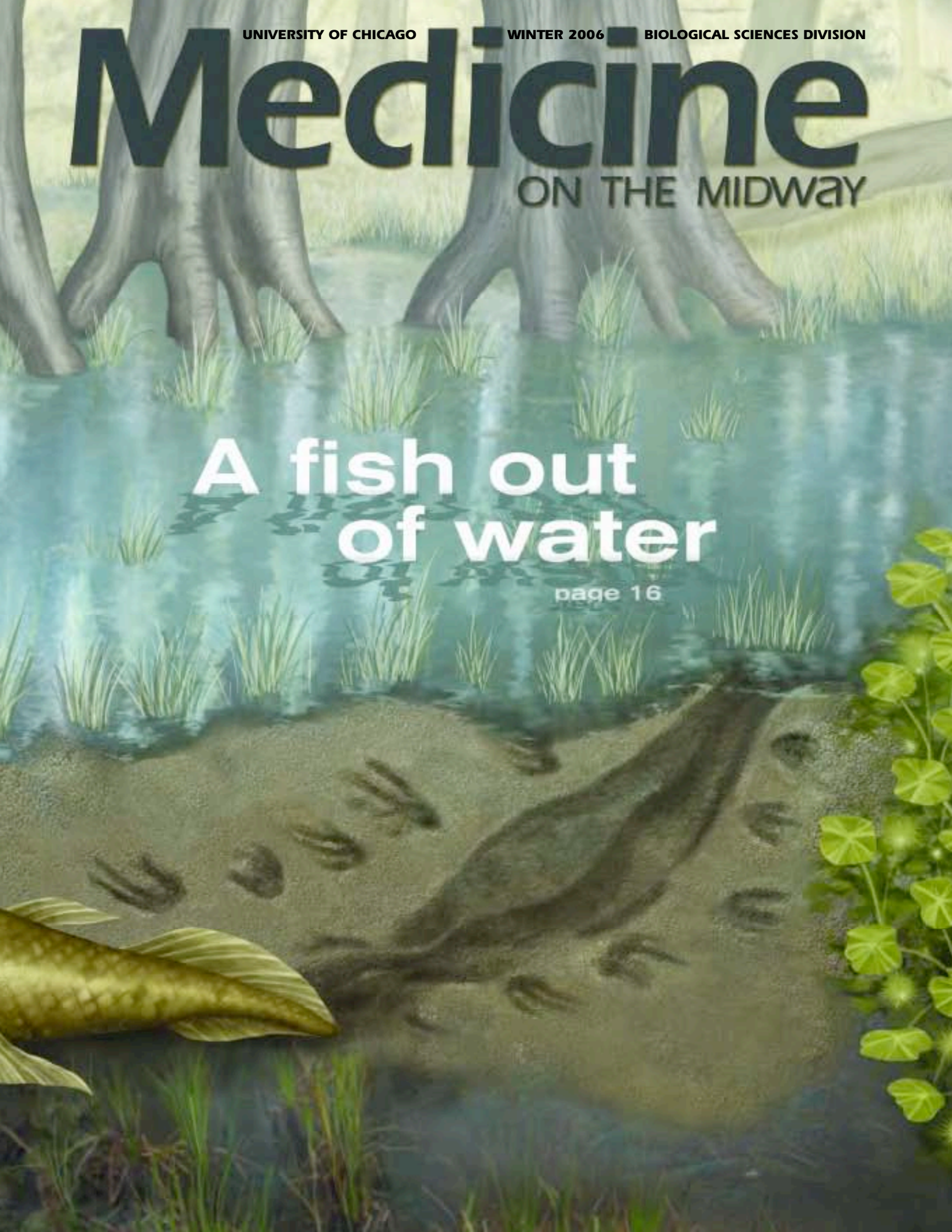


# Medicine

ON THE MIDWAY

## A fish out of water

page 16





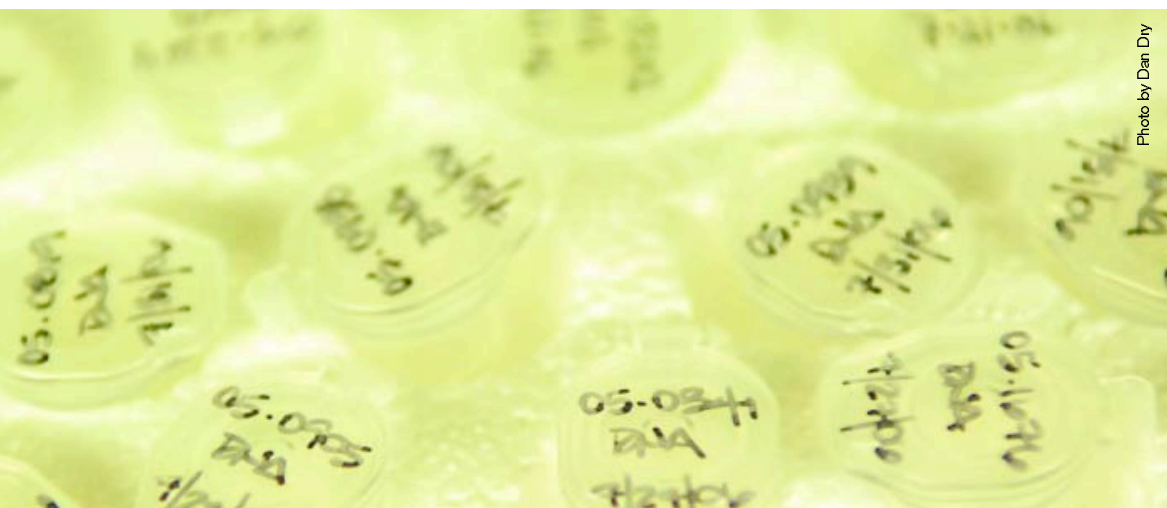


Photo by Dan D'Arcy



# MOLECULAR MEDICINE to the rescue

by Katie Scarlett Brandt

Lilly Jaffe is not keen on publicity. A petite girl with long, brown hair and big, brown eyes, Lilly can beam a broad smile when she's happy—and lose it in an instant when she becomes the focus of too much attention.

This aversion may exist because for her entire life—six whole years so far—she's been followed by an entourage that includes, at alternating times, her mother, father, the school nurse, a blood glucose gauge and insulin shots. It's all for her benefit, of course, and necessary for children like Lilly with Type 1 diabetes, but a lot of constant and concentrated attention for one little girl nonetheless.

Until a couple of months ago, meals in the Jaffe household involved math to calculate Lilly's carbs and compute her insulin needs. Play dates always included mom who would suspend games to draw Lilly's blood for glucose checks. Family outings were never completely worry-free because Lilly's blood sugar levels could rise or fall to dangerous highs or lows unexpectedly. And at school, time between lessons or lunch meant visits to the nurse.

And then Lilly's life changed.

Initially the idea of change worried Lilly, and she resisted. Diagnosed when she was just a month old, Lilly's life revolved around insulin shots or her pump: a pager-size device attached by a tiny catheter into her hip that delivered constant, low doses of insulin into her body.

But Lou Philipson, a University of Chicago endocrinologist, suggested this summer that Lilly's specific type of diabetes might be controlled with pills instead of pump.

*And then*

Lilly Jaffe holds her mom's hand while visiting the doctors and nurses who helped her switch from an insulin pump to medication that enables her to produce her own insulin. *Inset:* Lilly with University of Chicago endocrinologist Lou Philipson.



*Lilly's life changed.*

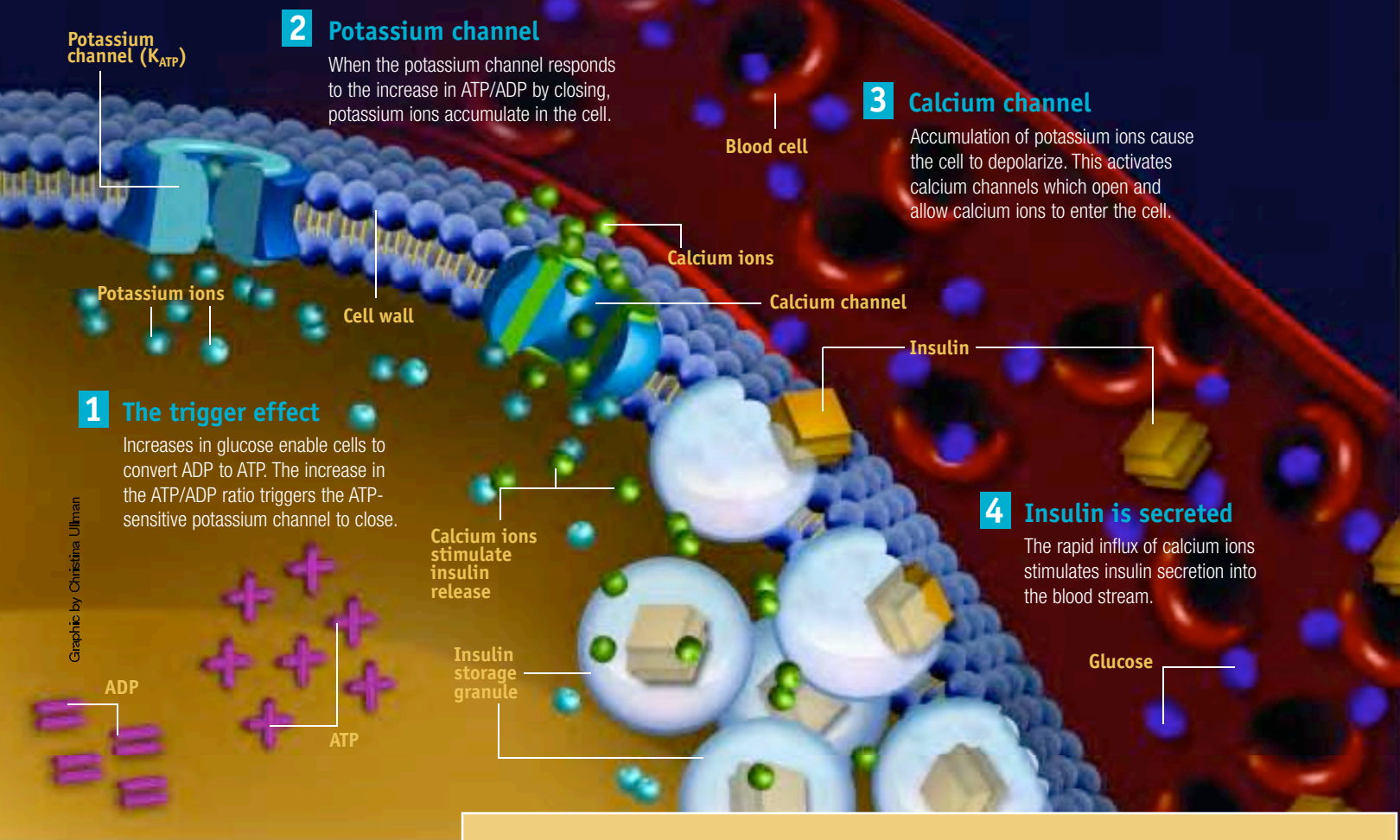


Photos by Yvette Dostani



# GLUCOSE METABOLISM

One small glitch in a long chain of events can disrupt glucose metabolism, producing symptoms that mimic Type 1 diabetes.



Graphic by Christina Ullman

Lilly didn't immediately embrace the idea. "She found comfort and security in that pump," said Laurie Jaffe, Lilly's mom. But where Lilly found apprehension in the new treatment, her parents saw hope instead.

Michael Jaffe, Lilly's dad, had heard Philipson speak about the relatively unrecognized treatment at a presentation for the Chicago chapter of the Juvenile Diabetes Research Foundation. Afterward, Michael approached Philipson and described his daughter's case, which led to Lilly having her genes tested. One spit sample and a couple weeks later, Philipson and his Chicago colleague, geneticist Graeme Bell, announced that one of the two particular strands of Lilly's genes involved in her insulin secretion showed a mutation.

She was a perfect monogenic diabetic candidate for oral drug treatment.

## Diagnosis and discovery

The oral drugs that the doctors proposed belonged to a family called sulfonylureas. Since the 1970s, Type 2 diabetics have used

On Aug. 3, 2006, the *New England Journal of Medicine* published Hattersley's findings and scientists around the world began to see that treatment—though not a total cure—was possible through these drugs.

those same drugs to help manage the disease, but nobody realized that the drugs also could play a major role in Lilly's type of diabetes. Even British scientist Andrew Hattersley didn't realize what he was on to when, three years ago, he began researching potassium channels in infants diagnosed with diabetes before 6 months of age.

On Aug. 3, 2006, the *New England Journal of Medicine* published Hattersley's findings and scientists around the world began to see that treatment—though not a total cure—was possible through these drugs. "To date we have examined over 280 patients diagnosed before 6 months of age and found over 140 patients with this type of diabetes," he said.

When Lilly's doctor diagnosed her six years ago, nobody saw this coming. Laurie had taken Lilly for her well-baby one-month check up. The doctor looked her over, pronounced her as perfect a baby

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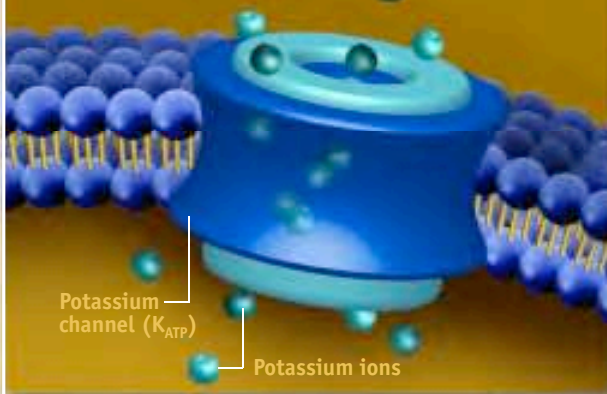


Photo by Yvette Dostajni

The Jaffes—(from left) Charlotte, Laurie, Nathan, Lilly and Michael—stand outside the Clinical Research Center.

### MALFUNCTIONS OF THE POTASSIUM CHANNEL

Gene mutations may cause the potassium channel to be less sensitive to ATP. As a result, the channel stays open, allowing potassium to continually flow out of the cell. Without these signals, insulin is not secreted and glucose levels rise.



as could be and left the room while Laurie bundled Lilly and herself into their jackets. But before they left, the doctor returned, and Laurie could read the concern creasing his face. Lilly's urine sample showed high levels of glucose, meaning her body either wasn't producing or wasn't using insulin the way nature intended in order to break down sugars.

Since that day, Laurie said, "We've always believed in our hearts that there would be a cure someday, but we thought it would be 15 years down the line."

### *sleeping cells*

Only 2,000 to 2,500 people in the United States have the same type of diabetes as Lilly, scientists estimate. It occurs in some infants diagnosed with Type 1 diabetes before 6 months of age and, in very rare instances, between 6 and 12 months.

In typical Type 1 diabetes, the immune system, for some reason, attacks and destroys the pancreas's beta cells responsible for making insulin. Type 1 diabetics like Lilly, (about 1 in 200,000 live births), have a normal number of insulin-secreting cells, but, Philipson said, "for all intents and purposes, the cells have been asleep for [their] entire lives."

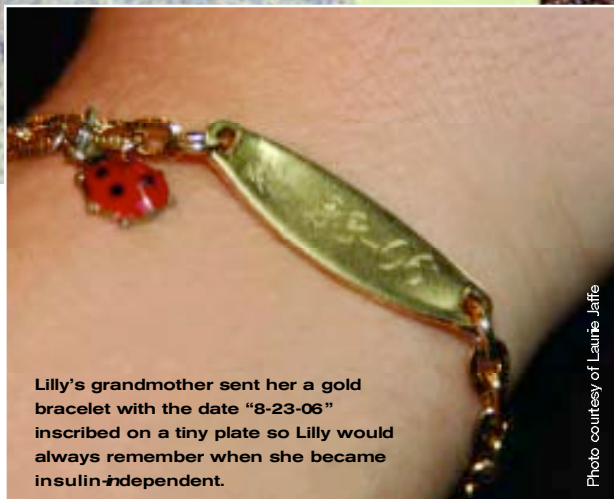
They "sleep" because the ions responsible for waking them up never do. In a fully functional beta cell, glucose metabolism leads to increased amounts of ATP, an energy-storing molecule in the cell. The increases in ATP cause the potassium channels along the cell's wall to close. Because they're closed, potassium ions build up within the cell, and when those reach a certain level, they prompt the calcium channels—also along the cell's wall—to open. As the calcium ions enter, they alert the cell that it's time to begin insulin secretion.

The mutation in diabetes cases like Lilly's happens in one of two possible genes, either *KCNJ11* or *ABCC8*, and affects the potassium channel. Chicago's Deborah Edidin, Lilly's pediatric endocrinologist, suspected Lilly had a mutation, but it was Jaffe and Philipson's chance meeting that put the transition in motion.

Lilly's K<sub>ATP</sub> channels are less sensitive to ATP build-up and therefore don't close and keep the potassium ions from exiting. So the potassium ions don't accumulate, the calcium ions never surge in signaling the cell to secrete insulin, and Lilly's insulin levels remain unreadable.

When Bell tested Lilly's DNA for the mutation, he looked at *KCNJ11* first, where mutations are more common. "It's absolutely critical to test DNA first because if you just take people off insulin, they could become very ill or even die," Philipson said. The test for mutations in the *KCNJ11* gene costs \$10, and for the *ABCC8* gene, which is much larger, the test costs about \$200.





Lilly's grandmother sent her a gold bracelet with the date "8-23-06" inscribed on a tiny plate so Lilly would always remember when she became insulin-independent.

Photo courtesy of Laurie Jaffe

## Continued questions

With these tests, Bell can find the mutation. Philipson's drug treatment then can help the patient make the transition away from insulin injections. But lots of questions still remain. For instance, no one is quite sure how some infants manage to survive for two or four or six months before diagnosis.

They also don't know why these drugs work better in younger people. Although, according to Hattersley, the oldest patient to be transferred from insulin to pills after a neonatal diagnosis was in his mid-50s. Why it works with some adults but not others is not yet known. And in another case, the transition worked in a son, but not his mother. Hattersley and colleagues cite the case in the *NEJM* paper.

Because of those cases, scientists aren't positive that the sulfonylureas will prove effective for Lilly's entire lifetime. However, Philipson said, even if it only works for 10 or 20 years, medical research may catch up with her. The field has advanced with such speed in the past few decades that virtually everyone who has contributed to the research of ion channels and sulfonylureas in insulin secretion—people from England, Japan, the United States and elsewhere—is still alive, so continued advancement is highly likely.

And already molecular medicine has progressed to a point where, if or when Lilly decides to have children of her own, scientists likely will be able to test the DNA in her eggs to see which ones are capable of producing babies without diabetes. Such knowledge carries with it both tremendous promise and ethical considerations.

"It's becoming more and more common to link genetics with health, but it's not always good," Philipson said of genetic testing that can indicate whether patients are prone to certain disorders, such as stomach, prostate or breast cancers. "Do we want to know?" Philipson poses. "Do we want the insurance companies to know?"

## "Going off the diabetes"

Those questions can come later, though. For now, Lilly is still a 6-year-old girl with diabetes who plays soccer and dances ballet.

Less than two weeks before she began first grade, she packed her clothes and her doll, Jess, and headed from her family's lake house in Michigan to the medical center. At first, her hospital stay was stressful. In just nine days, Lilly completely abandoned the security of her pump for a totally foreign method—initially five pills (now three) twice daily. She also had to adjust to full days of school, instead of kindergarten's half-days.

She transitioned "beautifully," Laurie said. "We told her she could sleep with her pump, and even name it, but she lost interest pretty quickly."

A month after her hospital stay, sitting at her family's kitchen counter, Lilly took a break from coloring to watch her brother Nathan, 8, pull a clear plastic box of tomatoes from the refrigerator. Around her wrist hung a delicate golden chain bracelet with her name and the date "8-23-06" inscribed on a tiny plate. Her grandmother had sent it in a wrapped box with a card, congratulating Lilly and encouraging her to always remember when she became insulin-independent.

The oven clock read 4 p.m., and after a long day of school—filled with organizing pictures into consecutive order and sounding out letters—the tomatoes looked appealing.

“Mom, can I have one?” Lilly asked as Laurie rinsed the fruit. She consented.

This time Lilly ate “without me hovering over her,” Laurie said. The constant blood sugar checks have decreased from more than a dozen daily to only two, once in the morning and once at night; her average during the first weeks of September was an ideal 114.

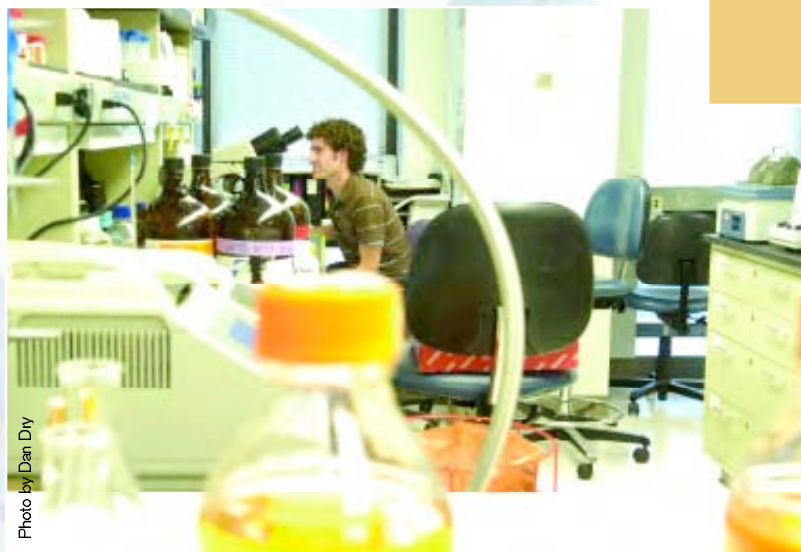
“Every day I get up and I hope that everyone on these drugs is OK,” Philipson said. “It’s amazing to me that this works with only taking the pills twice a day.”

Ironically, despite her initial reluctance, Lilly’s transition—now complete—proved easier for her than for her parents. “It’s a challenge to be able to relax again,” Laurie said. “Emotionally and physically for so many years we were on high alert.”

Her older brother Nathan confides, “It’s like she never had diabetes.” But to 5-year-old sister Charlotte, it seems like Lilly is finally “going off the diabetes.”

## *A dose of bravery*

To Philipson, Lilly and her family are heroes: brave to attempt the switch and brave to let Lilly’s picture and story appear on the front page of one of the nation’s best-known newspapers, the *Chicago Tribune*, less than a month after the transition.



The story traveled beyond national borders. Since it ran this past Sept. 11, Philipson has received roughly half a dozen e-mails daily from around the world. A woman from Albania was representative of most: “As every shocked parent whose children suddenly suffer from a diagnosis such as this,” she wrote, “we felt desperate, angry and betrayed. But, we strongly feel, we are more than ready to make every effort to make it easier for [our son] and hopefully resolve this problem.”

A month after Lilly left the hospital making her own insulin, Philipson sat at his desk checking his e-mail. By 9:30 that morning, he already had received two e-mails from people looking for any possible hope. One woman’s child was diagnosed at 15 months, and although Philipson knew that there was virtually no chance that the child would have the right form of Type 1 for the switch, he replied to the e-mail personally, just as he has to every message he has received so far. However, Bell has identified two more cases, and both are being prepared for the transition. Their families sought out the Chicago team after learning of Lilly’s story.

Lilly wants to help, too. One day, during her week in Chicago’s Clinical Research Center, Lilly sat up in bed asking about all her friends with diabetes—among them her cousin Sarah, babysitter Charlie and friend Jessie. She wanted to know if they’d be able to switch to pills too. Laurie said that Lilly wants everyone to feel the same independence that she now enjoys.

“Every day I get up and I hope that everyone on these drugs is OK. It’s amazing to me that this works with only taking the pills twice a day.”

—Lou Philipson, University of Chicago Endocrinologist

## **NEW DIABETES CENTER OPENS**

A new Comprehensive Diabetes Center, officially launching in early 2007, represents “a brand new approach to managing diabetes,” said University of Chicago endocrinologist Lou Philipson.

The center brings together endocrinologists, nephrologists, podiatrists, nutrition counselors and other diabetes experts within the Duchossois Center for Advanced Medicine.

Until now, many patients had to travel from clinic to clinic. The new center will accommodate patients seeking second opinions, participating in clinical trials, consulting with researchers and more.

For more information, contact the center’s executive director, Peggy Hasenauer, at 773-834-4789 or [peggy.hasenauer@uchospitals.edu](mailto:peggy.hasenauer@uchospitals.edu).

—KSB