SCIENCE NEWS of the week

Diabetes Autoimmunity Seen, Stopped

Early use of a potent immune-system suppressor could stop the destruction of insulin-producing cells in diabetics, some of whom may then be able to discontinue insulin injections, according to reports this week on two recent clinical trials. Scientists say the findings, based on studies with the drug cyclosporine, strongly support the theory that diabetes is an autoimmune disease.

At this week's international conference on diabetes in St. Louis, John Dupré of the University of Western Ontario in London presented the results of a clinical trial using cyclosporine to treat type I diabetes. The most severe form of the disease, type I diabetes usually begins during childhood or adolescence, and currently affects about 1 million patients in the United States. Symptoms appear when islet cells in the pancreas stop producing enough insulin to process sugar, and treatment generally requires repeated insulin injections.

In a recently completed study of 188 patients at 12 diabetes centers in Canada and Europe, cyclosporine "unequivocally" increased the rate of remission, Dupré told SCIENCE NEWS. "At one year," he says, "about 25 percent of the patients on cyclosporine are off insulin, compared to about 10 percent on the placebo." The group also noted that patients treated earlier (within two weeks of beginning insulin use) did better, with 30 percent in remission compared to 3 percent of the controls.

These results follow a preliminary study reported in 1984, in which Dupré and his co-workers had found that about half the 41 diabetics tested could discontinue insulin therapy if given cyclosporine, a drug normally used to suppress organ rejection following transplantation. This "unexpectedly high rate of remission" persisted during the year-long study, says Dupré. He adds, however, that because most patients relapsed after cyclosporine therapy stopped, such therapy likely would have to continue indefinitely.

Another clinical trial, at the St. Vincent de Paul Hospital and other institutions in Paris, supports the concept that early intervention with cyclosporine gives better results. The scientists presented their data at the Second International Congress on Cyclosporine this week in Washington, D.C. Of 40 patients given cyclosporine, 27 were able to discontinue insulin injections an average of 48 days after the onset of therapy. The results indicate that those who did not respond had had the disease longer.

Encouraged by such results, some scientists are asking whether cyclosporine therapy should be started immediately after the diagnosis of type I diabetes, to halt additional destruction of islet cells by what appears to be an autoimmune response. But the answer is complex, says Robert E. Silverman, chief of diabetes programs at the National Institutes of Health in Bethesda, Md. He said in an interview that "the data are good, but what they mean is still very much an issue of debate in the [scientific] community."

He is concerned that physicians will treat young diabetics with cyclosporine, which can be toxic and is approved worldwide only for transplantation use and treatment of an eye disease. This, coupled with the probability that cyclosporine therapy in diabetes must continue for the life of the patient, could affect cyclosporine's usefulness in this disease, even though doses given diabetics may be lower than those used following transplants. Silverman compares this use of cyclosporine, with its broad immunosuppression, to hitting "a bull's-eye with a bazooka." This form of immunotherapy for diabetes may be quite practical in the future, he adds, "but probably . . . with a drug more specific to . . . diabetes." — *D.D. Edwards*

THA trials suspended, research probed

Food and Drug Administration (FDA) investigators are looking into the quality of early research on a highly publicized experimental drug for Alzheimer's disease. Clinical trials of the drug, called tetrahydroaminoacridine or THA, were suspended late last month after some patients developed signs of liver toxicity.

Originally reported to improve memory in some Alzheimer patients, THA was considered by many to be the most promising treatment yet for the incurable disease (SN: 9/5/87, p.149). The recent suspension of tests, however, raises doubts about the drug's ultimate potential. And allegations that the original research results were embraced prematurely may temper the current movement for speedier approval of experimental drugs.

"It illustrates a problem," says Paul Leber, head of the FDA's drug review division for neuropharmacological drugs. On the one hand, the agency is under pressure to speed the approval of drugs that show signs of effectiveness against incurable diseases. On the other hand, he says, referring to the new findings of liver toxicity, "I'm glad we had only 50 or so patients in this trial, and not 50,000."

The federal government last month initiated the clinical trials jointly with Warner-Lambert Co. of Morris Plains, N.J., following the publication last November of research in the NEW ENGLAND JOURNAL OF MEDICINE. That research, by Arcadia, Calif., psychiatrist William K. Summers and his colleagues, found significant THA-associated memory improvement in Alzheimer patients. The new trials, which were designed in part to determine what dosage levels might be appropriate for use against Alzheimer's, were to include more than 300 patients. Fewer than 50 were treated before the trials were suspended, after liver enzymes in some patients became elevated from 6- to 20-fold — a "substantial signal" of liver toxicity, Leber says.

Liver damage is not uncommon in clinical trials of new drugs, and in many cases is reversible. Indeed, previous trials with other experimental drugs have been restarted after patients' enzyme levels returned to normal, Leber says. But those elevations were generally less severe than the levels encountered with THA, he adds, and there is some concern that the liver damage might be occurring at drug concentrations lower than those necessary to treat Alzheimer's.

The suspension of trials follows months of controversy regarding the methodology and conclusions of Summers's original research. The June 18 NEW ENGLAND JOURNAL OF MEDICINE ran five letters critical of the research and raised questions regarding his involvement in a for-profit corporation that had started offering experimental THA treatments for $12,000 per year. Summers replied in the same issue that a nonprofit entity is being incorporated to take over the business of providing such treatments.

The FDA investigation into Summers's work has reportedly been going on for several months.

Marshall Molloy, manager of media relations for Warner-Lambert, says his company has for some time been aware that "there was a level of discussion" within the FDA concerning Summers's work. Nevertheless, he says, "Given the total body of evidence, we believe that continued interest in the drug is warranted."

Leber, too, doesn't discount the possibility that THA may progress to further trials. However, he says, nothing more will be done until the liver toxicity problems are better understood. "There's no rush," he says. "This drug is no miracle." — *R. Weiss*