National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes Mellitus Interagency Coordinating Committee
Update on Current and Planned Initiatives

Building 31C, Conference Room 6C10
9000 Rockville Pike
Bethesda, Maryland

March 21, 2005
Summary Minutes

WELCOME AND INTRODUCTIONS

Allen Spiegel, M.D.; Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, Maryland

Dr. Spiegel welcomed members of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) and guests. Dr. Spiegel said this was an opportunity to exchange views on joint activities of DMICC member organizations. He pointed out that the U.S. Department of Health and Human Services (DHHS) recently released *Diabetes: A National Action Plan*, to focus the attention of health professionals, businesses, schools, and researchers on steps necessary to reduce the impact of diabetes on society. This initiative will be of interest to DMICC members.

TYPE 1 DIABETES INITIATIVE AND THE SPECIAL FUNDING PROGRAM

Judith E. Fradkin, M.D.; Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, NIH, Bethesda, Maryland

Dr. Fradkin reviewed the implementation status of recommendations from the January expert panel planning and evaluation meeting on the Special Statutory Funding Program for Type 1 Diabetes Research. She noted that the panel focused on ongoing projects being supported with the special funds. One recommendation of the expert panel was to initiate a broader review of the entire state-of-the-science regarding type 1 diabetes with an emphasis on new and emerging opportunities that could be pursued with the special funding (slide 3). To implement this recommendation, the NIDDK is spearheading a new strategic planning effort in type 1 diabetes research. Dr. Fradkin suggested that this strategic plan (slide 5) framed around the six goals that have guided the use of the special funds: (1) Identify genetic and environmental causes of type 1 diabetes. (2) Prevent or reverse type 1 diabetes. (3) Develop cell replacement therapies. (4) Prevent or reduce hypoglycemia. (5) Prevent or reduce complications from type 1 diabetes. (6) Attract new talent and apply new technologies.

The DMICC will be the entity responsible for coordinating the strategic plan with the help of working groups that are being established for five of the six goal areas (slide 6). The working groups will identify major research advances in type 1 diabetes research that have occurred since 1998 and identify emerging opportunities in these areas of research that can be pursued by the

NIH or other DHHS agencies in the next 10 years (slide 7). Dr. Fradkin presented the preliminary timetable for the initiative and asked for cooperation from each of the DMICC organizations in making this a priority initiative (slides 8-9). Dr. Spiegel stressed the importance of DMICC member organizations' commitment to supporting the development of the strategic plan in the areas that are key to the missions of their specific organizations. It is not expected that all organizations will want to be involved in all areas of the research. This strategic plan will contribute to the development of the final report on the use of the special funds that will be submitted in January 2007 to the U.S. Congress.

A second recommendation from the expert panel included support for "self-assembled" teams of scientists to tackle specific barriers in type 1 diabetes research (slide 10). Dr. Fradkin suggested that challenges to be pursued by these teams include: (1) the development of assays and biomarkers useful for assessing the response to immunomodulatory interventions in type 1 diabetes; (2) development of methods to image beta-cell mass and immune infiltration of the pancreas; (3) development of biomarkers for complications; and (4) development of outcome measures that could enable complications trials to be conducted with shorter durations and/or fewer patients. Funding will be available for this research using the P20 grant mechanism, and successful projects will receive 3 years of funding beginning in fiscal year (FY) 2006 (slide 12).

Other recommendations of the expert panel included the establishment of External Advisory Committees for existing consortia and resources (slide 13) and a plan to enhance coordination among existing consortia and resources (slides 14-15). As a first step for enhancing consortia coordination, a meeting will take place in May 2005 in Boston in conjunction with the Federation of Clinical Immunology Societies (FOCIS) meeting. There also will be more focused coordination meetings involving subsets of related consortia and networks. One of these will involve TrialNet, Immune Tolerance Network (ITN), and Clinical Islet Transplantation (CIT) consortium investigators. The Type 1 Diabetes Genetics Consortium (T1DGC), Genetics of Kidneys in Diabetes Study (GoKinD), Family Investigation of Nephropathy and Diabetes (FIND) study, and the Epidemiology of Diabetes Interventions and Complications (EDIC) Genetics Study consortia will hold a joint meeting in July. At the next meeting of The Environmental Determinants of Diabetes in the Young (TEDDY) consortium, representatives from the Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically At Risk (TRIGR) and National Immunization Program (NIP) will meet to discuss standardization across studies. Dr. Fradkin asked each of the DMICC organizations that have consortia or resources participating in the type 1 diabetes funding effort to identify scientists from the consortia to participate in these meetings.

Dr. Spiegel thanked Dr. Fradkin for the presentation and added that there are many exciting collaborative investigations taking place around the country for both type 1 and type 2 diabetes.

UPDATES BY DMICC MEMBERS

Health Resources and Services Administration (HRSA)

Suzanne Feetham, Ph.D., R.N., F.A.A.N;, Senior Advisor, Office of Director, Bureau of Primary Health Care (BPHC), Acting Director Division of Clinical Quality,BPHC , HRSA, Bethesda, Maryland

Dr. Feetham provided background information on the HRSA (slides 3-14) and collaborations currently being implemented in the HRSA that include diabetes components (slide 15). The Diabetes Detection Initiative (DDI) operates in 10 regions around the country within primary health care clinics, most of which are HRSA federally qualified health centers (slide 16). The DDIs have distributed more than 600,000 diabetes risk tests resulting in a 40 percent increase in the screening of blood glucose tests; results of these tests identified approximately 5,000 new cases of diabetes. Approximately 90 percent of patients served in HRSA clinics have incomes more than 200 percent below the poverty level.

The HRSA Health Disparities Collaboratives, a national effort to improve health outcomes among medically underserved people, have been successful in focusing collaborative efforts in this population (slide 23). Outcomes of the collaboratives, which focus on patient/health center goals, are increasing community partnerships. An important lesson learned in the development of these collaborations is that there must be system change when creating prevention collaboratives because the health centers have to intervene in the health of every patient who enters the center rather than just those with a disease (slide 28). The Diabetes Prevention Program (DPP) is a model of a prevention collaborative that is investigating system change (slides 29-31). Dr. Feetham presented data on patients participating in the DPP that showed baseline data and results, which indicated that it is possible to identify patients at high risk for diabetes who then can be managed in a primary care center (slides 32-41).

The Sentinel Center Network (SCN) is a collaboration among the HRSA, the Johns Hopkins University, and the Morehouse School of Medicine (slides 44-67). The primary goal of the SCN is to provide information to the HRSA and centers to assess health center practice patterns and outcomes on patients who use the centers. Over one million patients are participating in the 52 SCN health centers; 6.2 percent of total participants have diabetes.

During the discussion period, Dr. Feetham said that intervention through training and information distribution within the health centers has been one of the most significant reasons for system change. It was noted that all six goals should be addressed at the same time for maximum effectiveness. An assessment of the outcome of the DPP is incomplete and may take a number of years before enough data are available to make an accurate evaluation. Dr. Feetham also explained that the reason for the small differences in diabetes prevalence by race and ethnicity in this study may result from the disproportionately high number of low-income patients in the centers.

Veterans Health Administration (VHA)

Leonard M. Pogach, M.D., M.B.A.; Veterans Administration National Program Director for Diabetes, East Orange Veterans Affairs Medical Center, East Orange, New Jersey

Dr. Pogach presented information from the VHA perspective on systematizing quality improvement and quality innovation for persons with diabetes. Diabetes is just one part of the VHAs efforts to improve health care among American veterans. More than 1 million of the estimated 5 million veterans who use the VHA have diabetes (slide 2). Dr. Pogach presented

data showing that the VHA population has high levels of risk factors for chronic diseases such as cardiovascular disease, chronic kidney disease, stroke, and mental health disorders.

Since 1997, the VHA has instituted patient care principles that are some of the most forward looking in the nation. These include: (1) assignment of patients to an identified primary care provider; (2) development of evidence of explicit clinical care guidelines for common conditions, including diabetes; (3) development of performance measures and contracts for directors in the system; (4) development of a national electronic medical records database with local customization capabilities; (5) initiation of a translational research initiative, the Quality Enhancement Research Initiative; (6) the adoption of telemedicine, including home-based telemedicine and teleretinal imaging (slide 3). Examples of clinical reminders were given to show the types of systems the VHA has implemented to encourage veterans to keep appointments (slide 4). A sample of the electronic medical record used to allow physicians to get real-time data also was presented (slide 5).

The VHA's diabetes performance measures for FY 2004 indicate that the VHA is doing very well in improving screening and interventions compared to indemnity plans (slides 6-8). Long-term outcomes are being tracked for some conditions, and it appears that complications from diabetes have remained constant from FY 1999 to 2003, except for a decrease in amputations (slide 9). It is expected that innovations will continue to be implemented within the VHA (slide 11).

National Institute of Child Health and Human Development (NICHD)

Gilman D. Grave, M.D.; Chief, Endocrinology, Nutrition, and Growth Branch, Center for Research for Mothers and Children, NICHD, NIH, Bethesda, Maryland

Dr. Grave provided information on ongoing initiatives of the NICHD for diabetes research. The Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically at Risk (TRIGR) has 73 sites in 15 countries that will test the hypothesis that infants, who are genetically at risk according to human leukocyte antigen (HLA)-type, can be prevented from getting diabetes in the next 10 years if they are weaned to a hydrolyzed cow milk formula (Nutramigen) instead of a non-hydrolyzed formula (Similac). So far nearly 1,300 of the targeted enrollment of 2,032 infants have been enrolled and randomized.

Another initiative is DirecNet, which has five centers in the United States and a centrally located glucose-monitoring laboratory in Minnesota. DirecNet is investigating glucose monitors to determine if improvements can be achieved in monitoring high and low glucose levels with the Glucowatch or with the Continuous Glucose Monitoring System. A new subcutaneously implanted monitor called the Navigator is being investigated in a study of 30 children. This monitor uses the glucose oxidase method to assay glucose levels in interstitial fluid 1440 times per day. Another investigation will use glucose monitors to document the effect of exercise on the basal insulin requirements of children on insulin pumps and the best strategies to avoid late night hypoglycemia.

Dr. Grave reported that he has become interested in helminth infections (e.g., hookworm and filarial worm) and their possible role in preventing type 1 diabetes and other autoimmune diseases. A recent open label study by Robert Summers et al [*Gut 2005; **54**:87-90]* reported that 80 percent of 29 patients with regional enteritis who ingested sanitized ova of pig whipworm went into remission. It has been shown that helminth infections are antiinflammatory and that a pentasaccaride found on the surface of the ova triggers an increase in interleukin-10 and other anti-inflammatory cytokines. Interestingly, similar oligosaccharides are found in breast milk and may account for antidiarrheal effects in breast-fed infants. How surface oligosaccharides on microbes, parasites and their ova interact with the immune system of the intestine is an emerging field of study that may have application in diabetes research.

Dr. Spiegel suggested that Dr. Grave contact Dr. Steve James at NIDDK to discuss the helminth findings because Dr. James is studying parasitic interactions in Crohn's disease. There is a "hygiene hypothesis" that suggests autoimmune diseases such as asthma and possibly type 1 diabetes are increasing in incidence as a more clean and sanitized environment is achieved. Much of this is speculative but may be worth pursuing.

National Center for Research Resources (NCRR)

Richard Knazek, M.D.; Contractor for the Division of Clinical Research Resources, NCRR, NIH, Bethesda, Maryland

Dr. Knazek provided an update on the Islet Cell Resource (ICR) Center Consortium; the consortium partners include NIDDK, NCRR, and the Juvenile Diabetes Research Foundation (slide 1). The mission of the ICR is to generate and distribute Good Manufacturing Practices (GMP)-grade human pancreatic islets to clinical investigators for transplantation into patients who have severe type 1 diabetes mellitus (slide 2). Additional goals of the ICR are optimizing the methodologies and technologies for generating the islets and determining the characteristics of the cells that will allow successful transplantation. In the past few years, the ICR has expanded its mission to include distribution of islet cells for basic research. The islets are available to investigators at no charge, which is very advantageous for increasing islet research (slide 3). Dr. Knazek explained the ease with which investigators may apply to take part in this research, which begins with an application at http://icr.coh.org/.

National Heart, Lung, and Blood Institute (NHLBI)

Cristina Rabadan-Diehl, Ph.D.; Program Official, Vascular Biology Research Program, Division of Heart and Vascular Diseases, NHLBI, NIH, Bethesda, Maryland

Dr. Rabadan-Diehl described a program that was funded fully by the type 1 diabetes fund and involves investigation of the cardiovascular (CV) complications of diabetes. She reported on a joint meeting between NIDDK and NHLBI in 2003 that recommended support for mechanistic studies of the vascular wall and endothelial dysfunction and the onset and progression of CV complications and type 1 diabetes. As a result, NHLBI and NIDDK issued an initiative, Progression of CV Disease in Type 1 Diabetes that invited applications for investigations in this area. Of 49 applications, eight projects were found to be highly meritorious and currently are

being funded. Among these eight projects are investigations of vascular disease and cardioneuropathy.

In addition, two clinical studies also are being supported by the initiative. One is using an existing cohort of the Coronary Artery Calcification in Type 1 (CACTI) Diabetes Study, which investigates the role of inflammation and immune responses in the progression of coronary artery calcification, as well as the role of insulin resistance and the metabolic syndrome in accelerated atherosclerosis among patients with type 1 diabetes. This cohort also will be used to characterize the morphology of coronary plaque and the arterial wall remodeling processes. The investigators also will reanalyze past studies such as the Epidemiology of Diabetes Complications Study to determine if there are data that can be utilized for understanding the relationship of diabetes and clinical arteriosclerosis and the incidence of clinical coronary artery disease.

The second study, Coronary Artery Disease and Renal Disease in Type 1 Diabetes, will investigate the role of insulin resistance. This study will investigate whether individuals with both coronary artery disease (CAD) and overt nephropathy have greater insulin resistance than those with CAD or nephropathy alone, or with neither of these conditions.

Dr. Spiegel concluded by commenting that one of the NIH Roadmap P20s is investigating the relationship between diabetes and the heart and stressed that it is important that NHLBI be aware of this ongoing study.

NIDDK Office of Minority Health Research Coordination (OMHRC)

Lawrence Agodoa, M.D.; Director, OMHRC, NIDDK, NIH, Bethesda, Maryland

Dr. Agodoa provided background information on the Diabetes Based Science Education in Tribal Schools (DETS) initiative, which originally was discussed at the DMICC in 2000. At the time, there was concern about the high incidence and prevalence of diabetes in American Indian and Alaskan Native communities, especially in light of data showing that diabetes was rare in these communities until approximately 50 years ago (slide 2). The DETS program grew out of these discussions to target diabetes education toward children in these communities. Goals of the initiative include educating children on healthy lifestyles and risk factors for diabetes, with an emphasis on maintaining balance among families and their communities; increasing understanding of the process of developing scientific and community knowledge in relationship to health, diabetes, and maintaining balance; and encouraging interest in health science professions among American Indian and Alaska Native children (slides 3-10)

A pilot study was conducted for one year in science classes for grades K-12 (slides 11-15). The science curriculum being developed is being aligned with national and state teaching standards and benchmarks, is culturally sensitive, and includes hands-on science-based materials that reflect traditional learning styles emphasizing visual, spatial, and perceptual modes of learning (slide 12).

In discussions, it was pointed out that obesity also is a severe problem in tribal communities and this is being addressed in DETS as part of diabetes education. It was suggested that DETS

investigators should consider contacting investigators from the Diabetes Prevention Program (DPP) because they may be able to add their perspectives on working with these communities.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Judith Fradkin, M.D.

Dr. Fradkin commented that many of the diabetes initiatives at NIDDK have been discussed at previous DMICC meetings, and she would focus on only a few activities related to the priority area of obesity and type 2 diabetes in children.

On September 26-27, 2005, a meeting will be held on the effects of the intrauterine environment and specifically maternal diabetes, obesity, and associated metabolic changes on the future risk of offspring developing diabetes and obesity.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, which compares three approaches to treating type 2 diabetes in children, began recruitment one year ago. A school based prevention study to address risk factors for diabetes in middle school aged children has conducted pilot and feasibility studies and has developed important information on the prevalence of risk factors in this population. A full trial is under development for possible implementation in September 2006.

In addition, the National Diabetes Education Program, a joint effort of the NIDDK with the Centers for Disease Control and Prevention, is creating a new campaign that focuses on women with gestational diabetes and their offspring. The purpose of the program is to encourage obstetricians and gynecologists who are caring for women, and family physicians and pediatricians who are caring for children, to ascertain a history of gestational diabetes and implement the kinds of interventions that were successful in the DPP.

Dr. Fradkin asked Dr. Thomas Eggerman, Director of the Islet Transplantation Program, NIDDK, to comment on a recent meeting in Chicago on islet transplantation that involved staff from NIDDK, NIAID, and NCRR. A significant outcome of the meeting was the decision to coordinate the efforts of several groups and standardize data fields. This will minimize the amount of time investigators spend on data submission to multiple groups involved in collection of islet transplantation data.

CLOSING REMARKS
Judith Fradkin, M.D.

Dr. Fradkin thanked Dr. Saul Malozowski for his service to the DMICC and welcomed Dr. Sanford Garfield, who will be replacing Dr. Malozowski as DMICC Executive Secretary.

Dr. Fradkin asked DMICC members for suggestions for topics for future DMICC meetings. It was suggested that a future meeting focus on recent data on young adults related to changing risk factors for diabetes and cardiovascular disease, particularly increases in the prevalence and incidence of obesity in this group. Novel approaches such as the “polypill”—combining in a

single pill multiple agents (e.g., high blood pressure, high cholesterol, and diabetes)—should be considered, including what this may mean for diabetes prevention.

Dr. Fradkin thanked participants for their presentations and comments. The meeting adjourned at 3:35 p.m., E.S.T.