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Chairman Lieberman, Senator Collins, and Members of the Committee, as Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I thank you for your invitation to testify at this hearing on type 1 diabetes. 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. For each of the past several years, NIH has invested over $1 billion in diabetes research. This investment is complemented by the support and efforts of our research partners—academic institutions around the U.S., HHS' U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and patient-advocacy groups—with whom we share the goals of preventing, treating, and ultimately curing type 1 diabetes. Through collaborative and coordinated research efforts, we are making critical strides toward these goals. Today, I will highlight recent advances and future opportunities in type 1 diabetes research, including research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program*).

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 monitor their food intake and physical activity in order to manage their blood glucose levels. 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. The disease greatly affects the quality of life of people with type 1 diabetes

and their families. Furthermore, we now know that type 1 diabetes diagnoses are on the rise, and that the disease is occurring in children at younger ages than before, often appearing during infancy.

IMPROVING THE OUTLOOK FOR PEOPLE WITH TYPE 1 DIABETES

Research in type 1 diabetes has made a tremendous impact on the health and quality of life of people with the disease. NIDDK's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive blood glucose control, beginning as soon as possible after diagnosis, can prevent or delay diabetic complications of the eyes, kidneys, nerves, and heart. The DCCT concluded in 1993, but its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continued to follow participants to determine the long-term effects of prior intensive versus conventional blood glucose control. In a recent report, the researchers compared overall rates of eye, kidney, and cardiovascular complications in DCCT/EDIC participants. After an average of 30 years with type 1 diabetes, participants in the DCCT/EDIC intensive control group had lower complication rates than participants in the conventional control group. Improved control over a 6 year average study time yielded health benefits that last for decades. Since the study began in 1983, the prognosis for people with longstanding type 1 diabetes has greatly improved due to major improvements in glucose monitoring and insulin delivery. This progress has accelerated in the past decade. For example, several continuous glucose monitoring devices now approved by the FDA give real-time information for tracking and trending of glucose levels, helping people with type 1 diabetes supplement the management of their blood glucose to help control their disease. Because of these insights and improvements in diabetes care and therapy, people with type 1 diabetes are

living longer, healthier lives than ever before and experiencing lower rates of disease complications. For example, only about 70% of people diagnosed with type 1 diabetes in the 1950's survived for 25 years with the disease compared to about 95% for those diagnosed in the 1970's. Indeed, the Joslin Diabetes Center in Boston, Massachusetts, has a Medalist Program that recognizes individuals who have lived with type 1 diabetes for 25, 50, and 75 years with a special award to commemorate their dedication to lifelong diabetes management. Just last month Joslin awarded one of these medals to a man on his 90th birthday—the first American known to live 85 years or longer with type 1 diabetes. These inspiring accomplishments don't stop with a medal; many of the 50-year medalists have volunteered to participate in an NIDDK-funded study to identify factors that protect from the development of eye and kidney disease. It's exciting to report that through research, the outlook for people with type 1 diabetes continues to improve.

Still, the burden of living with diabetes is enormous, so it is critical to build on research progress to find ways to prevent and cure the disease. For example, advances in research have led to blood tests that can now predict the risk of developing the disease in relatives of people with type 1 diabetes. Building on this knowledge, we are now able to launch clinical trials to test new prevention strategies. Until prevention and cure are possible, improved outcomes will depend on improving devices to monitor and control blood glucose levels. Advances in continuous glucose monitoring are expected to help people of all ages. To build on these developments, research on how to best help people use new technologies is key toward moving this treatment strategy into practical use.

Pursuit of the research goals to prevent, treat, and cure the disease involves partnerships among scientists—with diverse backgrounds and expertise from many academic institutions— as well as partnerships among many of the Institutes and Centers of the NIH, the FDA, the CDC,

and patient-advocacy groups. Patient-advocacy groups, like the Juvenile Diabetes Research Foundation International, are instrumental in facilitating and in contributing support to many of these collaborative research endeavors. By complementing research efforts supported by the NIH and CDC, patient-advocacy groups are key partners in our battle against type 1 diabetes. Without question, the most important partners in these efforts are people with or at-risk for type 1 diabetes who volunteer and participate in clinical research. Their commitment to help improve diabetes care, not only for themselves but for future generations, inspires us. The clinical research we conduct would not be possible without their enthusiastic participation and dedication.

Research to prevent, treat, and ultimately cure type 1 diabetes requires a multi-pronged approach. The NIH focuses on research at all the stages of the disease: to prevent the onset of autoimmunity; to stop the autoimmune attack once it has begun; to preserve beta cells early in the course of the disease; to improve glucose control in people with established diabetes; to restore beta cell function in people who have significant beta cell loss; and to prevent, arrest, and reverse complications. Through this multifaceted strategy, we can achieve a comprehensive understanding of the disease process, and form a foundation for future advances in treatment, prevention, and approaches to a cure. I would now like to share with you some of the exciting progress that has been made in type 1 diabetes research.

UNDERSTANDING THE CAUSES OF TYPE 1 DIABETES TO PREVENT ONSET OF AUTOIMMUNITY

Type 1 diabetes is caused by a complex combination of genetic and environmental factors that lead to the development of “autoimmunity”—a preclinical sign of type 1 diabetes.

Understanding the causes of the disease is essential toward preventing onset of autoimmunity and type 1 diabetes and curing the disease. Just a few years ago, only three genes involved in development of type 1 diabetes were known. Today, as a result of efforts from the NIDDK-led Type 1 Diabetes Genetics Consortium (T1DGC) and other researchers, nearly 50 genetic regions are known that influence risk for type 1 diabetes. This group of researchers came together to collect information and DNA samples from families with type 1 diabetes to identify common genetic risk variants as well as the rare risk variants. The Consortium has collected over 38,000 DNA samples, and continues to add to our understanding of the genetic influences of the disease. NIDDK is also supporting efforts to pinpoint the specific, causal genetic variants among the identified genetic regions, as well as critical studies to determine how identified variants influence risk of developing the disease. These variants, as well as studies of their functions, may lead to targets for therapeutic and prevention strategies, potentially in a personalized manner.

Importantly, we know that not every person with high genetic risk goes on to develop type 1 diabetes, indicating that there is a factor—or factors—in the environment that interact with the genetic risk. Studies also show that the number of people diagnosed each year with type 1 diabetes is on the rise; increasing environmental exposures might account for these trends in diagnosis of type 1 diabetes. Determining the environmental factor or factors is critical to understand the disease process and to develop prevention strategies. For example, if research determines that a virus is involved, a vaccine to protect against the virus could be developed. Or, if a dietary factor is involved, a dietary intervention could be designed. Toward identification of environmental triggers, the NIDDK supports a bold, long-term initiative known as The Environmental Determinants of Diabetes in the Young, or TEDDY. TEDDY researchers are

following newborns until they are 15 years of age, and recently completed enrollment of over 8,600 after screening over 425,000 newborns to identify infants at high genetic risk to develop type 1 diabetes. For a decade and a half, investigators—aided by devoted parents—will regularly collect information about the child's diet, illnesses, vaccinations, allergies, and other life experiences. Biological samples are being collected as well and will be used for studies to identify early markers of the disease. Importantly, children enrolled in the study are now developing autoimmunity and type 1 diabetes at the predicted rates, indicating that the study is on track and poised to make a major contribution to type 1 diabetes research.

This achievement represents tremendous progress toward amassing the largest set of data and samples in the world on newborns at risk for autoimmunity and type 1 diabetes. To ensure that we learn as much as possible from these samples and maximize our investment in TEDDY, samples from the study will be made widely available to researchers. Already TEDDY investigators are using newly developed technologies emerging from the NIH Human Microbiome Project to study the microbiomes of these children to determine whether viral or bacterial-based treatments could be used to prevent the disease. Importantly, the benefits of TEDDY are expected to extend more broadly to include people with celiac disease, a digestive disorder caused by autoimmunity directed at gluten proteins in wheat and other grains. Celiac disease and type 1 diabetes share some genetic susceptibility factors, and many people have both diseases.

While TEDDY is a prospective, long-term investment to find the environmental causes of type 1 diabetes, scientists in The Trial to Reduce IDDM [insulin dependent diabetes mellitus] in the Genetically at Risk (TRIGR), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), are testing whether a dietary intervention can reduce

the risk of diabetes-associated autoimmunity or type 1 diabetes. A small pilot study, conducted by the Finnish arm of this trial, recently reported the promising finding that children who received the intervention had fewer diabetes-associated autoantibodies than children who did not receive it. Prevention strategies will also be informed by knowledge of who is developing diabetes. The CDC-led Search for Diabetes in Youth (SEARCH) is providing important information on the number of U.S. children in certain areas with diabetes, the rates of development of childhood diabetes, and whether these rates and the clinical course of diabetes in children and youth are changing over time. By building on critical SEARCH findings, researchers may be able to design interventions that can prevent or delay disease onset in at-risk individuals and interventions to reduce risk for complications of diabetes.

TESTING STRATEGIES TO STOP THE AUTOIMMUNE ATTACK AND PRESERVE BETA CELLS

Simple blood tests for the presence of preclinical markers of type 1 diabetes can now accurately predict the risk that relatives of people with type 1 diabetes will develop the disease within 5 years. This important advance means that people can now be screened for risk of type 1 diabetes. In the future, this could lead to identifying people who may be most able to benefit from a prevention strategy. Today, toward that goal, it means that people with high risk identified by screening are eligible for trials to test promising prevention strategies. For example, NIDDK's Type 1 Diabetes TrialNet is an international clinical research network focused on prevention in individuals at risk for type 1 diabetes and is currently conducting trials of potential prevention agents.

In addition to preventing the disease, it is important to identify ways to halt or reverse disease progression after onset. This could result in preservation or restoration of a person's insulin-producing capacity. Results from clinical trials have suggested that preserving remaining beta cell function in people with type 1 diabetes can have dramatic, long-term health benefits. Toward this goal, TrialNet also conducts trials testing therapies in newly diagnosed patients, frequently in collaboration with the National Institute of Allergy and Infectious Diseases' (NIAID) Immune Tolerance Network (ITN). Several agents have now been proven effective in slowing the progress of type 1 diabetes and preserving beta cell function, but these effects wane over time. The next step will be trials of combinations of agents that are individually effective to determine if the beta cell preservation can be extended when the agents are used concurrently. Collectively, TrialNet and ITN have 8 ongoing trials testing therapies in newly diagnosed people. One trial, a collaboration between TrialNet and the NICHD-led Diabetes Research in Children Network, is testing whether intensive blood glucose control upon diagnosis can preserve the ability of a person's pancreas to produce some of its own insulin. This trial employs a "closed-loop" system—a continuous glucose monitor linked to an insulin pump—in the hospital within a week of diagnosis. Patients are then sent home with an insulin pump and a continuous glucose monitor to use as part of the trial for the next 2 years, and investigators will determine whether this approach is able to delay progression of the disease.

DEVELOPING AN ARTIFICAL PANCREAS TO IMPROVE GLUCOSE CONTROL

A high priority for research is the development of new tools and technologies to improve the ability of people with type 1 diabetes to more precisely control their blood glucose levels. 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. Importantly, artificial pancreas technology could help people safely achieve the tight blood glucose control associated with preventing or delaying life-threatening disease complications. Thus, this technology has high potential to have a positive impact on patients' health and quality of life, alleviate an enormous amount of patient burden, and improve long-term health outcomes. Working closely with our partners at FDA, we are pursuing research to develop the artificial pancreas and ensure that these technologies are safe and effective for people with type 1 diabetes. I'm pleased to share with you some of the progress that has been recently made in this area.

An important question has been whether all the data provided by these technologies can actually help people achieve better blood glucose control. A recent study demonstrated that automated, real-time feedback of blood glucose control, glucose variability, and risk of dangerously low blood glucose levels resulted in improvements in long-term glucose control and reduction in episodes of low blood glucose levels. Research like this—to understand how to best help people take advantage of these technologies—is vital to improving the health of all people with type 1 diabetes.

In an exciting technical advance, investigators reported promising results from tests of a bi-hormonal closed-loop artificial pancreas, one that delivers both insulin and another hormone—glucagon—to more finely reproduce the activity of the human pancreas. This innovative strategy was developed by a bioengineer who, upon learning that his infant son had developed type 1 diabetes, switched his research focus to type 1 diabetes. In another recent report, researchers looked at overnight closed-loop insulin delivery in people with type 1

diabetes following two different real-life scenarios. In one, people had an "eating in" meal that mimicked a night of eating a medium-sized meal at home. In the other scenario, people had an "eating out" meal—a larger meal at a later hour. In both scenarios, a closed-loop system was able to improve glucose control and reduce the risk of dangerous drops in blood glucose levels overnight. Testing the closed-loop system technology in real situations that people find themselves in daily is critical to its development, and this advance marks a step toward moving closed-loop systems outside the clinic. This study used continuous glucose monitors that were derived from an NIDDK grant to a small business, highlighting the importance of fostering small business innovation in this field.

Our partners in industry are critical to the growing momentum toward an artificial pancreas. In addition to NIDDK small business grants that laid the groundwork for continuous glucose monitors, another company, SmartCells, Inc., who also received support from NIDDK small business grants, made substantial progress in preclinical development of a new formulation of insulin in which insulin release is automatically responsive to fluctuating blood glucose levels. This product—called SmartInsulin—has the potential to lower the risk of low blood glucose and improve glycemic control. Merck & Co, Inc. recently acquired SmartCells, placing this novel technology in a position to be developed to its fullest potential. NIDDK continues to stimulate and support innovative research on technologies that may lead to the development of the artificial pancreas through solicitations to the small business community. In addition, based on input from a recent meeting of scientific experts, NIDDK will support partnerships between diabetes researchers and bioengineers to promote training and career development in this exciting and emerging field. Through the development of these unique partnerships, we hope to

recruit more bioengineers into diabetes research and create many more success stories in the future.

RESTORING BETA CELL FUNCTION

Although insulin therapy is life-saving, it is not a cure. Therefore, a major goal of type 1 diabetes research is to vigorously investigate ways to replace beta cells destroyed by the disease and restore beta cell function. One strategy for replacing beta cells is islet transplantation. Clinical trials are ongoing to study and refine islet transplantation technology. The Clinical Islet Transplantation Consortium (CIT), jointly led by NIDDK and NIAID, has launched 7 studies to find methods that have higher success rates and fewer risks. To date, 363 participants have enrolled in these trials in North America, 66 of whom have received a transplant as part of these trials, and the investigators have begun the long-term follow-up protocol for these patients. Outcomes with islet transplantation continue to improve, and may ultimately lead to more widespread use of this treatment strategy for individuals with type 1 diabetes.

Investigators are also pursuing novel strategies to replace islets without the need for donor pancreata and toxic anti-rejection drugs. Basic research has increased the understanding of how pancreatic cell types develop, the events involved in development and regeneration of the pancreas, and the factors required for normal function and development of the beta cells. This knowledge is essential for the goals of growing beta cells in the laboratory for transplantation into people and coaxing other cells in the body to become beta cells—thus eliminating the need for transplantation all together. Research in this field has been accelerated by the NIDDK-led Beta Cell Biology Consortium (BCBC), a unique, team-based approach to solve the challenges of developing cell replacement therapy. Exciting advances from the BCBC continue to bring the

field closer to this goal. It is through studies in the BCBC that a key factor necessary for making the insulin-producing beta cells—a factor called Rfx6—was identified. Researchers now know that they will have to ensure that Rfx6 is present in order to successfully generate beta cells from precursor cell types in the laboratory. Another group of BCBC investigators discovered that by increasing the levels of a protein called Pax4 they could coax established alpha cells—another pancreatic cell type—into becoming beta cells in mice. Other BCBC scientists observed spontaneous conversion of alpha cells to beta cells in adult mice that were engineered to lack beta cells. These discoveries—of a critical factor for beta cell development, and that adult pancreatic cells have the potential to convert to beta cells—generate a fuller picture of pancreatic development and plasticity and may pave the way toward new cell-based therapies for diabetes.

PREVENTING, ARRESTING, AND REVERSING COMPLICATIONS

Persistent elevation of blood glucose levels, despite insulin therapy, slowly damages the body's organs and can lead to life-threatening diabetes complications. Until prevention or cure of type 1 diabetes is possible, intensified research toward preventing and treating the complications of the disease is critically important. Diabetes has multiple effects on blood vessels. While a paucity of small blood vessels contributes to poor wound healing in people with diabetes, in the eye, diabetes leads to excessive new blood vessel formation. Basic research on the growth of new blood vessels led to the discovery of a key regulator of blood vessel growth. Because tumors require a blood supply for growth, a drug that inhibits this regulator, and thus new blood vessel growth, emerged from research on cancer and is now an FDA-approved treatment for metastatic colon and lung cancer. These important advances from basic and clinical research set the stage for the biggest advance in diabetic retinopathy, a devastating eye

disease, in 25 years. Investigators in the National Eye Institute-led Diabetic Retinopathy Clinical Research Network (DRCR.net) compared a version of the cancer drug—ranibizumab—in combination with the standard therapy—laser treatment—to laser therapy alone for the treatment of diabetic macular edema, a swelling in the eye that often accompanies and aggravates diabetic retinopathy.

The results from this landmark comparative effectiveness trial demonstrated that the combination therapy was substantially better than laser therapy alone at treating diabetic macular edema. Nearly half of the patients who received the combination treatment showed a substantial improvement in vision after 1 year, compared to 28 percent receiving only laser treatments. As a result, in the future, this class of drugs could become the new standard of care for diabetic macular edema. The DRCR.net continues to test new therapies for the full spectrum of people with diabetic eye disease to treat this debilitating complication of diabetes.

The Diabetes Control and Complications Trial (DCCT), which provided dramatic evidence that type 1 diabetes-related complications of the kidneys, eyes, and nerves can be prevented or greatly delayed through intensive blood glucose control, continues to yield important, life-saving data through the follow-on EDIC study. Comprehensive and meticulous data collection of DCCT/EDIC participants for more than 25 years, with participation rates of about 95 percent, has created an unparalleled resource of individuals with type 1 diabetes that is ideal for study of the clinical course of diabetes and its complications and for the validation of endpoints that can facilitate future drug development. For example, using genetic data from DCCT/EDIC participants, researchers recently identified a gene region associated with regulating blood glucose levels. Understanding how a person's genetics influences blood

glucose control is important for personalizing therapy to provide the optimal care to each individual.

Cardiovascular disease is increased up to 10-fold in people with type 1 diabetes and contributes to reduced life expectancy. EDIC investigators also pioneered use of new noninvasive diagnostic tools, such as ultrasound, to measure the thickness of the carotid artery in people with type 1 diabetes. This allowed them to investigate the long-term effects of intensive blood glucose control on the progression of atherosclerosis, and show that early initiation and continued maintenance of intensive blood glucose control can slow progression of atherosclerosis. By validating new analytical tools for early detection of cardiovascular disease before events occur, the results of EDIC are paving the way for future trials that are smaller, shorter in duration, and less expensive to conduct. This long-term investment in research has and continues to pay major dividends, resulting in improvements in the health of people with diabetes.

EMERGING OPPORTUNITIES IN TYPE 1 DIABETES RESEARCH

Recruiting talented new researchers with different areas of expertise to type 1 diabetes research is critical to our goals to prevent, treat, and cure the disease. Management of diabetes in children is particularly arduous and requires an exceptional level of effort from the children, their families, and their health care providers. These extraordinary clinical care demands make it challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers. Moreover, there is a long process of training and career development before a new independent investigator is ready to obtain grant support and lead a research laboratory. Through support from the *Special Diabetes Program,* a cadre of pediatricians specializing in

childhood diabetes received such training and career development. I'm pleased to report that a recent evaluation of this program showed that, of the 28 pediatric endocrinologists who received training under the program, 27 of them—96 percent—remain in academic science. Many of them have also successfully competed for independent funding to conduct research. The success of this program led NIDDK to recently issue a solicitation announcement for the next round of the program, and also plan to develop similar programs in other fields, such as bioengineering and behavioral research.

These scientists will be well poised to take advantage of emerging scientific opportunities, such as those identified in the recently released Diabetes Research Strategic Plan, spearheaded by the NIDDK. This Plan will serve as a scientific guidepost to NIH, other federal agencies, and to the investigative and lay community by identifying compelling opportunities for research on diabetes and its complications. The Plan addresses research advances, key questions, and extraordinary opportunities in 10 major diabetes research areas, and reflects the efforts of the scientific community, patient-advocacy groups, and Federal staff. In addition, NIDDK recently solicited input from experts from outside the NIH on ideas for the use of funds resulting from the recent extension of the *Special Diabetes Program*. This meeting served as a critical source of input for NIH to ensure the most scientifically productive use of the funds.

Finally, I am pleased to report that NIDDK also recently released an Evaluation Report on the *Special Diabetes Program.* Analysis of projects supported by the funds from 1998 through 2010 revealed that over 2,500 publications, nearly 40 patents, and countless scientific resources have resulted from projects supported by the *Special Diabetes Program*. The *Program* has fostered clinical research as well as stimulated recruitment of new investigators to the field

of type 1 diabetes research. Research supported by the *Program* has resulted in important scientific advances and benefits to the health and quality of life of people with type 1 diabetes.

CONCLUDING REMARKS

I am grateful for the opportunity to share with you today these few examples of recent advances and ongoing research efforts in type 1 diabetes research. We continue to be inspired by the dedicated efforts of individuals affected by type 1 diabetes, and by organizations that represent them. We look forward to continuing to partner with these organizations and our sister Federal agencies on research efforts to combat type 1 diabetes and its complications. We are grateful for the full range of support that NIH has received for type 1 diabetes research. We will continue to be diligent in our fight against diabetes to help all the children at this hearing 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.

Thank you Mr. Chairman, Senator Collins, and Members of the Committee for your attention. I will be pleased to answer any questions you may have.