Testimony
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United States Senate

Development of an Artificial Pancreas: Will New Technologies Improve Care for People with Diabetes and Reduce the Burden on the Health Care System?

Statement of

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Chairman Collins and Members of the Committee, as Deputy Director and Acting Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I appreciate the invitation to testify at this hearing regarding the potential of new technologies to improve care for people with diabetes and help reduce the burden of diabetes on the health care system. On behalf of the NIDDK and the other Institutes and Centers of the National Institutes of Health (NIH) within the U.S. Department of Health and Human Services, I am pleased to report to you on recent technological advances that are paving the way toward an "artificial pancreas," a treatment approach to help patients with diabetes manage their disease more effectively, and on the outlook for research furthering this technology. I would like to thank the Senate for its continuing interest in new and emerging technologies that may improve the health of many Americans with diabetes, and I would particularly like to acknowledge your leadership, Chairman Collins, in focusing the Senate's attention on biomedical research and many other issues that are important to diabetes patients and their families.

Need for Improved Treatment Options for Diabetes

Diabetes is a chronic disease affecting nearly 21 million Americans. Without medical care, people with diabetes cannot control the levels of glucose (sugar) in their blood. Diabetes lowers average life expectancy by up to 15 years, significantly increases a person's risk for heart disease and stroke, and is the leading cause of new adult-onset blindness, kidney failure, and lower limb amputations. In 2002, the total cost of diabetes was estimated at $132 billion.[1] This estimate included both direct medical costs and the

[1] Hogan P, Dall T, Nikolov P; American Diabetes Association. Economic costs of diabetes mellitus in the US in 2002. Diabetes Care. 2003;26:917–932.

indirect costs due to loss of work, disability, and premature mortality. The NIH maintains a vigorous, multifaceted research program on diabetes so that we may harness scientific discovery toward diabetes prevention, treatment, and, if possible, a cure.

Most patients struggling with blood glucose control have either type 1 or type 2 diabetes. Both forms of diabetes involve malfunctions in the body's system for maintaining appropriate blood glucose levels and both also share the same complications.

Type 1 diabetes strikes mainly in childhood and adolescence and was formerly known as juvenile diabetes. In this form of the diabetes, the body's immune system destroys its own insulin-producing beta cells, which are found in clusters called "islets" within the pancreas. Without insulin, the body cannot regulate glucose in the blood or utilize it for energy. To prevent glucose levels from rising dangerously—and threatening life—patients require administration of insulin in the form of injections or *via* an insulin pump. They must also carefully monitor their food intake and physical activity in order to manage the disease.

Type 2 diabetes is more commonly diagnosed in adulthood, although we are now witnessing an alarming increase of this disease in children. It is strongly associated with overweight and obesity, and disproportionately affects minority populations. In type 2 diabetes, the body's ability to respond to insulin is impaired. This form of the disease can often be managed with oral medications, diet, and exercise, but patients can ultimately "exhaust" their insulin-producing beta cells and become dependent upon insulin treatment to control their blood glucose levels.

Landmark NIH-supported clinical trials have proven that achieving good glucose control is vital to preventing or delaying the devastating and costly health complications

of diabetes. Results from the Diabetes Control and Complications Trial (DCCT) revealed that close control of blood glucose levels could dramatically prevent or delay the eye, kidney, and nerve complications in type 1 diabetes patients. The findings of this trial paved the way to studies that replicated these impressive results in patients with type 2 diabetes. Moreover, a follow-up investigation in the DCCT patients—the Epidemiology of Diabetes Interventions and Complications (EDIC) study—recently showed that close control could cut the risk of heart disease and stroke in half. These results are critically important because people with diabetes have a 2- to 4-fold increased risk for heart disease compared to those without the disease, and type 1 diabetes patients in particular are at a 10-fold greater risk. Unfortunately, although we possess the scientific knowledge that close glucose control can confer these tremendous health benefits, we have lacked the tools to transform this knowledge into optimal health care. Less than half of diabetes patients are able to achieve good glucose control using current treatment methods. Type 1 diabetes patients and others dependent on insulin face unique challenges. In the effort to achieve good control, every day they must endure multiple, painful finger sticks to carefully monitor blood glucose, and intensive use of insulin to control it—steps which are inconvenient, painful, and invasive. Moreover, intensive insulin treatment places patients, especially children, at increased risk for episodes of dangerously low blood sugar, or hypoglycemia. This frightening condition can lead to immediate and severe injury, coma, and even death. Hypoglycemia is particularly troublesome at night, adding to the burden of care. Thus, patients and their families must walk a tightrope between the prospect of dreaded complications on one side, and the fear of dangerous episodes of low

blood glucose on the other. Additional impediments to close glucose control include treatment costs and lack of knowledge about diabetes self-management.

To overcome the limitations of current insulin therapy, researchers have long sought to develop an "artificial pancreas." In essence, this is a system that would mimic, as closely as possible, the way a healthy pancreas "senses" changes in blood glucose levels and responds automatically to secrete appropriate amounts of insulin. As a safety feature, the device would also provide alerts when blood glucose levels drop too low or rise too high. While not a cure, an "artificial pancreas" has the potential to significantly improve diabetes care and management and to alleviate patient burden. Importantly, it could bring to full application the knowledge gained from NIH clinical trials that close glucose control can prevent or delay the devastating complications of diabetes. This is a key goal for research.

Today, I am pleased to report that—with recent technological advances, many made possible by NIH-supported research in academia and industry—the first steps have been taken toward "closing the loop" between glucose sensing and insulin delivery, thus laying the foundation for a true artificial pancreas.

Continuous Glucose Monitors: First Steps Toward An 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. The NIDDK pursued these opportunities in collaboration with the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Center for Research Resources (NCRR), the National Institute of Child Health and Human Development (NICHD), and other NIH components. 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, non-invasively 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 Food and Drug Administration (FDA). These devices represent a significant improvement over the first devices approved by the FDA in 1999. I am pleased to note that NIDDK support was instrumental in technology development for two of them, the Medtronic and Abbott

continuous glucose monitors, the latter of which is still under FDA review. 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 or not 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 "real time" to patients. This information allows 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 additional improvements in these devices can be expected with further 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 NIDDK 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 implement the recommendations from the DCCT/EDIC and other clinical trials that will enable them to achieve significant risk reduction for heart disease and eye, kidney, and nerve damage. We are hopeful that, by observing how their glucose levels fluctuate throughout the day and night and by reducing their risk for the dangerous low blood glucose reactions that currently limit diabetes control, patients using these devices will be able to 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. For example, in one recent clinical trial in insulin-dependent patients with either type 1 or type 2 diabetes, participants who used a continuous glucose monitor spent, on average, 21 percent less time hypoglycemic, 23 percent less time hyperglycemic, and 26 percent more time in a healthy target range for blood glucose levels, when compared to trial participants not using the devices. Even more encouragingly, continuous glucose monitor use reduced the duration of hypoglycemia by 33 percent, and of severe hypoglycemia by 38 percent. 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 overaggressive or lenient management.

Continuous glucose monitoring devices are currently FDA-approved for use by adults 18 years of age and older. Yet, many insulin-dependent patients are children and adolescents, who are particularly susceptible to episodes of dangerously low blood glucose, especially at night. Already new insights about this issue have been gained from the Diabetes Research in Children Network (DirecNet), a multi-center clinical research network led by the NICHD and supported by the NIDDK. DirecNet 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, DirecNet has carried out several independent and scientifically rigorous studies to determine the true benefit of new continuous glucose monitoring technologies, including their accuracy, efficacy, and effectiveness. Using the new continuous glucose monitors, this network found, for example, that exercise much earlier in the day increases the risk of nocturnal drops in blood glucose, yielding the practical suggestion of increased bedtime snacks on days when children with diabetes were particularly physically active. Without the commitment of DirecNet to perform such research, it could be many years before studies would be conducted in the pediatric population. The initial 5-year project period for DirecNet ends in 2006, and steps are being taken to ensure that its research agenda continues to move forward.

Prospects for the Future

While currently available continuous glucose monitoring devices do not yet fully close the loop, they are an extremely important milestone in research toward developing an automated, artificial pancreas that can alleviate the burden of care for patients and

their families and reduce costly and debilitating health complications of diabetes. To continue the pace of progress toward an artificial pancreas, the NIDDK and other NIH Institutes and Centers are fostering basic and preclinical research on new technologies for both continuous glucose monitors and insulin delivery; algorithms to link glucose monitors and insulin pumps; research to better understand how the body normally senses low glucose and how this is altered in diabetes; and clinical studies to optimize and evaluate current and emerging technologies for use by patients. Recent advances on these fronts include clinical evaluation of an implantable glucose monitor for long-term use in patients and studies of first-generation closed-loop systems that use currently available technologies.

To assess the state-of-the-science of glucose-sensing and insulin-delivery technologies, the NIDDK, together with Juvenile Diabetes Research Foundation International, the American Diabetes Association, and the FDA, convened a scientific workshop in December 2005, entitled "Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop." The workshop brought together basic scientists from engineering and the biological sciences, clinical investigators, and industry officials who are developing new monitoring systems. Participants discussed progress and the technical difficulties of different technologies, optimal targets for normal glucose levels, and initial testing of closed-loop systems. FDA representatives discussed the criteria and regulatory steps involved in approval of new devices. Although a fully automated closed-loop system will require more years of development, the workshop generated an insightful dialogue on the practical considerations for an intermediate artificial pancreas that may have external or internal glucose sensors and may require some patient input

during meals and exercise, but could be automated during other activities--especially during sleep. The NIDDK is incorporating the outcomes of this meeting in its research planning efforts.

Conclusion

I am grateful for the opportunity to share with you these highlights of progress in the development of an artificial pancreas for diabetes treatment, and ongoing research efforts. The NIDDK continues to foster exciting new opportunities for the research community to intensify the study of the treatment prevention and cure of diabetes and its complications. We have just released a new Strategic Plan for Type 1 Diabetes Research that includes strategies directed at improving glucose control and reducing hypoglycemia, and that will help inform research program development for new technologies. This plan was developed under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee, which will continue to coordinate efforts in this area across the NIH and with other relevant Federal agencies.

Diabetes can wreak havoc on a person's health, family, and finances. Over the past several decades, technological advances have reduced the treatment burden on patients, improved disease management, and reduced premature mortality from type 1 diabetes. In a lifetime, some patients went from complicated, imprecise urine-based glucose tests to accurate, though often painful, finger sticks and pager-sized blood glucose readers, and from injections of insulin extracted from animals to continuous infusion, via a pump, of optimized biosynthetic insulins. We can now foresee a future when treatment technology will be so advanced it will be nearly invisible to the patient, while providing increased

health benefits. We will continue to foster research to achieve that goal. I am pleased to answer any questions you may have.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
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Biographical Sketch

Griffin P. Rodgers, M.D., M.A.C.P.

Dr. Griffin P. Rodgers is the Acting Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health, a position he has held since March 6, 2006. As Acting Director, Dr. Rodgers oversees a national research program in diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases, the goal of which is to improve the health and quality of life for all Americans. In addition to this current appointment, Dr. Rodgers has served as Deputy Director of the NIDDK since 2001. An active researcher, Dr. Rodgers also is Chief of the Clinical and Molecular Hematology Branch of the NIDDK's Intramural Research Program.

A native of New Orleans, Dr. Rodgers received his undergraduate, graduate, and medical degrees from Brown University in Providence, Rhode Island. He was an intern, resident and chief resident in internal medicine at Barnes Hospital and the Washington University School of Medicine in St. Louis, Missouri. His fellowship training in hematology was in a joint program of the National Institutes of Health, The George Washington University, and the Washington Veterans Administration Medical Center. Dr. Rodgers has also recently received a Master of Business Administration degree with a concentration in the Business of Medicine from The Johns Hopkins University in Baltimore, Maryland.

Dr. Rodgers is widely recognized for his contributions to the development of the first effective—and now FDA-approved—therapy for sickle cell anemia. He has served as the principal investigator in clinical trials to elevate pharmacologically fetal hemoglobin to counteract the deleterious molecular and cellular effects present in the red cells of these patients. Dr. Rodgers' basic research has focused on understanding the molecular basis of how these drugs induce gamma-globin gene expression. His laboratory also focuses on the identification and characterization of early markers of hematopoietic stem cell lineage-specific differentiation, and on the application of hematopoietic stem cell-based approaches to thalassemia and sickle cell disease, including transplantation and gene therapy strategies.

Dr. Rodgers has been honored for his research with numerous awards, including the Public Health Service Physician-Researcher of the Year and Hildrus A. Poindexter Awards, the Richard and Hinda Rosenthal Foundation Award, the Arthur S. Fleming Award, and Mastership in the American College of Physicians, among others. Dr. Rodgers has served as Distinguished Lecturer and has delivered several named lectures nationally and internationally. He has published over 150 original research articles, numerous reviews, book chapters, books and monographs. He is a member of the editorial board of several scientific journals.

Dr. Rodgers served as Governor to the American College of Physicians for the Department of Health and Human Services, and is a member of the American Society of Hematology, the American Society of Clinical Investigation, and the Association of American Physicians. He is the Chair of the Hematology Subspecialty Board, and is a member of the American Board of Internal Medicine Board of Directors.

Continuous Glucose Monitoring

For every 1 percent fall in HbA1c—a measure of blood glucose control over time--there is a 37 percent reduction in eye, kidney, and nerve complications

Tight glucose control cuts heart disease in half in patients with type 1 diabetes

Only about 44 percent of people with diabetes achieve recommended glucose control with current technology and medications

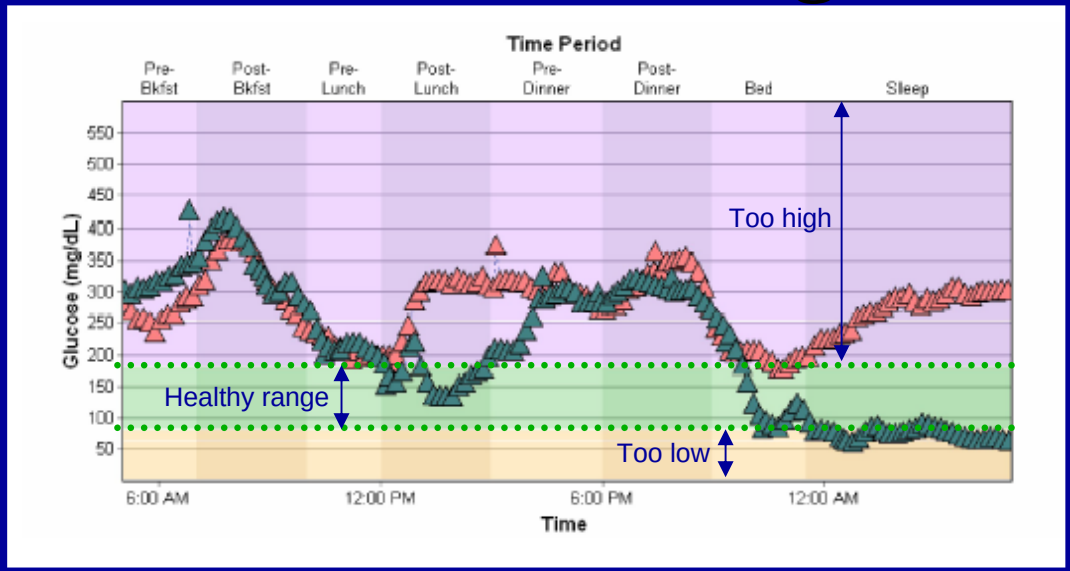
Continuous glucose monitors facilitate tight control of blood glucose levels

Improvement in Glycemic Control with Continuous Glucose Monitoring

Baseline Profile

(2 days)

HbA1c 7.2%



13 Week Follow-up Profile

(2 days)

HbA1c 6.8%