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A HISTORY OF BEING INNOVATIVE AND FUN



Dr. Denise Faustman attempts to understand why autoimmune diseases come in clusters. (Jonathan Wiggs/Globe Staff)

By Billy Baker, Globe Correspondent

Had the mice she'd been studying for two decades been deaf all along? If Dr. Denise Faustman's latest hypothesis was correct, they would have had to be. So she conducted a rather unscientific experiment: She went into her lab and had an assistant clang pots and pans together next to their ears. The mice never heard a thing.

Those deaf mice - a normal weight, diabetic strain that have been a staple for autoimmune researchers for decades - were just part of a bigger theory that she thinks researchers have been missing all along. In a new paper she co-authored, Faustman argues that organs involved in autoimmune diseases such as diabetes and multiple sclerosis play an accomplice role in the diseases' onset. The theory challenges the long-held belief that autoimmune diseases are caused solely by a defective immune system.

While this latest study is generating attention, it's nothing compared to the brouhaha - and personal attacks - that clanged through the medical community the last time she proposed a paradigm shift in the way we think about autoimmune disease.

In 2001, Faustman said it was possible to cure type 1 diabetes in mice with a two-step treatment that blocked their immune systems from destroying their insulin-making beta cells; new beta cells then grew back, and the mice were

no longer diabetic. After her announcement, many in the medical community - including some of her own Harvard colleagues - lashed out at her findings, and accused her of cruelly raising the expectations of those suffering from the disease.

Instead of funding her proposal to test the theory in human clinical trials, the Juvenile Diabetes Foundation bankrolled three independent studies to test her results.

By 2006, those studies were in. And it turned out that Faustman was right.

Now, a colleague at Massachusetts General Hospital, Dr. David Nathan, is set to attempt to transfer her work to humans.

If the trials work - well, Faustman doesn't want to speculate. Medical history is filled with treatments that have worked in animals but failed to translate to humans.

On a recent day, she chose to talk instead about the new paper, published in the journal *Immunology and Cell Biology*; this one, she expects, will go down easier than the last.

"It's just basic science," she said of the study, which was an attempt to understand why autoimmune diseases come in clusters; having one can make you more likely to get another. It was known that patients with type 1 diabetes also have high rates of Sjogren's syndrome - an autoimmune disorder that attacks the glands that produce tears and saliva - and conditions associated with hearing loss and tongue abnormalities.

Before, researchers were convinced that the immune system's misfiring was causing these collateral problems. Faustman's team wondered - and proved with the mice - that these related organs were abnormal before autoimmune disease set in.

She concluded that the target tissues themselves are accomplices in the onset of autoimmune disease, at least guilty "of second-degree murder," as Faustman put it.

"This study is just fun science," she said. "The lightbulb has gone off, and hopefully now people will start digging into the developmental biology on these tissues."

Faustman, who turns 50 this year, is director of the immunobiology lab at Mass. General and an associate professor at Harvard Medical School. She doesn't look the part of a steely crusader.

She's small, perky and has a chronic case of the giggles, which poured out of her as she explained why she decided to become a doctor.

"I hated my pediatrician," she said. "I thought he was way too serious. So I thought, 'I'll become a doctor and change this stern image.'"

At Washington University in St. Louis, Faustman enrolled in an MD/PhD program, and studied with Paul Lacey, who was working on a plan to fight diabetes by transplanting insulin-producing islet cells from a donor pancreas into a patient. "I thought diabetes would be cured by the time I finished my PhD," she said.

When it wasn't, she came to Boston in 1985 to do an internship and residency at Mass. General - still sticking with the plan of becoming a less-stern practicing physician. During a rotation through a diabetes clinic she came upon a patient with a foot ulcer.

"I picked up this woman's leg and there was this huge crater," she remembered. "And I knew immediately that she was going to lose her leg. I knew this woman cared for foster kids, and that would probably be over when she lost her leg. So I said, 'What am I doing? I'm just sitting in this clinic looking for bad things with no way to change the bad things.' Two weeks later, I was back in the lab for good."

Eva Mezey, the head of the adult stem cell unit at the National Institute of Dental and Craniofacial Research, and a long-time Faustman supporter, said she deserves credit for taking the heat and standing by her research. "The gist is that she was right, and she really is on a pretty strong path to doing something about diabetes that hasn't been done before.

"Her idea cost her a lot. She made some big enemies on the way. But she's a tough scientist, and she went after what she thought was right."

And if her idea fails in human clinical trials, Faustman said that's something she can deal with, because she believes that without that risk there will be no big reward.

"There's little motivation in the research world to translate back to humans," she said. "If you put your neck out to translate, everybody is going to know when you fail."

"But," she added, "that's why I left the clinic for the lab."

FACT SHEET

Hometown: Royal Oak, Mich.; lives in the Back Bay.

Family: Her two sons, James, 15, and Morgan, 13, are students at Dexter Academy.

Education: Received a bachelors degree in zoology and chemistry from the University of Michigan in 1979; earned an MD and a PhD in molecular biology from Washington University in St. Louis in 1985.

Hobbies: She enjoys rowing on the Charles River with her sons. "I like to think of it as a cross between yoga and swimming. You listen to the water, and it's very tranquil, but if you don't focus, you're going into the Charles," she says.