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Eggerman said. “In the meantime, patients with severe hypoglycemia can benefit.”

But Remuzzi said that while he would like to see research on islet transplantation continue, patients should be offered this experimental therapy only in the context of a randomized controlled trial that compares the outcomes of patients with islet transplants with those who remain on insulin therapy or those who have received a

whole pancreas transplant. “We have a moral obligation to start these activities only in the context of controlled trials,” he said.

Others, including Hering, disagree, noting that because the field is evolving very quickly, it would be better to wait until it has advanced further before launching such expensive trials. “Once we have an unlimited supply of tissue and maybe a next-generation immune therapy, then a

prospective randomized clinical trial should be performed, absolutely,” he said.

Bromberg also noted that the huge costs of controlled trials have been an obstacle for the field. In the meantime, he suggested continuing human studies—within limits. “For the foreseeable future, islet transplantation should still be done; it should be done in the few centers who do it extremely well and have a lot of experience.” □

Artificial Pancreas May Soon Be a Reality

M. J. Friedrich

THE PAST 40 YEARS HAVE PRODUCED enormous advances to help people with type 1 diabetes keep their glucose levels in check. Still, even with devices such as insulin pumps to deliver the hormone and continuous glucose monitoring sensors to check blood glucose levels every few minutes throughout the day, many patients still experience wide fluctuations in their glucose levels or have trouble reaching their blood glucose targets, noted Aaron Kowalski, MD, director of research at the Juvenile Diabetes Research Fund (JDRF), New York City, referring to recent research (JDRF Continuous Glucose Monitoring Study Group. *N Engl J Med.* 2008;359[14]:1464-1476).

The solution may lie with yet one more technology: a device designed to mimic the pancreas by automatically responding to changes in glucose levels in the body. Long sought by the diabetes community, this artificial pancreas would take information directly from the continuous glucose monitor and respond with an appropriate dose from the insulin pump—in other words, making dosing decisions without involving the wearer. While not a cure, such a device could be thought of as a “bridge to the cure,” said Kowalski.

CLOSING THE LOOP

For the last few years, researchers have been testing the concept of “closing the loop” between the continuous glucose monitor and the insulin pump with a computer algorithm that calculates rates of insulin delivery. Preliminary studies using off-the-shelf insulin pumps and continuous glucose monitoring sensors have suggested that in research settings, closed-loop systems that automatically dispense insulin can achieve better control of glucose levels than open-loop systems in which a person makes dosing decisions (Steil G et al. *Diabetes.* 2006;55[12]:3344-3350).

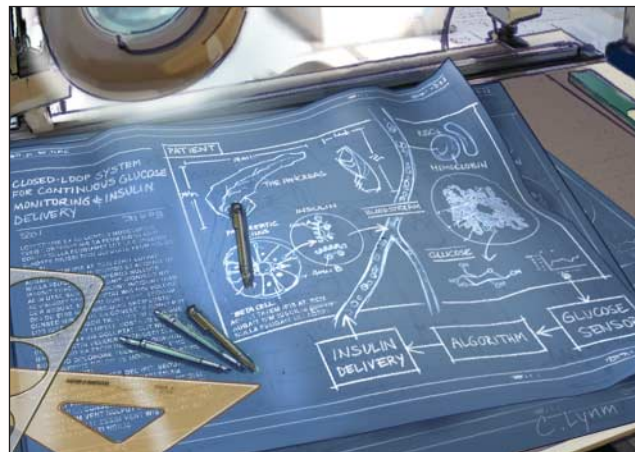
Such promising results prompted the JDRF to push the research forward by launching its Artificial Pancreas Project

3 years ago. In 2006, the US Food and Drug Administration (FDA) designated the artificial pancreas a priority within its Critical Path Initiative (<http://www.fda.gov/oc/initiatives/criticalpath>).

Realistically, a complete closed-loop system is a number of years away. The introduction of this technology is likely to be gradual, evolving from simpler applications to fully automated glucose control. But, noted Kowalski, the potential is high for delivering a system of this type that could transform diabetes care.

OBSTACLES TO OVERCOME

Not surprisingly, safety is the main concern about a device that automatically dispenses a substance as potent as in-



Scientists are working to develop an artificial pancreas that uses a computer algorithm to process readings from a continuous glucose monitor and direct an insulin pump to deliver insulin at appropriate rates.



sulin. Top diabetes researchers, engineers, and mathematicians are working together to create a road map for bringing the technology safely to patients outside the laboratory, said Kowalski.

One issue is that the accuracy of available continuous glucose monitoring sensors has room for improvement. People who use them rely on finger sticks to confirm glucose values before making adjustments to their insulin. In closed-loop systems, the readings from these sensors will be used differently, to make frequent but very small adjustments. And built-in fail-safe mechanisms will alert the wearer to inaccurate readings or malfunctions and allow human overrides of dosing decisions.

Another concern is that in current closed-loop systems, insulin delivery occurs only after glucose levels start to rise. This is in contrast to a healthy pancreas, which begins secreting insulin when a person smells or even thinks about food. "So you're always chasing after the blood sugars a little bit and always playing catch-up," explained Stuart Weinzimer, MD, associate professor of pediatrics at Yale University Medical School, New Haven, Conn.

Another issue is that rapid-acting insulin does not act as rapidly as one might hope, said Irl Hirsch, MD, professor of medicine at the University of Washington, Seattle. It can take 90 minutes for insulin injected subcutaneously to do its job, which is too slow to make immediate changes, he said.

Researchers are working on smarter-acting insulins, such as a glucose-responsive insulin, which is released in the body only when glucose rises above a certain level. This drug may reduce the number of required insulin injections to one per day. Although promising, this approach is a few years away from clinical testing.

Glucose-responsive insulin, which can be thought of as a nanoartificial pancreas, could be an important tool in diabetes control but the timeline for bringing this to market appears longer than that for the artificial pancreas, ex-

plained Kowalski. The scientists at JDRF are looking at different timelines for different approaches, including stem cells, which would be the ultimate solution, he said. But at this point "the mechanical looks faster than the nanomechanical, and both will happen sooner than the biological solution" he said.

INTERMEDIATE STEPS

Meanwhile, in the short term, a semi-closed, or hybrid, loop may help to address at least some of these challenges. The hybrid-loop system includes a computer algorithm but also allows some input from the patient.

Last year Weinzimer's group published results from a study involving 17 adolescents with type 1 diabetes that compared 8 participants who were on closed-loop control with 9 participants on hybrid-loop control who injected themselves with small priming boluses of insulin before meals (Weinzimer SA et al. *Diabetes Care*. 2008; 31[5]:934-939). The hybrid-loop control group showed improved glucose control, with their mean blood glucose levels being 135 mg/dL compared with 141 mg/dL among those on fully closed-loop control.

Further refinements are needed because postprandial glucose levels were still not completely normalized in the participants following the hybrid-loop protocol, said Weinzimer. Still, he added, "we showed that with only a little simple human intervention we could improve control."

Study coauthor William Tamborlane, MD, professor and chief of pediatric endocrinology at Yale and insulin pump pioneer, emphasized that even a fully closed-loop system will not be completely automatic because the person will have to perform operations such as calibrating the sensor and making sure the pump is working.

The Yale researchers are continuing to explore fully closed-loop systems in ongoing experiments. In one study, now enrolling individuals, they are looking at whether such a system is robust enough to deal with short-term

bursts of exercise. "Subjects will be admitted to the hospital where they will exercise moderately for about an hour wearing the closed loop and we'll see what happens to their blood sugars," said Weinzimer.

Another pilot feasibility study is looking at whether adding the adjunct drug pramlitide to the regimen of a person on a closed-loop system can give normal glucose control. Pramlitide is a synthetic form of the naturally occurring hormone amylin that smoothes out glucose spikes in people with type 1 diabetes. The drug works primarily by slowing gastric emptying, which can slow down carbohydrate absorption. "Instead of getting these big glucose spikes, you tend to get more modest, longer-duration spikes that are a little easier to control," said Weinzimer.

VIRTUAL TESTING

The linchpin of the artificial pancreas is the computer algorithm, which translates glucose sensor data into insulin dosing instructions for the pump.

There are essentially two competing schools in algorithm development for the closed-loop system. The Yale researchers have been using a system called proportional integrative derivative (PID) control that uses feedback control to maintain normal glucose levels. The alternative is model predictive control (MPC), a more sophisticated approach that models the glucoregulatory system, tunes the release of insulin to predicted glucose excursions, and can be tailored to each individual through the input of personal information such as weight and glucose and insulin levels.

Although pumps and sensors have FDA approval, the computer algorithms that connect the two devices must still be rigorously tested. Traditionally, animal models have been used to assess the feasibility of using algorithms for human trials, but last year the FDA accepted a computer simulation environment for the testing of these algorithms that was developed by a team led by Claudio Cobelli, PhD, professor of bioengineering at the Univer-



sity of Padova, Italy, and Boris Kovatchev, PhD, director of the diabetes technology program at the University of Virginia, Charlottesville.

The result of 10 years of data collection and research, this system is essentially a computer simulator of the human metabolic system that is equipped with the in silico images of 300 people with type 1 diabetes: 100 children, 100 adolescents, and 100 adults, said Kovatchev. This approach, referred to as in silico modeling, is cheaper and quicker than animal testing. “We can do trials in 10 minutes that would have taken years of animal experimentation,” he said.

As a case in point, in only 3 months of using the in silico modeling system, Kovatchev’s group received FDA approval to conduct a clinical trial of a fully closed-loop system using an MPC algorithm that is personalized for each individual. Similar approvals based solely on in silico testing were issued for parallel clinical trials in Italy and France.

When these trials are completed, each of the 24 individuals with type 1 diabetes will have undergone two 24-hour admissions involving identical eating, sleeping, and activity patterns. The first admission is an open-loop session in which glucose levels are controlled by the individuals; the second admission is under automatic closed-loop control. The results of the two admissions for each individual will be compared to determine which approach achieved better glucose control.

“Closed loop looks like it can do so much better, particularly overnight,” remarked Kovatchev, referring to preliminary results from 12 individuals that were reported at the Diabetes Technology meeting in Bethesda, Md, last November. The most interesting effect was a dramatic 5-fold reduction in the number of hypoglycemic episodes observed overnight.

One crucial step in development of the artificial pancreas is prevention of overnight hypoglycemia, which seems

within reach with this approach, noted Kovatchev. The team’s next goal, called control to range, is to reduce the number of hypoglycemic and hyperglycemic episodes and keep patients within a target glucose range for a greater percentage of the time.

NONTECHNICAL HURDLES

As researchers work to meet these technological challenges, ensuring that the current devices are covered by health insurance is also key.

University of Washington’s Hirsch noted, “Because of the JDRF study (see above, *N Engl J Med.* 2008;359 [14]:1464-1476) we’re finally starting to see more reimbursement for continuous glucose monitors, which is important.”

But he added that reimbursement should not stop at technology. “There’s a great need to reimburse physicians and nurse educators for time spent educating and following up with patients on using the technology successfully,” he said. □

FDA Warns Against Shared Insulin Pens

Bridget M. Kuehn

AFTER IMPROPER USE OF INSULIN pens at two hospitals put more than 2000 patients at risk of contracting a blood-borne disease, the US Food and Drug Administration (FDA) is warning clinicians and patients about the risks of sharing insulin pens and cartridges.

The agency issued the warning in March after it became aware that medical personnel at two Army hospitals had used multidose insulin pens intended for use by a single patient on multiple patients. According to the FDA, although the staff at the two hospitals reportedly changed the disposable needles used in the devices between patients, the pen itself or the insulin cartridge might have become contaminated, putting subsequent patients at risk.

In late January, officials at William Beaumont Army Medical Center in El Paso, Tex, became aware that between August 2007, when multidose insulin pens were first used at the hospital, and January 2009, staff were using the same insulin pen for multiple patients, according to a February press release from the hospital (<http://www.wbamc.amedd.army.mil/documents/PressReleases/02062009.html>). Such use may have put the 2114 diabetic patients admitted to the hospital during that period at risk.

The press release also noted that the discovery led them to review of the use of these devices at all Army facilities, and that review revealed that the device also had been improperly used at the Bayne-Jones Army Community Hospital in Fort Polk, La. However, 15 or fewer individuals may have been put

at risk in that facility. Both hospitals are contacting these patients and offering them screening for hepatitis B, hepatitis C, and HIV.

A notice has been sent to all Army medical facilities by the Army Surgeon General that emphasizes insulin pens are only to be used on a single patient, and additional training has been instituted for staff using these devices, according to the Texas medical center’s press release.

Some of the patients at risk from these incidents have tested positive for hepatitis C, but it is not known whether they were infected by a contaminated insulin pen or if they had undiagnosed hepatitis C prior to these incidents, according to the FDA’s alert (http://www.fda.gov/cder/drug/InfoSheets/HCP/insulin_pensHCP.htm#). □