GOAL IV

PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Hypoglycemia is the major obstacle to achieving the tight glucose control that has been proven to reduce the deadly complications of type 1 diabetes. To overcome this obstacle, the *Special Statutory Funding Program for Type 1 Diabetes Research* has supported multifaceted efforts ranging from fundamental research to understand how the body recognizes and defends against hypoglycemia and how diabetes impairs this defense, to applied research in partnership with industry to develop technology for continuous glucose monitoring and automated insulin delivery, and has established a clinical network to test the latest technology that can stabilize glucose levels and prevent or reduce hypoglycemia in children with diabetes.

Research supported by the *Special Funding Program* has concentrated on helping patients manage their blood glucose levels while also avoiding the terrifying acute dangers of abnormally low blood glucose (hypoglycemia). Excessive treatment with insulin relative to food intake and physical activity can cause blood glucose levels to fall dangerously below a minimal threshold required to fuel the body's activities, particularly brain function. The immediate effects of hypoglycemia can be severe, including changes in cardiovascular and central nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and death. Thus, the potential for hypoglycemic episodes has limited the use of intensive insulin therapy protocols that are known to reduce the risk of long-term diabetic complications, such as eye, heart, and kidney disease. Even with newer forms of insulin that provide more control, hypoglycemia remains an extremely serious, life-threatening concern.

Normally, a drop in blood glucose triggers the body's warning system to release stress hormones, including adrenaline, and to stimulate a part of the nervous system that raises glucose and results in symptoms such as shaking and sweating. However, in diabetic individuals who experience repeated episodes of hypoglycemia, these counter-regulatory mechanisms are impaired so the typical signs and symptoms disappear. These affected individuals do not recognize, and therefore cannot correct for, the low blood glucose—a syndrome known as hypoglycemia unawareness. A vicious cycle is initiated as each hypoglycemic event makes it more likely these compensatory signals will fail in the future, leading to another unrecognized hypoglycemic event. Patients, especially children, are particularly vulnerable to hypoglycemia unawareness while they are asleep. Therefore "nocturnal hypoglycemia" is a primary concern and the source of many anxious nights for parents of type 1 diabetes patients who stay awake to check on the well-being of their children throughout each night. To better understand the causes of hypoglycemia, the *Special Funds* have supported multiple initiatives that explore the integration of glucose sensing information in the body or that measure or image changes in brain function. By discovering the mechanisms involved in the body's reaction to hypoglycemia, scientists may be able to develop therapies that break the vicious cycle of recurrent hypoglycemia.

The widespread introduction and use of reliable, accurate, and relatively "user-friendly" glucose self-monitoring devices and portable insulin pumps have transformed the management of type 1 diabetes in the past two decades. The future holds enormous promise following the recent introduction of continuous glucose monitors—a major advance representing the culmination of years of NIH and *Special Funding* research and industry partnerships. The *Special Funds* also support a clinical trial network for reducing hypoglycemia in children. This network tests the effectiveness of these new technologies and employs the new technologies to learn about how daily activities such as sleeping and exercise affect blood glucose. The network is providing information to help bring to fruition a "closed-loop" insulin delivery system or artificial pancreas that may be on the near horizon to relieve patients from frequent painful finger sticks and injections, and the ubiquitous fear of hypoglycemia. Successful islet transplantation has also reduced the incidence of hypoglycemic episodes significantly, and the progress toward making that therapy a reality for more patients was discussed in the previous chapter.

HIGHLIGHTS OF SCIENTIFIC PROGRESS

While numerous significant advances have emerged since the beginning of the **Special Funding Program**, *many of the research efforts to prevent or reduce hypoglycemia in type 1 diabetes are still in progress, and the full impact of these projects will not be realized for several years. The advances made possible by the* **Special Funding Program** *thus far are therefore only the beginning of the scientific gains that can be expected in the future.*

Approval of New Glucose Monitoring Technologies: In April 2006, the FDA approved a continuous glucose monitoring device paired with an insulin pump for use in patients over age 18. Additional continuous glucose monitors developed by other manufacturers with NIH support are either under FDA review or have recently been approved. Instead of frequent, painful finger sticks, sensors inserted under the skin constantly take glucose measurements, whether the patient is awake or asleep, and trigger an alarm if levels become too high or too low. NIH support contributed to the development of each of these devices. This major technological advance represents the culmination of years of effort by HHS and the *Special Funding Program* in bringing together and funding collaborations of clinicians, engineers, and basic biologists from industry and academia to develop both the technology underlying the glucose sensors and the algorithms used to assist insulin delivery decisions. The new continuous glucose monitoring devices are a major milestone in the future development of an artificial pancreas. They have the potential to dramatically improve patients' ability to control glucose levels—key for preventing complications. They can also improve quality of life by reducing the need for frequent monitoring and alleviating the fears that patients and their parents have of nocturnal hypoglycemia.

Practical Steps To Avoid Nocturnal Hypoglycemia: Despite the many long-term complications of diabetes, many children with diabetes and their parents express the greatest fear of nighttime hypoglycemia (please see patient profiles in this chapter) or "dead-in-bed" syndrome. This phenomenon of low blood glucose during sleep despite having normal levels before bed prompts many parents to wake up in the middle of the night to check their child's glucose level. Recent data using continuous glucose monitoring have shown that low glucose levels are even more common than previously thought, but low levels sometimes go back up before the morning blood glucose check. The Direct Research in Children Network (DirecNet) Consortium has examined factors that contribute to nocturnal hypoglycemia in children. Using the new continuous glucose sensors, investigators found that exercising in the late afternoon caused a delayed nighttime drop in glucose levels and nearly tripled adolescents' risk for nocturnal hypoglycemia relative to exercise-free days.

Exercise is important for these children, particularly in keeping blood glucose from rising too high, but these findings point to the importance of adjusting patients' diabetes regimen on active days. This work yields the practical suggestion of increased bedtime snacks on days when children with diabetes are particularly physically active even if the bedtime glucose measurement is not low.

Counteracting Hypoglycemia: The pancreatic islets are comprised of several cell types. The counterpart to the insulin-producing beta cell is the glucagon-producing alpha cell. Just as insulin injections control high blood sugar, glucagon injections can be used in an emergency to raise glucose levels that fall dangerously low after insulin therapy. These dangerous episodes of hypoglycemia reflect the failure of the body to trigger normal warning systems (like adrenaline and glucagon) that wake the patient and increase blood sugar in response to hypoglycemia. Glucagon is the major counter-regulatory hormone that causes blood glucose to be released by the liver to raise the blood sugar. Researchers have long recognized that patients with type 1 diabetes do not secrete

glucagon in response to hypoglycemia, despite their ability to secrete glucagon under other circumstances. New findings suggest that a decrease in intra-islet insulin is necessary for glucagon secretion, explaining why the protective glucagon response is impaired in type 1 diabetes.

Protecting the Brain from Hypoglycemia: Therapies designed to protect the brain from injury due to hypoglycemia require a basic understanding of brain fuel usage and its adaptation to recurrent episodes of hypoglycemia. Recent progress has revealed how glucose and other fuels are transported into the brain despite a blood-brain barrier that blocks most molecules from entry. Surprisingly, new measurements show that glucose levels bathing the brain are only 25 percent of those in blood, which indicates that the glucose supply is very tenuous, particularly during hypoglycemia. Recent studies in rodents suggest that glucose transport into the brain may be increased by prior exposure to hypoglycemia and that brain glycogen ("starch") may also serve as a short-term fuel reserve to partially protect the brain from injury. Studies in patients suggest that hypoglycemia may induce the brain to more efficiently use other (non-glucose) fuels to meet its energy needs. Ironically, while these adaptive mechanisms do partially protect the brain from being damaged by impending hypoglycemia, they attenuate the ability of the individual to actually recognize and respond to hypoglycemia quickly (i.e., before dangerously low glucose levels impair brain function). This work explains how responses to hypoglycemia, which are beneficial in the short term and acutely protect the brain from damage, set the stage for a vicious cycle in which the brain becomes progressively less able to recognize and initiate action to halt future occurrences of hypoglycemia.

Mapping Metabolic Sensing: Maintenance of normal glucose balance (homeostasis) not only depends on the pancreas to release hormones in response to glucose levels, but also requires the communication of signals from all over the body with the brain, as well as within the brain itself. The *Special Funding Program* has propelled significant advances that revealed where and how the brain measures the body's metabolic status. To measure glucose levels in the blood, cells with specialized molecular sensors—some of which are similar to those used by the pancreas—line vessels that lead to the liver and brain, as well as the gastrointestinal tract. These peripheral sensors are linked to groups of specialized glucose sensing nerve cells (neurons), which are localized within a distributed, interconnected network within the brain, including the hypothalamus, forebrain, and hindbrain. Functional brain imaging and electrophysiology techniques have allowed neurobiologists to map the activity of these brain regions. To help the brain integrate different signals, some of these same brain neurons also respond to a variety of metabolic substrates (e.g., lactate, ketone bodies, fatty acids) and hormones (e.g., insulin, leptin, corticotropin releasing hormone), which are involved in the control of metabolism in the body. Identifying molecules and pathways for metabolic sensing may lead to targeted drug development to reduce hypoglycemia.

Brain Function Not Permanently Damaged by Hypoglycemia: The landmark Diabetes Control and Complications Trial (DCCT) found that tight control—while reducing complications—increased the risk of severe hypoglycemia three-fold. There was fear that in addition to its dangerous short-term effects—confusion, irrational behavior, convulsions, and unconsciousness—hypoglycemia might also lead to a long-term loss of cognitive ability. Twelve years after the conclusion of the DCCT, researchers report results of a study in which patients were evaluated using the same neuropsychological tests administered during the DCCT trial. The tests analyzed problem solving, learning, immediate memory, delayed recall, spatial information, attention, psychomotor efficiency, and motor speed. The tests revealed no link between multiple severe hypoglycemic reactions and impaired cognitive function in people with type 1 diabetes in the study. The lead

investigator concluded that while acute episodes of hypoglycemia can impair thinking and can even be life-threatening, patients with type 1 diabetes do not have to worry that such episodes will damage their mental abilities and impair their long-term abilities to perceive, reason, and remember. With the help of the *Special Funds*, DCCT patients continue to be followed more than 20 years after the study was launched and to provide valuable insights about diabetes and its treatment.

EVALUATION OF THE MAJOR RESEARCH TRIAL NETWORK TESTING TECHNOLOGY TO PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

With the increase in Special Funds *that became available in FY 2001, unique, innovative, and collaborative research consortia, clinical trials networks, and resources for the diabetes research community were launched. This section evaluates the progress of these ongoing efforts thus far and describes the impact that the efforts have already had—and have the potential to have—on type 1 diabetes patients.*

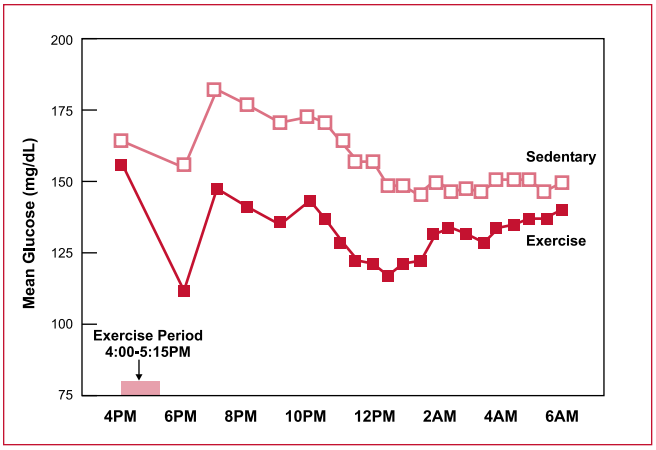
Diabetes Research in Children Network (DirecNet)

DirecNet is a multicenter clinical research network investigating the use of technology advances in the management of type 1 diabetes in children and adolescents. DirecNet is also developing a better understanding of hypoglycemia, the dangerous drops in blood sugar that can lead to seizures, loss of consciousness and, in extreme cases, coma or death. Specific goals for DirecNet have been to: (1) assess the accuracy, efficacy, and effectiveness of devices that continuously monitor blood glucose levels in children with type 1 diabetes, the population of patients at highest risk for consequences of hypoglycemia; (2) determine the optimal utilization of continuous glucose monitors in the management of diabetes in children; (3) determine the extent to which exercise contributes to the risk of hypoglycemia; (4) assess the impact of continuous glucose monitoring on quality of life for the child and family; (5) develop tools to incorporate continuous glucose monitors into diabetes self-management; (6) evaluate and develop distinct, age-appropriate treatment approaches to type 1 diabetes in children; (7) characterize the daily blood sugar profile of nondiabetic children with continuous monitoring; and (8) develop statistical methods for the analysis of continuous glucose monitoring data.

Highlights of Progress

The progress that DirecNet has made as of March 1, 2006, includes:

- Successful completion of six protocols on children with or without type 1 diabetes, with one more in progress, and one pending initiation.
- Demonstrated that counter-regulatory hormone responses to spontaneous nocturnal hypoglycemia are blunted throughout the nighttime period with or without antecedent exercise.
- Showed that the risk of hypoglycemia can be markedly reduced in insulin pump-treated patients by suspending the basal insulin infusion during exercise.
- Demonstrated that continuous glucose monitoring is a better method compared with 8-point glucose profiles as an outcome measure to assess glucose variability in diabetes clinical trials.
- Developed and tested new treatment satisfaction and adherence measures for use in clinical trials of continuous monitoring systems.
- Developed standard algorithms for patients and clinicians to use to adjust basal and bolus insulin doses based on continuous glucose monitoring data.
- Determined sensor accuracy, sensitivity, and specificity of first generation continuous glucose monitors in detecting hypoglycemia.



Effects of exercise on nighttime hypoglycemia: Data from the Diabetes Research in Children Network (DirecNet) show children's mean blood glucose levels on sedentary days (open squares) and exercise days (solid squares). Blood glucose levels are similar in the two groups up to the point of exercise (4:00 p.m.), but the children who exercised had lower glucose levels during the evening and overnight period, and hypoglycemia developed more often on the exercise days than on the sedentary days. This study suggests that food intake and insulin administration need to be adjusted on the evenings of days on which children are active, to help avoid overnight hypoglycemia. *(Reprinted from* J Pediatr *(147) Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzimer SA, Buckingham BA, Kollman C, Xing D, Ruedy KJ; Diabetes Research in Children Network (DirecNet) Study Group. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus: 528-534, 2005, with permission from Elsevier.)*

Anticipated Outcomes

In the absence of a functioning pancreas, diabetes patients are unable to respond to changes in blood sugar levels with insulin release. Over the past 80 years, improvements in technology have allowed patients to measure glucose levels and calculate the amount and variant of insulin to inject. These technological advances have saved many lives, but are far from perfect. The static measurement of glucose levels does not account for changes in diet or activity; there is a lag time between injecting insulin and its effect on the body; and too much injected insulin can lead to dangerous hypoglycemic episodes. The fear and danger of hypoglycemic episodes impede patients from achieving optimal control of blood sugar levels despite definitive evidence from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Trial that rigorous control can prevent diabetes complications. To address these issues, DirecNet has been testing the next generation of technologies: sensors that continuously monitor glucose levels and sound an alarm if levels cross certain thresholds; measurements that are sensitive to the rate of glucose change, not just the absolute amount of glucose; and insulin pumps that control insulin delivery under the skin. The ultimate goal of the network is to "close the loop" between automatic glucose level measurements and appropriate insulin delivery responses. The ideal artificial pancreas would relieve the patient of the burden of constantly testing and adjusting glucose levels. The role of DirecNet is to determine if the new technologies are safe and effective, particularly for use in children.

DirecNet is a prime example of the interface between industry, academia, health care, and government-sponsored research. DirecNet has carried out independent and scientifically rigorous studies to determine the true benefit of new monitoring technologies. Without the commitment of DirecNet to perform these studies, it could be many years before the manufacturers of these devices would be willing to conduct studies in the pediatric population. The DirecNet group is well positioned to assess new devices for their accuracy, as well as their clinical usefulness in the home environment.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of DirecNet at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- DirecNet is an independent and scientifically rigorous program that has published and recruited well.
- An important undertaking of the network was to define a child's normal glucose profile.
- DirecNet could benefit from the participation of external scientists with expertise in hypoglycemia.

- Currently, islet transplantation studies are appropriately limited to adults. However, as the field of cell-based therapies progresses, the goal is to apply these therapies to children. When safer and more effective cell-based therapies are developed, DirecNet investigators could be crucial in designing a clinical trial to compare the efficacy of different cell-based therapies. Therefore, the panel stressed that having this network infrastructure in place could be valuable for future projects.

Actions Taken in Response to Expert Panel Recommendations

DirecNet took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Make Plans for Future Directions if the Pilot Studies Do Not Yield Promising Results (Such as the Therasense Navigator)

- Recent DirecNet pilot studies with the Navigator monitoring system have yielded extremely promising results, and project directors expect that the Medtronic Guardian RT and other second and third generation sensors will also offer new research opportunities. The next phase of this research network will begin with the recompetition of the current network. It is expected that the new cooperative research network will evaluate a wide range of factors and mechanisms contributing to hypoglycemia and will set up clinical trials to test novel therapies and prevention strategies designed to focus on hypoglycemia prevention in type 1 diabetes. To further assist in this effort, the NINDS will be participating with the NICHD and the NIDDK in this next phase of the network, as neuroscience and neuroimaging measures will be added to the studies of hypoglycemia.

Recommendation: Broaden the Scope of DirecNet

- The recently-completed exercise studies and planned hormonal counter-regulation studies reflect the broader scope of DirecNet's highly productive research activities. Furthermore, in 2007, DirecNet will be renewed by soliciting competitive proposals, in response to a Request for Applications (RFA) that will significantly broaden the scope of research.

Recommendation: Study the Barrier of Linking Glucose Monitoring with Insulin Delivery ("Closing the Loop")

- The next step toward the development of a closed-loop system will be to develop the communication between the continuous glucose monitoring technology and the subcutaneous infusion pump, a device that can function like an artificial pancreas. DirecNet has demonstrated an improvement in continuous glucose monitoring technology in the past 4 years, especially at low glucose levels. As these systems become available, DirecNet will be well positioned to test their efficacy in children, adolescents, and young adults with type 1 diabetes.

Recommendation: Test DirecNet Technologies in Adults with Type 1 Diabetes

- The next phase of DirecNet, starting in FY 2007, will include such studies in adults.

Recommendation: Encourage Participation of External Scientists with Hypoglycemia Expertise

- The 2007 research solicitation will add an advisory group of outside experts. The NIH has already convened a panel of scientists with hypoglycemia expertise to obtain input on the 2007 research solicitation.

Recommendation: Organize a Workshop To Obtain Input on Future Directions of DirecNet from Experts in Hypoglycemia, Pediatric Diabetes, and FDA Regulations

- A workshop is planned in the next fiscal year (Summer 2007) to determine future directions of the Network.

Recommendation: Create a Network of Investigators To Aid in Design of Clinical Trials To Compare the Efficacy of Cell-Based Therapies

- The 2007 research solicitation encourages such therapies to be tested in clinical trials. Studies of cell-based therapies will therefore be a priority in the discussions of future clinical trials.

Ongoing Evaluation

The DirecNet Data and Safety Monitoring Board (DSMB) is an independent group of experts who meet every 2 months to review clinical research protocols in the Network and to advise the DirecNet Steering Committee (SC). The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy; and (2) make recommendations to the DirecNet Steering Committee concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data, as well as relevant background knowledge about the disease, technology, or patient population under study. Meetings involve DSMB members as well as DirecNet investigators, coordinating center staff, and NIH representatives. The advisory role of the DSMB will be replaced by a separate Protocol Review Committee in the next funding period.

DirecNet Administrative History

Date Initiative Started	2001
Date *Special Program* Funding Started	2001
Participating Components	NICHD, NIDDK
Website	http://public.direc.net

DirecNet consists of a Coordinating Center, five pediatric diabetes centers, and a central laboratory.

EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

In addition to the clinical trial network previously described, the **Special Funding Program** *supported investigator-initiated research projects addressing particular challenges and opportunities identified by the NIH with the aid of scientific experts at workshops and advisory meetings. Often these recommendations were disseminated to the research community in a Request for Applications (RFA) or Request for Proposals (RFP). (For a list of initiatives supported by the* **Special Funding Program***, please see Appendix 1.) The NIDDK conducted a Grantee Survey (see Appendix 5) to evaluate the impact of the* **Special Funding Program** *on investigators with research project grants principally supported by the* **Special Funds***. The survey was used as a tool to assess the research accomplishments (e.g., publications, resulting patents, impact on patients' health), research collaborations, and impact that the* **Special Program** *had on careers of investigators supported by it. Data from this survey are found in the "Assessment" chapter.*

Impact of *Special Funding Program* on Extramural Grantees

Principal investigators who received grants related to hypoglycemia responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- "Since the completion of this project, I have been recruited to head a major biomedical imaging initiative (>$40 million effort) focusing on metabolic and functional imaging. In this context, I am committed to pursue this line of research and strongly motivated to expand into other challenges in type 1 diabetes research, such as imaging beta cell mass."
- "We have made the development of this sensing motif the highest priority of our laboratory. Our work in this area won the American Association of Clinical Chemistry Zigi Zering Award."
- "I am a tenured professor in a university department of bioengineering and this award had little direct effect on my career. Nevertheless, I could not have done the research without the award. The award was instrumental in recruitment of an MD-PhD student who has been involved in the work and intends to further some of the outcomes in his research and patient-care career."
- "Possession of this grant was essential in my promotion to Associate Professor. Results of this grant have spurred continued research in type 1 diabetes, and were the basis of two grant submissions currently under review. Contacts with diabetes researchers resulted in my participation in an NIH study section."
- "This long-term (5 year) R01 has helped significantly to provide stable funding for my lab, and has significantly increased my interest in the field of diabetes and hypoglycemia. This grant has considerably altered my career funding from more basic mechanisms of neuronal functioning to clinically relevant topics."
- "This grant has been very influential in my academic career. It has enabled me to recruit personnel, to develop my research basis, and to remain in the field of type 1 diabetes research. It was also the first major step I made in becoming an established investigator in this field. Without this grant I would probably have returned to clinical medicine."

DEVELOPING BETTER WAYS TO TREAT DIABETES: A CLOSED LOOP ARTIFICIAL PANCREAS

An artificial pancreas based on mechanical devices requires, at a minimum, three basic components: a continuous blood glucose sensor, an insulin delivery system, and a way to link the two in a loop. Such a system would automatically turn the measurement of blood glucose levels into a practical, precise, and "real-time" insulin-dosing system for patients. Technology that can replace intermittent finger sticks with continuous, accurate measures of blood glucose levels is a key element. Whereas conventional methods of testing glucose levels provide only snapshots in time, a continuous glucose monitoring device, by contrast, can reveal the dynamic changes in blood glucose levels that are the bane of close control and, in turn, can enable responsive insulin delivery in a way that mimics the exquisitely timed responsiveness of a normally functioning pancreas.

The NIH has accelerated the pace of research on glucose sensing technologies through research solicitations and investigator-initiated projects. Over the last decade, these efforts have led investigators in academia and industry to explore a variety of approaches to continuous glucose monitoring, including devices to measure glucose in body fluid extracted from skin, in eye fluid using a contact lens as a sensor, noninvasively with optical sensing of glucose in the blood, and with minimally invasive sensors inserted into the skin. Researchers have also been exploring the benefits and drawbacks of sensors designed for external use versus more permanent, fully implantable devices. Studies have also focused on validating and optimizing the different technologies. These multifaceted approaches have borne fruit. New continuous glucose monitoring devices from three companies (Medtronic, Inc., DexCom, and Abbott Laboratories) have recently been approved or are currently under review by the FDA. These devices represent a significant improvement over the first devices approved by the FDA in 1999. NIH support was instrumental in technology development for all of them. The devices employ a similar basic approach in their technologies: a slender sensor that can detect the biochemical reaction of glucose with an enzyme (glucose oxidase) present on the sensor tip. Inserted under the skin, these minimally-invasive sensors take glucose measurements every few minutes, whether the patient is awake or asleep, and trigger an alarm if levels become too high or too low. Importantly, both current glucose readings and glucose "trends" indicate whether blood glucose levels are increasing or decreasing—and how quickly—and are reported in "real time" to patients. This information permits patients to take immediate action to avoid low and high blood sugar episodes. Finger sticks are not entirely eliminated because they are needed for calibrating the devices and for directly measuring blood glucose levels before adjusting an insulin dose. However, the burden of care can be significantly reduced and further improvements in these devices can be expected with additional research and development.

One of the FDA-approved devices (Medtronic, Inc.) has been "paired" with an insulin pump through a wireless transmitter so that information about current and past glucose readings is displayed on the pump, making it easier for the patient to adjust the insulin dose. This pairing does not constitute an artificial pancreas. However, it does represent the first step in joining glucose monitoring and insulin delivery systems using the most advanced current technology. To help "close the loop," the NIH is supporting research on the algorithms that will be needed to enable "proactive" insulin dosing by the insulin delivery device based upon current glucose monitor data, insulin usage data, and patient trend data.

Although the new continuous glucose monitors are not fully integrated into an artificial pancreas, they represent an important opportunity, for now, to help patients better manage their disease and reap the proven benefits of achieving close glucose control. Continuous glucose monitors may be especially helpful to patients to prevent "excursions" into high and low glucose levels on a daily basis, which may go undetected in long-term assessments of glucose control, but which researchers now believe may silently contribute to long-term health complications.

Already, patients using the new devices have been shown to reduce time spent in excessively high and low ranges of blood glucose. However, the wealth of data these devices offer means that patients will need to be well trained in order to achieve their optimal benefits and to avoid over-aggressive management.

New insights about the use of continuous glucose monitoring technologies have been gained from the Diabetes Research in Children Network (DirecNet), which is investigating the use of technological advances in the management of type 1 diabetes in children and adolescents. It seeks to determine if the new technologies are safe and effective, particularly for use in children. Thus far, the Network has carried out several independent and scientifically rigorous studies to determine the true benefit of new continuous glucose monitoring technologies, including their accuracy and efficacy. Without the commitment of DirecNet to perform these studies, it could be many years before studies would be conducted in the pediatric population.

Using Advanced Technology To Help Control Glucose Levels

It's the middle of the night, and the Burkhalter family of Jacksonville, Florida, is sleeping more soundly and peacefully than they have in a long time because of a newly-developed technology called a continuous glucose monitoring system, or CGMS. This promising device is being tested by their 14-year-old daughter, Casey, as part of a research network, called the Diabetes Research in Children Network (DirecNet), sponsored by the NICHD, NIDDK, and the *Special Funding Program*.

Casey has type 1 diabetes. The device she is testing monitors her blood glucose levels almost constantly throughout the day. It's when Casey is asleep at night, however, that the CGMS is a lifesaver for her and her family. Should Casey's glucose levels become too high or too low, the CGMS sets off an alarm that alerts her parents to take action. If her glucose level is too low, the Burkhalters give Casey orange juice to raise her blood glucose levels; if it's too high, they administer insulin through Casey's insulin pump.

Caring for children with diabetes requires great diligence, and CGMS technology has the potential to ease some of that burden. "Prior to Casey using the CGMS," says Casey's mother, Leslie Burkhalter, "my husband and I would wake up every 2 hours to prick Casey's finger and check her glucose levels." Their nightly vigil was part of an all-out effort to keep their daughter's blood glucose levels as close to the normal range as possible to prevent diabetes-related seizures and other complications.

NIDDK-supported research—including the landmark Diabetes Control and Complications Trial (DCCT) and a follow-up study, the Epidemiology of Diabetes Interventions and Complications Study (EDIC)—demonstrated that intensive blood glucose control offers remarkable long-term benefits when it comes to preventing or delaying the damage diabetes can have on a patient's eyes, kidneys, and nerves, as well as the harm the disease can inflict on large blood vessels that can lead to heart attacks and strokes.

Casey and Leslie Burkhalter

Most people with diabetes report checking their glucose levels every couple of hours, at best. The CGMS device Casey is testing is designed to provide, among other valuable information, glucose readings every minute—without a finger prick. The hope is that this technology will enable people of all ages with diabetes to better gain control over their blood glucose levels and reduce their risk of diabetes complications.

"I want to tell the world about this device," says Mrs. Burkhalter, who works in sales and is also actively involved in the Juvenile Diabetes Research Foundation (JDRF).

About the Continuous Glucose Monitoring System

In 2006, new continuous glucose monitoring devices were approved for use in adults. In 2007, a device was approved for use in children. However, Casey wears her monitor because of her participation in the DirecNet study, which is investigating the potential use of CGMS technology and its impact on the management of type 1 diabetes in children. She received her CGMS when she enrolled in the study in December 2005.

Casey's CGMS comes with a 5-day sensor, a transmitter, and a wireless receiver with a built-in glucose monitoring system. The tiny glucose sensor is placed just under the skin of Casey's abdomen. This procedure is similar to inserting the catheter of an insulin pump, is quick, and usually is not very painful. Tape is used to hold it in place. When used during the day, the wireless receiver allows Casey to attach the monitor to a belt or the waistline of her pants. When she goes to bed, she leaves it on her night table. The system automatically records an average glucose value every minute for up to 5 days, at which time the sensor needs to be replaced and repositioned on Casey's abdomen.

Casey's CGMS, when connected to a computer, also provides charts and graphs that indicate trends in her glucose levels over time and how often her glucose levels may be out of range. Although Casey's blood glucose control was excellent when she entered the trial, while wearing the CGMS she was able to further improve her blood glucose control without causing hypoglycemia. The family had great comfort knowing Casey's blood glucose level all the time and in real time.

"This technology is unbelievably helpful in controlling glucose levels. It's a huge step toward an artificial pancreas," says Mrs. Burkhalter. She is referring to the day when glucose monitoring and insulin delivery technologies merge, allowing insulin pumps to not only recommend proper insulin dosages, but automatically deliver them as well.

The Burkhalters' Vigil Before the CGMS

Casey was diagnosed with diabetes at about age 10 and a half. Her 18-year-old brother, Tyler, was diagnosed with the disease in November 1999. "Both came as a surprise," says Mrs. Burkhalter. "There is no other history of diabetes in our family."

Night after night of awaking every 2 hours to check Casey's levels was taking its toll on the family. "It created a lot of wear and tear on my husband and me," says Mrs. Burkhalter. "Lack of sleep was making us both irritable and cranky. However, we didn't want Casey to go into a diabetic seizure in her sleep, and fortunately, she never has."

The CGMS has provided the Burkhalters with more than just a good night's sleep. It has provided their daughter with a new attitude toward managing her diabetes.

Casey, whom her mother describes as outgoing and determined, is also an athlete who plays basketball, rides horses, and is a member of a crew team—all rigorous physical activities that can make controlling glucose levels even more difficult than normal.

"I hate having my fingers pricked (to check glucose levels), and the calluses they make aren't very attractive," says Casey. "With the CGMS, I only need to prick my finger, on average, once instead of 7 to 12 times a day." Casey adds that her CGMS is easy to wear "because it's not technically connected to me." At night, she keeps the transmitter on her nightstand. Should its alarm beep, "my parents don't even need to wake me."

As helpful as it may be, the technology is not perfect. There can be as much as a 10-minute delay between sensing and reading out glucose levels, and every 5 days, when the sensor needs replacing, it takes 10 hours to recalibrate, both of which timeframes users would like to see shortened, says Mrs. Burkhalter. Making the device smaller would also make it more convenient, she adds.

Participating in DirecNet

The Burkhalters learned about the DirecNet CGMS study when, in the fall of 2005, Mrs. Burkhalter read an article in *Countdown*, a publication of the JDRF, entitled, "Artificial Pancreas: How Close Are We to Closing the Loop?" It piqued her interest, and shortly thereafter she spoke with Casey's endocrinologist, Dr. Nelly Mauras at the Nemours Children's Clinic, one of the five participating centers, who recruited Casey into the study and started the ball rolling. Casey was

one of the first 30 children in the U.S. to participate in this DirecNet study. Today there are about 100. "One reason Casey is a good candidate for the study is that she recognizes when her blood glucose level is low during the day but, unlike Tyler, not at night," says Mrs. Burkhalter.

The Burkhalters have been extremely pleased with their participation in the DirecNet study. "We believe in the potential of this technology and very much appreciate how those running the study have provided information to us, as well as taken information from us," says Mrs. Burkhalter. "We've recommended the study to many of our friends, and several of their children are now participants." Tyler, the Burkhalter's son, is not a study participant. "He's averse to wearing anything, including an insulin pump, and unlike Casey, he doesn't seem to mind the finger pricks as much. But he's beginning to change his mind [about using a CGMS]," says Mrs. Burkhalter.

Five clinical centers presently participate in DirecNet: Yale University, The Barbara Davis Diabetes Center (Denver), Nemours Children's Clinic-Jacksonville, University of Iowa, and Stanford University. For more information on participating in DirecNet, please visit: http://public.direc.net/

What It Is Like To Care for a Young Child with Type 1 Diabetes

The day after two-and-a-half-year-old Hannah Beauregard was diagnosed with type 1 diabetes, her parents, Doug and Mary, were being trained at their local hospital by a team of medical personnel on how to measure Hannah's blood sugar level. Blood sugar is measured in milligrams per deciliter of blood. Although people with diabetes have higher than normal blood sugar levels, they can also occasionally experience dangerous episodes of seriously low blood sugar. "At one point," Doug recalls, "I told the medical team that I must be doing something wrong because the monitor read 20 (milligrams per deciliter)." The proper target range for Hannah, if she hasn't eaten recently, is substantially higher. Before he knew what was happening, attending residents whisked Hannah from his arms and out of her hospital bed into what Doug can only describe as a "little emergency-type" room. "They shut the door and would not allow me in," he vividly recalls.

What Doug didn't know at the time was that Hannah was being administered a medication that acts like "instant sugar." Because Hannah's blood sugar levels had dropped precipitously, this treatment was necessary to prevent her little body from going into a coma. What Doug did quickly realize was that having a child with diabetes was going to alter life for the Beauregard family dramatically.

"You Are Not Alone"

Doug Beauregard is a third grade teacher and longtime soccer coach. His wife, Mary, is a registered nurse. Given their professions, one would think that they should know a thing or two about children and medical care—and they do—a great deal. But having a young child with type 1 diabetes is often as difficult for them as it is for anyone else. "You are not alone," Doug wrote recently in an e-mail to another parent seeking advice on how to

Hannah Beauregard

deal with a toddler with type 1 diabetes who was refusing to eat after taking her insulin. "We're facing the same problem with Hannah."

People with type 1 diabetes must carefully monitor their blood sugar levels throughout the day to determine when they need to eat, and administer insulin, either through injections or an insulin pump, to help their bodies use the sugar from carbohydrates in food. Both steps are also necessary to help keep blood sugar levels within a healthy target range. A constant challenge faced by people with type 1 diabetes is matching food intake, physical activity, and insulin doses in order to maintain healthy blood sugar levels. For example, although too little insulin leads to high blood sugar (hyperglycemia), administering too much insulin for the body's needs at a given time can cause blood sugar levels to fall too low (hypoglycemia). Dramatic rises and drops in blood sugar levels can have immediate and life-threatening consequences, and need to be avoided. Moreover, research has shown that carefully controlling blood sugar levels over the long term is crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, and nerve disease, and cardiovascular disease.

Controlling Sugar Levels Is a Constant Chess Match

Carefully controlling blood sugar levels, especially in a young child with type 1 diabetes, is no easy task. Just ask the Beauregards.

According to Doug, since November 14, 2002, the day Hannah was diagnosed with type 1 diabetes, he and Mary have had few uninterrupted nights of sleep. "If Hannah snores, whimpers, cries, moves, or whatever, we wake up," he says. "We can tell by the way she is sleeping if her blood sugar is low or high. If I think it is low, I will check her. If not, I try to comfort her."

Since Hannah was diagnosed, the Beauregards have been relatively successful at developing systems for keeping Hannah's blood sugar levels within a normal range, especially at night when levels tend to drop, a phenomenon called nocturnal hypoglycemia.

To compensate for sugar level drops over the night, Hannah's parents try to put her to bed with a high enough blood sugar level so that she will wake up in the normal range. At least that's the goal, but it's a lot easier said than done. "It's a constant chess match," says Doug. "Her body makes a move; we make a counter move."

For example, physical activities tend to decrease blood sugar levels. Hannah's activities, like playing soccer, end at about 7:00 p.m. To bring her sugar level up before she goes to bed, which is around 9:30 p.m., the Beauregards usually give Hannah a snack—a fruit snack, sometimes followed by a protein-rich food.

"There are many nights, however, when Hannah will wake up, get out of bed, and tell us she's hungry," says Mary. "I'll check her levels and find that she's in a low but not dangerous range. I'll give her something to bring her level up a bit so she can safely get through the night. It's as if her body is talking to her and telling her what she needs."

But there are no hard and fast rules to this chess game. Hannah can go to bed with an acceptable blood sugar level on one night and wake up with a higher sugar level, but on another night, she might wake up with very low blood sugar, even if she started at the same point.

Then there are the real "Sugar Monster" nights when, according to Doug, there are no obvious reasons why Hannah's blood sugar will surge. Last spring, for example, Hannah lay in her bed crying uncontrollably, with a very high blood sugar level. Doug gave her extra insulin to bring her level down, and 15 minutes later she stopped crying, was peaceful and sound asleep. "But we worried about her all night and wondered what her numbers would be like in the morning," says Doug. In addition, the Beauregards run the battle of having to prick Hannah's little fingers yet again to test her sugar levels—fingers that have already been pricked thousands of times. "It's a question of whether we have faith in what we did," says Doug. "Controlling Hannah's sugar is really an art, not a science, and there are days I wish we didn't have to go through all of this," adds Doug.

As a result of such diligence, Hannah's hemoglobin A1c (HbA1c) tests have nearly always been good, between 6.9 and 7.1, which lowers Hannah's risk for complications from type 1 diabetes. These tests are administered by her endocrinologist and are a good indicator of average blood sugar levels over a 3-month period.

It's obvious that Doug and Mary love Hannah dearly. Doug, in particular, has made it his mission to tell everyone he can about Hannah and how special she is. "No one is responsible for Hannah's having type 1 diabetes. It's just part of her life, and we love her for who she is," says Doug, who actively tries to help other parents whose children have this life-threatening disease.

In many ways, Doug is the consummate communicator. The very first night that Hannah was diagnosed, Doug was on the Internet searching for local support groups. Today, their

family attends a support group near their hometown of Plainwell, Michigan. The group consists of families of children with type 1 diabetes who range in age from 2 to 13 years old. Doug also frequently exchanges e-mails with people around the world, from Argentina to Newfoundland. "We are all seeking answers for our children," says Doug. "We learn a lot through each other's experiences and mistakes."

What About All of Those Finger Pricks and Shots?

It is hard enough for adults with type 1 diabetes to take all of the steps necessary to take care of their disease. Therefore, the questions remain: How does a parent convince a small child with type 1 diabetes that enduring finger pricks to test blood sugar levels and shots to administer insulin, several times a day, is necessary in order to stay alive and healthy? How do parents feel about having to administer those finger pricks and shots?

To help the whole family adjust to Hannah's new health needs, the Beauregards introduced Hannah to a friend—a fluffy brown teddy bear named Rufus. Rufus™, The Bear with Diabetes, was given to Hannah by the organization Childrenwithdiabetes.com. Within hours of their meeting, Rufus became Hannah's fast friend. Rufus is designed so that he, too, needs to have his fingers "pricked" and to be given "shots." It wasn't long before Hannah was administering "shots" to Rufus. After finger pricks to test for sugar levels, both Hannah and Rufus would have their fingers wiped and a special Band-Aid® applied. When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

Everyone in Hannah's family—except 2-year-old Evan—knows how to care for her, including her 14-year-old brother, Ryan. "Ryan is really good with his little sister," says Mary. "Yes, they fight and can drive us crazy at times, but Ryan and members of his soccer team know how to test Hannah's blood sugar level," adds Doug.

The good news is that the older Hannah gets, the more choices she can make for herself to help balance her diet, physical activities, and insulin injections so that she can maintain healthy control of her blood sugar levels. As Hannah becomes more independent, it is becoming easier for her parents. Doug recounted an experience in which he encouraged Hannah in learning about the foods she needs to eat in order to obtain the proper amounts and balance of nutrients she requires at each meal, including carbohydrates. Says Doug, "At dinner the other day, Hannah said she was full. I told her that she needed to eat so she would get her carbs (carbohydrates). Hannah then asked, 'Dad, does my bread have carbs?' Yes, I told her. 'How about my meat?' No, I said. 'I guess I will eat my bread then,' she said." Hannah recognized the need to have her carbohydrates to stay healthy. The Beauregards try to make Hannah feel in control of her diabetes as much as possible by giving her choices. "We also always have a fallback food just in case Hannah doesn't want to eat what we have for dinner," Mary adds.

As much as Doug and Mary sometimes feel they have things pretty much under control, "It's not easy being a parent of a child with diabetes, and it never will be," Doug says. The kindergarten Hannah attends, for example, was leery at first about having a student with Hannah's disease, so the Beauregards had to educate the staff about diabetes and what to do if Hannah's blood sugar level became too low or too high. "Part of the problem," says Doug, "is that Hannah isn't always cooperative when her blood sugar level is low." The family has shied away from day care. When Hannah was not in pre-school, Doug's mother, Elizabeth—who is as well trained as Doug and Mary in how to care for Hannah—spent 2 or 3 days a week at the Beauregard home. Doug adds that when he is at work, "my students know that if my cell phone rings, it's something important."

In Short, Life Is a Constant Vigil

Hannah is growing up to be an adorable little girl whose life will be in constant jeopardy until a cure is found for her type 1 diabetes. Until then, she will be required to take insulin every day of her life to survive.

"We're not angry that Hannah has (type 1) diabetes," says Doug. He and Mary just want to tell everyone they can about their little girl. "Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength."

"We need to be strong for every child with diabetes," says Doug, "because without their parents, they won't make it."

Hope Through Research

To balance the long-term risks of developing complications associated with hyperglycemia with the short-term dangers of hypoglycemia, patients with type 1 diabetes and their families must perpetually face a chess match of measuring sugar levels and reacting to them with insulin or sugar. The *Special Funding Program* supports multiple avenues of research that are helping patients improve their blood sugar control and avoid hypoglycemia.

As a result of insulin therapy for type 1 diabetes, many patients experience low blood sugar at night during sleep, a phenomenon known as nocturnal hypoglycemia. Sleep can be a particularly dangerous time because it inhibits the normal adrenaline responses that are usually triggered when blood sugar drops below a threshold level; the adrenaline and nervous system responses are needed to warn patients that they are in danger. Nearly half of all episodes of severe hypoglycemia occur during sleep and, in extreme cases, can lead to coma or seizures that can result in fatal cardiac arrhythmia (disturbed heartbeat).

Despite measuring blood sugar levels just before sleep, type 1 diabetes patients often find it difficult to predict the profile of blood sugar during the night. Research that explores the relationships among diet, behavior, insulin therapy, and the nocturnal sugar profile will make it easier to predict and prepare for changes in blood sugar during the night. For example, a DirecNet study has already provided vital information required to adequately manage active adolescents with type 1 diabetes to avoid precipitous declines in blood glucose after exercise, particularly to prevent the dangers of nocturnal hypoglycemia.

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE *SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH*

The Special Funding Program *has fueled the emergence of a wide range of research opportunities. Opportunities that have largely been made possible by the* Special Funding Program *have been excerpted below from the Type 1 Diabetes Research Strategic Plan (see Appendix 6).*

Brain and Peripheral Nervous System Mechanisms of Hypoglycemia

Define the Mechanisms and Modulators of Metabolic Sensing:

- Identify and elucidate the mechanisms involved in glucose sensing in the brain.
- Determine the hormonal and metabolic modulators involved in glucose sensing.

Elucidate Brain Alterations in Response to Hypoglycemia:

- Determine alterations in brain metabolism and function induced by recurrent hypoglycemia.
- Prevent hypoglycemia-induced brain injury and promote protective adaptations.
- Identify potential genes involved in individual susceptibility to hypoglycemia.

Develop New Strategies To Prevent or Reverse Hypoglycemia-Associated Autonomic Failure (HAAF):

- Elucidate the mechanisms of HAAF.
- Identify the clinical consequences of HAAF.
- Develop and test therapies to restore counter-regulation.

Clinical Interventions To Prevent or Reduce Hypoglycemia

Control Hypoglycemia Through Behavioral Therapies:

- Refine and link behavioral interventions and algorithms that predict risks of hypoglycemia.
- Evaluate behavioral approaches to preventing nocturnal hypoglycemia.

Close the Loop—Develop the Tools Required for an Artificial Pancreas:

- Optimize use of continuous glucose monitors.
- Develop algorithms needed to link glucose monitors with insulin delivery.