Testimony
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Progress and Plans in Type 1 Diabetes Research

Statement of
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Chairman Lieberman and Members of the Committee, as the recently appointed Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I appreciate the invitation to testify at this hearing on type 1 diabetes, entitled "The Juvenile Diabetes Research Foundation (JDRF) and the Federal Government: A Model Public-Private Partnership Accelerating Research Toward a Cure." 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 (HHS), I am pleased to report that we are vigorously pursuing research on type 1 diabetes and its complications—along with the JDRF and other research partners with whom we share important goals. Such partnerships have helped to synergize and propel research to combat this disease. Through collaborative and well-coordinated research, we are gaining insights into the molecular mechanisms underlying disease development, testing promising therapies to prevent and treat the disease and its complications in people, and striving for a cure. Today, as requested by the Committee, I will discuss recent advances and future opportunities in type 1 diabetes research, including research supported by the Special Statutory Funding Program for Type 1 Diabetes Research. I will also address the Committee's interest in our plans if the Special Diabetes Program is not renewed.

Type 1 diabetes strikes mainly in childhood and adolescence. It is an "autoimmune" disease, in which the body's own immune system attacks and destroys the insulin-producing beta cells found in clusters called "islets" within the pancreas. To survive, people with type 1 diabetes require daily administration of insulin in the form of injections or via an insulin pump. They must also monitor their food intake and physical activity in order to manage the disease. Even with continuous and vigilant management, patients are still susceptible to developing serious, long-term complications that can damage the eyes, kidneys, nerves, heart, and other organs.

Today, I will be describing some of the strides forward that we have made with respect to improving the lives of people with type 1 diabetes. For example, continuous improvements in therapy, as a result of research, have contributed to recent findings that people with type 1 diabetes are living longer, healthier lives than ever before. Prevention efforts are reducing rates of diabetic kidney disease in people with type 1 diabetes. New continuous glucose monitoring technologies are helping patients control their blood glucose levels, which is key for preventing disease complications. Blood tests can predict the risk of developing the disease in relatives of people with type 1 diabetes; this knowledge has enabled the launch of clinical trials testing new prevention strategies. It is imperative to build on these successes and continue basic and clinical research to further improve patients' quality-of-life and to seek ways to prevent and cure the disease.

The NIH is focused on six broad goals in type 1 diabetes research, which are to: (1) understand the genetic and environmental causes of type 1 diabetes; (2) prevent or reverse the disease; (3) to develop cell replacement therapy as a cure; (4) prevent or reduce hypoglycemia (low blood sugar), which limits tight control of blood glucose; (5) prevent or reduce complications; and (6) attract new talent and apply new technologies to research. Through this multifaceted approach, we can obtain a comprehensive understanding of the disease process—the foundation for future advances in treatment, prevention, and approaches to a cure.

Relative to each of the six research goals, I would now like to highlight recent research progress, as well as ongoing efforts in unique, innovative, and collaborative research consortia and clinical trials networks. These efforts have involved not only partnerships among scientists with complementary expertise from multiple academic institutions, but also partnerships among many of the Institutes and Centers of the NIH, HHS's Centers for Disease Control and

Prevention (CDC), and patient-advocacy groups. JDRF has played an instrumental role in facilitating and in contributing support to many of these collaborative research endeavors. Most of these efforts are being pursued with some contribution under the Special Diabetes Program, about which you asked me to testify today.

Understanding the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes is caused by a combination of genetic and environmental factors. We already know some of the major genes that predispose people to develop type 1 diabetes, and additional key genes have recently been identified. Further discovery of the genes involved in type 1 diabetes will provide new targets for prevention and therapy, as well as help us predict more accurately who will develop the disease. To this end, we established the "Type 1 Diabetes Genetics Consortium" to collect genetic material from 2,800 families with two or more siblings having type 1 diabetes. The Consortium has already recruited over 2,400 families for this study, and recruitment is ongoing. It also conducted one of the largest linkage studies ever performed for a common disease and found several genetic regions associated with type 1 diabetes risk, which researchers are further exploring.

We know much less about the environmental factors that trigger onset of type 1 diabetes in genetically-susceptible individuals. To address this question, an international consortium is identifying infants at high-risk for developing type 1 diabetes and following them through adolescence to search for environmental factors that may trigger disease. This long-term, NIDDK-led study, called "The Environmental Determinants of Diabetes in the Young," or "TEDDY," has enrolled over 3,000 newborns, and recruitment is ongoing. This study is making significant progress toward amassing the largest data set and samples on newborns at-risk for autoimmunity

and type 1 diabetes anywhere in the world. To maximize the return on the investment in TEDDY, samples from the study will be made widely available to researchers worldwide. Importantly, TEDDY may also contribute to understanding the development of celiac disease, which is an autoimmune disease primarily affecting the gastrointestinal tract. Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Thus, TEDDY may not only benefit people with, or at-risk for, type 1 diabetes, but it can also benefit people with celiac disease and other autoimmune diseases. NIH's National Institute of Child Health and Human Development (NICHD) leads another effort, called the "Trial to Reduce IDDM [insulin-dependent diabetes mellitus] in the Genetically At Risk," or "TRIGR," which is examining a specific environmental factor, cow's milk, in development of type 1 diabetes.

We are learning, for the first time, how many children in the U.S. have type 1 and type 2 diabetes. The Search for Diabetes in Youth Study, which is supported by CDC and NIDDK, has reported the first national data on the prevalence of diabetes in youth: one of every 523 youth had physician-diagnosed diabetes in 2001. Now that this baseline assessment of diabetes rates in children nationwide has been completed, the study is poised to evaluate trends in diabetes incidence and progression over time.

Preventing or Reversing Type 1 Diabetes

To spur the testing of promising new strategies to prevent, delay, or reverse progression of type 1 diabetes, the NIDDK leads a clinical trials network, the Type 1 Diabetes TrialNet. Several clinical trials are under way. For example, TrialNet recently launched a trial to test whether oral insulin administration can prevent type 1 diabetes in a subset of people who have high levels of a certain disease marker—anti-insulin antibodies. TrialNet also launched a trial to

determine if a drug, called rituximab, could prevent further insulin-producing beta cell destruction in people newly-diagnosed with type 1 diabetes. The TrialNet infrastructure is critically important for testing emerging therapies for disease prevention and early treatment.

The Immune Tolerance Network (ITN), led by NIH's National Institute of Allergy and Infectious Diseases (NIAID), is conducting several clinical trials to test therapies to reverse disease in newly-diagnosed patients with type 1 diabetes. For example, ITN is testing an agent, called anti-CD3, which has shown promising results with respect to halting disease progression.

Research is also ongoing to image pancreatic beta cells in order to monitor type 1 diabetes disease progression and response to therapy. Toward this goal, researchers recently used imaging technology to visualize both normal beta cells and transplanted islets *in vivo* in rat, mouse, pig, and baboon models of the disease. In one method, a compound that could be imaged was injected into the animal model, bound to a protein found in beta cells, and could be detected on an image of the pancreas. In another method, an iron compound was taken up into isolated islets prior to transplantation and was visible using magnetic resonance imaging (MRI) technology. The first approach permitted the researchers to noninvasively monitor beta cell destruction as the laboratory animal transitioned from a healthy to a disease state, and the second method showed where transplanted islets go and how long they live. Both approaches are being tried in type 1 diabetes patients. If successful, the approaches could be tremendously useful in monitoring disease progression and response to therapy. Finally, an MRI method has been developed that can visualize the inflammation associated with onset of type 1 diabetes. This approach is being investigated in animal models and newly-diagnosed patients.

Research is also ongoing to identify biomarkers of autoimmunity in type 1 diabetes. Biomarkers are measurable molecular, biological, or physical characteristics that indicate a

specific underlying physiologic state. Biomarkers are critically needed to predict disease risk, to monitor disease, and to monitor autoimmune responses during therapeutic intervention.

Developing Cell Replacement Therapy

Insulin therapy is a poor substitute for the body's exquisitely precise regulation of blood glucose by insulin-producing pancreatic beta cells. In contrast to insulin administration, a real cure could emerge from cell-based therapy, such as the transplantation of insulin-producing cells. Scientists participating in the Immune Tolerance Network successfully replicated the "Edmonton Protocol" for transplanting human pancreatic islets. The results showed that, a year after the final treatment, 44 percent of the transplant recipients no longer needed insulin injections. An additional 28 percent had partial islet function, which was associated with resolution of hypoglycemic unawareness (a condition in which people cannot recognize early symptoms of dangerously low blood glucose). Insulin independence did not persist indefinitely in most cases, and less than a third of the people who had been freed from insulin after one year remained so by two years. However, individuals with functioning islets had improved control of their type 1 diabetes, even though they still needed to take insulin injections. The results of this study extend the demonstration that islet transplantation may become an alternative to whole pancreas transplantation. They also highlight the continued need for safer, more tolerable anti-rejection therapies.

To further bolster research efforts on islet transplantation, the NIDDK and NIAID co-sponsor an ongoing Clinical Islet Transplantation Consortium. To expedite progress and promote safety in islet transplantation, an islet transplant registry publishes an annual report with comprehensive and current data on all islet transplants performed in North America.

A major barrier in the field of islet transplantation is an inadequate supply of islets. The NIDDK teamed with NIH's National Center for Research Resources (NCRR) and the JDRF to form Islet Cell Resource Centers, which provide human islets for both clinical transplantation and basic research studies. In addition, we are accelerating research on many aspects of beta cell development and function with the goal of increasing the supply of islets for transplantation. A key component of this effort is the NIDDK-sponsored Beta Cell Biology Consortium. Researchers in this Consortium have created numerous research tools, such as mouse models, antibodies, cell lines, and gene chips, that are not only propelling research progress within the Consortium, but are also accelerating research progress in the broad diabetes research community. For example, the Consortium developed "promoter" chips, which are available to the scientific community and contain over 35,000 regulatory regions on mouse DNA.

In addition, the NIAID leads a research consortium that is studying methods for transplanting islets from pigs to non-human primates. Xenotransplantation, which involves the transfer of cells, tissues, or organs from one species to another, may eventually help to alleviate the shortage of islets available for transplantation.

Another barrier that limits widespread use of islet transplantation is the lifelong immunosuppressive drug treatments that are required to prevent rejection of transplanted islets, as well as recurrence of the underlying autoimmunity that caused type 1 diabetes initially. Scientists are testing approaches to altering the immune system in human transplantation studies. These new approaches may be safer or have fewer side effects than the drugs currently used. Other efforts involve testing novel methods to induce immune tolerance after transplantation into non-human primates.

Researchers are also studying alternative strategies to restore beta cell mass and function. For example, research in beta cell regeneration is determining if adult beta cells could be coaxed to form more beta cells, or if other resident cell types could be directed toward a beta cell fate.

Preventing or Reducing Hypoglycemia in Type 1 Diabetes

Perhaps the most distressing, acute complication in people with type 1 diabetes is hypoglycemia. It is caused by excessive treatment with insulin relative to food intake and physical activity. The potential for hypoglycemic episodes has impeded the use of intensive insulin therapy even though major clinical trials have shown that such therapy can significantly reduce the risks of longer-term diabetic complications. A major goal of research is to "close the loop," to link glucose monitoring and insulin delivery. Researchers are laying a foundation for an "artificial pancreas" that would mimic the body's own insulin-sensing and insulin-delivery mechanisms. While not a cure, an artificial pancreas has the potential to significantly improve diabetes care and management and to alleviate a patient's burden.

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. This progress has come in the form of new continuous glucose monitoring technologies. These devices have recently been approved for use in adults and children by the Food and Drug Administration (FDA) within HHS. They reveal the dynamic changes in blood glucose levels by assessing glucose levels hundreds of times per day and displaying trends so patients can see if their levels are rising or falling. Alarms warn the patient if blood glucose becomes too high or too low. This revolutionary technology can make it easier for patients to accurately determine how much insulin or food they need to keep blood glucose at healthy

levels, and it can enhance their ability to achieve the tight control necessary to prevent disease complications.

The NICHD leads a network, called "DirecNet," which has carried out several independent and scientifically rigorous studies to determine the benefit of new continuous glucose monitoring technologies. Using the new technologies, DirecNet researchers found, for example, that exercise much earlier in the day increases the risk of nocturnal drops in blood glucose. This finding resulted in the practical suggestion of increased bedtime snacks on days when children with type 1 diabetes are particularly physically active.

Preventing or Reducing the Complications of Type 1 Diabetes

The complications of diabetes affect virtually every system of the body; diabetes and its complications can shorten average life expectancy by up to 15 years. Recent studies have brought good news: people with type 1 diabetes are living longer and healthier lives than ever before. Data from Allegheny County, Pennsylvania, have shown that the long-term survival of children with type 1 diabetes has greatly improved over time. The prognosis continues to improve, with a reduced likelihood that kidney failure, diabetic nerve damage, and death will occur, as research has led to continuous improvements in therapy.

The NIH is fostering exciting new opportunities to intensify the study of diabetic complications. Because people with both type 1 and type 2 diabetes develop complications, research on the complications of type 1 diabetes can also benefit people with type 2 diabetes, and vice versa.

The landmark NIDDK-supported Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels is extremely effective in preventing

complications affecting the eyes, kidneys, and nerves. Long-term results from the follow-on study to the DCCT now show that intensive therapy also dramatically reduces the risk of heart disease, which is the leading cause of death in people with diabetes. Results also showed that a finite period of good glucose control provides benefits years down the road. Thus, patients and physicians are advised to start intensive therapy as early as possible following diagnosis.

Recently-reported results have brought more good news for people with type 1 diabetes: recurrent episodes of severe hypoglycemia associated with intensive glucose control appear not to affect patients' long-term cognitive function. Even though the acute effects of hypoglycemia are very worrisome, this result is reassuring to patients and to parents of children with diabetes.

Prevention efforts are having dramatic and positive effects on rates of diabetic kidney disease in people with type 1 diabetes. The incidence rate of end-stage renal disease in Caucasians under 30 years of age with diabetes, most of whom have type 1 diabetes, is about half the rate seen in the late 1980s and early 1990s. Credit for recent gains likely goes to implementation of strategies to prevent kidney disease, including improved management of diabetes.

Type 1 and type 2 diabetes together are the leading cause of new blindness in people 20-74 years old. To combat this devastating complication, NIH's National Eye Institute supports the "Diabetic Retinopathy Clinical Research Network," which is conducting multiple protocols to identify new prevention and treatment strategies for diabetic eye disease.

In the area of diabetic foot ulcers, researchers found that a new technology, which measures the oxygenation of tissue surrounding the wound, could accurately predict whether a foot ulcer will heal. Based on these results, the FDA recently approved the new technology for use by healthcare providers. Because foot ulceration precedes the majority of lower-limb

amputations, finding new ways to predict healing could lead to personalized treatments to reduce the burden of this complication.

Development of animal models is key to preclinical drug development. Thus, another focus of research is a program to develop animal models that replicate development of diabetic complications in humans. This program has generated numerous promising models for studying complications involving the heart, kidneys, and nervous system.

In addition to clinical studies, basic research is under way to identify the genes that may increase a person's susceptibility to developing complications of diabetes. This knowledge can help predict which patients are prone to them, as well as illuminate new targets for prevention and therapy. It could also lead to personalized therapies for people who have a genetic susceptibility to developing certain complications. Researchers are also studying angiogenesis, or new blood vessel formation, as it relates to diabetic complications.

Attracting New Talent and Applying New Technologies to Research on Type 1 Diabetes

Type 1 diabetes research spans a broad range of scientific disciplines. For this reason, a cadre of exceptionally talented and dedicated researchers is needed to bring expertise to bear on scientific challenges. As research is being done in the laboratory, or at the “bench,” there is a need to rapidly move those results to the clinic, or “bedside,” to benefit patients directly. Thus, the NIH is sponsoring “bench-to-bedside” initiatives, in which teams of basic scientists and clinical researchers work together on translational research projects focused on type 1 diabetes. Researchers supported through this initiative have demonstrated in a mouse model of diabetes that the incidence of diabetes could be significantly delayed by using genetically-engineered cells expressing certain immunosuppressive molecules. Scientists have also demonstrated that

kidneys of diabetic mice have reduced levels of a protein that blocks blood vessel formation. These and other insights are increasing our understanding of type 1 diabetes and its complications, which is leading to new therapeutic targets and strategies.

Another important translational research effort is the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program. T1D-RAID has provided resources for preclinical development of several therapeutic agents that are being tested in clinical trials.

T1D-RAID and the other research consortia and networks that I have described feed into an integrated and comprehensive research pipeline. This pipeline facilitates research to: identify promising therapeutic targets and agents in the laboratory; generate animal models that mimic human type 1 diabetes and its complications; test promising agents in these animal models; and test promising therapies in people. An example of an agent that has moved through this research pipeline is called lisofylline. In a mouse model of type 1 diabetes, treatment with lisofylline after islet transplantation was shown to protect the animals from recurrence of the underlying autoimmunity that initially caused the disease. Because of these promising results, T1D-RAID manufactured lisofylline for testing in humans. The Clinical Islet Transplantation Consortium will soon be testing lisofylline in a human islet transplantation clinical trial. This is just one example of how the NIH not only supports the fundamental, basic research that leads to novel discoveries, but also supports a critically important research pipeline to translate promising results that could directly benefit patients.

Future Directions

Looking to the future, in order to inform the program-development process for NIH-supported type 1 diabetes research in the years ahead, the NIDDK spearheaded a strategic

planning effort under the aegis of the Diabetes Mellitus Interagency Coordinating Committee. This planning process culminated in the development of a Type 1 Diabetes Research Strategic Plan, which was released in August 2006. With extensive input from external scientific and lay experts, the Plan highlights recent advances in the field, and sets forth objectives for future research on type 1 diabetes and its complications.

The letter of invitation to this hearing asked me to address which programs and/or initiatives might be reduced or ended if the Special Diabetes Program is not renewed by Congress. Those decisions have not yet been made; however, we will continue to seek the advice of external scientific and lay experts in helping us to prioritize our efforts. One of our highest planning priorities is to maintain our commitment to clinical studies, which involve patient volunteers. Another priority is to maximize the Program's long-term investment in major research consortia and networks that are poised to make important research progress, or that are likely to produce discoveries that would be otherwise unattainable.

Conclusion

I am grateful for the opportunity to share with you these few examples of recent advances and ongoing research efforts. We continue to be inspired by the dedicated efforts of individuals affected by type 1 diabetes, and by organizations that represent them, such as the JDRF. We look forward to continuing to partner with the JDRF on research efforts to combat type 1 diabetes and its complications. We are grateful for the full range of support the NIH has received for type 1 diabetes research. We continue to be diligent in our fight against diabetes so that we can help all the children in this room and the many other Americans whom they represent here today.

Improving their quality-of-life—with the ultimate goal of curing their disease—is the driving force behind our efforts.

I will be pleased to answer any questions you may have.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
Biographical Sketch
Griffin P. Rodgers, M.D., M.A.C.P.

Dr. Rodgers is the 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 April 1, 2007, after holding the post of Acting Director for one year. As 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. Prior to leading the Institute, Dr. Rodgers served as its Deputy Director from 2001, a position that he still holds. An active researcher, Dr. Rodgers also is Chief of the Molecular and Clinical 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.

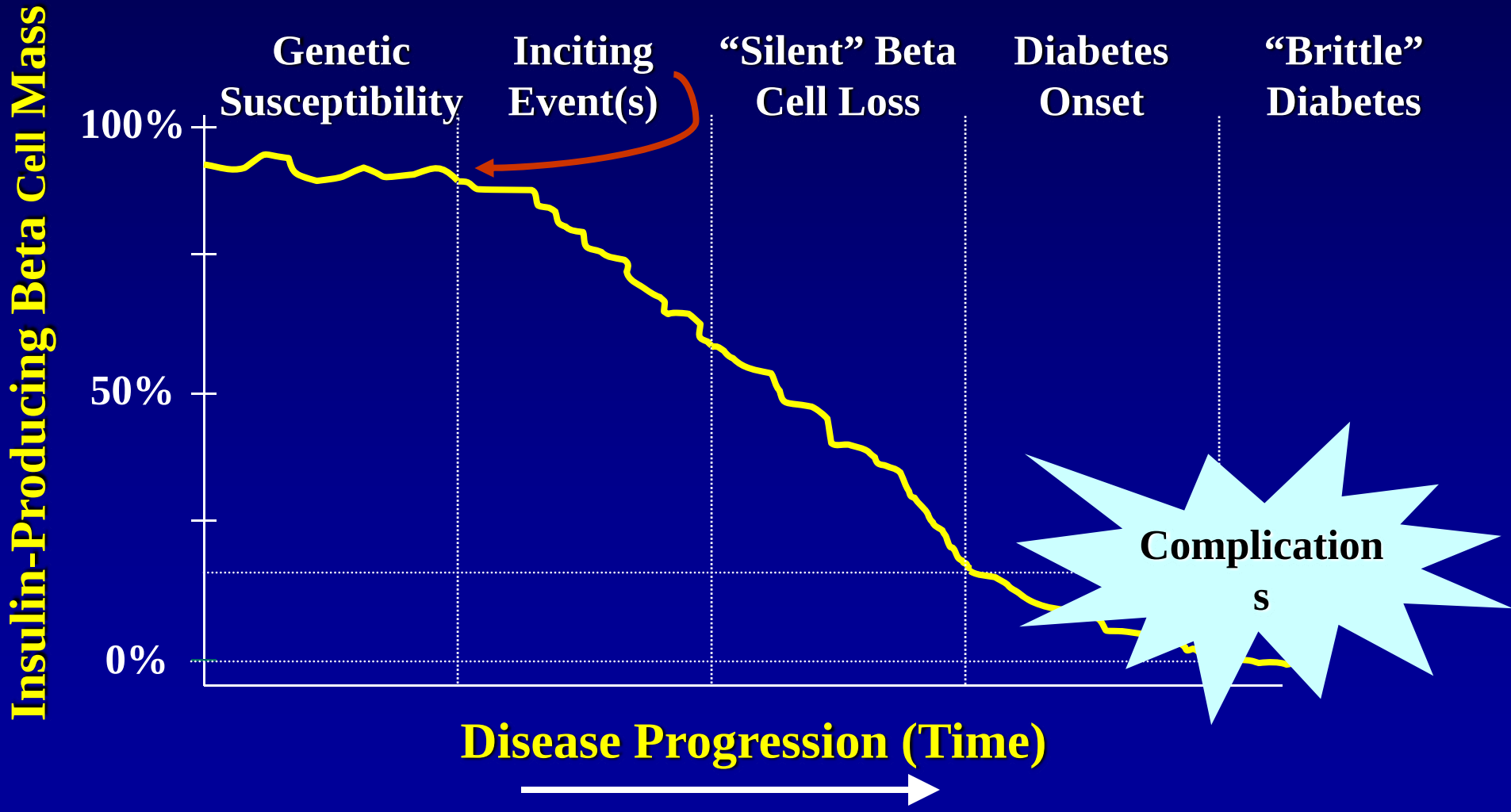
Dr. Rodgers is widely recognized for his contributions to the development of the first effective—and now Food and Drug Administration-approved—therapy for sickle cell anemia. He has served as the principal investigator in clinical trials to elevate pharmacologically fetal hemoglobin to counteract the 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. Flemming 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 for 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.

Type 1 Diabetes: A Slowly Progressive Autoimmune Illness



Continuous Glucose Monitoring

For every 1 percent fall in HbA1c—a measure reflecting a patient's blood glucose control for the preceding two to three months—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