

Miracle unfolds for diabetic girl

Genetic discovery allows 6-year-old to swap insulin pump for readily available pill

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When Lilly Jaffe, 6, gleefully disconnected her insulin pump from her hip last month, her mother, Laurie, forced herself to be brave.

Lilly was cutting the lifeline to the hormone that had kept her alive since she was a month old. That was when she was diagnosed with Type 1 diabetes, meaning she would always need insulin injections.

But thanks to advances in molecular medicine, doctors had reason to believe that Lilly could be weaned off the shots. Because scientists recently had identified the genetic mutation that causes her condition, they knew why her body was not making insulin and they had a way to fix it: a readily available drug.

Now Lilly no longer needs insulin shots to control her blood sugar. Instead, she takes five sulfonylurea pills twice a day.

"Our family is watching a miracle unfold," Jaffe said. "For me, the simple act of removing the battery from her pump and putting it away in a drawer was surreal."

The kind of diabetes Lilly has is rare, so the discovery will help relatively few children. But scientists say it is an example of how genetic discoveries are beginning to allow doctors to treat the root causes of a disease instead of its symptoms.

Constant monitoring required and for families like Lilly's, the benefit is life-changing.

"We could never let our guard down, having to monitor her closely and constantly," said Jaffe, who lives in the north suburbs. "That meant glucose checks 10 times a day, even at night, and three to five daily insulin injections, not to mention analyzing every bite she ate."

Two years ago, Lilly had two nighttime seizures caused by low blood sugar. "It's sobering dealing with that kind of fragility and intensity day after day," her mother said.

"Now, though, she's so proud, so happy, so excited. She's just thrilled, for the first time, to be like her friends and her brother and sister."

Diabetes affects an estimated 20 million Americans, and the number is growing by 1.3 million new cases a year. It is the leading cause of blindness, end-stage kidney disease and amputations.

Between 90 percent and 95 percent of diabetics have Type 2, in which the body fails to use the insulin it makes. This type often can be controlled by close monitoring, weight control and oral drugs, including the sulfonylurea class, developed decades ago to enhance insulin secretion for Type 2 patients.

In Type 1 diabetes, which affects about a million Americans, the body stops producing insulin and it must be supplied by injections. Most cases result when the body's immune system destroys its own insulin-producing cells in the pancreas.

In rare instances, such as with Lilly, the insulin cells are intact, but a genetic mutation prevents them from working. The sulfonylurea drugs correct that defect.

"As long as they take their pills, it's like trading a severe case of Type 1 diabetes for a mild case of Type 2," said the girl's physician, Dr. Louis Philipson, director of the Comprehensive Diabetes Center at the University of Chicago. "It's comparable to swapping influenza for the sniffles."

The mutation was first identified by a research team led by a British researcher, Dr. Andrew Hattersley of Peninsula Medical School in Exeter. Over the last two years he has studied the genes of patients diagnosed with diabetes before the age of 6 months.

In a study published in the *New England Journal of Medicine*, Hattersley and colleagues showed that nearly half of these patients have a mutation in one of two critical genes that work together to form a channel, or valve, that regulates the flow of potassium ions in and out of insulin-producing cells.

Normally, as glucose from food builds up in the bloodstream, the channel is cut off, causing potassium to accumulate in the cells. That, in turn, triggers the opening of another channel, for calcium. As calcium ions flow into the cells, they respond by secreting insulin.

The mutation--thought to affect as many as one newborn out of 200,000--causes the potassium channel to remain open regardless of blood sugar. As a result, insulin secretion is drastically reduced, to undetectable levels in Lilly's case.

This new understanding of the process at the molecular level convinced researchers that they could fix the chemical short-circuit. Hattersley showed that sulfonylurea drugs help close the potassium channel when needed, allowing cells to respond to glucose levels and make insulin.

Philipson's colleague Graeme Bell, a professor of medicine and human genetics at the U. of C., has been tracking down diabetes genes since 1990.

"We thought [Type 1 diabetes] was one disease, but if you look at it really closely, it turns out to be much more complicated, and knowing the genetic and molecular causes in an individual, you end up treating it in a radically different way," Bell said.

Lilly is the fourth person to be treated this way in the U.S. and one of fewer than 100 in the world. But researchers suspect about 2,000 people in the U.S. have her kind of Type 1 diabetes and could benefit if diagnosed and treated early in life.

"The kids are treated with insulin, they're doing just fine, and that's that," he said. "The case never gets revisited."

When Bell suggested that Lilly get tested for the genetic mutation, her family tried not to get its hopes up.

"Lilly spit in the cup and we sent it back and tried to forget about it," Jaffe said. "This disease is an emotional roller coaster. We were determined not to get excited."

When the DNA test came back positive, things began to move swiftly. Lilly was admitted to the U. of C.'s Clinical Research Center on a Monday, "and we began to give her low doses of sulfonylurea and gradually reduce her insulin," Philipson said.

Lilly was scared at first; she had to stay in the hospital while everyone focused on her, constantly testing her blood and adjusting the insulin level as successively larger doses of the oral drug took effect.

"By Friday, she was skipping down the hallway," Jaffe said.

Lilly now has the freedom to be a normal, active child. She can go to sleepovers or play dates without mom coming along to do blood sugar tests and operate her pump. She can eat snacks without counting carbohydrates or testing her blood. The Jaffes don't even keep insulin in the house anymore.

"We hope and pray that Lilly's story will bring hope to all those who suffer with diabetes," Jaffe said.