DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Juvenile Diabetes – Examining the Personal Toll on Families, Financial Costs to the Federal Health Care System, and Research Progress Toward a Cure

Witness appearing before the
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Statement of the Director

National Institute of Diabetes and Digestive and Kidney Diseases

Chairman and Members of the Committee: As Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), I appreciate the opportunity to testify at this hearing on type 1 diabetes, held in conjunction with the "Children's Congress" of the Juvenile Diabetes Research Foundation International (JDRF). On behalf of the NIDDK and the other Institutes and Centers of the National Institutes of Health (NIH), I am pleased to report that we are aggressively pursuing research on childhood diabetes and its complications. We are gaining insights into the underlying causes of disease development, working diligently toward more effective treatment and prevention strategies, and striving for a cure.

Type 1 diabetes is the form of the disease that strikes mainly in childhood and adolescence; it affects approximately one million Americans. Patients require daily insulin administration and must carefully monitor their food intake and exercise in order to manage the disease. Even with continuous and vigilant disease management, patients are still susceptible to developing serious, long-term complications. Although we have a much greater understanding of the disease than we did a decade ago, we still need to carry out both basic and clinical research to find new ways to improve the quality-of-life for type 1 diabetes patients, whether through advances in insulin delivery, islet transplantation, or other avenues. Research is the key to a cure.

The NIH is focused on six broad goals in type 1 diabetes research: (1) to understand the genetics and environmental causes of type 1 diabetes so that we can identify who is at risk for developing the disease; (2) to prevent or reverse the disease; (3) to develop cell replacement therapy as a cure for diabetes; (4) to prevent or reduce hypoglycemia (low blood sugar) which limits tight control of blood sugar; (5) to prevent or reduce complications; and (6) to attract new research talent to the field. The research we undertake to achieve these goals is supported by both our regular appropriation and by the Special Statutory Funding Program for Type 1 Diabetes Research. Research teams are vigorously studying different aspects of the disease, such as interactions between genetic and environmental factors, the development and function of the insulin-producing beta cells of the pancreas, and how the misdirection of the body's immune defense system can be corrected to spare the beta cells from immune attack. Because of the complexity of the disease, investigators with diverse expertise are attacking the disease from many different angles. Through this multifaceted approach, we can attain a comprehensive understanding of the disease process--the foundation for future advances in treatment, prevention, and approaches to a cure.

Relative to each of our six research goals, I would now like to highlight some of the specific advances and initiatives that have been made possible through the Special Funding Program. We have deployed the special funds to create unique, multidisciplinary consortia to tackle the major obstacles to developing methods to prevent and cure type 1 diabetes. These 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, the Centers for Disease Control and Prevention (CDC), the JDRF, and the American Diabetes Association (ADA). I will highlight selected examples of our major

efforts. Further information and additional examples are presented in a new "Report on Progress and Opportunities" to date under the Special Funding Program, which began in fiscal year 1998 and will continue through fiscal year 2008. This important interim assessment is based on input from external scientific and lay experts, grant recipients, and NIH staff involved in the program.

Understanding the Genetics and Environmental Causes of Type 1 Diabetes

Type 1 diabetes is caused by a combination of genetic and environmental factors. Identifying these factors is key to both prevention and cure. Already we know some of the major genes that predispose patients to develop type 1 diabetes, but identification of other key genes will provide new targets for therapy. To this end, we have formed a collaboration to collect genetic material from 7,500 families in which one member has type 1 diabetes. This material will be an invaluable resource to investigators in their search for culprit genes. We know much less about the environmental factors that trigger onset of type 1 diabetes in a genetically susceptible individual. To address this question, an international consortium will use our knowledge of key genes predisposing to type 1 diabetes to identify infants at high risk for developing the disease and follow them through adolescence in a search for environmental factors that may trigger disease onset. We call this study "Triggers and Environmental Determinants of Diabetes in Youth," or "TEDDY." The Special Funding Program has also allowed us to address the important issue of whether rates of development of type 1 diabetes in America are changing over time. The NIDDK and the CDC are supporting a population-based registry to define the prevalence and incidence of diabetes in

children. This project, entitled "SEARCH," will identify children with diabetes in six regions of the country and will help us understand how the disease strikes and unfolds.

Reversing or Preventing Type 1 Diabetes

To spur the testing of promising new strategies to prevent, delay, or reverse progression of type 1 diabetes, the NIDDK, in conjunction with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the ADA, and the JDRF, has established a clinical trial network, the "Type 1 Diabetes TrialNet," consistent with a major recommendation of the congressionally-established Diabetes Research Working Group. Teams of diabetes experts and immunologists will test promising new therapies that may preserve the ability to make insulin in those newly diagnosed with type 1 diabetes and actually prevent the development of the disease in individuals at high risk based on genetic and immunologic tests. The NIAID-led Immune Tolerance Network will partner with TrialNet in efforts to test promising interventions and strategies to prevent or reverse type 1 diabetes. An international trial addresses the role of environmental factors in the development of type 1 diabetes. The NICHD-led "Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically-At-Risk," or "TRIGR," will compare the development of type 1 diabetes in infants who are weaned onto a hydrolysate of cow's milk formula *versus* standard cow's milk formula.

Developing Cell Replacement Therapy

Insulin therapy, via daily injections or a pump, 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. Just this month, researchers participating in the Immune Tolerance Network, led by NIAID, reported the preliminary results from a study in which the islet transplantation protocol pioneered in Edmonton, Canada, was replicated at nine sites. Although the success rates varied among the centers, this study showed that the new procedure can relieve some patients of the burden of daily insulin injections. However, the immunosuppressive drugs of the new protocol do carry significant side effects and the long-term results of the procedure have yet to be established. This confirmation of the success of the Edmonton protocol offers great hope to the diabetes community of investigators, patients, and families and will stimulate further research to improve the procedure. Nonetheless, there are still some barriers in the field of islet transplantation that could limit its widespread use in clinical application, such as: (1) inadequate supplies of islets and (2) imperfect methods to prevent transplant rejection and recurrent autoimmunity.

To make the promise of islet transplantation a reality for those with type 1 diabetes, we are accelerating research on many aspects of beta cell development and function with the goal of creating an unlimited supply of islets for transplantation. A key component of this effort is the NIDDK-sponsored Beta Cell Biology Consortium. This collaboration is providing scientists with access to information, resources, technologies, expertise, and reagents that are beyond the means of a single research effort. It represents an unprecedented effort to delineate each step in the pathway that leads to formation of beta cells with the unique capacity for appropriately regulated insulin secretion and to develop methods to create unlimited supplies of these vital cells.

We are also supporting research to develop alternatives to the lifelong immunosuppressive drug treatments that are currently required to prevent rejection of transplanted islets as well as recurrence of the autoimmunity that caused type 1 diabetes. In addition to the efforts of the Immune Tolerance Network and other NIAID-funded investigators, preclinical work is being pursued in promising animal models. The NIDDK and the NIAID, through the Autoimmunity Centers of Excellence and the Prevention Centers for Autoimmune Diseases, support multidisciplinary basic and clinical research in type 1 diabetes and other autoimmune diseases. Another research consortium is pursuing methods to induce immune tolerance to transplanted kidneys and islets in non-human primates to achieve long-term graft survival. This approach would avoid lifelong immunosuppressive therapies that can have deleterious and often life-threatening side effects.

Key new resources have been developed to spur islet transplantation research. A network of islet cell resource centers will improve methods of islet isolation and provide islets to researchers nationwide. A newly created transplant registry will collect and analyze data from all islet/beta cell transplants performed in the U.S. and Canada. This effort will expedite progress and promote safety, as this technology advances at an accelerated pace after the success of the Edmonton protocol. Through this multifaceted bench-to-bedside approach combining shared resources, collaborative fundamental basic research, preclinical development in animal models, and multicenter clinical trials, the NIH is aggressively pursuing every avenue toward progress in islet transplantation that can directly translate into potential therapies for type 1 diabetes patients.

Reducing or Preventing Hypoglycemia in Type 1 Diabetes

Perhaps the most distressing, acute complication of type 1 diabetes is hypoglycemia, or low blood sugar. 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. Some diabetes patients are also at risk for a condition called "hypoglycemia unawareness," in which they have difficulty recognizing the symptoms of hypoglycemia and are, therefore, more vulnerable to adverse outcomes. Hypoglycemia is a particular problem in young children, who may not be able to realize and communicate their symptoms to parents. For these reasons, we have made a greater understanding of hypoglycemia and new approaches to mitigate this problem a key goal to be pursued through the Special Funding Program, and have established research programs to address these important issues.

We have established a network, called "DirecNet" (led by NICHD), to test recently-developed glucose sensors in children with type 1 diabetes to determine their value in reducing the risk of hypoglycemia. Already, DirecNet has compared two new devices, which had not been previously tested in children. These approaches--as well as the support of basic and clinical studies of hypoglycemic complications, and glucose-sensing and insulin-delivery technologies--are all directed toward improved management of the disease.

Preventing or Reducing the Complications of Type 1 Diabetes

The complications of diabetes affect virtually every system of the body. Diabetes increases the risk of blindness, kidney failure, chronic wounds and skin ulcers, nerve pain

and other neurological problems, lower limb amputation, heart disease and heart attacks, stroke, high blood pressure, gum disease, and pregnancy-related problems. Diabetes and its complications can shorten average life expectancy by up to 15 years. Costs to the nation are in excess of $130 billion annually in health-related expenditures. The NIDDK continues to foster, through the Special Statutory Funding Program for Type 1I Diabetes Research and through our regular appropriation, exciting new opportunities for the research community to intensify the study of many diabetic complications. A particular focus of the program has been on the development of tools needed to enhance clinical research, such as the development of biomarkers which can predict the development of complications and can serve as outcome measures allowing clinical trials to be conducted more efficiently and less expensively. Another focus has been on the development of animal models that faithfully replicate development of complications of diabetes in humans. These models are essential for preclinical drug development.

In addition to clinical studies, basic research is under way to identify the genes that may increase a person's susceptibility to developing the eye and kidney complications of diabetes. Identifying the genetic basis of these complications will reveal new targets for therapy.

Attracting New Talent to Research on Type 1 Diabetes

Type 1 diabetes research spans an extraordinarily broad range of scientific disciplines. For this reason, a cadre of exceptionally talented and dedicated researchers is needed to bring expertise to bear on understanding, treating, preventing, and curing type 1 diabetes. As more research is being done in the laboratory, or “bench,” there is a need to

rapidly move those results into the clinic, or "bedside," to directly benefit patients. For this reason, the NIH is sponsoring "bench-to-bedside" initiatives, which form partnerships among basic and clinical scientists. In addition, we are supporting the research training and career development of pediatric endocrinologists. Due to heavy clinical demands, it is especially challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers, yet their clinical expertise is invaluable to type 1 diabetes research. The NIDDK, in collaboration with the ADA and the JDRF, is supporting research training and career development programs in pediatric endocrinology at institutions whose environments, mentors, and programs should make them particularly effective in enhancing the number of independent investigators who can contribute to research in this area.

I am grateful to share with you these few highlights of the Special Statutory Funding Program for Type 1 Diabetes Research. With the recent completion of the Human Genome Project, we are living in a new and exciting era of scientific research. We intend to take full advantage of the new technologies and information that have emerged to realize greater progress in diabetes research. Diabetes is a devastating illness for patients and their families, especially when it strikes in infancy, childhood, or adolescence. We continue to be inspired by the dedicated efforts of patients and their families, by organizations such as the Juvenile Diabetes Research Foundation International. We are thankful for the full range of appropriations for type 1 diabetes research. We continue to be vigilant in our fight against diabetes so that we can help all the children in this room; they are the real motivation behind all of our efforts. I am pleased to answer any questions you may have.