National Institutes of Health (NIH) and Juvenile Diabetes Research Foundation (JDRF) Workshop in Collaboration with the Food and Drug Administration (FDA)

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Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop

Summary Report

OPENING REMARKS

Judith Fradkin (NIH) opened the workshop with an update on a recent meeting of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) focused on ways to improve hemoglobin A1C (HbA1C) levels in type 1 diabetes patients. The DMICC noted that tight glucose control is critical if patients are to benefit from the results of the Diabetes Control and Complications Trial (DCCT), which showed that lower HbA1C is associated with sharply reduced risk of developing complications. Optimal HbA1C levels of 7 percent or lower are difficult to maintain, however, especially in young children and adolescents who are at increased risk of severe hypoglycemic episodes from intensive insulin management.

Steve Gutman (FDA) commented that FDA regulation of glucose monitors requires the Agency to consider the environment of their use and other human factors. FDA, however, wants to be a partner in bringing new devices to market by allowing scientific advances to drive the technology forward rather than creating regulatory obstacles.

With both a wife and a son living with type 1 diabetes, Michael White (JDRF) is well aware of the need for new tools for achieving optimal glucose control while minimizing frightening hypoglycemic episodes. JDRF has made a commitment to fostering the development of an artificial pancreas that can address this critical need in diabetes management. The main goals of the JDRF Artificial Pancreas Project include developing artificial pancreas technologies that improve glycemic control; ensuring broad patient access to new technologies; and supporting a thriving, competitive market for next-generation devices.

Scott Campbell (American Diabetes Association [ADA]) noted that a closed loop system—while not a cure—would have a great impact on diabetes care and management.

OPTIMAL TARGETS: WHAT LEVELS OF BLOOD GLUCOSE SHOULD WE BE SHOOTING FOR?

William Tamborlane, M.D., Yale University (on behalf of Robert Sherwin, M.D.)
Hypoglycemia: The Barrier to Effective Insulin Therapy

The DCCT revealed the tradeoff of intensive insulin therapy—the risk of long-term complications was reduced drastically, but the acute risk of hypoglycemia rose in its place. About one-half of hypoglycemic episodes occur at night—"nocturnal hypoglycemia"—which undermines good diabetes management as patients or their caregivers relax control because of a fear of becoming hypoglycemic during sleep. Moreover, severe hypoglycemic events with recognizable symptoms only hint at the true magnitude of the problem; asymptomatic hypoglycemia is common, especially during sleep. It is important to note that the DCCT was conducted in the 1980s and 1990s, when type 1 diabetes patients were not using the rapid acting insulin formulations for pump therapy that are available today.

Problem 1: Improved glucose control worsens hypoglycemic awareness. The introduction of CSII (continuous subcutaneous insulin infusion or an "insulin pump") to U.S. patients in 1979 first revealed the issue of hypoglycemic unawareness—or the loss of normal warning signs of low blood sugar, such as sweating or shakiness. Type 1 diabetes patients appear to have an acquired defect in their epinephrine response to hypoglycemia. Moreover, hypoglycemic unawareness creates a vicious cycle in which each new episode of hypoglycemia reinforces the problem of unawareness. To date, the only way to reverse hypoglycemic unawareness is the meticulous avoidance of hypoglycemia over several weeks.

Problem 2: pharmacokinetics and pharmacodynamics of regular insulin compound the problems of intensive therapy. They can skew each other easily, especially in adolescents who require a large pre-meal bolus due to the natural insulin-resistant state of puberty.

Research is underway to determine if frequent episodes of hypoglycemia lead to impaired cognitive function in type 1 diabetes patients. However, no simple test is available to quantify the amount and degree of hypoglycemia exposure, nor is it easy to separate the adverse effects of hyperglycemia and hypoglycemia.

Ultimately, no treatment will reliably prevent hypoglycemia until feedback control of insulin delivery is based on real-time measurements of fluctuations in plasma glucose.

Michael Brownlee, M.D., Albert Einstein College of Medicine
Hyperglycemia and Diabetic Complications

Hyperglycemia causes microvascular damage through four independent mechanisms: polyol pathway flux; increased AGE (advanced glycation endproduct) formation; PKC (protein kinase C) activation; and hexosamine pathway flux. At first these pathways seemed to have no common element, and clinical trials to block the pathways individually have been disappointing. It is now clear, however, that the different pathways have a single upstream mechanism: the overproduction of mitochondrial free radicals, which enter the nucleus and damage DNA. Small blood vessels in particular are susceptible to damage from excess glucose.

Hyperglycemia also causes macrovascular damage, as evidenced by a recent study of type 1 diabetes patients with an average age of 42 years that uncovered atherosclerosis in the entire study population. Type 1 diabetes patients have hyperglycemia-induced insulin resistance, which reduces the ability of endothelial cells to eliminate fatty acids. Oxidation of the accumulated fatty acids damages the large blood vessels.

In the Epidemiology of Diabetes Interventions and Control (EDIC) Study—the long-term followup of the DCCT cohorts—two patient groups with identical HbA1C levels during EDIC displayed divergent rates of retinopathy that correlated with their level of glucose control during the DCCT. In addition, a study showed that normal subjects lost prostacyclin synthetase activity for 24 hours after just 4 hours of a hyperglycemic clamp. Thus, even a short period of high glucose has lasting effects for the next day. It is possible that every hyperglycemic episode activates a damaging "threshold" that does not shut down for 24 hours or longer. Understanding this phenomenon of "hyperglycemic memory" is critical to optimizing glucose management.

Without closing the loop between glucose sensing and insulin delivery, patients can reduce the risk of complications by as much as two-thirds with intensive insulin therapy. Improving insulin pump technology and closing the loop can impact diabetes management even more.

Christopher D. Saudek, M.D., Johns Hopkins University
Clinical Trial Design

A mechanical, closed-loop system requires three elements: the insulin delivery device, the glucose sensing device, and a linking algorithm.

The greatest risk from a closed-loop system is the possibility of catastrophic hypoglycemia caused by uncontrolled insulin delivery. The implanted insulin pumps were designed with that in mind, and no case of uncontrolled insulin delivery has been seen since trials began in 1986. The implanted pumps are approved for use in France, but have not been submitted to the FDA for routine use in the United States. Why not? Trials have been piecemeal and have not generally been conducted at academic centers. Moreover, the impression of manufacturers is that the market is not large enough to be profitable, and reimbursement is uncertain. Technical issues with the electronics and insulin aggregation also have contributed to the slow pace of development, but these largely have been overcome. There is strong accumulated evidence, here and in France, that open implanted pumps are safe and highly efficacious.

Several continuous glucose monitors now are available, with FDA approval having been achieved or close. Current devices require daily calibration and have other issues that will require further development. Some have been used to suggest a dose of insulin from external insulin pumps, and some provide useful alarms if glucose is too low or too high. The technology is improving, but none of the current continuous sensors is robust enough to be used without backup finger stick measurements, much less to drive a closed-loop system.

For a truly closed-loop system, a linking algorithm must be developed that allows the insulin delivery component to respond quickly to an appropriate degree as blood sugar levels change. Redundant safety mechanisms must be built in and, even then, normal control of blood glucose

levels will not be attained, because the normal pancreas responds to multiple cues, not just a rise in blood glucose. Incretin hormones, a "cephalic phase," and dietary protein, for example, all play small but significant roles in regulating insulin secretion. Patient input may be needed, for example, signaling the start of a meal.

How "perfect" is necessary? What levels of glycemia must be attained? Based on current data, even moderately close-to-normal glycemia (e.g., 60–130 mg/dl) certainly would eliminate all symptoms and acute complications of diabetes, and probably would entirely eliminate the dreaded long-term complications. This would be an enormous achievement.

Discussion

- Data in aggregate suggest that insulin pumps reduce the frequency and severity of hypoglycemic episodes. Implantable insulin pumps are more effective in this regard than external insulin pumps.
- It is unlikely that diabetes management will shift directly from the current relatively poor control for most patients to a perfect closed-loop system. Continual refinement and improvement, however, could have a large impact.
- HbA1C levels represent an average of glucose control over a 3-month period. A patient with frequent, extreme swings in glucose levels still can have a reasonable HbA1C result. It is not clear whether this glycemic variability contributes to vascular damage.

WHERE DO WE STAND?

Richard Bergman, Ph.D., Keck School of Medicine, University of Southern California

Insulin has three major functions: increase glucose uptake by muscles, decrease glucose secretion by the liver, and suppress the release of fat.

Natural glucose regulation is not a closed loop, but a complex, multilayered system. Peripheral tissues and the brain use many signals, such as free fatty acids (FFAs), to communicate with the pancreas and affect insulin secretion. Glucose monitoring alone does not completely replicate how the body regulates metabolism through the complex interplay of hormones. Moreover, an optimized artificial pancreas would have to simulate the biphasic nature of insulin secretion as well as the timing of insulin activity, which is delayed as insulin moves from the plasma into the interstitial tissue between cells.

Pancreatic beta cells are adaptive, continuously changing in response to new physiological conditions. For example, during the third trimester of pregnancy, insulin secretion increases while insulin sensitivity is reduced. When a person becomes more insulin resistant, beta cells up-regulate to increase insulin secretion and the liver clears less insulin, allowing more insulin to circulate through the body. The signal that triggers beta cells to compensate for insulin resistance is not known, although FFAs are postulated to be the feedback signal that causes beta cells to increase their sensitivity. GLP-1 increases insulin secretion indirectly through the liver and brain, which in turn signal the beta cells. In an artificial system, it might be helpful to infuse

GLP-1 along with insulin. The portal vein rather than interstitial tissue is the ideal location for insulin administration.

The long-term goal in developing an artificial pancreas is to improve feedback to the system. In addition to measuring glucose, it would be helpful to consider integrating an insulin sensor, an FFA sensor, and an algorithm to estimate glucose clearance.

William Tamborlane, M.D., Yale University
Fast Track to Make an Artificial Pancreas a Reality for Children with Type 1 Diabetes Mellitus (T1DM)

An artificial pancreas is essential because:

- Present methods of diabetes treatment improve, but do not normalize, blood glucose levels;
- The burden of care is extremely high;
- Islet cell replacement therapies are limited to small segments of the population and are not well-suited for children with T1DM because of the excessive morbidity related to immunosuppression.

Researchers are pursuing the development of both external and implanted insulin pump designs. External insulin pumps have been in use for decades, and increasing numbers of children with type 1 diabetes are opting for pumps over injections. New models continue to be improved, with basal and bolus doses available in tiny increments. Smart pumps have dose calculators, and some have a wireless link to glucose meters. Studies have demonstrated the benefits of pumps in infants and toddlers. Although hypoglycemic episodes are reduced among pump users, the problem must be eliminated entirely. The alternative—an implanted pump—has several practical disadvantages, such as the need for a surgical procedure to implant the device, complicated refill protocols, possibility of pump failure, and the potential for catheter blockage. Weak evidence suggests that implanted pumps might be more effective than subcutaneous ones. Experience with implanted pumps in children is very limited.

Development of glucose sensors also must consider whether the optimal design is an internal or external device. The limitations of the Continuous Glucose Monitor System (CGMS) were that the data were not available in real time, the measurements were not accurate enough, and the cable connection was inconvenient. Similarly, the GlucoWatch had several drawbacks, including skin irritation, accuracy problems, and measurements being affected by sweat or motion. Most significantly, children with diabetes were not willing to use the device.

The Diabetes Research in Children Network (DirecNet) has evaluated the FreeStyle Navigator glucose monitoring device, and other real-time glucose-sensing systems have been developed. These new-generation devices provide real-time glucose readings, improved accuracy, alarms that signal high or low glucose values, and the ability to transmit data directly to a pump.

To create a closed-loop system using data from a glucose monitor, algorithms must be developed that alter the rate of insulin delivery based on continuous glucose monitoring data. Preliminary studies have been carried out with the PID algorithm, which varies the rate of insulin delivery in a manner that is Proportional, Integrative and Derivative. Initial testing of an external closed-

loop system used a laptop computer to receive data from a sensor and calculate the proper insulin dose which, in turn, is transmitted to a pump. The first pediatric patients using a closed-loop system demonstrated generally good glucose control. Control was not perfect, however, especially at breakfast. Glucose control was good at other meals and at night.

From these preliminary studies, researchers have learned that exaggerated post-meal excursions arise from lags in carbohydrate absorption and other factors. It may be possible to compensate for this with hybrid, semi-automatic control that allows the patient to prime with a conventional pre-meal bolus of insulin to account for most of the carbohydrates in the meal. Other issues, such as potential sensor errors, could be addressed by setting glucose targets at slightly higher than normal. Developing a hybrid open/closed system might be an achievable first step on the way to a fully closed device.

Jeffrey Joseph, M.D., Thomas Jefferson University
Mechanical Artificial Pancreas: Current Issues and Future Directions

The blood glucose excursion of a nondiabetic person following a meal and exercise has a narrow range and a small standard deviation. A nondiabetic person's glucose response to the second meal of the day can be completely different from that of the first meal, even if the meals themselves are identical. The healthy pancreas, liver, and intestine work in concert to provide exquisite blood glucose control.

Our goal is to develop a device that safely and effectively controls the level of glucose in patients who are insulin deficient (T1DM) or insulin resistant with beta-cell dysfunction (T2DM), over a wide range of real-life situations. An artificial pancreas combines a CGMS, a computer control algorithm, and an insulin delivery system to automatically control glucose levels in the physiological range with a low risk for hypoglycemia.

A closed-loop system will have to measure glucose as frequently as every minute or two to recognize when a meal is being eaten so that insulin can be delivered quickly. Time delays in sensing the acute rise in glucose levels following a meal and time delays in the absorption of insulin from the subcutaneous tissue make it very difficult to achieve near normal blood glucose control using current artificial pancreas systems. One way to overcome this limitation is to have the patient interact with the artificial pancreas system- signaling the onset of food consumption, exercise, or sleep (semiclosed loop).

Attributes of an ideal glucose sensor include:
- Near continuous measurement;
- Specificity for the glucose molecule;
- High sensitivity, especially in the hypoglycemia range;
- Minimal physiological delay in glucose sensing;
- Minimal physical delay in glucose sensing;
- Point accuracy;
- Direction accuracy;
- Rate-of-change accuracy;
- User-friendly calibration;

- Stability-limited change in output signal unrelated to glucose level; and
- Robustness when used in the real-world setting; sensor array will provide redundancy

A wide variety of glucose sensor technologies are under development. The distal tips of needle-type sensors are implanted for 3 to 5 days in the loose connective tissue below the skin. The enzyme glucose oxidase provides specificity for the measurement of glucose. Molecular glucose is oxidized to produce hydrogen peroxide, resulting in the generation of electrons. The sensor generates an electric current that increases or decreases in direct response to a change in the interstitial fluid glucose level. Although small pore membranes attempt to protect the enzyme and electrodes from biofouling, the sensor exhibits acute changes in sensitivity when inserted into tissue. Sensors typically are recalibrated to a reference blood glucose measurement several times per day to improve accuracy and precision. Each sensor provides a glucose measurement every 1 to 5 minutes, with rate of change and direction of change information, and programmable alarms for hypo- and hyperglycemia. Medtronic Diabetes, Dexcom Inc., iSense Corporation, and Abbott Corporation are developing miniature needle-type sensors for short-term CGM.

Another CGM technology requires insertion of a dialysis catheter with small-sized pores into the loose connective tissue below the skin. A glucose-free solution (dialysate) typically is infused from outside of the body into the catheter at a slow rate. Glucose in the interstitial fluid partially equilibrates with the glucose-free dialysate inside the catheter. The glucose-containing fluid is pumped outside of the body to an external flow-through enzyme-based glucose sensor. The slow movement of dialysate limits the frequency of glucose measurements to six or less per hour. The *ex-vivo* glucose sensor exhibits superior stability and can be calibrated automatically using external glucose standards. Roche Diagnostics and Menarini Group are developing this type of sensor for short-term CGM.

Long-term glucose sensors typically require surgical implantation in the body. Dexcom Corporation is developing a miniature sensor that is implanted in the loose connective tissue under the skin. The sensor uses the enzyme glucose oxidase to measure glucose in interstitial fluid. A multilayered porous membrane has been developed to maintain vascular tissue in close proximity to the sensing region while minimizing biofouling of the enzyme and electrodes. Data are transmitted to an external module that displays the glucose value and trend information. Diabetic patients implanted with the Dexcom sensor have used the real-time glucose information to improve blood glucose control and minimize hypoglycemia. Formation of fibrous tissue and loss of vascularity have limited long-term function.

Medtronic Diabetes is developing a vascular catheter-type sensor that is implanted long-term in the superior vena cava of the body. The distal tip of the sensor has two electrodes that measure the partial pressure of oxygen in venous blood. One of the oxygen sensors is covered with the enzyme glucose oxidase and a porous membrane that ensures the availability of oxygen in excess of glucose. The differential change in oxygen is measured to provide an accurate and precise measurement of glucose. The sensor has demonstrated satisfactory sensitivity and long-term stability. Data are transmitted to an external module that displays the glucose value and trend information. Unfortunately, the harsh environment of blood causes biofouling of the protective

membrane, enzyme, and electrodes, leading to premature sensor failure. The invasiveness of the surgical procedure prohibits frequent removal and re-implantation.

Animas Corporation is developing an implantable optical sensor based on near infrared absorption spectroscopy. A miniature sensor head is implanted around the outside of an artery or vein to provide a fixed path length. Small optical fibers are used to direct the near infrared (NIR) energy into the bloodstream to provide spectra of whole blood with a high signal-to-noise ratio. Spectra measured at numerous discrete wavelengths in the NIR region provide specificity for glucose. High collection efficiency provides sufficient sensitivity, even in the hypoglycemia range. Spectra are analyzed using a universal calibration model to provide an accurate glucose measurement. Because NIR energy easily can pass through any protein or fibrous layer that coats the optical windows, the technology has the potential to overcome the biofouling issues that plague enzyme-based sensors. The sensor is connected via a flexible optical fiber and wires to an implantable module that contains the light source, electronics, battery, and telemetry. An external unit (resembling a wrist watch or pager) will display the glucose value and trend data. Programmable alarms are designed to warn the patient of impending hypo and hyperglycemia.

An artificial pancreas requires a computer control algorithm that can provide the appropriate dose of insulin at the appropriate time in relation to changing physiology and external events (meals, exercise, and device malfunction). A variety of control strategies (e.g., PID, model predictive control [MPC]) have been developed. Safe and effective artificial pancreas function may require that the algorithm parameters be adjusted in real-time, based on changes in insulin sensitivity.

A computer controller will need to consider:

- Current and past glucose measurements;
- Physiological and physical (sensor) time delays;
- Pharmacokinetics of insulin absorption from tissue;
- Pharmacodynamics of insulin's actions—glucose utilization, inhibition of hepatic glucose release;
- Changes in insulin sensitivity;
- Time and composition of meals—closed loop vs. semiclosed loop;
- Other sensor inputs to controller to detect and quantify meals, exercise, illness;
- Safety; and
- Artificial pancreas function when the sensor or insulin pump malfunctions.

Medtronic Diabetes (formerly MiniMed Inc.) and French scientists successfully demonstrated the feasibility of an integrated artificial pancreas system in type 1 diabetic humans. The Medtronic intravascular glucose sensor was connected to an implantable insulin pump programmed with a PID closed-loop control algorithm. The long-term implanted artificial pancreas system measured the concentration of glucose in venous blood and delivered regular insulin into the peritoneal cavity on a minute-by-minute basis. The type 1 diabetes subjects were not able to maintain their blood glucose levels in the acceptable range (80 to 180 mg/dl) using traditional open-loop insulin delivery methods. During several half-day periods of time, the artificial pancreas system was able to use closed-loop controls to provide superior glucose control without hypoglycemia during fasting and meals. Medtronic has completed similar

closed-loop studies using a subcutaneous glucose sensor and rapid-acting insulin delivered into the subcutaneous tissue. The algorithm has been able to partially compensate for the time delays caused by subcutaneous sensing and insulin delivery.

Safety issues may require an artificial pancreas system to provide a bolus or infusion of glucagon to prevent or treat hypoglycemia. The need for glucagon must be determined in clinical trials of specific artificial pancreas systems.

We should not expect perfect blood glucose control from early artificial pancreas systems. The first artificial pancreas system to be commercialized probably will be used to control glucose levels during sleep. This should be accomplished easily by automatically adjusting basal insulin delivery. Closed-loop glucose control following meals and exercise will be more challenging. The data, however, suggest that an automated artificial pancreas system based on a robust model of human physiology, insulin physiology, and analysis of frequent glucose measurements should provide glucose control that is superior to current open-loop methods. Of course, the diabetic patient always will be required to supervise the artificial pancreas system to confirm proper function and convert to open-loop methods when the system fails.

Guido Freckmann, Institute for Diabetes Technology
Semi-Closed Loop Algorithms: Practical Experience

Currently available fast-acting insulin analogs show peak action after about 45–60 minutes and a duration of action of some hours. Results from continuous glucose monitors reflect physical and physiologic delays between changes in blood glucose and interstitial glucose to the insulin action profile. Because of the delay in peak insulin activity and the currently unavoidable delays inherent in obtaining interstitial glucose values, closed-loop control based only on glucose levels is very difficult at mealtime. A semiclosed loop system would allow the patient to tell the device about upcoming meals. The patient, however, may not reliably notify the system of upcoming meals, which would leave the system "chasing" the blood glucose elevation caused by a meal. Patient variability in assessing the carbohydrate count of the meal also may affect the function of an open-loop system. Therefore, training in carbohydrate counting would be important for optimal system performance. Good overnight closed-loop control already is achievable. In a clinical setting, semiclosed loop therapy based on continuous glucose monitoring has been shown to be possible. For better meal control, feedforward and feedback must be developed. In addition to meal control issues, parallel administration of other hormones that regulate glycemic control also may need to be considered.

Discussion

- DirecNet is developing strong, scientifically valid studies because the network controls both the study design and the resulting data. DirecNet has experienced good cooperation with the companies that provide the devices for testing.
- The time lag between glucose levels in interstitial fluid and in blood is not an "error," but reflects normal physiology. The time difference comes from measuring in the interstitial fluid instead of blood and seems to increase during periods when glucose levels are changing

rapidly. In addition, there are technical time lags in some devices. When comparing an open loop with a fully closed loop, the interstitial lag might not be important.

- An improved fast-acting insulin with very quick peak action and short duration of action is the most important prerequisite for the development of a glucose-driven closed-loop system. Using currently available insulin and subcutaneous delivery, meal input to the algorithm is necessary if the goal is near-normal postprandial control. Further development of algorithms and especially strong, significantly valid studies for testing closed-loop and semiclosed loop algorithms must be done.

TECHNICAL CHALLENGES

W. Kenneth Ward, M.D. (Legacy Health System)
Amperometric Glucose Sensors: Design Factors and Biological Issues

One issue regarding implanted sensors is finding ways to ensure that the signal being measured is glucose-specific. To avoid creation of a "glucose" signal from nonglucose-oxidizable compounds, it is necessary to use a membrane that allows the passage of hydrogen peroxide but blocks the larger molecular weight interferents.

Glucose oxidase is necessary to create the peroxide signal that originates from glucose and oxygen. In our studies of fully implanted devices, glucose oxidase functioned for at least 30 days. Ultimate failures were caused by electronic malfunctions and battery failure, not enzyme loss.

Another drawback of implanted devices is the potential for error or delay in measurement caused by a foreign body capsule forming around the device. One solution would be to promote blood vessel growth into the outer portion of the device using VEGF or other growth factors. Similarly, fibrinogen can bind to an implant and attract macrophages. It may be possible to prevent the fibrinogen from binding to polymer by using a "passivating" protein. Areas for future investigation include both engineering efforts (miniaturization, new biomaterials) and biological efforts (blocking pro-inflammatory cytokines, inhibiting normal fibroblast action, slow release of angiogenic cytokines, and passivating proteins).

Francis Moussy, Ph.D., University of South Florida
Glucose Sensor Biofouling

A sensor implanted in a rat worked well for 56 days but its performance declined over time, mostly because of tissue reactions. Implanted sensors are plagued by unreliability and progressive loss of function, caused mainly by changes in the properties of surrounding tissue. Proteins and fibrin deposited during hemostasis interfere with device function. Research is underway to determine the specific contributions of inflammation, fibrosis, and blood vessels to biosensor function and lifespan; and to develop a combination of approaches to control or limit these reactions.

"MicroImager" digital autoradiography allows researchers to quantify diffusion through tissue reactions. Sometimes the sensor itself fails; other times, loss of function is caused by tissue reaction. Blood vessel density around a sensor seems to influence sensor function strongly, even in the presence of a fibrous capsule. Efforts are being made to control the tissue reactions as well as to induce angiogenesis around the sensors to improve their function. Injection of plasmids carrying the VEGF gene at the implanted site is being tested as a strategy to promote angiogenesis. Another approach involves applying a collagen scaffold onto the biosensor, which could help anchor the sensor and allow blood vessels to grow into it.

B. Wayne Bequette, Ph.D., Rensselaer Polytechnic Institute
Algorithms for Continuous Glucose Monitoring and Control

Sensor noise and sensor drift are known to occur over time. Sensors should factor out the noise while predicting where glucose levels are going. Optimal Estimation theory, developed during the 1950s, and the Kalman filter are being applied to evaluate whether a change in glucose levels is real or due simply to measurement noise. A long, solid foundation of control and estimation theory can be used in developing the algorithm for a closed-loop device.

Lessons learned to date include:

- Both feedback and feedforward control should be used. If a patient is about to consume a meal, he or she can infuse an insulin bolus in advance.
- Model Predictive Control—Find the current and future insulin infusion rates that best meet a desired future glucose trajectory, and initiate the infusion. At the next sample time, correct for model mismatch, and perform a new optimization.
- Challenges remain, such as: ease of tuning, time-varying behavior, adaptability, and robustness to meal uncertainty.

William Clarke, M.D. (University of Virginia Health System)
Statistical Considerations

It is important to have more than single-point accuracy in glucose measurements; knowing the direction and rate of blood glucose changes also is critical.

One possible solution is an Error-Grid Analysis that:

- Quantifies the clinical accuracy of continuous glucose sensors by estimating both absolute blood glucose value (point accuracy) and change in blood glucose (rate accuracy);
- Takes into consideration inherent interstitial time lag;
- Is applicable to both Error Grid Analysis and consensus Error Grid point accuracy;
- Requires the distribution of blood glucose levels similar to those routinely observed in type 1 diabetes.

Each meter would receive two accuracy estimates: point accuracy, according to traditional Error-Grid Analysis, and rate estimation accuracy, which follows the logic of the Error Grid but plots reference vs. estimated rate of blood glucose change.

Outcome evaluation of new devices will be needed to determine if new strategies are equivalent or superior to current therapy. How will this be measured? Glycemic averages do not tell the whole story. Although two people might have the same HbA1C value, one person may stay within the optimal glycemic range most of the time, while the other experiences wildly fluctuating glucose levels and suffers more health consequences. Moreover, the blood glucose scale is skewed, so averages can be misleading. This may be illustrated by comparing the mean and "clinical center" blood glucose level. The "clinical center" is approximately 100 mg/dl, and the numerical center (i.e., mean) is different. Since they are not the same, blood glucose readings are skewed and must be transformed logarithmically prior to statistical analyses.

Discussion

- Meals create a rapid rise in blood glucose. Because of this meal disturbance, it may be necessary to deliver a rapidly acting insulin bolus in an open-loop fashion *before* a meal. From a practical standpoint, an advantage to a fully closed-loop system is that it would not require the patient to remember to take the pre-meal dose—patients do not always remember to take boluses.
- Even a device requiring an open-loop pre-meal insulin dose would be a big improvement over current care. Such a system could be called a "hybrid" system; that is, basal insulin delivered by closed loop and meal-related insulin delivered by open loop.
- A closed-loop system need not be completely implanted. The next step might be to implant the insulin-delivery portion and have the sensor be external.

INDUSTRY PERSPECTIVE: ROUNDTABLE DISCUSSIONS

Kerstin Rebrin, Abbott Diabetes Care

<u>Hurdles in moving toward fully automated insulin infusion</u>:

Companies have not yet seen any return on their significant investment in subcutaneous glucose sensors. Therefore, it is not clear who would provide resources for further advanced products. It is rare to come across companies or investors with support for long-term commitments. Nevertheless, clinicians are asking for modified devices to perform research studies toward fully automated insulin infusion. It is important to note that any modified device, or even any marketed device used within an automated closed-loop setup, would be considered an investigational device of significant risk (21 CFR § 812 "… for a use of substantial importance in diagnosing, curing, mitigating, or treating disease…."). In addition, any sensor commercially available in the United States at this point has been approved for adjunctive use only; i.e., any treatment decision should be made based on confirmative capillary measurements. Although physicians would be able to use available devices off-label within their responsibility, companies must follow product development and regulatory requirements strictly if investigational devices are knowingly provided for off-label use. Also, treatment decisions are the physician's or possibly patient's responsibility. The transformation of such decisionmaking into a mathematical algorithm, however, requires complex systems control theory and engineering skills. This is an unusual situation, and industry-academic collaboration is absolutely vital. The extent of activities needed to fulfill regulatory requirements often is underestimated outside of

industry. Someone has to move a closed-loop device down the regulatory path, which perhaps will take at least as much effort as developing the algorithm *per se*. It probably should be taken into account however, that although the use of such a device might not fully alleviate the occurrence of hypo- or hyperglycemia, it could be much safer than any of the other treatment options available today.

Based on my experience, I believe strongly that the subcutaneous glucose signal is appropriate to serve as an input signal for an artificial pancreas. Abbott Diabetes Care has developed a 5-day subcutaneous sensor that has the status of an investigational device under FDA review for approval. The suggested label of this device is "adjunctive," i.e., can not yet be used as full replacement for regular monitoring. Nonetheless, studies performed recently by Abbott to demonstrate the safety and efficacy of the device reveal that the signal is very stable over the 5-day period and that it certainly has potential to be used as input for a closed-loop system.

Garry Steil, Medtronic

A totally external system, as opposed to an implantable system, has emerged as the front-runner for closed-loop insulin delivery, at least in the near term. Today, two philosophies exist for developing the system. The first envisions an "incremental path," in which a series of small changes are made to existing products; the second envisions an "accelerated path," in which research studies on completely automated systems are performed on an ongoing basis. Medtronic is pursuing both approaches. In the incremental approach, patients would continue to calculate their dosages in much the same way as today's standard of care, but with glucose sensors and algorithms progressively taking on more of the control—starting with sensor-based recommendations to give boluses or suspend delivery, followed by auto-suspend and/or auto-bolus, etc. In the accelerated approach, algorithms derived from control theory, and a detailed understanding of physiology, are used to take control of insulin delivery on a minute-to-minute basis. In the accelerated pathway there is little or no patient interaction, no predefined basal rates, no carbohydrate-to-insulin ratios, etc. It can be argued that the latter approach is less susceptible to user error, more desirable to patients themselves, and, even with an imperfect sensor, may prove to be more effective than today's open-loop therapy. Ideally, the technology might develop to a point where an imperfect sensor would be no more problematic than today's failing or disconnected catheter—problems that routinely are diagnosed by patients and corrected easily. The key is to find ways to build in safeguards and still fast-track development of the closed loop. NIH-supported studies already have generated data showing that algorithms based on the "accelerated path" can lead to 24-hour completely automated closed-loop insulin delivery systems. Studies performed in adults have demonstrated excellent nocturnal control, but with higher than desired peak postprandial glucose levels (Steil et al. Diabetes:55 3344-50 2006). Subsequent studies in pediatric patients have shown that the higher than desired postprandial peaks can be corrected by adding a small bolus in advance of a meal (Weinzimer et al. Diabetes 55 (supplement l): 413P, 2006). An algorithm using a meal bolus is not a completely closed-loop system; however, if the use of a small meal bolus becomes the only controversy, we might still consider ourselves 95 percent of the way to achieving a closed-loop insulin delivery system. The incremental pathway favored by industry still provides a viable path forward; however, it has been through NIH's support of research studies that the "accelerated pathway" has gone forward.

Jim Brauker, Ph.D., DexCom, Inc.

DexCom is a small company focused on developing a continuous monitor system. The company is working on two sensors, short-term and long-term. The STS (short term sensor) Continuous Glucose Monitoring system currently is under review at the FDA. (Note: The STS was approved by the FDA in March 2006.) We believe in and support the vision of linking continuous monitoring systems with insulin delivery systems. DexCom's philosophy is that "closing the loop" can best be achieved with an "open architecture" that would allow access to DexCom continuous data for pumps and other technologies that may become important for diabetes management.

To encourage a safe, careful approach that sets realistic expectations and maintains credibility, we propose a staged technology progression that moves methodically in appropriate steps:

1. Communication/Display
2. Confirmed adjustments—patient would confirm the device's suggestions.
3. Auto shut-off/hypoglycemia prevention—alarm and stop delivery of basal insulin until acknowledged or resolved by patient.
4. Auto bolus/hyperglycemia prevention—alarm and automatically bolus insulin to cap off the excursion.
5. Automated closed loop

Matthias Essenprais, Roche

Roche is looking at how present tools can be used better, and at developing better monitoring modalities. The company has decided to take a stepwise approach and has invested in microdialysis, which it views as a reliable technology that can be applied to clinical research.

Discussion

- Dr. Mann: The inclination to proceed in a slow, stepwise manner always will exist, but if we go all out for the closed loop, we could be in clinical trials within 3 years. A completely closed-loop system for nighttime control only may serve as a logical compromise between the two pathways.
- Audience: What is the barrier now? Sensor stability and reliability still can be improved, and the delay in insulin absorption from the subcutaneous site continues to be an obstacle for a closed-loop system. Determining what to do with all of the data provided by continuous sensing also remains challenging when effecting changes in open-loop therapy.
- Dr. Brauker: There are two very complex technologies: one (pump) has proved itself on the market, while the other (sensors) is in the early stages. Patients adapt to pump use very well, but we do not know how they will adapt to sensors.
- Audience: Other issues—education, legal, reimbursement, etc.—are as important as the scientific challenges.

- Audience: The limiting factor in performing closed-loop insulin delivery research has been the sensor. The field needs technical developments, with supporting human clinical trial studies, more so than conceptual development.
- Audience: Preliminary studies show that the closed-loop system can work better than current care, but much thought will need to go into answering the question, What exact studies need to be conducted to let people use these systems?
- Audience: If the two new sensors that provide real-time readings prove accurate, should we move to closed-loop trials in children or adults? Ideally, a closed-loop system should be usable in both adult and pediatric patients.

REGULATORY CONSIDERATIONS: COMMENTS AND ROUNDTABLE FROM FDA

Steve Gutman, M.D., Office of *In Vitro* Diagnostics
The quality of a submission to the FDA determines the length of time the Agency will take in review.

Patricia Bernhardt
The FDA reviews submissions as a team and will determine an acceptable tradeoff between quantity and quality of data.

Anthony Watson
The FDA wants to be responsive to stakeholders. The Agency should be involved from the first step to help avoid some of the regulatory hurdles that will arise. While a technology is being studied, the FDA needs to know that patients are not being treated as guinea pigs. The FDA is comfortable with the infusion side of these devices, although they are problematic because of the human factor—patients may not understand the rationale behind the software. Putting the sensor and pump together is different than evaluating them separately.

Ron Kaye, **Human Factors Group**—"Human factors" is a science derived from engineering and psychology that studies how humans actually use their devices. About one-third of device reports received by the FDA mention human error. Almost one-half of recalls involve design problems. It looks like the artificial pancreas will evolve through a series of steps. Questions to be addressed include: Will patients over-rely on the system? How do we keep operator problems to a minimum? What about implanting and explanting, or purging and refilling the devices?

Discussion

- The investigator who initiates a study is responsible for the conduct of that study.
- Review of these devices is expedited at the FDA, which recognizes their importance to personal and public health. The speed of review, however, ultimately will depend on the quality of the submission. A good submission could be reviewed in 180 days, whereas a problematic application could take 3 years and result in precautionary labeling.
- The FDA wants to ensure that important information that the user may not know is on the label of the device.

- Sponsors understand a product best and are responsible for stating the intended claim for a product and then backing it up with strong data. It often is better to make a narrow claim at first and to expand it later if desired. The FDA is not necessarily "locked into" using the HbA1C as the endpoint for efficacy.