



Rest easy. An artificial pancreas will protect diabetics from low blood sugar while sleeping.

can't consume it, and liver and fat tissue can't store it for later use. Type 1 diabetics, whose condition develops early in life, lack insulin because their own immune system has attacked insulin-producing cells in their pancreas known as β cells. (Another form of diabetes, type 2, usually affects older people and results from insensitivity to insulin rather than a lack of it.)

MEDICINE

A Pancreas in a Box

Sophisticated sensors, insulin pumps, and algorithms may help give type 1 diabetics a more normal life while researchers work on a cure

One morning last April, a woman named Jane checked out after an overnight stay in Addenbrooke's Hospital in Cambridge, U.K. She had spent 24 hours connected by tubes to several medical devices—mostly bored, she says, but also “mildly apprehensive.” Now, she was taking them home to do something she hadn't done for 3 decades, something that she and the rest of the world's 30 million type 1 diabetics are never able to do: forget about her diabetes.

The devices—an insulin pump, a blood glucose sensor, and a computer about the size of a paperback book—make up a prototype of what researchers call an artificial pancreas. Together, they replicate the function of the pancreas that is lacking in diabetics: producing insulin in response to rises in blood glucose level. Groups in Europe, the United States, and elsewhere are now testing such systems in small groups of patients, hoping to show that the technology can work efficiently and safely. If so, it could transform the lives of diabetics, improving their health and allowing them something closer to an ordinary life. After controlling her diabetes with blood tests and injections for most of her life, having an artificial pancreas “would be magical,” Jane says.

With its tubes and needles and gadgets, an artificial pancreas is not an elegant solution to the problem of diabetes. But research-

ers say it could provide a valuable stopgap until effective biological treatments—or even cures—come along. The principle is simple: Connect a commercially available glucose sensor to a commercially available insulin pump via a computer programmed to interpret the sensor readings and decide how much of the drug is needed. But implementing it has turned out to be far from straightforward. Controlling the level of sugar in the blood from outside the body is fiendishly difficult because sensors are slow and error-prone, while injected insulin can take hours to have an effect and overdoses can be fatal. For a person with diabetes, used to calculating insulin doses multiple times every day and dealing with the consequences, handing over that responsibility to a computer is daunting. Patients may be clamoring for such a solution, but researchers will have to convince them that it is safe.

Glucose, ingested in the form of sugar and other carbohydrates, is the body's energy source. But without the hormone insulin to help glucose out of the bloodstream and into cells, muscle and brain

Before the discovery of insulin in the early 1920s, type 1 diabetics would simply wither away, fall into a coma, and die within months or years. In the developed world at least, today's diabetics (including the writer of this article) can live a relatively normal life—although one dominated by a never-ending round of blood sugar tests, usually achieved with a finger prick to draw blood and an electronic meter, insulin injections, and meals carefully weighed to estimate how much carbohydrate is being eaten.

The consequences of getting it wrong can be severe. Give slightly too much insulin and glucose in the blood drops to low levels. Starved of fuel, the brain first shows symptoms similar to drunkenness, followed by unconsciousness and even death. Allow sugar levels to get too high and the syrupy blood can damage delicate blood vessels, leading to long-term complications that include heart disease, blindness, kidney failure, and limb amputation. Completely uncontrolled blood sugar leads to a coma

and a trip to the hospital by ambulance, which is how many type 1 diabetics find out that they have the disease. So living with diabetes is a continual balancing act: trying to keep blood sugar levels close to those of a normal person using sporadic and erratic information (finger-prick tests) and inadequate tools (injected insulin).

Researchers worldwide are working on biological



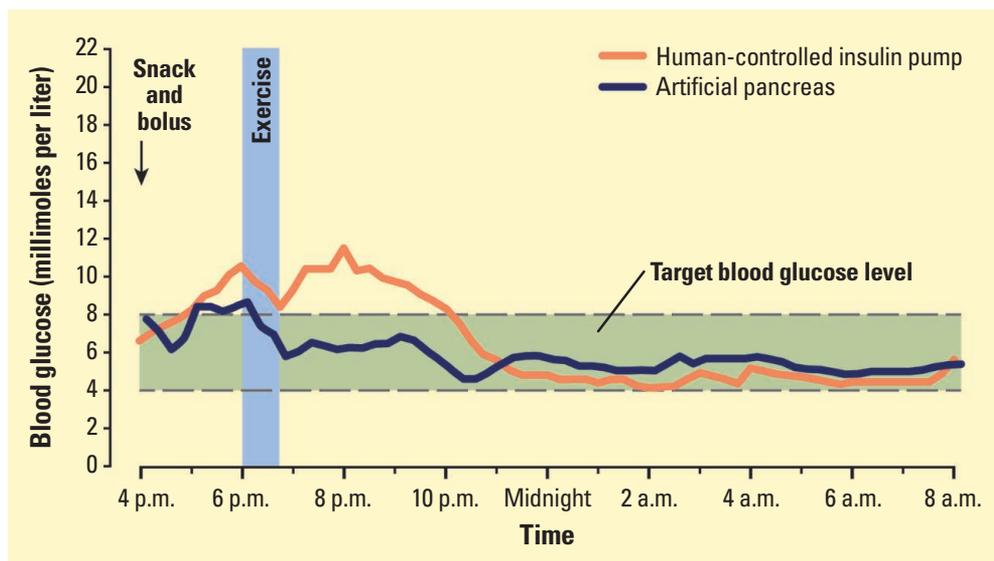
“We're trying to do this invisibly and automatically. But we need faster insulin and we need faster [sensors].”

—FRANK DOYLE,
UC SANTA BARBARA

cures for type 1. But progress is slow, and it could be many years or even decades before they are ready for widespread use. So, over the past decade, many researchers and physicians have begun working on a technological solution—the artificial pancreas—to fill the gap. Their job has been made easier by huge advances in diabetes management—

tests do—but again, because of their high cost very few diabetics now use them.

“The advent of a portable, reliable CGM was the missing link” that encouraged funders to take the idea of an artificial pancreas seriously, says Aaron Kowalski, vice president for treatment therapies at JDRF, a worldwide diabetes research foundation.



On target. A diabetic’s main goal is to keep his or her blood glucose level within the same levels as a normal person. An artificial pancreas does this better than manual control, with fewer potentially dangerous excursions.

new types of insulin, insulin pumps, blood glucose sensors—introduced by drug companies and medical device manufacturers.

The first insulin pumps that patients could take home and manage themselves emerged in the 1980s. Today’s models, the size of a pager, pump insulin via a thin tube into the body through a cannula: a needle or tube inserted a few millimeters into subcutaneous tissue, usually in the stomach area. Pumps trickle in tiny doses of insulin—known as a basal dose—day and night, just as a pancreas does. Meals call for a much larger and immediate dose of insulin, known as a bolus, which patients program into the pump depending on how large the meal is. Pumps provide better control of blood sugar levels than insulin injections do, but their high cost has limited their popularity.

Pumps don’t eliminate the need for finger-prick glucose testing, but continuous glucose monitors (CGMs) do. Introduced in the late 1990s, these devices use a sensor that projects through the skin into the interstitial fluid between cells and measures its electrical characteristics to determine blood glucose levels. A transmitter attached to the body sends the results to a handheld receiver. CGMs give better real-time data on blood glucose levels than finger-prick

JDRF set up an artificial pancreas project in 2006 to fund research in centers and companies in the United States and Europe.

But it was the medical device industry that took the first step. In 2009, device manufacturer Medtronic released the most basic type of artificial pancreas system: an insulin pump able to receive signals from a CGM transmitter. The hybrid device isn’t smart enough to control blood sugar to within a narrow range, but it can avert emergencies. The company adapted it to set off an alarm when blood sugar gets low; if no action is taken, the system simply stops the basal insulin dose for 2 hours.

Such a system is ideally suited to dealing with low-glucose events—otherwise known as hypoglycemia or “hypos”—during the night. Nighttime hypos are particularly worrisome because people are unaware they are happening and respond too slowly or not at all, which can result in coma or hypoglycemic seizures. Medtronic’s system was approved for use in Europe relatively quickly; the U.S. Food and Drug Administration (FDA), which is more cautious about medical devices, followed suit in September 2013.

Medtronic’s system can stop hypos from getting worse, but it doesn’t prevent them in

the first place. For that, you need an intelligent algorithm that can analyze what a user’s blood sugar is doing and predict what it will do in the future. Groups around the world have been working on such algorithms for a number of years.

Algorithms fall into three main types. The simplest is a common feedback loop used in the industrial control industry called a proportional-integral-derivative (PID) controller. This looks at a user’s past and current blood glucose level and, based on the rate of change, calculates the best insulin dose to restore a target glucose level. “It’s very simple, very intuitive,” Kowalski says, but many now think PID controllers are too simplistic for the complex array of factors involved in controlling blood sugar, including food ingested, the slowness of insulin absorption, amount of insulin already in circulation, and exercise.

Many groups are working on a second algorithm type, which forecasts future blood sugar levels on the basis of the diabetic’s own physiology. Such model predictive control (MPC) algorithms “incorporate a model of insulin and carbohydrate absorption, tuned to the particular patient,” says Lalantha Leelarathna of the Institute of Metabolic Science at the University of Cambridge in the United Kingdom. The third type of algorithm attempts to replicate how a physician would advise a patient to control his or her blood sugar and applies the recommendation using fuzzy logic, which makes decisions based not on binary yes-no answers but on truth variables that range between 0 and 1. “We took our experience and incorporated it into an algorithm,” says Moshe Phillip of the Schneider Children’s Medical Center of Israel in Petah Tikva.

Researchers are now testing these more advanced systems by inviting subjects for short stays in the hospital. In 2013, several teams let subjects take the systems home for a few days, as Jane did, or test them in hotels or at a children’s “diabetes camp.” Not all the results of these trials have been published yet, but Kowalski says that “the results have been amazing, showing a dramatic decrease in hypos and hypers [high blood glucose] and a positive effect on the social aspects of diabetes,” such as a freedom from worry and a chance to lead a “normal” life.

Some of the systems tested were designed to be used only at night. “Night is the most dangerous time,” Phillip says. Some parents

rise several times every night to test a sleeping child's blood sugar. The "Glucositter" system that he and his team are developing "will change the quality of life for parents," he says.

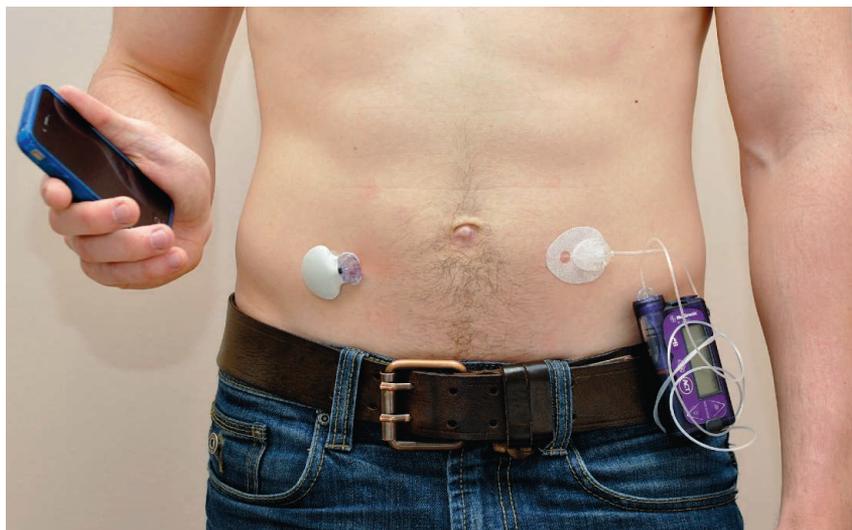
Systems designed to work round the clock, however, still require some input from the user to deal with daytime activities such as eating or exercise. The huge influx of carbohydrate in a meal poses perhaps the biggest challenge. In a nondiabetic person, the β cells in the pancreas are relatively dormant between meals. Other cells known as α cells take charge and produce a hormone called glucagon, a sort of anti-insulin that signals the liver to release stores of glucose to keep the body ticking over. When the person sees and smells food and knows that a meal is on the way, the body starts getting ready. The brain turns off the α cells and sets the β cells producing insulin, which in turn tells the liver to switch from secreting glucose to storing it. Within 10 minutes, the body is primed and ready to digest the meal.

In a diabetic, the body can't prepare in this way. And because injected insulin can take up to 2 hours to reach peak activity, a patient's blood sugar level often rises above the target range in the hours after a meal before leveling off as the insulin takes effect. With an artificial pancreas, the situation is even worse because the CGM takes time to detect the meal: half an hour or more for the carbohydrate to reach the bloodstream, 15 minutes for it to reach the interstitial fluid where it can be detected, and another 6 to 15 minutes for signal processing. Algorithms also have trouble gauging the size of a meal from the scanty information the CGM provides early in the digestive process. So the device could easily administer too much insulin and—because the hormone remains active in the body for up to 4 hours—trigger a hypo hours later.

To get around this problem, some researchers require users to warn the system that a meal is on the way. The artificial pancreas can then either base a dose on a user's estimate of how much carbohydrate he or she is about to eat, or simply administer a starter dose of insulin and then top

up as necessary once blood sugar readings begin to rise. Users may soon be able to assist the system by taking a premeal puff from an insulin inhaler. The drug company MannKind Corp. has developed a very quick-acting inhalable insulin called AFREZZA. FDA turned AFREZZA down for approval in 2011 because the agency wanted more information, but MannKind resubmitted the product in October and hopes for approval in April 2014.

Such approaches help reduce postmeal blood sugar peaks and later troughs. Many researchers, however, want to provide a fully hands-free system. "We're trying to do this invisibly and automatically. But we need faster insulin, and we need faster CGMs," says chemical engineer Frank Doyle of the University of California, Santa Barbara. Companies are working on ways to speed insulin into the bloodstream by altering its molecular structure or using drugs or small electric heaters to change the properties of skin and tissue.



Technological fix. In an artificial pancreas, a glucose sensor (on stomach, left) transmits readings to a controller (here in a smartphone), which instructs an insulin pump to administer the required dose.

Perhaps the fastest approach is to inject insulin straight into the abdominal cavity near the liver and pancreas, where it can get to work instantly and signal the liver to halt releasing glucose before a meal. "This would speed up considerably what you can do with a fully automatic system," Doyle says. The pharmaceuticals company Roche has developed a permanent injector called DiaPort, but because of the complications of a permanently inserted device, only a tiny number of diabetics now use it.

Others are working on making CGMs faster and especially more reliable. Current systems are not only slow to respond but can

also make mistakes. Miscalibration, a dislodged sensor, or a loss of sensor sensitivity can cause spuriously high readings of blood glucose, resulting in a serious hypo. "Outliers are the main problem," says Kowalski, who believes developers will have to use techniques from critical systems engineering, such as redundant sensors and failure analysis, to spot erroneous readings.

Alternatives to the electrochemical signals now used to detect glucose could also yield better CGMs. Some makers are developing sensors that shine light through the skin and look for wavelengths that glucose absorbs. Other systems inject proteins that fluoresce in the presence of glucose and use light sensors to spot the telltale glow. JDRF is now working with several companies to develop a single sensor that uses both electrochemical and optical techniques as a fail-safe.

Another safety mechanism employs a pump that can separately dispense both insulin and the anti-insulin hormone glucagon. When blood glucose readings dip too low, a squirt of glucagon quickly brings them up again. A team at Boston University tested the idea using two pumps in 2013 with "very, very impressive results," Kowalski says. JDRF is working with the device manufacturer Tandem Diabetes Care on a dual-hormone pump. Right now, glucagon is not stable in solution for long periods, but drug companies are working on a reformulated long-lasting version of the hormone.

Whether developers will ever get to a fully automated system that diabetics can insert and forget remains to be seen. But "we shouldn't let perfect be the enemy of good," Kowalski says. Stuart Weinzimer of the Yale University School of Medicine agrees: "We don't need these things to be perfect. It doesn't matter what system is best. Just make them available to market and let clinicians decide." As for those who stand to benefit from an artificial pancreas, Jane says, all that matters is that the devices work. In that case, pump and tubes notwithstanding, "it will feel like not having diabetes."

—DANIEL CLERY