived for 11 years and a patient with Alpha-1-antitrypsin deficiency has survived 5 years. In Wilson's disease, copper accumulates in the body; after liver transplants several recipients have had normal copper levels for years. In Alpha-1-antitrypsin deficiency, the liver seems unable to excrete the products of its flawed synthesis, and in some patients liver injury ensues from Alpha-1-antitrypsin accumulation. The product does not accumulate after the transplant.

But the application and exploitation of this technique has been tricky. "We needed better ways to prevent rejection," Starzl says. "The margin between effective and lethal immunosuppression has been too narrow."

Now Starzl describes the use of the fungal drug Cyclosporin A as "a new and advisably revolutionary technology." The drug effectively suppresses the immune system without harming the bone marrow, the source of immune system cells. When Starzl and colleagues at Pittsburgh used the drugs in combination with brief steroid treatment, they had 100 percent 6-month survival of transplanted kidney; the conventional therapy survival is only 60 percent. Cyclosporin A has been similarly successful for transplants of other organs, including the recent dramatic heart-lung surgery. Starzl says the incidence of viral, fungal and bacterial infections is much less than with conventional immunosuppression therapy.

After transplanting 25 kidneys with the new drug regime, Starzl turned again to livers. Using Cyclosporin A, the success rate was high from the start. Approximately 80 percent of all these liver recipients survived at least one year, and of Starzl's most recent liver transplants, 14 out of 15 patients have survived.

Bone marrow transplantation has also been used as treatment for genetic disorders and other diseases. It has been successful in treating 20 otherwise fatal diseases including leukemia (SN: 2/14/81, p. 104), aplastic anemia and severe combined immunodeficiency diseases, which include at least six genetic disorders. Robert A. Good of the Memorial Sloan-Kettering Institute in New York reports that the number of bone marrow transplants performed is increasing exponentially. More than 400 will be done this year.

The use of these transplants is severely limited because the donor must be a relative matched to the recipient in tissue type for the major histocompatability characteristics. A brother or sister is most likely to match (each has a 25 percent chance), but sometimes another relative only partially matched will do. If the donor is not sufficiently matched, the transplanted bone marrow will attack its new host.

"It has been possible to eliminate the remaining major hazard of marrow transplantation," Good now says. He describes a "trick" to allow transplants of bone marrow from a donor whose histocompatability characteristics do not match the recipient's. In the normal immune system some cells arising from stem cells in the bone marrow travel to the thymus gland where they are endowed with the surface markers that confer tissue type. With his new technique, Good separates these marked cells from the stem cells in the bone marrow just before the transplant. The cells with the surface markers can be made to clump together with a soybean compound and with the red blood cells of sheep. "The trick is to get rid of all committed cells, the bad guy cells, and transplant only stem cells," he says.

With this technique Good has been able to perform bone marrow transplants across major histocompatibility barriers in rats, mice and monkeys. In the first clinical trial, Good reports 10 "very high risk" young patients received "totally mismatched" bone marrow transplants from their parents. None suffered a graft versus host reaction. Other laboratories are trying different approaches to eliminating rejection problems occurring in bone marrow transplants (SN: 2/14/81, p. 104). □

Treating the cure: Problems with pesticides

Dockworkers in California prompted U.S. health officials to reexamine hazards of battling the Mediterranean fruit fly, when they refused this month to handle fruit sprayed with ethylene dibromide (EDB), a fumigant known to cause cancer and reproductive defects in animals.

In response to a petition submitted by the workers' union and growing concern among California health officials that federal restrictions of the chemical may be too lax, the Occupational Safety and Health Administration has set up a task force to investigate EDB. Twenty industrial hygienists have been sent to Texas, Florida, California and Hawaii in a 30-day study of the risks to workers exposed to varying levels of the fumigant.

"There exists convincing and voluminous scientific evidence demonstrating [EDB] to be a potent carcinogen at levels far below those allowed under the present OSHA standard," wrote R. V. Durham, director of the Safety and Health Department of the Teamsters Union, in a September 2 petition sent to OSHA. "EDB has also been found to be mutagenic and have adverse effects on male reproduction."

Both OSHA and Environmental Protection Agency officials agree that in high enough doses the 15 million pounds of EDB sprayed on U.S. grain and fruit each year poses a health threat to workers, but where the "acceptable level of exposure" line should be drawn is being debated. EDB is employed as a backup protective chemical to malathion against the Medfly. Current federal standards permit EDB levels in the air surrounding fumigated fruit of 20,000 parts per billion—a standard more than 100 times too high, according to Richard Wade, deputy chief of health for California's OSHA.

"There have been probably 100 to 200 studies done on EDB that all indicate it's a powerful carcinogen," Wade told SCIENCE NEWS. He cited a 1977 recommendation by the National Institute of Occupational Safety and Health and 1980 findings of the National Cancer Institute as evidence that "the existing federal standard is just unconscionable." The state agency set its own maximum acceptable level of 130 ppb on September 23.

Wade suggests more careful flushing of chambers after fumigation, provision of well-ventilated trucks and storage areas for the fruit in transit, and shielding of workers with protective clothing and equipment as measures that could sufficiently mitigate dangers of the fumigant. Four to eight days after fruit is sprayed with EDB, Wade says, evaporation of the fumigant substantially reduces the health risk to a consumer, though traces are detectable in fruit 22 days after fumigation. The greater danger to workers arises, he says, from a build-up of the chemical in refrigerated trucks and storage areas that are often poorly ventilated. □