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After Initial Rejection, Scientists Back Work On Cure for Diabetes

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When Denise Faustman announced that she had cured mice of diabetes, funders didn't exactly beat a path to her door, and colleagues didn't shower her with hosannas.

To the contrary. After her 2001 breakthrough, Dr. Faustman, an associate professor of medicine at Harvard Medical School, couldn't interest drug companies or the Juvenile Diabetes Research Foundation in supporting the bold next step she proposed: testing in people a version of what cured the mice.

When she published a similar study two years later, reaction from colleagues wasn't much better. Two fellow Harvard diabetes experts sent a letter to the New York Times, which had run an article describing Dr. Faustman's work, calling the claim that she was the first scientist to cure diabetes in mice "patently false." They also apologized to people with diabetes "on behalf of Dr. Faustman" for "having their expectations cruelly raised." JDRF, getting flak for not funding her, circulated the (unpublished) letter to show that the scientific verdict on her results was far from unanimous, explains spokesman William Ahearn.

But JDRF did approve grants to three competing teams, including one led by an author of the critical letter, to attempt to replicate Dr. Faustman's work. Now all three are announcing they have confirmed the aspect of her study that is the basis for a clinical trial planned at Harvard. By keeping the mice's immune system from destroying their insulin-making beta cells, the three report in today's issue of the journal Science, they got beta cells in some (but not all) of the animals essentially to come back from the dead, curing their diabetes.

In the three studies -- from the University of Chicago, Harvard and Washington University -- about one-third of diabetic mice were cured. They had normal blood-sugar levels even though they had only a few beta cells. "Autoimmune diabetes can be reversed," the Chicago team says. It isn't clear why only some mice were cured, but scientists are working on getting higher response rates, says Chicago's Anita Chong, who speculates that tweaking the treatment might help.

Biomedical science has a long history of mouse cures that never become human cures, but this one may be different. The mice had long-established diabetes, due to the same mechanism that causes Type-1 diabetes in people: the immune system's destruction of beta cells. Without enough functioning beta cells, there is too little insulin to keep blood sugar in check. That can lead to blindness, kidney failure and amputations. Although a number of treatments keep mice from

developing diabetes, "few can induce its reversal," wrote Dr. Chong's team.

In the 2003 study that the three labs tried to confirm, Dr. Faustman and colleagues gave diabetic mice a compound that destroys killer T-cells. They also transplanted cells from the spleens of healthy mice into diabetic mice. The transplants bloomed into beta cells, they reported.

That suggested the spleen contains adult stem cells that can morph into specialized cells. Dr. Faustman attributed the cure largely to this, landing her smack in the middle of the stem-cell debate. The juvenile diabetes foundation and a number of scientists argue passionately for research on human stem cells obtained from embryos. Some who oppose that research for ethical reasons talk up the potential of adult stem cells.

None of the three teams found that transplanted spleen cells differentiated into beta cells. "Denise Faustman was extremely helpful to us in duplicating her protocol, but it's possible we did something wrong, and so can't absolutely rule out the possibility that the spleen contains stem cells that can become beta cells," says Chicago's Louis Philipson.

For patients, it may not matter. Harvard's David Nathan will soon launch a clinical trial, funded with some of the $11.5 million grant the Iacocca Foundation gave Dr. Faustman when others turned her down. It will not use spleen cells. It will inject diabetic volunteers only with a compound called BCG; like the one given to mice, it stimulates the immune system in a way that eliminates T-cells that attack beta cells. With the T-cells gone, they hope, surviving or regenerated beta cells will yield enough insulin to reverse diabetes.

That a diabetes-ravaged pancreas contains enough beta cells to support a cure is arguably better news than finding that spleen-cell transplants are key. Harvard's Diane Mathis and her colleagues discovered that even in mice with long-established diabetes, there is "substantial beta-cell mass, which can be rejuvenated/regenerated to reverse disease." If so, then cell transplants, from cadavers or embryonic stem cells, wouldn't be necessary. But she cautions that earlier trials of BCG have failed.

"The good news is that all three groups cured mice as we did," says Dr. Faustman. "They showed that it was due to regeneration in the pancreas, and that's the beauty of it: The animals' own pancreas did this."

She still thinks transplanted cells from the spleen might produce beta cells. "The pancreas is too smart to cure itself in only one way," she says. "I think there will be many sources of regeneration, and we're only at the beginning of understanding what they are."

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