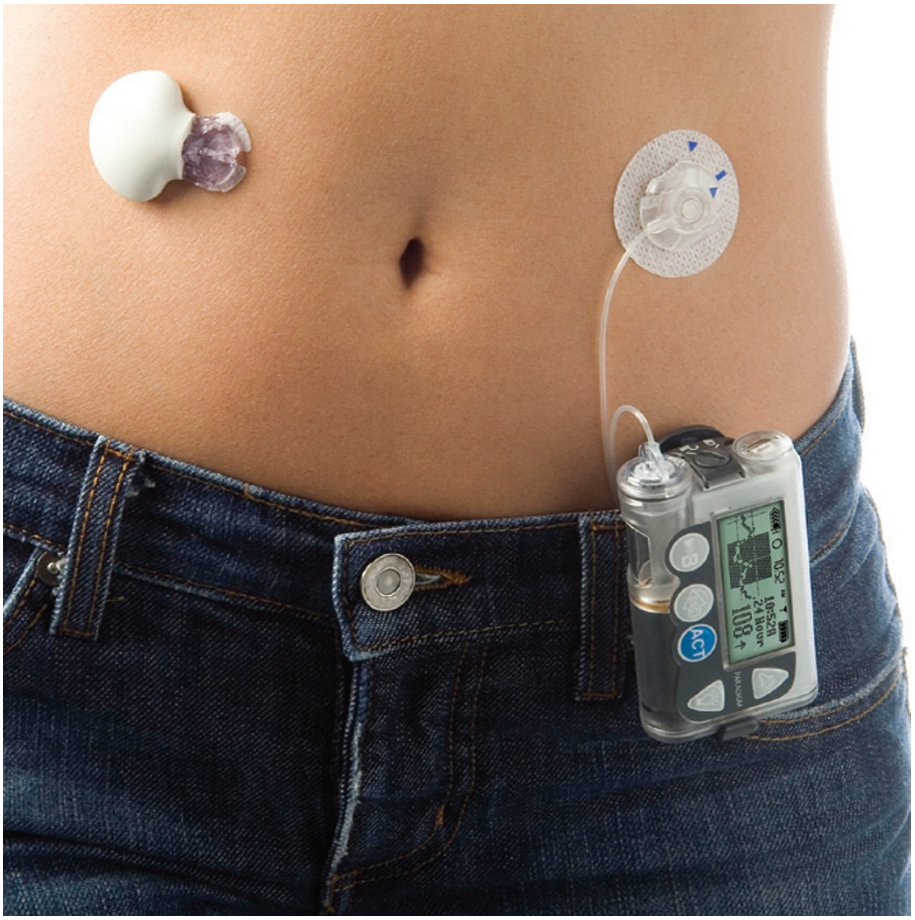

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Software may soon close the loop between glucose sensors (left) and insulin pumps (right).

MEDICAL DEVICES

Managed by machine

Artificial pancreases promise to take the decision-making — and human mistakes — out of managing type 1 diabetes.

BY ELIE DOLGIN

Leah Moynihan lifts her shirt to reveal half a dozen devices strapped to her midriff: four glucose sensors and two hormone pumps attached to her belly and a pack of remote controls slung across her chest. On this Saturday in February, Moynihan is wired up to test what could be a major advance in the treatment of type 1 diabetes (T1D): a bionic pancreas that automatically dispenses the right amount of insulin in response to fluctuations in blood glucose levels.

"It looks like chewing gum and paper clips right now," admits Kendra Magyar, a research nurse at Massachusetts General Hospital (MGH) in Boston who has type 1 diabetes herself and is helping to run the trial. "If it all works out, it'll get smaller and less invasive."

The current standard of care for treating T1D leaves much to be desired. Typically, people prick their fingers several times a day to monitor their blood sugar levels. They then try to regulate their blood glucose, either by eating sugary foods if blood sugar levels are low (hypoglycaemia) or by injecting themselves with insulin when glucose levels spike. Two types of wearable devices that help people manage the condition have recently hit the market. One, the continuous glucose monitor, is a tiny sensor placed just under the skin that checks sugar levels automatically every few minutes. The other is an insulin pump about the size of a mobile phone that attaches to a fine needle implanted under the skin to deliver the missing pancreatic hormone at the click of the button.

The trouble is that both systems still require people to decide for themselves if, when and how to get their blood sugar levels back into the normal range — and a wrong decision can be deadly. People with T1D suffer an average of two episodes of symptomatic hypoglycaemia per week, and as many as 10% of deaths in this patient group are caused by insulin-related complications. "When you look at the care and the burden of type 1 diabetes — testing and correcting 24 hours a day — it really is unbelievable," says Dana Ball, programme director for the T1D programme at the Helmsley Charitable Trust, a New York-based non-profit organization that is partly funding the MGH trial. "A more sophisticated device would be incredible."

For Moynihan, a nurse practitioner at the nearby Mount Auburn Hospital in Cambridge, Massachusetts, who has lived with T1D for close to three decades, such a device could not come soon enough. Diabetes "interferes with my life every day, all day long", she says. "So it gives me some hope that there will be more than my having to think about how much insulin I need to take or whether I need a snack."

IN THE LOOP

To improve the quality of life for people with T1D and help prevent diabetes-related premature death, several researchers are designing automated systems that close the loop between glucose monitors and insulin infusion devices by transmitting information wirelessly from a sensor to an insulin pump. These closed-loop artificial pancreases rely on advanced control algorithms — mathematical formulations run on software — to make therapeutic decisions and accurately regulate blood sugar in real time with minimal human input. "This is an unprecedented kind of technology in which you're handing over therapeutic decisions to software," says Ed Damiano, a biomedical engineer at Boston University in Massachusetts involved with the MGH trial. "As soon as it's available, it will make the current standard of care obsolete."

Artificial pancreases trace their roots back more than 35 years to the Biostator, a device introduced by Indiana-based Miles Laboratories in the late 1970s. The refrigerator-sized controller relied on intravenous blood readings and intravenous infusions of insulin, which meant its use was limited to the hospital. Still, the Biostator proved that such a closed-loop platform was possible. Products that were more portable soon followed, but the surgical procedures needed to implant the sensors and

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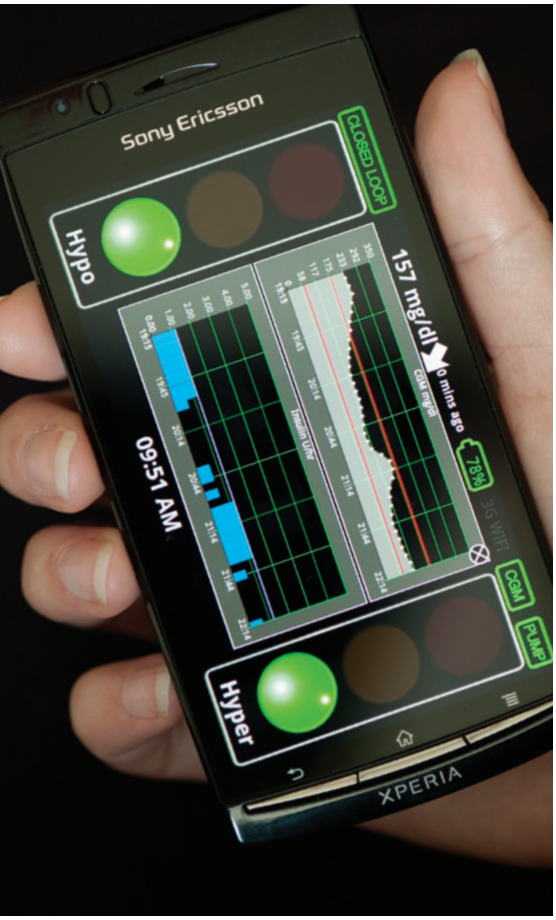

Closed-loop algorithms can run on smartphones; this version shows insulin delivery and glucose level.

MELODY KOMYEROV FOR BOSTON UNIVERSITY

pumps deep inside the body, among other safety and usability problems, prevented their broad commercialization.

Closed-loop devices for use in the home took a big step forwards about ten years ago, with the roll-out of glucose sensors that could be implanted beneath the skin. The first-generation devices provided only retrospective data that could be analysed after the fact to inform disease management. But in 2005, Medtronic, a medical device company based in Minneapolis, Minnesota, began selling the Guardian RT, which relayed glucose results every five minutes. Subcutaneous devices had already been available for insulin delivery for decades. Now all that was missing was the link between the two.

IT TAKES TWO

To spur the development of algorithms that could make therapeutic decisions, the JDRF, a New York-based non-profit foundation, initiated the Artificial Pancreas Project in 2005. This multimillion dollar initiative brought together diabetes researchers and businesses determined to make the artificial pancreas a reality. Around the same time, the US Food and Drug Administration (FDA) identified the artificial pancreas as a top priority and, together with the US National Institutes of Health, formed the Interagency Artificial Pancreas Working Group to identify and work through any clinical and scientific challenges. Meanwhile, government funding bodies in the United States and Europe, as well as many medical device companies, started spending tens of millions of dollars to encourage the development of an artificial pancreas.

In the wake of rapid progress, a handful of independent research groups launched human clinical trials, and several algorithms are being tested (see 'Control issue'). For the most part, studies have been conducted under the controlled confines of the hospital setting, often with participants hooked up to laptop computers and intravenous backup systems that limit their mobility, as Moynihan was. But some investigators have taken their devices to the next level.

At the Princess Margaret Hospital for Children in Perth, Australia, Medtronic is running its algorithm on a BlackBerry smartphone. In Italy and France, researchers are using mobile phones and tablet computers to conduct trials in hotels — not hospitals — with doctors and engineers in separate rooms in case safety problems arise. "The patients wanted to go home with it," says Eric Renard, a diabetes specialist at Montpellier University Hospital in France who is leading the hotel-based trial. "After only a few hours, they say they're completely different. Never before have they had this feeling that they don't have to think about their disease." In March 2012, the FDA approved a similar trial using the same technology at the University of Virginia in Charlottesville and at the Sansum Diabetes Research Institute (SDRI) in Santa Barbara, California.

In the United States, some investigators have also started experimenting with systems that try to improve how the artificial pancreas works. For example, Damiano's team and an independent group in Portland, Oregon, are using a pancreatic hormone called glucagon to help raise blood glucose when too much insulin has been delivered and blood sugar levels start to plummet. At Yale University School of Medicine in New Haven, Connecticut, researchers are adding pramlintide, a synthetic version of another human hormone called amylin, to help slow the absorption of nutrients from the gut as glucose levels rise after mealtimes. The Yale group has also tested a patch that heats the skin before insulin release to increase blood flow to the site in order to speed up the hormone's uptake. Given the inherent lag times associated with subcutaneous insulin absorption, "you're going to have a problem with catch up", says Stuart Weinzimer, a paediatric endocrinologist who is leading the Yale trials. "Anything you can do to speed up insulin delivery or slow down glucose absorption will help."

"Never before have patients had this feeling that they don't have to think about their disease."

A RISKY PROPOSITION

Although developers of artificial pancreases have differing opinions about the best closed-loop design, all agree that safety must remain a top priority as more authority is handed over to the device. "Hypoglycaemia is extraordinarily dangerous. You lose consciousness and then you have seizures and you die if someone doesn't help you," warns Steven Russell, a diabetes specialist at MGH who is collaborating with Damiano on the trials in Boston. "Giving over control entirely to a machine is a high-risk proposition," he says, making it imperative that the process be "done properly".

To help make the safe transition to a fully closed-loop system that requires minimal human input, many experts and companies are advancing hybrid control algorithms that are only partly automated. "We want to take iterative steps to closing the loop," says John Mastrototaro, vice-president of global medical, scientific and health affairs at Medtronic's diabetes division in Northridge, California.

The first such product could be Medtronic's Paradigm Veo, an insulin pump that automatically turns off when a sensor reports that glucose levels have fallen below a certain level. Already available in Europe, this 'low glucose suspend' system is now undergoing in-home testing in the United States, and is expected to receive regulatory approval in 2013.

Subsequent partly automated systems will probably benefit from technological improvements. The next logical step is a predictive low-glucose sensor that anticipates declining glucose levels, rather than relying on a hard cut-off point as the Paradigm Veo does. Then maybe there will be a device that automatically increases the insulin rate when blood glucose levels rise above a certain threshold, followed perhaps by a fully closed-loop system that only works when people are asleep, thereby avoiding

Ed Damiano checks the readings on his son David's continuous glucose monitor.

UNIVERSITY OF VIRGINIA PATENT FOUNDATION

CONTROL ISSUE

The algorithm method

Diabetes researches and clinicians generally agree that a safe and effective artificial pancreas should provide better treatment than the current standard of care. But the bioengineers behind the systems don't agree on the best type of algorithm to control the closed-loop devices.

In one camp sit the advocates of so-called 'proportional-integral-derivative' (PID) controllers, a simple strategy widely used in feedback control in settings ranging from missile steering to automobile cruise control. For artificial pancreases, PID-based algorithms use glucose values and rates of change to make calculations of insulin dosing. Gary Steil, a former Medtronic engineer who is now developing his own algorithms and running clinical trials at Children's Hospital Boston in Massachusetts, says that the PID approach best emulates how the body's insulin-producing beta cells manage glucose naturally, as they simply react to blood glucose levels and then spit out hormones as needed. "Everything in this algorithm is linked to something that the beta cell does," Steil says.

But others endorse a more predictive strategy to make up for the unavoidable time lags associated with subcutaneous glucose sensing and insulin release. Known as 'model-predictive control', this method tries to plan several moves ahead in someone's glucose control based on past actions and responses. According to Boris Kovatchev, director of the University of Virginia Center for Diabetes Technology in Charlottesville, this level of built-in prediction is vital to ensure patient safety. "Safety cannot be reactive," he says. "It's too late to be reactive."

Some researchers, however, say this whole debate around control theory techniques is a red herring. "Algorithms aren't the issue," says Ken Ward, an endocrinologist at Oregon Health and Science University in Portland. "If we had a really reliable sensor and reliably fast insulin, I think the artificial pancreas would work with any number of algorithms." — *E. D.*

ELIE DOLGIN

Leah Moynihan gives her bionic pancreas a test ride.

the confounding factors of meals, stress and exercise, all of which can complicate blood glucose management. Importantly, all these hybrid devices would be automated some of the time but still maintain some degree of human input in the intervening periods.

"This is the Wright Brothers at Kitty Hawk when everyone wants to go to the Moon," says endocrinologist David Klonoff, medical director of the Diabetes Research Institute at Mills-Peninsula Health Services in San Mateo, California, who has been involved in the Paradigm Veo's in-hospital trials. "It's a first step, but you've got to start somewhere."

"We all have this goal of a fully automated system," says Howard Zisser, director of clinical research and diabetes technology at the SDRI. "But we need to harvest some of this low-hanging fruit," he says of semi-automated systems, which can be put into practice more easily. What's more, he adds, "it will be easier to convince the regulatory authorities that an artificial pancreas can readily help people with type 1 diabetes."

Getting to that point, however, could be a long and bumpy road, especially in the United States — as shown by the slow path to approval for low glucose suspend systems. To speed the approval process along, in October 2011 the JDRF launched a campaign to convince the FDA, which was drawing up guidelines on artificial pancreases at the time, to create a clear and reasonable path to approval for closed-loop devices. "The reason we're putting pressure on here is because there is a critical unmet medical need," says Aaron Kowalski, research director of the JDRF's Artificial Pancreas Project. "We all want safe and effective products, but we also appreciate that people with diabetes are struggling now and the technology exists to help them do better."

The response to the JDRF appeal was overwhelming. In only three weeks, more than 100,000 people signed a petition — and the FDA paid attention. In December 2011, the agency released draft guidelines in which it promised to be flexible on trial sizes, durations and clinical endpoints needed for approval of an artificial pancreas. "There is no magic number or glucose level that the FDA believes is necessary to approve these devices," says Charles Zimliki, chair of the FDA's Artificial Pancreas Critical Path Initiative. "We're really trying to say: 'Come in and talk to us as you're developing these systems.'"

In February 2012, Damiano and Russell did just that. They met with FDA officials to discuss setting up five-day trials at MGH with their algorithm running on an iPhone. "Subjects will have free run of the entire hospital campus," Damiano says. After that, they hope to run 12-day trials involving MGH staff with type 1 diabetes; these study volunteers would go about their jobs at the hospital as normal while wired up to the device, and would even be able to sleep at home while still connected. Then, the Boston team plans to conduct one- to two-week trials with children at diabetes camps, followed sometime in 2014 by pivotal long-term outpatient trials.

Through it all, Damiano remains confident that a fully closed-loop device will make it to market sometime before his son, who was diagnosed with T1D in 2000 at just 11 months of age, graduates from high school. "Before my son goes to college, he has to wear one of these things," he says. "Or else I'm going with him." ■

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