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Putting Up with Self

Critics warned of bad experiments and false hope. But Denise Faustman seems to be right about a strategy to regrow insulin-making cells killed off in diabetes

By Philip E. Ross

- Showed that the insulin-producing function of islet cells may be restored in type 1 diabetes. Later she presented data for true islet regrowth and suggested that transplanted spleen cells convert to functional islets.
- Type 1 diabetes results from an autoimmune attack on islet cells, as distinct from type 2 diabetes, in which the body becomes resistant to the effects of insulin.

Five years ago Denise Faustman stunned the biomedical world--and not in a good way, it seemed. She declared that she had cured diabetic mice by getting them to regrow their insulin-producing beta cells, a finding that, if it could be translated to humans, would spare the million-odd Americans with type 1 diabetes their daily needle pricking and insulin dosing. Since her announcement, the academic establishment has given Faustman little money and a lot of flak. Researchers complained that they could not replicate the experiments and that the Harvard Medical School researcher had cruelly raised hopes that would only be dashed.

Faustman's vindication, however, finally seems to be at hand. In March three groups reported separately in *Science* that they had repeated Faustman's protocols and reproduced her most important result, stopping the disease process in about half their mice and getting the animals to recover normal function. "The results are fantastic, coming from these groups, which were each paid $1 million to spend three years showing that I was wrong," she remarks. "I mean, they were all funded by the JDRF."

The Juvenile Diabetes Research Foundation, the leading nonprofit source of research money in the field, had declined to back her work. The foundation states that it cannot fund all the research proposals it receives, but Faustman says that it had bowed to the tyranny of preconceived notions. Until recently, she says, it was taken for granted that once the beta cells are lost, they can never grow back. She had to go instead to a

foundation set up by Lee Iacocca, the former chairman of Chrysler Corporation, whose wife died of diabetic complications. In total, Faustman has raised $11 million and is preparing preliminary human trials of an adaptation of her mouse therapy.

The 50-year-old Faustman says her work also undermines an important rationale for a favored subject of diabetes research, embryonic stem cells. The hope has been to get these stem cells to turn into beta cells and thereby furnish an ample supply of the scarce tissue. The JDRF and many diabetes activists support research on such stem cells, but the Bush administration has curtailed federal funding for it after coming under pressure from some conservative and religious groups.

Faustman got her idea by chance while transplanting islets, the pancreatic bodies that contain beta cells, from normal mice into others that had lost theirs to type 1, or juvenile, diabetes. In this form, the immune system mistakenly attacks its own islets as if they were foreign invaders. Such autoimmunity--or inability to tolerate "self"--impairs the islets' function and eventually kills them. Patients must then inject insulin many times a day to control the fluctuating level of glucose in their blood.

To suppress the autoimmunity, Faustman injected mice with a cocktail of bacterial irritants called Freund's complete adjuvant, which made their bodies churn out a signaling chemical called TNF-alpha. This compound destroyed the activated immune cells, particularly those that targeted islets, so that when a surgeon implanted islets on the kidneys of each mouse, the transplants could take root, make insulin and restore normal blood sugar control.

That was when Faustman took a trip to the land of Serendip. "I wanted data for a figure showing how the blood sugar went up again after you take out the kidney with the islets in it," she recalls. The kidneys of two mice were removed, and "the day after the surgery, the mice were about 110 [milligrams of sugar per deciliter of blood--a normal reading], and both the animals were running around in the cage." In a 2001 paper she concluded that the mice had grown new islets.

Unfortunately, the cure was not permanent: the bad immune response returned. To eliminate the problem for good, Faustman borrowed an idea from the transplant specialists, who have found that liver or spleen cells can "reeducate" a graft recipient's immune system to treat the graft as native tissue. Here spleen cells from a nondiabetic mouse would teach a diabetic immune system how to be nondiabetic.

The ploy worked, and Faustman reported her results in *Science* in 2003. Her assertions provoked the criticism of a number of prominent researchers, including two Harvard - colleagues, Diane Mathis and Christophe Benoist. They wrote to the *New York Times* criticizing an appreciative report the paper had run on Faustman, and although the paper declined to publish the letter, a version circulated in the diabetes community.

Yet William Ahearn, spokesman of the Juvenile Diabetes Research Foundation, says it was the 2003 paper that attracted the foundation's interest. The JDRF was "particularly excited" by what Faustman now describes as a secondary finding: the evident conversion of some spleen cells into beta cells. Spleen cells are easier to come by than beta cells, and if they could do the job, Ahearn says, the JDRF wanted them. That is why it funded the three groups to repeat Faustman's work.

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Despite the positive results they announced in March, the three teams--from the University of Chicago, Washington University in St. Louis and the Joslin Diabetes Center (which included Mathis and Benoist)--nonetheless harbored doubts. They all sounded three sour notes: that they had cured only about half of their mice; that they did not know whether the mice had grown new islets or merely revived dormant ones; and that they had found no evidence that spleen cells had converted to beta cells.

But data announced this past June may allay those uncertainties. At the annual meeting of the American Diabetes Society in Washington, D.C., researchers from the medical schools of Keio and Osaka universities reported that they had substituted a tumor-

derived islet for Faustman's spleen cells. Because these islets carried the kind of peptide that spleen cells use to reeducate the immune system, they were able both to control blood sugar and to end the autoimmune response. The proof came when the tumor-derived islets died off and the mice remained healthy. They must have grown beta cells of their own.

A second group, led by the National Institutes of Health, reported curing seven out of eight mice not only of diabetes but also of Sjögren's syndrome, an autoimmune disease that attacks the salivary glands. The investigators demonstrated robust new growth of islets and their saliva-making equivalents, and by a painstaking procedure, they proved Faustman's final proposition--that spleen cells had converted to both islets and salivary tissue. Éva Mezey of the NIH did the job by staining the same slice of tissue in two ways, once to pinpoint the secretion (either of insulin or of saliva) and a second time to pinpoint the male, or Y, chromosome. Because the donors of the spleen cells were male and the recipients female, any cell with the Y chromosome must have started out as spleen.

Success in rodents, however, has so far not translated to humans. Researchers tried Faustman's therapy in patients with type 1 diabetes in Israel, using a TNF stimulant called BCG, which is much milder than Freund's complete adjuvant and has a long history of use in humans. The initially promising results failed to find confirmation in later trials in Canada and the U.S., a failure Faustman's critics have been quick to point out.

"But once we knew the mechanism," Faustman counters, "we went back and looked at the data and saw that the BCG dosage in Israel was 50-fold higher" than in the later trials. She says getting the correct dosage is all-important and plans to develop a biomarker to show whether the BCG is having even a subtherapeutic effect on the immune cells that target islets.

Faustman, who plans to test a version of her therapy herself in the clinic next fall, dismisses the criticism heaped on her work. "A lot of groups are working on this now," she says. "If imitation is the best form of flattery, then I'm flattered."