Appendix 5

SUMMARY REPORT OF THE APRIL 2000 ADVISORY PANEL MEETING

Advisory Meeting on the Use of FY 2001 Balanced Budget Act Funds for Type 1 Diabetes Research

National Institutes of Health

April 12, 2000

A panel of scientific advisors (*see Acknowledgements*) met with representatives of the National Eye Institute (NEI), National Human Genome Research Institute (NHGRI), National Institute on Aging (NIA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Neurologic Disorders and Stroke (NINDS), National Center for Research Resources (NCRR), Centers for Disease Control and Prevention (CDC), American Diabetes Association (ADA), and Juvenile Diabetes Research Foundation International (JDRF) to consider 22 proposals, totaling $57.65 million, submitted by the institutes and centers of the NIH and CDC for funding with $19.5 million to become available in FY 2001 under the provisions of the Balanced Budget Act of 1997.

Dr. Allen Spiegel, Director of NIDDK, asked the scientific advisors to determine which of these 22 proposals offer the best opportunity to develop knowledge that will lead to improved methods to prevent, treat, or cure type 1 diabetes. They were also encouraged to suggest other initiatives that could make important contributions toward advancing research on type 1 diabetes and its complications. Dr. Spiegel noted that institutes and centers had been encouraged to propose trans-NIH initiatives involving multiple components of the NIH and initiatives to which they were also willing to commit institute funds.

Eleven of the 22 proposals were recommended with the highest enthusiasm; a twelfth highly recommended project emerged from the discussion. To achieve a total recommended budget of $20 million in FY 2001, many proposals were reduced in scope and allocated less than the funds requested. The proposals selected and the amount of Balanced Budget Act funding in FY 2001 for each follow:

1. Comprehensive Atlas of Beta Cell Biology ($3.0M)

As initially proposed, this project included seven components. The committee recommended supporting five components as part of this project: online database to disseminate information arising from this project to the scientific community; development of a human beta cell line which maintains physiologic responsiveness to glucose and other factors involved in regulation of insulin secretion and cell growth and development; functional genomics and proteomics of the beta cell; development of monoclonal antibodies to cell surface components of the beta cell for use in stem cell identification; and functional imaging of the beta cell to detect changes in cell number, cell mass, function, and metabolism. The two additional components initially proposed as part of this initiative were recommended for inclusion as components of other proposals: diagnostic tools for beta cell transplantation was included in the human islet resource centers, and identification of SNPs for type 1 diabetes candidate genes was included in the Immune Response Diversity Project. It was recognized that the $3.0 million allocated from Balanced Budget Act Funds would not be sufficient to pursue all the components of this initiative found to have outstanding merit, and the NIDDK promised to provide substantial additional institute funds for this project.

2. Human Islet Transplantation ($2.5M)

As initially proposed, this project would fund regional resource centers to supply human islet cells to researchers for use in trials of human islet transplantation. The committee recommended incorporating into these resource centers the development of methods to assess the quality, purity, and viability of harvested islets in vivo and the determination of optimal methods of islet preparation, using tools developed from the functional genomics component of the Comprehensive Atlas of Beta Cell Biology Project. The committee also recommended that these resource centers screen donors for evidence of autoimmunity, and provide organs not suitable for use in islet transplantation to researchers for studies of pathogenesis of type 1 diabetes. Two million dollars in Balanced Budget Act funds were recommended for these components, with additional funding for the islet resource centers in FY 2001 to be provided from the NCRR. An additional $0.5 million was recommended to support an islet/beta cell transplant registry to collect and analyze data, both pre- and post-transplantation, from all institutions performing islet and beta cell transplants in North America.

3. Consortium for Development of Improved Animal Models ($4.0M)

This project focused on development of animal models of diabetes-associated micro- and macrovascular complications. The emphasis was on the mouse, but larger animals, such as swine and other species, were proposed as well. The committee strongly supported the research proposed, and recommended that, in addition to micro- and macrovascular complications, models useful for study of wound healing in diabetes be developed.

4. Immune Response Diversity Project ($1.0M)

This project integrates the genomics of host immunity with advanced bioinformatics to aid discoveries in immune mediated diseases. While this proposal was felt to be highly meritorious, concern was raised about the support of aspects of the proposal that appeared to lack a focus on type 1 diabetes with funds targeted for type 1 diabetes. Reduced funding was recommended to support components of the proposal specifically focused on type 1 diabetes, particularly identification of SNPs in type 1 diabetes candidate genes.

5. Preventive Vaccines for Autoimmune Diabetes ($3.0M)

This project was recommended without modification and with the highest priority. Additional regularly appropriated funds will be provided for this initiative.

6. Studies of New Therapies that Prevent or Reduce the Microvascular Complications of Diabetes ($1.0M)

Several promising new drugs are under development to prevent retinopathy and other microvascular complications. Some surrogate outcomes have recently been developed which can be used for short-term pilot studies to prevent retinopathy. This initiative would support small pilot studies of promising agents to aid in the transition from the bench to clinical investigation. Additional support for these pilot trials would come from NIH and industry funds.

7. Gene Therapy Approaches for Type 1 Diabetes and Its Complications ($1.0M)

The committee recommended that this project focus particularly on methods of targeting gene transfer to the beta cell in vivo, and on developing gene therapy approaches to prevention and treatment of complications, such as delivery of growth factors. Additional regularly appropriated funds will be required for this initiative.

8. Functional Genomics Approaches to Diabetes Complications ($1.0M)

As proposed, this initiative included two components, focused on hypoglycemia and microvascular complications. The committee strongly endorsed application of gene profiling techniques to studies of glucose sensing and noted that common mechanisms are involved in beta cell and brain glucose sensing. However, it was felt that this component of the initiative should be deferred until FY 2002 so that it can be developed in the context of recommendations from a planned workshop on hypoglycemia and the brain. One million dollars was recommended in FY 2001 to fund application of gene profiling technologies to peripheral vascular tissue to aid in understanding of microvascular complications.

9. Population-Based Registry for Diabetes in Children ($1.0M) and Pilot Programs for Population-Based Screening of Risk Factors for Type 1 Diabetes in Children Using State and Territorial Public Health Laboratories ($0.5M)

It was noted that there are a number of practical problems in developing population-based registries for diabetes in children in the U.S. Despite the uncertainty of success, the committee recommended that $1.0 million be allocated to support one or two pilot projects. Such registries are of critical importance in documenting the true incidence of type 1 and type 2 diabetes in children and in assessing changes over time in incidence and age of development of diabetes. It was felt that pilot programs for screening for risk of type 1 diabetes in the general population are feasible because assays are now available for use on dried blood spots, and the initiation of pilot studies was highly recommended.

10. Studies to Identify Genetic Associations in Patients with Microvascular Complications of Diabetes ($0.5M)

The committee noted that the NIDDK and the JDRF have recently initiated efforts to identify genes for diabetic nephropathy and recommended support for the initiation of studies to identify genes predisposing and contributing to the development of retinopathy. Additional regularly appropriated funds will be provided for this initiative.

11. Assessment of Oral Microflora and Immune Responses in Type 1 Diabetic Patients ($0.5M)

The committee recommended support of this initiative, which was developed based on recommendations from a recent workshop on oral complications of diabetes. Additional regularly appropriated funds will be provided for this initiative.

12. Evaluation of Use of Minimally-Invasive Glucose Sensors in Children ($1.0M)

Committee members proposed this initiative after considering a proposal to study the metabolic and developmental consequences of intensive insulin therapy in children. The committee felt that proposal was not feasible due to the very long follow-up which would be required and the likely changes in methods of glycemic control which would occur in the interim. Instead the committee recommended that new technologies should be evaluated in children. It was recommended that the use of recently developed minimally-invasive glucose sensors should be studied in children to assess their efficacy in achieving improved metabolic control and reducing the risk of hypoglycemia.