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# COUNTDOWN

An Artificial Pancreas

How Close

Are We To

Closing

The Loop?

The 40-year old idea of using a machine to replace the lost endocrine pancreas function in people with diabetes is approaching reality. Technology has finally caught up with the work of people like Dr. Arnold Kadish, who is credited with devising the first experimental closed-loop artificial pancreas in 1964. The idea evolved by 1977 into a machine still in use today, the Biostator.

BY WAYNE L. CLARK  
ILLUSTRATION BY DAVID CUTLER

**JDRF** Juvenile  
Diabetes  
Research  
Foundation  
International

*dedicated to finding a cure*

**T**he problem is, the Biostator is roughly the size of a dormitory refrigerator, and requires two catheters inserted in the patient. One draws out blood and measures the glucose level, and the other infuses the appropriate amount of insulin. Obviously not suitable for daily consumer use, it has found a home in clinical laboratories, where the ability to manipulate blood glucose levels is an important part of diabetes research.

The old idea of an artificial pancreas is new again. JDRF has made the development of a closed loop artificial pancreas one of its six research goals to be achieved within five years.

Over the past few years, JDRF has partnered with the U.S. Army and the National Institutes of Health (NIH) to further development and clinical applications of glucose sensing technologies, says Aaron J. Kowalski, Ph.D., scientific program manager for JDRF. "Private companies have been investing heavily in this area as well, and we have channeled our resources into complementary areas. We now plan to actively pursue opportunities in both research and advocacy that will speed progress towards closing the loop."

"The need is urgent," Dr. Kowalski says. "The 1993 Diabetes Control and Complications Trial (DCCT) and other research since then has shown that tight blood sugar control significantly reduces the risk of diabetes-related complications. However, tight control is extremely difficult to achieve and the majority of patients are not reaching recommended Hemoglobin A1C levels [HbA1c, a measurement used to reflect glucose levels over 8 to 12 weeks]. This must change."

Since 2001, JDRF has worked with the U.S. Department of Defense, along with the NIH and the National Aeronautic and Space Administration (NASA), in a project called Technologies for Met-

abolic Monitoring (TMM). The unique partnership combines JDRF's interests in glucose monitoring with that of the military in being able to remotely monitor the condition of soldiers in the field.

JDRF's contribution to the metabolic monitoring project has been to help the Defense Department identify research priorities and attract top researchers, and to lobby Congress for continued funding of the project.

technologies that will allow them to take better care of themselves, and to make that easier. We want to make this happen sooner."

"It won't be just research funding," says Lawrence Soler, JDRF vice president for government relations. "This effort will require both research and advocacy. For these new technologies to reach people with diabetes, we need to work in Washington, D.C. to help them

## A system that could be used for overnight hypoglycemia prevention would be a vast improvement for people with diabetes.

JDRF is also involved in securing federal funds for and providing input to the Diabetes Research in Children Network, or DirecNet. This national network of clinical centers is dedicated to researching the use of glucose monitoring technology and its impact on the management of type 1 diabetes in children. It is sponsored by the NIH, and its work includes assessing the optimal use of continuous glucose sensors, their accuracy, and their impact on quality of life.


"With the recent approval of a continuous glucose sensor and other exciting technologies in the pipeline, JDRF has carefully assessed the field to find opportunities to speed progress," Kowalski says. "A comprehensive plan was recently presented to the JDRF Board of Directors and we have already begun its implementation. With this plan, we want to ensure that people with diabetes will have access to safe and effective

get approved by the federal government and covered by government and private health insurance. We want a thriving marketplace that will encourage companies to develop an artificial pancreas and its components, bring them to market, and make them available to all people with diabetes."

The renewed emphasis on the artificial pancreas is welcomed by clinicians.

"This is particularly important for children and adolescents," says William V. Tamborlane, M.D., professor and section chief of pediatric endocrinology at Yale University, "because until there's a breakthrough in transplantation that doesn't require immunosuppression, you're not going to want to expose young people to immunosuppressive therapy."

Dr. Tamborlane also chairs the DirecNet Steering Committee, and has a long-standing interest in insulin pumps for children.



Immunosuppression is a concern because it carries long-term risks that can be as significant as those associated with a similar length of time on insulin therapy. Young children, who could benefit most from early islet transplantation, might be trading one disease for another.

Another reason for the uptick in interest in the artificial pancreas is the discovery that blood glucose control is important in surgical patients and intensive care patients, even those who do not have diabetes. Strong evidence indicates that high blood glucose, which can occur even in non-diabetic patients who are critically ill or have had major surgery, contributes to a higher incidence of infections. It also has a negative influence on blood pressure and increases clotting.

In light of these findings, biotechnology companies can consider a larger market for the artificial pancreas or its components, such as a continuous glucose sensor.

Add to this the increasing ability to miniaturize components, the improvement of short-distance wireless communications, and new fast-acting insulin analogs—as well as a renewed major infusion of support from JDRF—and the stage is set for a leap forward in the development of an artificial pancreas.

### THE MACHINE

The artificial pancreas must have three components: a sensor that continuously monitors glucose levels, an insulin delivery system, and computer program algorithms that calculate the correct insulin dose based on the sensor readings. The sensor has until recently been the most significant barrier to achieving a closed-loop system, but there is recent progress on several fronts.

The standard glucose meters used to check blood drawn with fingersticks make use of a chemical reaction in which the enzyme glucose oxidase reacts

with glucose. That same reaction forms the basis of the Medtronic MiniMed Continuous Glucose Monitoring System (CGMS), approved by the FDA in 1999. It continuously records glucose levels in the interstitial fluid—which lies between blood vessels and the cells, under the skin—by means of a glucose oxidase-plated platinum electrode. The sensor is worn for three days, and calibrated once a day with a standard blood glucose meter. The system doesn't display the information for the patient, but it is

downloaded in the physician's office at the end of the three days. The concept is similar to that of the Holter Monitor used to record heart activity over a period of time.

The CGMS has been used to help patients and physicians get a better picture of how blood glucose levels vary throughout the day and night, especially those "excursions" above or below the target range that may not be picked up by routine testing. It also has been valuable for clinical research, showing how



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blood glucose levels can be affected by medications, surgery, different insulin formulations, and other factors.

The lifetime of the glucose oxidase sensor is limited. As a foreign substance, it triggers the body's protective measures which slowly erode the sensor's accuracy. Like most subcutaneous catheters, such as an insulin pump catheter, it must be changed every few days in any event in order to avoid infection.

Medtronic MiniMed has developed a new continuous sensor based on the glucose oxidase reaction. The Guardian RT ("Real Time") received FDA approval in August 2005. The system records as many as 864 glucose readings during a three-day period, after which the sensor is replaced. The sensor wirelessly transmits readings to a monitor every 5 minutes. The patient reads the glucose value on the monitor's screen and decides on an insulin dose. Patients can set alarms to warn them of dangerously high or low levels, and all the information can be downloaded to a computer and displayed as reports and charts. The system needs to be calibrated twice a day using a standard blood glucose meter.

The company is currently testing a system that would tie the Guardian RT to an insulin pump. The pump would calculate a recommended dose, and the wearer would decide if it was appropriate. This is sometimes referred to as an "advise you" open loop system.

Abbott Laboratories, which acquired TheraSense and its FreeStyle product line in 2004, is developing the "FreeStyle Navigator." This system consists of a biochemical sensor that is inserted under the skin, a transmitter that snaps onto the sensor, and a pager-sized receiver. Information is transmitted wirelessly once every minute. The display shows glucose readings, arrows indicating the trend in the readings, and the rate of change in the trend. The FDA is currently review-

ing a "Pre-Market Approval" application for the product.

San Diego-based DexCom is developing the STS Sensor, which also consists of a sensor inserted under the skin, a wireless transmitter, and a receiver that displays continuous glucose readings and trend information. It also has high and low alerts. The sensor will need to be replaced every three days. The system is currently under FDA review.

DexCom is also working on a long-term sensor that would be implanted in a surgical procedure under local anesthetic and would last for a year.

There are other approaches under investigation in at least two dozen laboratories. Some are noninvasive or minimally invasive and measure the glucose in interstitial fluid. Others are intended to be implanted deep in the body, inside veins where they can measure blood glucose levels.

One minimally invasive method actually brings the interstitial fluids out of the tissue so they can be tested. A technique called reverse iontophoresis applies a weak electrical current to the skin, and pulls interstitial fluids out through the skin and into a measuring device. The Cygnus GlucoWatch G2 Biographer, introduced in 2001, uses this method. The device must be calibrated with a standard blood glucose meter when the sensor is changed, every 13 hours.

SpectRx, a Georgia-based company, is developing a technology that uses a laser to create microscopic holes through the outer layer of dead skin. The interstitial fluid then flows out of the holes into a patch that contains a standard glucose sensor. The results are displayed on a wireless meter.

A new generation of sensors also measures glucose levels in the interstitial fluids, but uses a different minimally invasive technology called microdialysis. A thin catheter is inserted into the sub-

cutaneous fatty layer under the skin. A perfusion fluid inside the catheter is in continuous contact with the interstitial fluid, and pulls glucose into the catheter. The perfusion fluid is then pumped out into a measuring device.

Light—or more accurately, infrared or near-infrared light—may prove useful as a noninvasive way to measure glucose. In theory, glucose either absorbs or scatters light differently than other constituents of the skin and subcutaneous tissue, and measuring the effect of a beam of light could provide the information to calculate glucose levels.


Among the companies working with near-infrared light is Sensys Medical. Their technology uses diffuse reflectance spectroscopy to detect how much light is absorbed by various molecules. Each type of molecule has its own absorption profile, so the idea is to measure the proportion of light absorption that corresponds to glucose.

A different kind of light, fluorescence, may eventually provide a means of glucose detection and measurement. GluMetrics is a California company that has developed a glucose sensing technology called GluGlow. This boronic-acid based substance glows in the presence of glucose. The company's first application will be a catheter tipped with GluGlow, that can be used to monitor hospitalized patients.

Animas is one of the companies "going deep" with glucose sensor technology. Their product is intended to be surgically implanted in the abdomen and will measure blood glucose levels by passing a light beam through a blood vessel.

### INSULIN PUMPS

Insulin delivery is the furthest along of the three artificial pancreas components. A true artificial pancreas clearly cannot rely on manual injections of insulin, so the advent of the insulin pump was a



critical step. The first prototype insulin pump was the size of a backpack and was worn as one. Since the first commercially available insulin pump was introduced in 1983, the machines have steadily become smaller, more accurate, and more user-friendly.

The pump created a revolutionary change in how people with type 1 diabetes receive their insulin. Instead of subcutaneous injections several times a day, the pump continuously infuses a “basal” dose of insulin through a very thin catheter inserted under the skin. The continuous infusion mimics a real pancreas. The pump wearer can give “bolus” doses to compensate for the carbohydrates they take in at meals, or suspend the basal rate if their blood glucose level is running too low. The user must still check blood glucose levels with a conventional meter, usually four to five times a day.

In July 2003, the FDA approved an integrated blood glucose meter and insulin pump from Medtronic MiniMed and Becton, Dickinson and Company. It combines the Paradigm 512 pump with the Paradigm Link Blood Glucose Monitor, which includes a dose calculator. This is an “open loop” system that still requires the user to test his or her blood with finger sticks, but the meter sends the data to the pump, which performs a calculation and recommends a dose. The user decides if the recommendation is correct, then pushes a button to tell the pump to deliver it.

In mid-2005, Deltec released a combination pump and monitor in a single unit. The catheter-based system consists of a blood glucose module that snaps onto an insulin pump and communicates with it wirelessly.

The latest variation is an “unterminated” pump that eliminates the need for a physical connection between the pump and the insertion point of the cath-

eter. The Insulet OmniPod consists of a small insulin-containing “pod” pump that sticks to the skin, and a unit that is both a glucose meter and a wireless controller for the pump. The device received initial FDA clearance earlier this year, and the company hopes to have it available in late 2005.

### **PUTTING IT ALL TOGETHER**

Once the loop is closed, the system must be flexible and “smart.” The ability to control blood glucose with an artificial pancreas is subject to the same issues as

any testing and insulin delivery system. In fact, control of blood glucose by any means other than the native pancreatic beta cell is complicated by food intake, physical activity level, stress, illness, and sleep. An artificial pancreas has to account for all these variables with a computer program.

“Even with current open-loop therapy, the transition from conventional fingerstick blood monitoring to continuous glucose monitoring will be difficult enough,” Dr. Tamborlane says. “When you’re deciding your pump dosage, you

## **DirecNet**

The mission of the Diabetes Research in Children Network (DirecNet) is to investigate the potential use of glucose monitoring technology and its impact on the management of type 1 diabetes in children. It is co-funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Child Health and Human Development (NICHD) and is made up of five clinical centers and one data coordinating center. JDRF is represented on the DirecNet Steering Committee and actively seeks continued federal funding for the network.

### *Current studies include:*

- A Pilot Study to Evaluate the Navigator Continuous Glucose Sensor in the Management of Type 1 Diabetes in Children
- The Effect of Basal Insulin During Exercise on the Development of Hypoglycemia in Children with Type 1 Diabetes
- Nocturnal Hypoglycemia Prevention Study

### *Previous studies:*

- The Accuracy of Continuous Glucose Monitors in Children with Type 1 Diabetes
- A Pilot Study to Evaluate the GlucoWatch 2 Biographer in the Management of Type 1 Diabetes in Children
- The Effect of Exercise on the Development of Hypoglycemia in Children with Type 1 Diabetes

### **DirecNet CENTERS**

- Barbara Davis Center for Childhood Diabetes, Denver, CO
- Nemours Children’s Clinic, Jacksonville, FL
- University of Iowa Carver College of Medicine, Department of Pediatrics, Iowa City, Iowa
- Yale University School of Medicine, Department of Pediatrics, New Haven, CT
- Stanford University, Division of Pediatric Endocrinology and Diabetes, Stanford, CA
- Data Coordinating Center: Jaeb Center for Health Research, Tampa, FL

**For more information, visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and search for ‘DirecNet’**

## CLOSING THE LOOP

won't be locked in to four, five, or six tests a day. You can actually see what your blood sugar is doing every five minutes. That's going to be challenging for doctors as well as patients because when you get all this information, you have to know how to deal with it."

Some believe that closing the loop might be simpler in many ways.

"When we asked ourselves how a patient would use all the information a continuous monitor could provide, it became difficult to come up with all

the various scenarios," says Darrell M. Wilson, M.D., professor and chief of pediatric endocrinology at Stanford University. "If they were on insulin glargine and lispro four times a day, how would they use the information? What would you tell somebody if it was an hour and a half after a meal and they had taken their humalog? Did you forget to give your shot? Did you underestimate your carbohydrates? Is this just a bad day?"

"That's why we wonder if it might be better to go ahead and close the loop,"

Dr. Wilson says. "Then you would be dealing with one or two algorithms. One of the advantages of closing the loop is that it 'steps over' the need to understand how best to use the information.

"Linking these pieces together is not trivial. If you consider that it's autopilot at that point, you have to be very sure that you're not going to risk a catastrophic failure. Even with an 'advise you' system, people will put a lot of faith in the system's advice, so you want to make sure it's good advice."

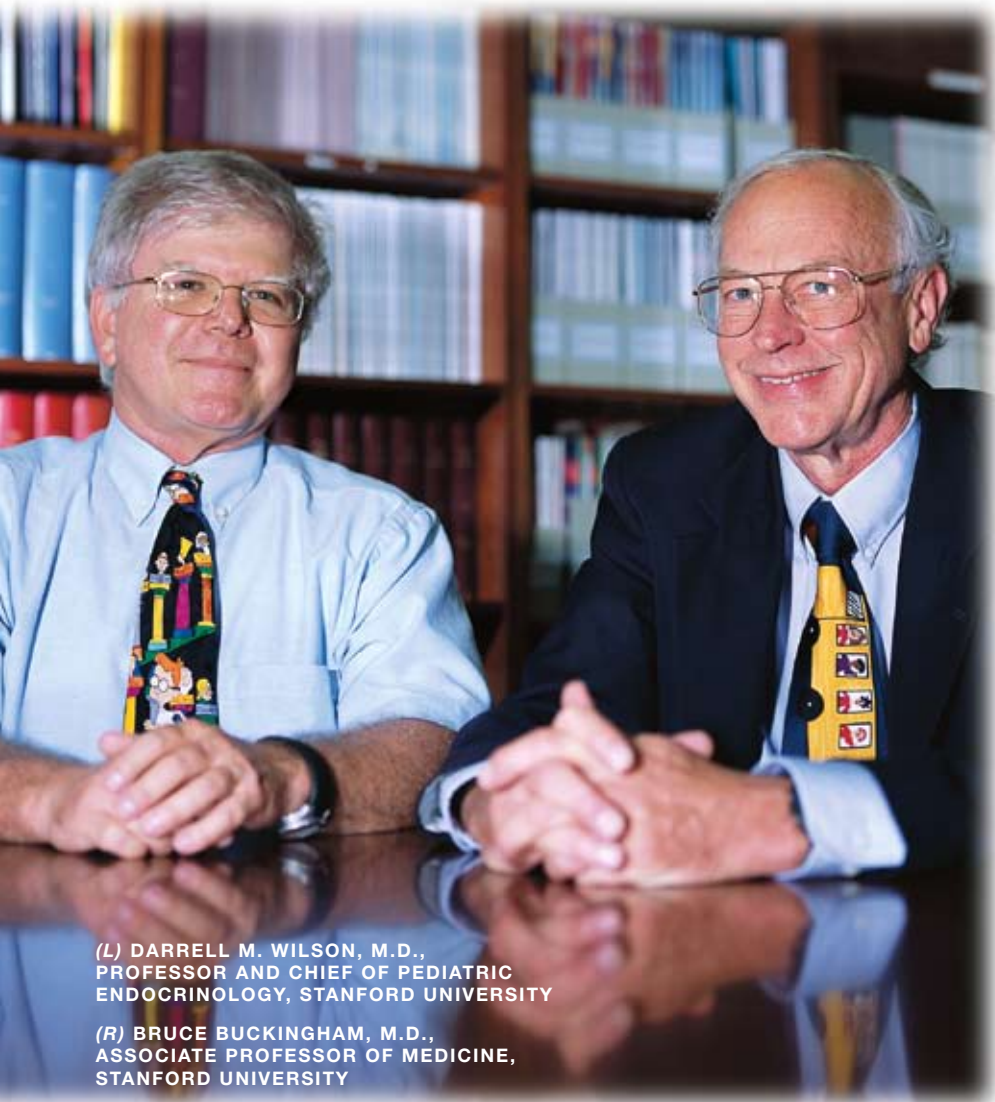
The problem with the accuracy of today's sensors, and the way they might be used to operate an insulin pump, is largely a matter of kinetics. Put another way, there are delays in the system in both measurement and insulin delivery for which an algorithm has to account.

"There is about a 10 to 15 minute delay before subcutaneously delivered insulin becomes effective," says Bruce Buckingham, M.D., associate professor of medicine at Stanford University. "But when you eat, your blood sugar goes up quickly, so you get a mismatch between the insulin you need and the insulin you get. Also, insulin delivered subcutaneously lasts about four to six hours, so if you deliver a lot of insulin to try to keep your blood sugar from going too high after a meal, then you may be at risk from the residual insulin causing a low blood sugar four to six hours later.

"There also is a delay for the sensor itself. Most of the sensors we have at present are subcutaneous, so there is a delay of anywhere from five or six minutes to 15 minutes as the glucose moves from the blood to the interstitial space."

What's more, the sensors are coated with a biocompatible membrane to stall the body's attempt to cover over the foreign body, and the membrane creates a 'sensor lag' of several minutes.

"If you're in a 'steady state', where you're not inducing a lot of changes,"



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Dr. Buckingham says, “the sensor does very well in closing the loop. It is the meal-related issues that are going to pose the challenge.”

On the other hand, despite the lag time, measuring interstitial glucose levels may be more relevant to what the body needs.

“For 25 years we have been using blood glucose measurements, and everyone’s used to them,” Dr. Buckingham says, “but the more important level may be the brain glucose. The interstitial fluid is in between the blood and the cells, so it has been suggested that the interstitial fluid more closely reflects what’s going on in the brain. It required a paradigm shift in our thinking when we made the transition from using urine glucose measurement and changed to blood glucose measurements to manage diabetes. It may be time to make another paradigm shift in how we think about glucose levels.”

### HOW GOOD IS GOOD ENOUGH?

When will the technology be far enough along to allow “closing the loop?”

“There are two schools of thought,” Dr. Wilson says. “One is that it has to be perfect, and produce results that reflect nondiabetic physiology almost exactly. The other is that we need a technology that is better than what we have now, that it doesn’t have to be perfect. I’m in the latter camp. If we can show a significant improvement in control, we would go a long way down the road to helping people with diabetes. Waiting for perfection ignores the difficulties that all our patients and families have with the current technology.

“If you had a reasonably reliable sensor that controlled a pump in a reasonable fashion, and you could stay within 25 points of target, you could set it at 125 and run between 100 and 150,” Dr. Wilson says. “There may be a few people managing that now, but the vast

majority are well outside that degree of variability.”

Even a system that could be used for overnight hypoglycemia prevention would make for a vast improvement in the quality of life of people with diabetes, especially children and their parents.

“If we can get results that are much better with the same effort or less effort, I think most of our patients and families would be happy with that,” Dr. Tamborlane says. “If a parent could know that they just have to turn a switch a night, and that the likelihood of getting low is minimal, they could sleep through the night. You could adjust for some inaccuracies in the sensors just by shooting for a higher target.”

To illustrate the point, Dr. Tamborlane poses the example of a closed loop system with a sensor that is much less accurate than the ones currently available, that reads 50 percent higher than the actual value. If the sensor was set to a target of 120 mg/dl, the lowest the actual blood glucose level could get would be 80 mg/dl before the pump stopped delivering insulin.

“I think most of my patients would be happy if they could wake up at 120 and know they’d go no lower than 80,” Dr. Tamborlane says. “Even if it was off by 50 percent, you’d still be safe. The more accurate the better, of course, but you have a margin of error.”

The artificial pancreas will almost certainly evolve over time, with the units becoming less of an intrusion for patients.

“It’s important to remember that we are in the first generations of these devices,” says Dr. Buckingham. “Current sensors and transmitting devices will become smaller. It may be possible to combine the insulin infusion set and the glucose sensor into a single, subcutaneously-inserted device, with the entire unit the size of a quarter on the skin sur-

face. A small, waterproof system would allow full daily activities, participation in sports, and could be used by young children as well as adults. Not many patients would wear a backpack all day to deliver insulin, but thousands—including infants and toddlers—use the small insulin pumps of today.”

The ultimate artificial pancreas, many believe, would be a system that could be

## We’re much closer than people think.

implanted within the body. That would remove not only the need for a person to actively manage it, but also would remove the external pump, meter, and sensor and the associated inconvenience of having them appended to the body. Other observers are skeptical.

“I’m not so sure about a fully implantable system,” Dr. Tamborlane says. “There are technical problems with it. The refill process, for instance, is like a mini-surgical procedure, because it has to be done under sterile conditions. I think the external route might be fine for most people.”

That hasn’t stopped some investigators from pursuing an implanted closed loop system. In fact, the first clinical trial of a fully-implanted artificial pancreas is underway in France. The trial is under the direction of Eric Renard, M. D., Ph.D., professor of endocrinology, diabetes, and metabolism at Montpellier Medical School in Montpellier, France. The system consists of a sensor that is implanted in a neck vein, and an implantable insulin pump connected to the sensor by a wire under the skin. Both devices are from Medtronic MiniMed.

## CLOSING THE LOOP

The first five patients who used the device for six months did well: the sensor was 95 percent accurate compared against finger-stick readings with conventional meters. Trial participants delivered their own insulin during most of the trial, based on the sensor readings. The researchers “closed the loop” for a two-day period, and found that the patients’ blood glucose levels stayed in the desired range 42 percent of the time, compared to only 21 percent of the time in patients using conventional meters to adjust insulin delivery.

The researchers then tested the closed-loop system using not only an algorithm to control the pump’s insulin delivery based on the sensor readings, but also a pre-meal bolus of insulin from the pump to address the problem of higher post-meal blood glucose levels. The protocol produced lower post-meal glucose levels and did not increase hypoglycemic episodes, which often occur when a person “overtreats” a high blood glucose level with extra insulin. Trial participants also stayed within the target range of 70 and 120 mg/dl nearly 50 percent more of the time.



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JDRF SCIENTIFIC PROGRAM MANAGER**

Longevity of the full-implant equipment is an issue that must be addressed, since the sensors last only nine months and the pump must be replaced roughly every eight years.

### WHAT'S NEXT?

The progress toward an artificial pancreas didn't follow the course many scientists thought it might.

“I think people have had a mindset that development of a new sensor would follow a particular pathway,” Dr. Wilson says. “First it would be available experimentally, then you’d use it retrospectively like the CGMS from MiniMed, and then you might use it as a nocturnal hypoglycemia detector or a meter replacement. Then, you would get to the point where you’d have an ‘advise you’ system, and finally you could close the loop.

“One thing that’s become clearer is that the idea of a hypoglycemia detector doesn’t play to the strengths of the current sensors,” he says. “They have less accuracy in the low ranges, so there’s a dilemma: the risk of too many false positive alarms. As a pump controller, however, if you set it to keep you at 150 and you’re off by 70 points, you’re still okay. With the current sensors, it makes sense to move more quickly to an application where you’re closing the loop, because you’re in the range where the sensors work better.”

A closed-loop system might not have to be “all or nothing,” either. For instance, there might be concern that the system would not react quickly enough to cover the rapid postprandial rise in blood glucose, because of the delays inherent in measuring the rise in interstitial glucose levels. No problem, says Dr. Tamborlane.

“You can adjust for postprandial highs by making it a semi-automatic sys-

tem,” he says. “Just do what our patients are doing now: give something of a bolus before eating, which wouldn’t have to be the whole amount you would normally take, and then let the sensor take over to do the fine-tuning.

“You don’t have to go from not very good to perfect,” Dr. Tamborlane says. “It’s a big step to go from not very good to very good. I think we’re much closer than people think. In the work we’re doing with children, that JDRF supports, we’ve already had five or six children go for over 36 hours on automatic control.”

JDRF has swung its support to the artificial pancreas, and not just for the sake of an artificial pancreas itself.

“The development of an artificial pancreas could actually contribute to our biological cure goals,” Dr. Kowalski says. “For instance, when you transplant islet cells, many of them die. There are a number of suspected reasons, but one of them could be the toxicity of hyperglycemia. If you could use an artificial pancreas to get a patient to euglycemia prior to the transplant, the patient might do better.”

There is already evidence that an artificial pancreas might extend the “honeymoon” period in new-onset diabetes. Research using the Biostator demonstrated some preservation of beta cell function. Beta cell regeneration is one of many avenues to euglycemia, and an artificial pancreas might help the regeneration process.

“I call the artificial pancreas the bridge to the biological cure,” Dr. Kowalski says. “It will have a major impact on people with diabetes while we get to solutions for beta cell regeneration, islet cell transplantation, or an islet supply. It will help forestall complications, help with the problem of hypoglycemia, and generally improve quality of life.” ●