For a Few Thousand with Diabetes,

A Significant Breakthrough

A recent discovery has shed light on a rare genetic condition, that will allow some people living with diabetes to unlock the ability to produce insulin naturally. While most of the millions of people living with type 1 diabetes will not be able to make the switch from insulin to a simple pill regimen anytime soon, there are thousands who have been told they have type 1 diabetes, for whom an accident of genetics is making the dream of insulin independence possible. >>

PHOTOGRAPHS BY STEVEN E. GROSS

Diagnosed with type 1 diabetes when she was just one month old, Lilly Jaffe spent the first years of her life getting used to insulin shots, frequent glucose checks, and the concern of her parents over her meals and whether she'd sleep through the night. The family quickly learned the daily issues familiar to any household living with diabetes.

Things improved when Lilly began using an insulin pump, her mother, Laurie, reports. But for the first years of the young girl's life, "There wasn't a night when Lilly or I slept through the night," Laurie says. She and her husband, Mike, were constantly on high alert with regard to Lilly's diabetes, along with every other responsibility required in a household of five—Lilly (now 7 years old) is the second of three children: older brother Nathan is 9, and younger sister Charlotte is 5; none of the other family members have diabetes.

These numbers may seem small, but they are significant—not simply because every sick child deserves compassion and care, but because the cases of monogenic diabetes are linked biologically to the overall type 1 diabetes population.

By the time Lilly was one year old, the Jaffes had become active members of JDRF's Illinois chapter, and therefore kept themselves up to date on research news, followed developments concerning potential treatments and clinical trials, and attended scientific presentations to hear about the latest developments first-hand.

In June 2006, Mike attended the chapter's annual meeting and was listening to one such research seminar by Dr. Louis Philipson, an endocrinologist at the University of Chicago.

Near the end of his talk, Philipson touched briefly on several different projects in the field, including work by a former colleague of his that was about to be published in the *New England Journal of Medicine*. Dr. Andrew Hattersley at the University of Exeter's Peninsula Medical School in the U.K. had found that people with a single-gene mutation who were diagnosed with type 1 diabetes before the age of six months were able to stop their insulin intake, thanks to a sulfonylurea drug known as glyburide, which is used regularly for type 2 diabetes.

Mike Jaffe was intrigued, and explained the details of his daughter's diagnosis to Philipson after the presentation. What was about to happen to the Jaffe family seemed so unlikely, and was to happen so quickly, that the family can't help but remember the exact date it all started: June 26, 2006.

THE DISCOVERY

For the past several years researchers have been investigating the likelihood that cases of diabetes diagnosed within the first six months of life are not type 1 diabetes, but are a form of monogenic diabetes (meaning a single gene is affected; type 1 diabetes is known to involve multiple genes). These diagnoses are very rare: monogenic forms of diabetes account for only one to two percent of all cases of diabetes in young people.

Researchers have identified three types of monogenic diabetes as the most common: permanent neonatal diabetes (PND) and transient neonatal diabetes (TND), as the names suggest, occur in the first six months of life. The third common type is maturity-onset diabetes of the young (MODY), usually detected in children or adolescents.

Further, there are several forms of each of these three types of monogenic diabetes. Dr. Hattersley and an international research team studied the most common type of permanent neonatal diabetes, which is caused by a mutation in the gene KCNJ11. In 2004, Hattersley's team found that this mutation accounted for up to half of all cases of PND.

(To clarify how rare this type of diabetes is: incidences of KCNJ11 mutations represent half of all cases of PND, which is one of the three main types of monogenic diabetes, and monogenic diabetes occurs in 1 or 2 out of every 100 cases of diabetes in the young.)

These numbers may seem small, but they are significant—not simply because every sick child deserves compassion and care, but because the cases of monogenic diabetes are linked biologically to the overall type 1 diabetes population. By focusing on unusual, monogenic forms of diabetes, Dr. Hattersley's lab has had a chance to explore key biological pathways in depth, pathways that may be implicated in the disease more broadly. The insights he has gained thus far have indeed revolutionized treatment for a small group of young patients who possess a very particular genetic quirk.

Hattersley's latest study focused again on KCNJ11. The gene mutation causes a disorder in a particular part of the surface of insulin-producing beta cells. This part of the cell, a potassium channel, plays a role in the chemical and electrical chain reaction that occurs when beta cells react to glucose, a chain reaction that ends with the cell's release of insulin. In people with the mutation, the potassium channel doesn't function correctly (it stays open when it should be shut), the chain reaction is halted, and insulin can't be released from inside the cell.

Without insulin being released into the bloodstream, it's easy to see why doctors would think a patient, even a newborn, had type 1 diabetes. That's how children like Lilly Jaffe were diagnosed.

"Once we understood the link between the gene and this particular pathway in glucose metabolism," says Dr. Hattersley, "we

Approaching one year of Lilly being insulin-free, Laurie Jaffe recalls how it all started:

When Lilly was diagnosed, JDRF reached out to our family before we could even contact the foundation. We were touched to receive the Bag of Hope with the teddy bear! Our hearts were warmed by the concern of so many at JDRF and those friendships have continued.

We were unexpectedly blessed last year. It has been an amazing experience, one that we believe will be shared one day by everyone who lives with diabetes. We are grateful to have shifted from a constant state of "high alert" to trusting that we don't have to worry about highs and lows. It has been an adjustment to accept that Lilly's body can now do what it wasn't able to do before.

During her treatment, Lilly asked if her friends with diabetes and her cousin (and now cousins–a second was recently diagnosed) will "go off their pumps too." It was heartbreaking to explain why they could not.

Our only regret is that everyone can't share in this particular breakthrough. Lilly's cure is only one piece of the diabetes puzzle. But thanks to JDRF, there are talented and dedicated researchers working to find those other pieces. Our family is more committed than ever to JDRF and funding research that will bring cures for our nieces and many friends who still battle diabetes.

If it weren't for JDRF, who knows when we would have found out about the cutting-edge research that helped our daughter? Research is making a difference... Lilly's cure is proof of that.

The Jaffe Family: Mom Laurie, Dad Michael, Nathan, Lilly and Charlotte

knew we were onto something important. For those with the mutated gene, we thought sulfonylurea therapy might help close the channel and restart insulin production."

"We hope and pray that Lilly's story will bring hope to all those who suffer with diabetes," said Lilly's parents. "This was Lilly's unique cure but there are many other cures on the horizon."

The study results showed that 90 percent of the patients given sulfonylurea to close the potassium channel were able to stop their insulin intake, lower their HbA1C levels after three months of treatment, and maintain improved glycemic control for one year.

"Our hypothesis turned out to be sound," Hattersley adds. "We benefited from insights and strategies borrowed from pharmaco-genetics, a discipline that connects the dots between genetic discovery and response to treatment."

For more information on testing for monogenic diabetes, visit:
www.monogenicdiabetes.org
www.diabetesgenes.org

CHANGE COMES OVERNIGHT (NEARLY)

When Dr. Philipson heard Mike Jaffe's story, the family was preparing to leave for a trip. A DNA test was sent to the family home; Lilly spit into a small, contact lens-sized container, and the package was shipped back to Dr. Philipson's lab the same day. "We were hopeful, but not very expectant," Laurie explains. On July 1 they were off on their planned vacation.

Ten days later, they received a phone call with the genetic results. The test confirmed that Lilly did in fact have the KCNJ11 mutation. For their vacation, Laurie and Mike had asked Philipson to provide them with all the published studies on monogenic diabetes, which they kept re-reading until they fully grasped the impact of Hattersley's work. As Laurie recounts: "It's hard to describe the flood of emotions we experienced. Of course we had always thought about a cure; we all do. And we hoped and prayed it would happen. But to be honest, we believed it would be in the future, possibly by the time Lilly went to college. We didn't expect it to come before she started first grade!"

Taking the next step was a challenge: while Mike and Laurie were certainly not fans of glucose checks, insulin pumps, and sleep-interrupted nights, they were at least well-practiced at it, compared to facing a little-known treatment for what was largely an unknown disease. Furthermore, they weren't sure where to begin: the Hattersley research was conducted largely in Europe, with only two participants from the U.S. There were hospitals and labs at the University of Chicago, but Lilly wasn't enrolled in any study that would get her access to the recommended drug. There might also be FDA or insurance hurdles to clear the use of the drug for a child.

In a few short weeks, Philipson pulled it all together, and Lilly was admitted to the clinical research center at the University of Chicago. "Dr. Philipson truly moved heaven and earth, jumping through bureaucratic hoops, to get Lilly's treatment started. He has a heart of gold."

Lilly entered the clinic on August 14, Laurie staying at her bedside, while the rest of the family moved into a nearby hotel. Lilly began taking the oral medication immediately, while the University of Chicago team continually monitored her blood glucose and adjusted her insulin pump as the drugs began to take effect. Each day, Lilly's dose of sulfonylurea increased, and by the end of the week, Lilly was secreting insulin for the first time in her life. Lilly left the hospital five days after being admitted, happy to be back with her brother and sister. Her parents continued her protocol at home, checking in regularly with Philipson. On August 23—before the start of school, and less than two months after Mike Jaffe met Lou Philipson—Lilly disconnected her insulin pump for the last time. She celebrated with an ice cream cone, and 90 minutes later had normal blood sugar.

Lilly no longer takes insulin, although Laurie and Mike keep some in the house just in case. Her dosage of the sulfonylurea drug amounts to three pills, taken twice each day. "We hope and pray that Lilly's story will bring hope to all those who suffer with diabetes," said Lilly's parents. "This was Lilly's unique cure but there are many other cures on the horizon."

Dr. Philipson is eager to insure that families with children who were diagnosed before six months of age are educated about the types of monogenic disease and the possible treatments. And while questions remain—some drugs work on younger patients, less so on older people—he's deeply involved in helping as many people as possible. And for all the potential of bitterness or recrimination that their child with diabetes doesn't match the monogenic profile, Philipson says: "I receive quite a few calls a week, most of them from parents of kids who do not fit the criteria, which is primary diagnosis before the age of about six months. Yet instead of being angry, every single person has words of encouragement for us, and thanks us for doing this work. That has made this an incredible experience."