

SUGAR



by ART JAHNKE

FIX

A diabetic child spurs a race for a bionic pancreas

For nearly 13 years, Ed Damiano would wake at night every two or three hours, steal into his son David's bedroom, and check the boy's blood sugar. If he'd overslept and missed his scheduled check, he would rush anxiously to David's side and lay a hand on his body, feeling first for the warmth that told him his boy was all right.

Damiano's concern was appropriate. Dead-in-bed syndrome, which takes the lives of the 6 percent of people with type 1 diabetes who die before the age of 40, is a bogeyman that haunts every parent of a child with diabetes. His background in biomedical engineering did not exempt him from the dread.

Next, Damiano, a College of Engineering associate professor of biomedical engineering, would do a quick blood stick in one of David's fingers or toes, draw some blood into a test strip, and wait for the glucose meter to return a number. If the number were too high, or rising too fast, he would give insulin; if it were low, or dropping too fast, he would wake his son and give him juice or lower the insulin infusion rate, or both. Then he would go back to sleep for two or three more hours.

Type 1 diabetes, which affects about two million people in the United States, is an autoimmune disease that destroys the pancreatic cells that normally produce insulin,

BU's Information Services & Technology helped biomedical engineer Ed Damiano build a user interface for iPhones that displays real-time blood glucose levels.



CYDNEY SCOTT

Damiano's aim in building a bionic pancreas for people with type 1 diabetes is to remove the human brain from the equation. An algorithm might work better, and certainly more consistently.

a hormone that allows the body to convert carbohydrates to energy. Instead of being put to work by muscles, the sugars build up in the blood, creating a toxic combination that if treated poorly over many years is almost certain to damage organs such as the kidneys and eyes, as well as blood vessels and nerves. The consequences before the discovery of insulin 90 years ago were even more dire: without the ability to draw upon the sugar in the blood, the body would inevitably waste away and starve to death.

David Damiano's type 1 diabetes showed itself at the extraordinarily young age of 11 months. Toby Milgrome, David's mother and a practicing pediatrician, will never forget the experience. "David had been a normal, happy little boy," she says. "He was learning to walk, pushing a wagon, and then one week he just seemed to be tired, and then one week he was refusing to walk. At the end of the week he was just kind of staring into space."

Milgrome took David to see one of her pediatric partners and requested some blood tests. "I had a few things in my mind," she says. "I was thinking diabetes, leukemia, and brain cancer, but I was hoping for nothing. I was hoping my partner would tell me that there was nothing wrong."

Hours later, the family learned that David was suffering from ketoacidosis, a symptom of diabetes. His extremely high blood glucose level was nearly 10 times what it should have been. They went straight to the hospital, where David was admitted to intensive care.

David's parents knew little about living with type 1 diabetes, but they learned fast. One of the first things they learned was that the available medical expertise was frustratingly limited. After disagreements with more than one endocrinologist about the best treatment, Milgrome and Damiano decided to put their son on an insulin pump, a disposable battery-operated device the size of a pocket watch that delivered relatively precise injections of insulin under the

skin. The technology had been available for about 10 years for adults, and most physicians were not yet persuaded that it was suitable for use with very young children.

"Now they will put little children on pumps," says Milgrome. "But the way they usually managed kids was, they'd get a couple of shots a day and their blood sugar would run around 180 to 250 mg/dl. The kids live and they have a life, but we weren't comfortable with that because of what we know about long-term complications. Some people said, 'Don't worry about it. He won't get any complications for 20 years.' But in 20 years, David would be only 21."

"WHEN YOU'RE sleeping, you're checked out. You

They also learned why there was little consensus about the best ways to maintain a healthy blood sugar count (between 70 and 120 mg/dl in people without diabetes): it's extremely hard to do. Without a functioning pancreas to keep things in balance, the amount of sugar in a person's blood climbs and dives in response to a variety of stimuli, such as the amount and intensity of a person's physical activity, state of mind, illness, stress, and many other factors, not to mention the hormonal changes of a growing child. An insulin dose that works fine one day may be ineffective or excessive the next day. Insulin dosing is an art form, Damiano says, and any given dose often defies simple prescriptive regimens.

AN EXQUISITE PIECE OF BIOLOGICAL MACHINERY

Damiano's expertise had been in the application of fluid dynamics and solid mechanics to physiological systems. He spent years doing mathematical analyses of blood flow in microcirculation and the fluid dynamics of the inner ear. But he is also an engineer, and engineers design systems to solve problems. In 2004, when David was five years old, Damiano set to work on something he knew he had to do: building a bionic pancreas.

He describes the natural pancreas as an exquisite piece of biological machinery, one that fine-tunes a body's glucose level both by lowering it (with minute amounts of insulin) and by raising it (with another hormone called glucagon). The real thing has many advantages that the man-made technologies now available cannot rival. For one thing, says Damiano, the pancreas releases its insulin and glucagon directly into the liver, where they can get to work immediately. Insulin

infusions under the skin with an insulin pump can take an hour or more to reach peak absorption.

But for Damiano, one of the most compelling advantages of a natural pancreas has as much to do with constancy as efficiency—a real pancreas is relentless—it works while you’re awake and it works while you sleep.

“Sleeping is the scariest part of all this,” he says. “It’s what put this project on a high-speed rail. It’s a very scary prospect that blood sugars could go low at night. When you’re sleeping, you’re checked out—you don’t want to check out permanently.”

Jeff Hitchcock, the founder of Children with

“Every morsel of food you eat, you think about it. Every time you go to sleep you think about it.”

Insulin dosing is normally done with extreme care, by the person with diabetes or by a guardian. For years, for example, Milgrome has been preparing David’s meals and snacks for school, and with each meal she includes a card detailing the carbohydrate content and insulin dose. She has also prepared a chart with insulin doses to be given for high blood sugar. But no chart can account for everything that might affect a young child’s blood sugar from day to day. As an additional measure, the nurse in David’s elementary school would call either Milgrome or Damiano five times throughout the day and read them their son’s glucose levels; they would then recommend an insulin dosage that may depart from the standard dose regimen, depending on a variety of other factors that needed to be considered.

Damiano wanted to remove the human brain from the equation. If a human could do it, he reasoned, an algorithm could do it, and it could possibly do it better, and certainly more consistently.

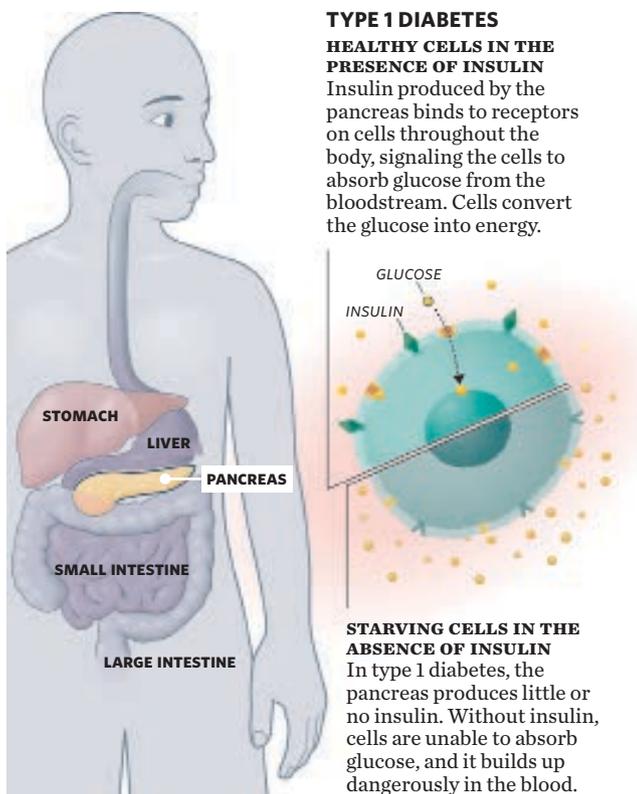
WEB EXTRA
Watch a video of Ed Damiano and his family talking about living with type 1 diabetes and his effort to build a bionic pancreas at bu.edu/bostonia.

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Diabetes, an online community promoting a better understanding of the care and treatment of the disease, shares a parenting history with Damiano. His daughter’s type 1 diabetes emerged when she was 24 months old.

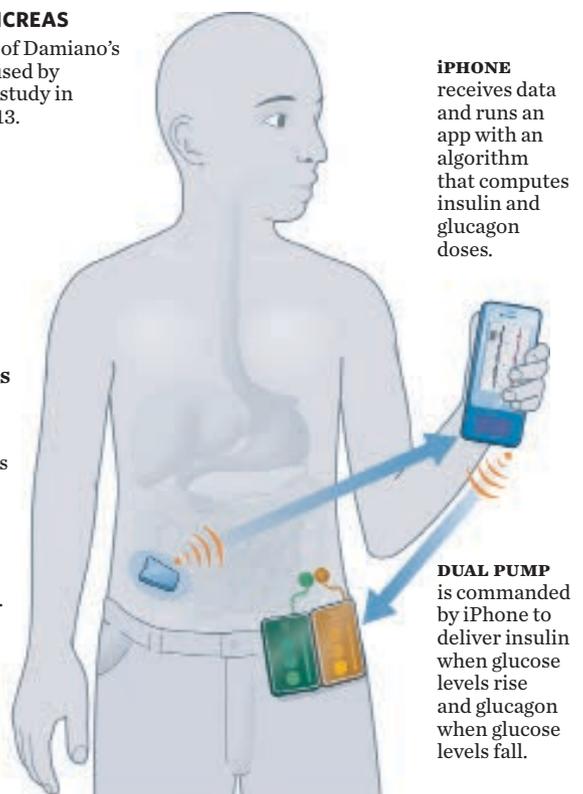
“Whatever you do in a life with type 1 diabetes is impacted by that diabetes,” says Hitchcock.

Ed Damiano’s bionic pancreas would free patients from much of the uncertainty involved in dosing.



BIONIC PANCREAS
This version of Damiano’s system was used by patients in a study in February 2013.

CONTINUOUS GLUCOSE MONITOR
measures glucose levels just under the skin and transmits the data wirelessly to an iPhone.



He envisioned a bionic pancreas as a trio of connected devices: a continuous glucose sensor, which could be worn on one side of the body just above the waist, a dual insulin and glucagon pump, which could be worn on the other side of the body, and a small computer, which could be built into the pump and would determine how much insulin or glucagon to administer.

By 2008, three companies in the United States were marketing continuous glucose monitors, a golf-ball-sized device with a sensor placed just under the skin of the abdomen that measures glucose levels every five minutes. Before that, people with type 1 diabetes managed their blood glucose levels with an insulin pump. Today, about one in four people with type 1 diabetes wears an insulin pump. The missing link has been a mathematical solution, an algorithm that would run on a computer or smartphone, analyzing glucose levels and determining how much insulin or glucagon the pump should administer.

“In the current embodiment of our system,” says Damiano, “glucose levels stream from a small sensor/transmitter unit worn by the person into a

receiver, and the receiver then passes data into an iPhone, where an app with our algorithm makes a therapeutic decision to dose either insulin or glucagon, with two small infusion pumps, every five minutes.”

Most important, the algorithm could do it while the wearer of the bionic pancreas sleeps, eliminating, at least in theory, dead-in-bed syndrome. Damiano knew exactly what he had

“THE MAIN goal is to get something in David’s

to do, and he knew when he wanted it done: by fall 2017, when David would be heading off to college.

FROM PIGS TO HUMANS

Working with Firas El-Khatib, an ENG senior research associate, Damiano started experimenting with pigs in 2005. Their first hurdle was fine-tuning the algorithm to churn out immediate and precise responses to the wild fluctuations of sugar in the pigs’ blood.

In spring 2006, Damiano gave a talk about their work at the Joslin Diabetes Center in Boston. When he left the podium, he was approached by Steven Russell, a physician and researcher at Massachusetts General Hospital (MGH), who understood the implications of the research. Russell said he wanted to help bring the technology to humans.

In 2008, with assistance from the Wallace H. Coulter Foundation, the Juvenile Diabetes Research Foundation, the Helmsley Charitable Trust, and the National Institutes of Health, Damiano, El-Khatib, and Russell began a series of human trials. In the first of these, 11 study subjects stayed in a hospital room with an IV in each arm for one day and one night and ate three high-carb meals. The first-generation version of the system controlled the subjects’ blood glucose for 27 continuous hours and used blood glucose sampled from one of the IVs as the input signal to the control system.

In a clinical trial at MGH, 11 adults with type 1 diabetes were hooked to the first-generation version of Damiano’s system for 27 hours and were supplied with three high-carb meals.



COURTESY OF ED DAMIANO

A second study, launched in 2010, used the second-generation version of the system, which relied on glucose levels sampled from a continuous glucose monitor placed just under the skin. Subjects spent two days in the hospital and had their glucose controlled for 51 continuous hours, eating six meals and doing the kind of light exercise that would send their glucose downward.

A third study, conducted last fall, validated the

hands before he leaves for college.”

performance of the second-generation system, which had been modified to accommodate both adults and adolescents. In that study, 12 adults and 12 adolescents followed the same protocol as in the second study.

One of the greatest challenges the researchers faced in developing their mathematical algorithms was devising a single system that could quickly and automatically adapt to meet the vastly higher insulin requirements of adolescents while at the same time not overdosing with too much insulin when determining the much lower insulin needs of adults.

This past February, Damiano and his colleagues got approval from the MGH Institutional Review Board to conduct their first outpatient study with the current iPhone-driven version of their bionic pancreas.

“Previous systems we designed all ran on a laptop computer,” Damiano says. “It hung on an IV pole, and there was a large contraption you had to pull around if you wanted to ambulate up and down the hallway. In lieu of this, we built the whole device into an iPhone platform, using a custom app that incorporates all the mathematics. We’ve built a user interface with the help of some of the folks at Information Services & Technology at BU, so there’s a nice graphical user interface that allows us to control the system and visualize real-time glucose levels.”

Because the system uses an iPhone, Damiano and El-Khatib could use the cellular network and a cloud-based service to view each experiment remotely on iPhones and iPads. They could also review every subject’s real-time glucose levels and all insulin and glucagon doses given to the subject by the device.

In their latest trial, 30 adult subjects wore the device for five days and five nights and were free to wander, iPhones in their pockets, around a three-square-mile area in Boston by day and sleep in a hotel next to MGH by night. Next, Damiano says, he will conduct a study in 32

children who will wear the device for five days and five nights in a diabetes summer camp in central Massachusetts.

The final study with an iPhone, scheduled for the first half of next year, will involve 48 adult subjects wearing the device at work and while sleeping at home for 12 days and 12 nights. In 2015, Damiano plans to conduct what he calls the pivotal studies, which will test the commercial product that he plans to build over the next 18 to 24 months. That product, he says, will embed all of the functionality of the current investigational device in a single dual-chamber pump.

“In the study’s final form, people with type 1 diabetes from across the country will wear the device for six months or so,” he says. “We’ll compare the glucose control our device was able to achieve in that cohort with the control a similar cohort was able to achieve when managing their own diabetes with their usual care over the same period of time. Our goal is to do those pivotal studies in 2015 so that we can submit the device to the Food and Drug Administration for review the next year, and hope for approval by 2017. That’s the goal—to get this done in about four years’ time. It’s very ambitious, but I think we can stay on track.”

Hitchcock believes that Damiano’s device will “remove the albatross that circles above everyone with diabetes” and will fundamentally change life with diabetes. “It will free you from constant mathematics every time you eat,” he says. “It will free parents from fear every day that their child will die every time the child goes to sleep. What Ed is doing is going to change the world.”

David, who is now an active eighth grader with a highly accurate jump shot, is, unsurprisingly, his father’s number one fan. “I know it’s really tough,” he says. “He’s been working on this for so many years. I know his motivation is me, but I know it’s more than me. It’s everyone with type 1 diabetes, and I think it’s really great. I’m really proud of him.”

“When we started this project, we were definitely focused on trying to build something that can take care of everyone with type 1 diabetes,” says Damiano. “But my main goal was also to get something in David’s hands by the time he leaves for college. That’s really why I’m doing this. I’m not particularly interested in glucose levels in people’s blood. It’s not an interesting thing to think about, but I have to think about it all of the time. It shouldn’t have to be that way. Ideally, no one should have to concern themselves with it, ever.” ■



An iPhone displays a patient's blood sugar levels and runs an algorithm that determines insulin needs.