Diabetes Mellitus Interagency Coordinating Committee

Fiscal Year 2003 Annual Report

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Diabetes Mellitus Interagency Coordinating Committee

Fiscal Year 2003 | Annual Report

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INTRODUCTION

In accordance with Section 429 of the National Diabetes Mellitus Research and Education Act, the Diabetes Mellitus Interagency Coordinating Committee (DMICC) prepares an annual summary report of its activities as well as other Federal research activities in the field of diabetes. It is submitted to the Secretary, Department of Health and Human Services (DHHS), and the Director of the National Institutes of Health (NIH). This is the annual report of the DMICC for Fiscal Year (FY) 2003.

LEGISLATIVE MANDATE

The DMICC was authorized by Public Law 93-354 and established in fall 1974; subsequent legislation modified some of the charges to the Committee. The legislative authority of the Committee is presented in Appendix A. The charge to the DMICC is to coordinate the research activities of the NIH and other Federal agencies relating to diabetes mellitus and its complications and to contribute to the adequacy and technical soundness of these activities by providing a forum for communication and exchange of information.

The Committee includes representatives from Federal agencies whose programs are relevant to diabetes mellitus and its complications. The chairman, designated by the Director, NIH, is the Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In FY 2003, the DMICC membership included representatives of 31 Federal organizations. A roster of Committee members as of the close of the fiscal year is included as Appendix B.

ACTIVITIES OF THE DMICC

The DMICC facilitates cooperation, communication, and collaboration among agencies that conduct or support diabetes-related activities. These activities may range from support for biomedical research to direct provision of health care services. The DMICC provides both a forum for initiating interactions and a mechanism for tracking progress.

ACTIVITIES OF MEMBER ORGANIZATIONS

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Agency for Healthcare Research and Quality (AHRQ)

http://www.ahrq.gov

The Agency for Healthcare Research and Quality continues to be involved in a broad range of activities related to improving the quality of health care, reducing its costs, improving patient safety, decreasing medical errors, and broadening access to essential services related to diabetes. These activities include the support of research and collaborations with others in the public and private sectors to improve outcomes for those with diabetes and to prevent the condition across the population.

Current Activities

Prevention - USPSTF. Through the work of the U.S. Preventive Services Task Force (USPSTF), recommendations for screening for type 2 diabetes and gestational diabetes were updated and released in 2003:

- The USPSTF concluded that the evidence is insufficient to recommend for or against routinely screening asymptomatic adults for type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose.

- The USPSTF recommends screening for type 2 diabetes in adults with hypertension or hyperlipidemia.

- The USPSTF concluded that the evidence is insufficient to recommend for or against routine screening for gestational diabetes.

Extramural Research. The Agency continues to fund and is involved with a large number of studies related to diabetes:

- Under a partnership with the Health Resources and Services Administration, AHRQ funded two studies to assess the impacts of the Health Disparities Collaboratives. Hundreds of Community Health Centers have been involved in the diabetes collaboratives, a learning process built on the Institute for Healthcare Improvement's methods for improving care and outcomes and the Chronic Illness Model. This project started in 2001.

- Under the TRIP II (Translating Research Into Practice II) and EXCEED (Excellence Centers to Eliminate Ethnic/Racial Disparities) initiatives, researchers are examining why disparities exist in the care and outcomes of minorities with diabetes and what can be done to reduce or eliminate them. Projects include an examination of the association between diabetes education programs and quality of care indicators in the Indian Health Service; implementation of successful managed care models of diabetes care in underserved populations; a community-based participatory research study aimed to improve processes of care for elderly African American diabetics; an evaluation of the impact of point-of-service testing of hemoglobin A1c on care and outcomes; and the development and evaluation of a culturally sensitive multimedia education program aimed at increasing diabetes-related knowledge, self-efficacy, and self-care for African American and Latino populations. Other ongoing studies include an assessment of diabetes care in community health centers, the effects of Navajo interpreters on diabetes outcomes, the effectiveness of an automated telephone disease management system for English- and Spanish-speaking patients, and an evaluation of the impact of changes in managed care policy towards reimbursement for glucose self-monitoring on utilization and outcomes.

In FY 2003 the Agency funded five new studies involving:

- Computerized interviews to assist secondary prevention in diabetes care (2003-2005).

- Evaluation of culturally appropriate primary health care, with particular attention to diabetes (2003-2004).

- Efficiency examination in diabetes care (2003-2004).

- Home care outcomes of expanded home health aide roles with particular attention to diabetes (2003-2007).

- Collaborative Management of Diabetes in Blacks (2003-2006).

Intramural Research. Staff at AHRQ are also involved in a number of intramural studies of diabetes. Investigators are using data from the Medical Expenditure Panel Survey (MEPS) to develop national estimates for medical visits, individual expenditures, and sources of payment for people with diabetes. Another study is identifying factors associated with multiple hospitalizations of diabetics using Healthcare Cost and Utilization Project data.

Dissemination of Evidence. AHRQ continues to work with individuals and organizations to ensure that the evidence-base is being employed. The Agency has maintained an initiative launched last year to strengthen partnerships with stakeholders across the health care spectrum. Under a partnership with the American College of Physicians– American Society of Internal Medicine, the Agency will be involved with broad efforts to improve the quality of care for type 2 diabetes. The Agency also continues its involvement with the National Diabetes Quality Improvement Alliance (formerly called the Diabetes Quality Improvement Project (DQIP)), an effort to develop uniform, core measures of diabetes performance that allow benchmarking across organizations and identify opportunities for improvement among health plans and providers. Reporting on DQIP measures is now required of managed care organizations by the Centers for Medicare & Medicaid Services (CMS) and results will be made publicly available.

Collaborative Work With Other Federal Agencies. AHRQ is a partner of the Centers for Disease Control and Prevention (CDC) in the National Public Health Initiative on Diabetes and Women's Health. AHRQ is a partner of CDC in the TRIP initiative as it relates to diabetes.

National Health Care Quality Report (NHQR) & National Health Care Disparities Report (NHDR). These reports were mandated by Congress starting FY 2003 and will be released to the public in January 2004. The first provides for the first time, a systematic picture of the quality of health care in America and highlights areas where improvement is needed. The National Healthcare Disparities Report shows where racial and ethnic inequities exist in health care delivery and what we can do to improve. In both, diabetes is a key priority area.

Products

- Program Brief: Diabetes Research Highlight. Released in April 2003.

- NHQR and NHDR – reports to be released in FY 2004.

- The Agency is currently developing a prototype "Workbook on Diabetes" for State leaders. The workbook is based on the methodology and findings of NHQR and NHDR. The major goal is to serve as a source of data and evaluation of performance including comparative rates among States. State leaders may be able to improve their performance by knowing where the gaps are and perhaps being able to follow best practices established by other States. Scheduled for publication in FY 2004.

- Evidence report on Best Practices on Diabetes. This is a systematic review of the literature currently under development by the University of California at San Francisco (UCSF)–Stanford University Evidence-Based Practice Center. It is scheduled for release in FY 2004.

Future Activities

Much of the work mentioned above will continue during the next fiscal year. It is expected that additional work will be funded under the Agency's Program Announcements (PAs) and Requests for Appications (RFAs). Priorities with particular pertinence to diabetes include translating research into practice, patient-centered care, patient safety and medical errors, and the relationship between systems factors and quality. In addition, work will continue on the evaluation of quality of care in diabetes and the identification of best practices (quality measures) as we develop on a yearly basis the NHQR and NHDR reports.

Center for Scientific Review (CSR)
http://www.csr.nih.gov

The Center for Scientific Review is a center within NIH, where a majority of investigator-initiated applications in diabetes and obesity areas are reviewed. The mechanisms of application support are the investigator-initiated individual project applications (R01s), High Risk/High Impact Pilot grant applications (R21s), Small Business Innovation Research Applications or Technology Transfer (SBIR/STTR), and Individual Fellowship Applications: Predoctoral (F31 and F30), Postdoctoral (F32), and Senior Fellowships (F33).

Under the above research support application mechanisms, pertinent areas that are covered fall into two main categories: Basic and Clinical Translational Research. Areas include: Beta Cell Biology, Islet and Pancreas Transplantation, Insulin Action, Insulin Resistance, Pathogenesis of Type 1 and Type 2 Diabetes, and also study of pathogenesis of obesity. These studies invoke molecular genetic, metabolic (which includes nutritional interventions), cell, biological, and histochemical approaches.

These applications are reviewed in several Integrated Review Groups (IRGs) within which individual subcommittees (study sections) are located. Each of these sub-committees (study sections) has definite expertise to review specific areas relevant to diabetes and obesity. Thus, the mission of CSR to activities of DMICC is central and pivotal through help in maintaining the quality of diabetes and obesity research in the Nation. The knowledge gained through these NIH-supported projects would help control/treat type 1 diabetes and type 2 diabetes and obesity in areas of the world where these diseases are prevalent.

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov

Mission, Vision and Structure. The mission of the Centers for Disease Control and Prevention and its diabetes program is to eliminate the preventable burden of diabetes through public health actions. These actions will occur within a vision of "healthier and safer people." While the mission and vision of public health efforts to eliminate the preventable burden of diabetes are the primary responsibility of the Division of Diabetes Translation (DDT) at CDC, several other programs at CDC, including nutrition and physical activity, laboratory science, cardiovascular disease (CVD), public health genetics, school programs, and so forth, are essential to the activities of CDC in diabetes. Further, other U.S. Department of Health and Human Services agencies, State and local health departments, private and professional organizations, minority entities, businesses and purchasers of care, etc., are also essential in the actions of CDC to address diabetes. While CDC's DDT is organized into an Office of Director and two branches—the Program Development Branch and the Epidemiology and Statistics Branch—activities within DDT are divided into those efforts that primarily address issues of "Knowing, Knowing Why, and Doing."

Current Activities

Knowing:
1. National Diabetes Surveillance System: CDC continues to strengthen and broaden various surveillance systems that increasingly provide a broader and more complete picture of diabetes in the United States. Efforts to expand the Behavioral Risk Factor Surveillance System (BRFSS) and its diabetes module, a re-designed National Health Interview Survey (NHIS), additional questions with-in the National Health and Nutrition Examination Survey (NHANES), expansion of the National Impatient Survey (NIS) system, and augmentation of the Indian Health Service's Clinical Surveillance System are examples of a broader and more complete set of surveillance systems to "know" the extent and nature of the diabetes burden. Within these and other systems, new topics (e.g., age of diagnosis, CVD risk factors, level of amputations) have been added. Finally, through CDC's online Morbidity and Mortality Weekly Report (MMWR) and other peer-reviewed journals, surveillance information is being more widely and rapidly shared.

2. SEARCH: The SEARCH project, directed by CDC and importantly co-funded by NIH, is well into its third year of establishing six registries for diabetes among youth throughout the United States. A uniform population-based registry system is now well in place, and both prevalence and incidence cases are being identified and characterized. Protocols and manuals of operations have been finalized, utilized, and now shared nationally and internationally on CDC's web site. Initial data indicates that the incidence projections for diabetes in youth 19 years or less underestimated the frequency of diabetes, and that it is likely that the number of persons with type 1 diabetes mellitus (DM) is likely to be greater than previously estimated.

3. Forecasting the Burden of Diabetes: Combining improved surveillance systems with newly developed computer modeling that can accept a variety of past trends related to diabetes and the general population and project changes into the future, several such projections have been accomplished, including (a) a clear sense of the size of the population burden of diabetes in 2050 based on cautious interpretation of data from the past decade (approx. 30 million persons with known DM); and (b) a precise estimate of the individual risk of developing type 2 diabetes if born in 2000 (overall, 1 in 3 chances). These projections provide an essential perspective regarding what the future will look like unless more effective preventive and control diabetes programs are put into action and also the financial and social implications of the present day diabetes epidemic.

4. U.S.–Mexico Border Diabetes Project: Given the increasing power of the global economy as well as the "internationalization of health and disease," it is important to expand surveillance and program efforts in cooperation with other countries that relate to the United States. Efforts over the past 4 years have resulted in population-based data from the U.S.–Mexican Border regarding prevalence of DM and associated risk factors and conditions from approximately 25,000 persons. Population-based household surveys have been completed, and data initially analyzed. The project, being conducted with four and six U.S. and Mexican states, respectively, the Mexican Health Ministry, Health Resources and Services Administration (HRSA), CDC, and others is now in the process of developing public health programs to improve the prevention and management of diabetes along the Border.

5. Vision Health in America: A number of vision abnormalities contribute to substantial loss of quality of life and disability among Americans, especially those in the aging population. Diabetes is one of these important conditions. Yet, there is no population-based surveillance system to both define and measure this burden. Under the leadership of CDC/DDT along with Prevent Blindness America (PBA), several existing surveillance systems, including the BRFSS and NHANES, are being expanded to increase information collected from a population basis regarding both the extent of poor health due to vision impairment, as well as the etiology of this vision impairment. These efforts are being coordinated with NIH/National Eye Institute (NEI) and CDC/National Center for Health Statistics (NCHS).

Knowing Why:

1. TRIAD: The Translating Research Into Action for Diabetes (TRIAD), a project directed by CDC and importantly, co-supported by NIH, is systematically examining structure, process, and outcomes of diabetes care in six large managed care organizations (MCOs) in the United States. TRIAD by intention includes a very large percentage of members from minority communities. Ultimately, quality of care and those factors that impair the delivery of quality of care have been identified. Eventually, structured interventions will be systematically applied in these different MCO settings to determine the improvement of delivery of care. Forty investigators are now involved in TRIAD.

2. Project DIRECT: This community-based diabetes intervention program, located in an African-American component of Raleigh, North Carolina, has been in place for approximately 8 years. Initially, following an extensive and population-based assessment of the status of diabetes in this community, interventions—primary, secondary, and tertiary prevention strategies—have been accepted by the community and applied. At present, both longitudinal and a follow-up cross-sectional assessment is being completed. DIRECT is the first comprehensive community-based project in the United States to address the growing burden of diabetes in an African-American urban city.

3. Health Services Research: This project is monitoring the delivery of efficacious preventive care services in the United States and identifying barriers to optimal diabetes care, especially at the systems level.

4. Primary Prevention of Diabetes–Formative Research: To inform communications and program development, CDC/DDT has completed extensive formative qualitative research to determine individual and community perceptions about primary prevention of type 2 diabetes, from within various communities of culture, businesses and managed care, the health care system, and individual health providers. This rich information has provided convincing data indicating that (a) different views of the possibilities and benefits of primary prevention exist among these various populations; and (b) very different strategies need to be developed to engage these various populations in effective programs to launch primary prevention programs.

5. Primary Prevention of Diabetes–Identifying Persons at Risk for Type 2 DM: Through cooperation with the University of Minnesota, large datasets are

being analyzed to establish simple indicators of individuals likely to develop DM and likely to benefit from behavioral interventions. Initial study indicates that "Enlarged Waist and an Elevated Triglyceride" (EWET) identifies individuals with insulin resistance and a high risk for subsequent DM.

6. Primary Prevention of Diabetes–Integrated Chronic Disease Models: Because the development of type 2 DM occurs in populations that also are at high risk for obesity, hypertension, CVD, etc., the integration at a State-level of models to deliver both preventive and management strategies needs to be identified. Five (5) State health departments have been funded to model different approaches to integrating chronic disease prevention, including type 2 diabetes, in an effort to ultimately combine coordinated interests in chronic disease control.

Doing:

1. Diabetes Prevention and Control Programs (DPCPs): CDC/DDT now supports 50 State programs, the District of Columbia, and 8 territories to apply public health programs in the management of diabetes mellitus, and since the past year, in efforts to develop and launch primary prevention strategies for type 2 DM. At present, 27/50 States have "Capacity Building" programs, and measurable progress has now been documented. In addition to primary prevention, the DPCPs also now include CVD prevention activities to persons with established DM, and in these efforts, they work very closely with State-based CVD programs. DPCPs continue to be the major venue for delivery of all CDC-directed public health programs in the United States.

2. Diabetes Collaborative: In cooperation with HRSA and various Community Health Centers (CHCs), CDC/DDT and DPCPs (47) are working closely with the Institute for Healthcare Improvement (IHI) to implement improved chronic care systems such that improved management of diabetes would result. The program has expanded to include now over 600 Community Health Centers, and data indicate (a) increased ordering of diabetes tests (e.g., A1c); and (b) improvements in "intermediate outcomes" such as A1c levels. Further, on a pilot basis at five DPCPs and CHCs, primary prevention strategies to identify those at risk for undetected diabetes and prediabetes have been implemented, and by using simple data sets of existing information, a very high percentage of members of CHCs (i.e., 25%), have been identified. The expansion of this primary prevention detections strategy as well as the implementation of primary prevention behavior programs is presently in place.

3. National Diabetes Education Program (NDEP): In cooperation with NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the NDEP continues to expand, moving now beyond improved glycemic and CVD regulation, to address the primary prevention of type 2 diabetes among those with prediabetes. In addition, improved use of Internet-based education programs for health systems, health care providers, businesses, and purchasers of care have been put in place. A more efficient and representative administrative structure of the NDEP, including the Executive, Steering, and Operations Committees, has been established. The DPCPs have become more active in the dissemination of NDEP materials and (a) greater attention to evaluation of the NDEP; (b) expanded interaction with the American Diabetes Association (ADA) and American Association of Diabetes Educators (AADE); and (c) greater emphasis on and attention to materials and programs for minority communities at risk for diabetes are all being implemented.

4. National Diabetes Prevention Center (NDPC): Recognizing the remarkable challenge of diabetes among American Indians, as well as the expanding efforts by the Indian Health Service (IHS) towards diabetes, CDC's NDPC has been formalized, staffed, and expanded in effort and partnership. The NDPC, located in Gallup, New Mexico, now develops materials, programs, and guidance for all Tribal Nations, usually in concert with each Tribe as well as IHS.

5. Business, Managed Care, Purchasers, and Model Contract Language: CDC/DDT accepts the important and necessary attention that the business community directs to DM. In this context, and working with various Schools of Law and Business, several programs have been developed and implemented that (a) facilitate the identification of the burden of diabetes in a business community; (b) inform purchasers of care concerning evidenced-based approaches to the management or prevention of type 2 diabetes; and (c) provide appropriate contract language about diabetes that must be included in State-based Medicaid RFAs (Requests for Applications).

6. National Public Health Strategies for Women and DM: This major new effort, begun approximately 2 years ago, has been further expanded in 2003 with two additional conferences to both delineate and assign important strategies for both the prevention and management of diabetes among women across the age-span. Working with its three major co-sponsors, ADA, APHA (American Public Health Association), and ASTHO (Association of State and Territorial Public Health Officials), CDC has now developed specific responsibilities for this national program to add a public health perspective to the typical clinical program for women with or at risk for diabetes mellitus.

Future Activities

1. Greater attention will be directed to integrate diabetes programs with other chronic disease efforts, such as nutrition and physical activity strategies; CVD programs; activities among youth, especially during school; and so forth. Categorical activities and programs will gradually be imbedded in larger, more financially supported chronic disease initiatives.

2. As programs at CDC in diabetes have grown, along with improved and expanded surveillance systems that are being developed, greater and more appropriate accountability efforts will be made.

3. Within the scientific efforts of CDC/DDT, increasing attention to projections of the diabetes burden, economic analyses, health services research, and the application of evidenced-based public health strategies will be implemented.

Centers for Medicare and Medicaid Services (CMS) [formerly HCFA]

http://www.cms.hhs.gov

Diabetes activities at CMS fell into several broad categories: evaluation of the quality of care provided to Medicare beneficiaries, national and State-level quality measurement and improvement projects designed to improve care for Medicare beneficiaries, beneficiary educational campaigns, and research to support quality diabetes care.

Current Activities

The Doctor's Office Quality Project is a component of CMS' Physician Focused Quality Initiative. The Physician Focused Quality Initiative builds upon ongoing CMS strategies and programs in other health care settings in order to: (1) assess the quality of care for key illnesses and clinical conditions that affect many people with Medicare, (2) support clinicians in providing appropriate treatment of the conditions identified, (3) prevent health problems that are avoidable, and (4) investigate the concept of payment for performance.

The Physician Focused Quality Initiative includes the Doctor's Office Quality (DOQ) Project, the Doctor's Office Quality Information Technology (DOQ–IT) Project, and several Demonstration Projects and Evaluation Reports.

- The DOQ Project has two goals. The first goal is to describe quality of care in the ambulatory setting in three domains: clinical performance, practice system assessment survey, and the patient experience of care survey. The second goal is to assess the feasibility of collecting doctors' office quality-of-care data.

- The goal for the DOQ–IT Project is to encourage physician offices to adopt electronic health record systems.

- The Demonstration Projects study the impact of new payment approaches and new types of services on beneficiaries, providers, health plans and States, and the Evaluation Reports validate the research and demonstration findings.

The Quality Improvement Organizations (QIOs) have been working to improve diabetes care in the following areas:

- Annual hemoglobin A1c testing.
- Biennial lipid profile.
- Biennial eye examination.

The QIOs are implementing quality improvement projects in physician offices to improve diabetes care for the above measures on a statewide basis as well as working intensively with approximately 5 percent of the physicians in their State to improve diabetes care by implementing interventions such as office system changes, patient care management registries, and flow sheets or reminder cards. Improving diabetes care will remain a focus as the QIOs move into their new contract cycle that will begin in 2005.

2003 National QAPI Project–Clinical Health Care Disparities (CHCD). One option for Medicare + Choice Organizations (M+COs) undertaking a 2003 QAPI Project is to focus on Clinical Health Care Disparities. With this project, an M+CO will choose a clinical focus area (of which diabetes is one option) and will focus interventions on a specific segment of their enrollee population that experiences disparities in care and treatment of this clinical area. More information about the QAPI Clinical Health Care Disparities projects can be found at *www.cms.hhs.gov\healthplans\quality*.

Methods for Increasing Communications With People With Medicare. The Center for Beneficiary Services has an agreement with the National Diabetes Educational Program (NDEP) to promote preventive services for people with Medicare. Currently our promotion efforts include the "Power To Control Diabetes Is in Your Hands" brochures, posters, Community Kits, and Practitioner Kits. We have also

prepared a new fact sheet that will advise people with diabetes about the new self-monitoring benefit and the medical nutrition benefit to supplement the "Power To Control" campaign. The fact sheet uses the existing cleared language from the CMS Publication #11022, "Medicare Coverage of Diabetes Supplies & Services."

Future Activities

2004 National QAPI Project-Diabetes. Medicare + Choice organizations undertaking a 2004 QAPI project have the option of conducting either the national diabetes project as defined by CMS or a regional collaborative project of their own choosing. The national project will allow the M+COs the option of selecting to focus on reducing disparities in care or focusing on the larger diabetic population. CMS encourages strong clinical performance in the care and treatment of diabetes by offering M+COs the opportunity to be exempt from this project if they have reached specific standards of clinical performance. Additional information regarding the 2004 QAPI National Diabetes Project and information regarding M+COs exempt from the project can be found at *www.cms.hhs.gov\healthplans\quality*.

Department of Health and Human Services (DHHS)
http://www.dhhs.gov

DHHS Office of Public Health and Science (OPHS)
http://www.hhs.gov/agencies/ophs.html

The Office of Public Health and Science (OPHS) within the *Office of the Secretary* serves as the focal point for leadership and coordination in public health and science across the U.S. Department of Health and Human Services, provides direction to program offices within OPHS, and through the Assistant Secretary for Health provides advice and counsel on public health and science issues to the Secretary. OPHS identifies innovative solutions to public health problems and issues and provides health policy advice to public health and other professionals and information to the public to improve the prevention and treatment of diseases including diabetes.

Highlights and future plans of the OPHS program offices are described below.

Current Activities

Steps to a HealtherUS Initiative: In April 2003, Secretary Thompson launched his prevention initiative, Steps to a *HealthierUS*, at a summit in Baltimore, Maryland. *Steps to a HealthierUS* builds on the President's *HealthierUS* initiative by focusing on prevention of chronic diseases, such as diabetes, obesity, asthma, heart disease, stroke, and cancer, and by encouraging Americans to make healthy food choices, increase their level of physical activity, and avoid tobacco use and exposure. A cornerstone of *Steps to a HealthierUS* is cooperative agreements, which were awarded in September 2003 to 12 grantees covering 23 communities. A second prevention summit is planned for April 29–30, 2004. The Office of Disease Prevention and Health Promotion within OPHS coordinates the *Steps* Initiative.

Secretary's Diabetes Detection Initiative: Finding the Undiagnosed: Plans were made for launching a nationwide initiative aimed at finding the more than 5 million persons with undiagnosed diabetes during FY 2003. The Office of the Surgeon General was one of the primary leads in developing this multi-agency initiative. The initiative's focus is to help people understand their risk for diabetes and assist high-risk people in linking the various health care systems for follow-up testing, if needed. The *Diabetes Detection Initiative* will be piloted in 10 locations around the country in FY 2004. The Surgeon General plans to appear at some of these sites to address the importance of diabetes prevention, detection, and appropriate treatment.

The Office of Disease Prevention and Health Promotion within OPHS serves as the overall coordinator of the national *Healthy People 2010* effort. Diabetes is one of the 28 *Healthy People 2010* focus area chapters. The diabetes focus area identifies 17 specific health promotion and disease prevention objectives aimed at achieving the goal of using prevention programs to reduce the incidence and economic burden of this disease and to improve the quality of life for people who have diabetes or who are at risk for it. A progress review on the diabetes focus area was held on December 18, 2002, and new data are added quarterly to the National Center for Health Statistics web site DATA 2010. The complete report on the review can be found at *www.healthypeople.gov/data/2010prog/focus05*, and *www.cdc.gov/nchs/about/otheract/hpdata2010/fa5/diabetes.htm*, a web page prepared by the National Center for Health Statistics that includes additional information about the review.

The Office of Minority Health (OMH) within OPHS seeks to improve the health of racial and ethnic minority populations through the development of health policies and programs that address health disparities and gaps. In FY 2003, OMH continued funding the following three grants and one cooperative agreement that targeted diabetes as a priority health issue:

1. *The Bilingual/Bicultural Service Demonstration Grant Program* funds 10 projects that target diabetes by utilizing promotores (lay health educators) to conduct education and outreach to the target population; by providing diabetes screening in community settings such as churches, schools, and work sites; by fostering case management to assist individuals with diabetes; by conducting workshops that encourage physical fitness and better nutrition; and by developing bilingual health education materials. The projects also reach health care providers to enhance the quality of care delivered to minorities with limited-English-proficiency (LEP) through cultural competency training and providing health care facilities with interpreters for LEP patients. During FY 2003, four projects were in their second year of operation, and six were in their third and final year.

2. *The Health Disparities in Minority Health Grant Program* is intended to demonstrate the merit of using local, small-scale programs to address health problems and issues that affect the health and well-being of local minority populations. Several of the projects within this program addressed diabetes prevention education, self-management education, and access to health care for defined minority populations.

3. *The Community Programs To Improve Minority Health Grant Program* fosters the use of a community coalition approach to health promotion and risk reduction as a means of reaching targeted minority populations. Project activities seek to improve the delivery of comprehensive diabetes care in the community through a patient-based care management model, health care provider education, and telemedicine technology. These demonstration programs are funded for 3 years.

4. *The American Indian Higher Education Consortium Cooperative Agreement* is a collaborative effort between the Centers for Disease Control and Prevention (CDC), the Indian Health Service Diabetes Program, OMH, and 10 Tribal Colleges and Universities.

Honoring Our Health: Tribal Colleges and Communities Working Together to Prevent Diabetes seeks to:

- Develop infrastructure for diabetes education and community mobilization.
- Establish diabetes-related curricula.
- Connect diabetes prevention to land preservation, aquaculture, gardens, and bison restoration.
- Develop diet-related curricula.
- Increase education, awareness, and the opportunity to practice good health behaviors.
- Support community health and wellness centers.
- Foster faculty development in diabetes-related fields.
- Stimulate capacity building for health-related research.

In November 2001, OPHS, in collaboration with the Office of the Secretary, initiated a partnership with the ABC Radio Networks to inform minority communities on ways to achieve better health and close health gaps with the rest of the U.S. population. In 2003, the National Institutes of Health, the Health Resources and Services Administration, the Centers for Medicare & Medicaid Services, and the Agency for Healthcare Research and Quality joined OPHS in sponsoring an extensive series of broadcast messages on ABC Radio featuring the Department's *Closing the Health Gap* messages. The campaign's initial focus on African-American health was expanded in FY 2003 to include other racial and ethnic minority populations. Specifically, OPHS and agency partners built an extensive series of web pages featuring the Department's Spanish language health education resources. In addition, five health fairs were held in FY 2003 that brought information and screening to 7,500 Hispanic consumers. Finally, a series of broadcast health messages was initiated including 60-second vignettes and 1-hour talk shows with Spanish broadcaster Radio Unica.

Another major component of the campaign, *Take a Loved One to the Doctor Day* encourages all Americans, especially minorities, to become more involved in their health care. Now established as the third Tuesday in September, *Doctor Day* took place on September 16, 2003. It drew more than 450 partners in 50 states, the District of Columbia, and Puerto Rico, and many of these partners sponsored local health screenings, fairs, and events at community health centers, including diabetes awareness and management activities. During the month of September 2003, ABC Radio Network ran 180 recorded PSAs on diabetes, 180 10-second live announcements on diabetes, and posted web-based information and links on diabetes. ABC Radio ran these spots on 240 affiliate stations of the ABC Urban Advantage Network, magazines, the Associated Press, and Scripps-Howard News Service. As a result of these campaigns and events, OPHS estimates that more than 33 million people had multiple exposure to DHHS minority health broadcast messages and more than 40 million people were exposed to DHHS minority health print messages.

The Office on Women's Health (OWH) within OPHS reviews current scientific knowledge to prevent, reduce, or delay onset, morbidity, and mortality of diabetes and its complications and serves as a forum to strengthen partnerships and identify collaborative opportunities.

OWH and the Coordinating Committee on Women's Health, which includes representatives from across DHHS agencies and staff offices, collaborated with the American Diabetes Association to convene a Women and Diabetes Town Hall at the Cannon House Office Building on May 20, 2003. Recognizing that

more than half of those diagnosed with diabetes are women, the Town Hall provided a forum for information on diabetes in the lives of women across the Nation and across the life span. It highlighted the National Diabetes Education Program's "Small Steps. Big Rewards," the first national diabetes prevention campaign that was launched on November 20, 2002. This initiative builds on results of clinical trials that demonstrated modest lifestyle changes can have a major impact on preventing the disease. The Town Hall was broadcasted via satellite around the country, with 77 sites participating. There were 1,579 user sessions on the Diabetes Town Hall web site. The House of Representatives' Women's Caucus and Diabetes Caucus were also partners in this effort.

The President's Council on Physical Fitness and Sports (PCPFS) stresses the health benefits of regular physical activity for all Americans, including people with chronic health conditions such as diabetes. Each November, PCPFS publishes a web site feature for the American Diabetes Month: "Physical Activity: A Key to Diabetes Control and Prevention," which includes information on physical activity for people with diabetes and links to other health web sites as well.

Federal Information Resources on Diabetes. The Office of Public Health and Science established and coordinates several Federal information resource centers with toll-free call centers and Internet portals that provide comprehensive and reliable health information about the causes, treatment, and prevention of diabetes. They include the National Health Information Center *(www.healthfinder.gov* and 800–336–4797*)*, the National Women's Health Information Center *(www.4woman.gov* and 800–994–woman*)*, the Office of Minority Health Resource Center (www.*omhrc.gov* and 800–444–6472*)*, www.*nutrition.gov*, and www.*fitness.gov*.

Future Activities

Two key initiatives for FY 2004 will be the launching and evaluation of the *Secretary's Diabetes Detection Initiative: Finding the Undiagnosed* and the FY 2004 *Steps to a HealthierUS Summit*.

In FY 2004, the Office of Minority Health will solicit applications for its three grant programs—1) Bilingual/Bicultural Service Demonstration Grant Program, 2) Community Programs To Improve Minority Health Grant Program, and 3) Health Disparities in Minority Health Grant Program.

Food and Drug Administration (FDA)
http://www.fda.gov

Division of Metabolic and Endocrine Drug Products
http://www.fda.gov/cder/dmedp

The mission of the Center for Drug Evaluation and Research of FDA is to facilitate the clinical development and delivery into the marketplace of safe and effective drugs for human use. The Division of Metabolic and Endocrine Drug Products works in collaboration with the pharmaceutical industry and academia in the area of drugs for the prevention and treatment of diabetes mellitus and its microvascular and macrovascular complications.

Current Activities

There are now available in the United States multiple insulin products, animal-sourced and recombinant, the latter category including native sequence human insulins and insulin analogues with rapid-acting or long-acting pharmacokinetic characteristics. At this time, there are no additional approved hypoglycemic agents for the treatment of type 1 diabetes, though the FDA is committed to working with sponsors on any and all promising therapies.

For type 2 diabetes (DM2), in the last near-decade, FDA has approved drugs in multiple mechanistic classes. This broadening of the therapeutic armamentarium in DM2 has revolutionized the management of this disease that is epidemic in our society. There is continued interest in drugs that impact insulin responsiveness by primary transcriptional activation, the so-called PPAR drugs, and FDA is committed to prudent developmental strategies for new drugs in this class and others. While many new drugs show promise in effecting improvements on glycemic control, the challenge in development and, with luck, post-approval, is establishing long-term benefits outweighing risks of monotherapeutic and combination therapeutic medical regimens, particularly in the cardiovascular system.

With the recognition of diabetes as a "risk equivalent" of coronary artery disease, the assessment of the effects of potential anti-atherosclerosis therapies on the natural history of the disease in diabetes and metabolic syndrome is important from the standpoint of understanding the totality of expected risks and benefits of these new drugs and, therefore, in guiding prudent, long-term, preventive therapeutic intervention strategies. The division is engaged in ongoing dialogue with industry and thought leaders in this area as new data emerge, in hopes of establishing scientifically rigorous methods for determining the cardiovascular benefits, if any, of primary antidiabetic, anti-obesity, and other risk-factor-modifying drugs.

Health Care Financing Administration (HCFA)
See **Centers for Medicare & Medicaid Services (CMS)**

Health Resources and Services Administration (HRSA)

http://www.hrsa.gov

The Health Resources and Services Administration manages several health care systems programs that include diabetes identification, education, prevention, or treatment.

Bureau of Primary Health Care

HRSA supports the Consolidated Health Center Program, a health system providing primary and preventive care to the underserved, which includes diabetes identification, education, prevention, and treatment. The health center program is managed in HRSA's Bureau of Primary Health Care (BPHC).

HRSA's Bureau of Primary Health Care established two strategic goals: to move toward the elimination of health disparities and toward a 100 percent access system for all Americans. The Health Disparities Collaboratives (HDC), started in FY 1999, seeks to: (1) generate and document improved health outcomes for underserved populations; (2) transform clinical practice through new evidence based models of care; (3) develop infrastructure, expertise, and multi-disciplinary leadership to improve health status; and (4) build strategic partnerships.

The HDC program originally focused on diabetes mellitus—to delay or decrease disease complications—by implementing an evidence- and population-based model of care, which relies on knowing which patients have the illness and helps them participate in their own care. It has six basic elements: support of patient self-management, clinical decisions support, delivery system redesign, a clinical information system, organization of health care, and strong partnerships with local government and community organizations. Additional clinical areas of focus have been added to the HDCs, including cardiovascular disease, asthma, depression, cancer, and prevention.

Current Activities

- 397 health centers participated or are in the initial learning year of the Health Disparities Collaboratives with a focus on diabetes.
- After completing the year-long collaborative, health centers continue to receive support—to promote the model of care throughout their organizations, bring change to clinics and measure its impact on the health of underserved patients.
- Orientation and training videos and brochures describe the program. A distance learning tool was created to assist with staff turnover at participating health centers. Health centers have integrated these tools in ongoing staff orientation programs, increasing sustained organizational changes.
- A software program was developed to meet the need for a comprehensive prevention and multiple disease clinical information system.
- The HDCs have brought positive national and international visibility to Health Centers and the work to improve health care outcomes in medically underserved and vulnerable populations.
- Depression screening is included in care of diabetes patients.
- Partnerships with other Federal agencies, State diabetes control programs, and private-sector organizations grow stronger.

Outcomes (through July 2003):

- Health centers continue to report on the shared key goal that 90 percent of patients with diabetes will receive two HbA1c tests annually, at least 3 months apart. Starting in 2000, a shared health outcome measure was added to all the diabetes collaboratives requiring them to report on control

of glucose levels (average HbA1c), and a self-management support measure. Additional measures focus on prevention of cardiac as well as microvascular complications, the latter including eye, kidney, and lower extremity disease.

- There are over 140,000 patient records in health center chronic disease registries that enable centers to track and better manage the delivery of health care. Of the patients in registries, 102,260 persons have diabetes and are tracked for diabetes care.

- The average HbA1c has decreased from 9.2 to 8.2 for nearly 24,000 patients in the Diabetes 1 Collaborative.

- The average HbA1c has decreased from 8.77 to 8.06 for more than 32,500 patients in the Diabetes 2 Collaborative.

- The average HbA1c has decreased from 8.63 to 8.03 for more than 8,500 patients in the Diabetes 3 Collaborative.

- The average HbA1c has decreased from 8.13 to 8.05 for more than 5,000 patients in the Diabetes 4 Collaborative.

- The aggregate for all 102,000 patients in diabetes registries shows the average percentage of patients with two HbA1c tests in 12 months increased from 24 percent to 37 percent in all the Diabetes Collaboratives as they disseminated the care model throughout the organization and the registry size grew to over 102,000. Thirty-nine percent or 39,780 patients have documented collaboratively set self-management goals.

Strategic Partnerships and Infrastructure Development:

- Nine cluster directors and 10 information systems specialists are employed by the five lead Primary Care Associations.

- Thirty State-based staff provide additional support to the centers.

- Primary Care-Public Health partnerships are highlighted as a programmatic success. The partnership with the Centers for Disease Control and Prevention (CDC) Division of Diabetes Translation continues to be strengthened.

  - 1999: 15 initial partnerships between State health department Diabetes Control Programs (DCP) and health centers working on the diabetes collaborative.

  - 2002: additional 15 partnerships formed between State health departments Diabetes Control Programs.

  - 2003: 48 partnerships between State health department Diabetes Prevention and Control Programs (DPCPs) and Health Centers working on collaboratives.

Since 2002, the Agency for Health Research and Quality has assisted with program evaluation strategy.

DHHS Diabetes Detection Initiative (DDI)

On behalf of HRSA, BPHC/HRSA is a major participant in the Secretary's Diabetes Detection Initiative. The DDI is a U.S. Department of Health and Human Services (DHHS) interagency activity to identify Americans with undiagnosed diabetes and to facilitate their participation in management programs that reduce diabetes complications. The Initiative centers around a self-assessment tool by which individuals in targeted communities will assess if they are at high-risk for having diabetes. The tool will encourage high-risk individuals to seek follow-up and treatment, if needed, with their primary care provider, a HRSA-supported health center, an Indian Health Service facility or Tribal clinic, or another safety net provider in their community. Starting in

November 2003, the DDI will be piloted in one State in each of the 10 DHHS regions across the Nation. Each State will plan a number of community events to market this program.

BPHC/HRSA has participated in the full range of activities related to the development and implementation of the DDI, including participation on the steering, operations, implementation, evaluation, and local planning committees. In particular, BPHC played a critical role in partnering with HRSA-supported State Primary Care Associations to locate and enlist participation of the HRSA-supported health centers and other safety-net providers within the targeted high-risk communities. As of November 2003, 16 HRSA-supported health center grantees (approximately 29 health center sites) and 14 other sites (Indian Health Service clinics, the Choctaw Nation Health Center with 4 satellite sites, hospitals, and federally qualified health centers) were confirmed implementation sites for the pilot.

Maternal and Child Health Bureau

The Maternal and Child Health Bureau (MCHB) administers maternal and child health (MCH) Block Grants to States to support programs that promote the health of all the Nation's mothers and children and ensure statewide systems of health care for the MCH population. Diabetes screening, education, prevention, and treatment programs may be supported through these grants.

Additional Title V activities, such as MCH research, training, genetic services, and MCH improvement projects, are supported under Special Projects of Regional and National Significance (SPRANS). While these activities may not specifically target Diabetes Mellitus, core elements of community systems of care serving children with special health care needs are addressed by the Program for Children with Special Health Care Needs. The Healthy Start Initiative to significantly reduce infant mortality in targeted communities also includes services addressing diabetes in mothers and children. In addition, MCHB promotes diabetes detection and care through school-based and school-linked health programs. Finally, the MCH Training Program provides training grants to graduate programs and professional schools to support teaching, research, and service activities that focus on women and children. Its Leadership Education in Adolescent Health (LEAH), public health nutrition, and pediatric nutrition grantee programs include diabetes education, and the Indiana LEAH is nationally recognized for their work in diabetes.

Special Programs Bureau

HRSA's Special Programs Bureau has been working with the Organ Procurement and Transplantation Network, the national system for matching donated organs with patients on the transplantation waiting list, to facilitate the allocation of pancreatic organs for use in pancreatic islet cell transplants in treating patients with type 1 diabetes mellitus. Approximately 30 investigational new drug (IND) applications are in effect for the use of islet cell transplants to treat type 1 diabetes mellitus.

HIV AIDS Bureau

Derangements of glucose metabolism, including both glucose intolerance and frank diabetes, have been associated with the use of highly active antiretroviral therapy to treat HIV infection. As part of comprehensive primary care, the Ryan White CARE Act-funded clinical programs provide monitoring, treatment, patient education, and nutritional counseling for this complication of HIV treatment. The AIDS Education and Training Centers provide education and training to clinicians regarding this recently described complication and rapidly disseminate information on new treatment strategies as they evolve.

Office for the Advancement of Telehealth

The Office for the Advancement of Telehealth has 39 active grantees that use telehealth technologies to provide a range of services to improve the management of diabetic patients. The Office has funded the Marshfield Medical Foundation to work with the Office for the Advancement of Telehealth's other grantees to create technical assistance materials for programs that wish to employ telehealth technologies in the management of diabetes.

Bureau of Health Professions

• *Division of Medicine and Dentistry*

Podogeriatric Cooperative Agreements: Podogeriatric Cooperative Agreements were signed with Griffin Hospital in Connecticut, University of Texas at San Antonio, Memorial Hospital of Rhode Island, and Ohio State University. In FY 2003, these programs received funding to develop an interdisciplinary podogeriatric curriculum and train primary care and podiatric residents in that curriculum. There was a focus on the medically underserved geriatric population with chronic conditions, such as diabetes, that limit their mobility and self-care abilities. These projects were initiated in FY 2001.

Family Medicine Residency Training Grants: University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School: This project, initiated in FY 2001, provided for the development of a Problem Based Learning (PBL) curriculum for use in family practice residency education based on 15 health priority areas of Healthy People 2010, one of which is diabetes.

Brody School of Medicine at East Carolina University: Diabetes-related objective: increase the knowledge base, skills, and confidence of family practice residents in caring for high-risk patients by using the strategies of care management and group visits to improve clinical outcomes. At the end of the curriculum, it is anticipated that the residents will understand effective strategies for managing chronic disease and high-risk conditions using care management and group visits. The chronic diseases and high-risk factors of focus in the curriculum include diabetes, obesity, and poor nutrition. This project was initiated in FY 2002.

Riverside County Regional Medical Center: Riverside County Regional Medical Center Family Practice Residency Program will develop three innovative, interdisciplinary curriculum initiatives that will better prepare residents for diverse and vulnerable patient populations. One of these initiatives was to develop and implement an interdisciplinary diabetes curriculum focused on uninsured Hispanic population. This project was initiated in FY 2003.

Physician Assistant Training Grant to the University of Kentucky PA Program: Diabetes-related objective: revise the Physician Assistant (PA) training program in order to fully integrate education in prevention of specific chronic medical conditions and to more effectively educate practicing providers in preventive medicine through an annual symposium in preventive medicine. Chronic medical conditions include obesity, diabetes, and cardiovascular disease. This project was initiated in FY 2003.

Family Medicine Academic Administrative Units Grant to the University of Southern California, Department of Family Medicine: This proposal sought to expand the research infrastructure and capabilities of the Department of Family Medicine in the Keck School of Medicine at the University of Southern California (USC-DFM) by forming a Practice-Based Research Network (PBRN) in inner-city Los Angeles and the surrounding underserved areas with at least 20 primary care sites. The PBRN will support research on issues ranging from epidemiological studies of cervical cancer and diabetes among Los Angeles' most vulnerable populations to studies of the most effective models for delivering care to these at-risk populations. The project was initiated in FY 2002.

Family Medicine Pre-doctoral Education Grant to Brown University School of Medicine, Department of Family Medicine: This proposal sought to develop an innovative, modular family medicine curriculum focusing on health disparities for the leading causes of mortality and morbidity and cross-cultural medicine. Using an interdisciplinary project team of family physicians, a pediatrician, educational specialists, a medical anthropologist and clinical epidemiologists, they are developing, implementing, refining, evaluating, and disseminating three modules on health disparities in cardiovascular disease, cancer, and diabetes mellitus. This project was initiated in FY 2001.

Faculty Development in Internal Medicine Grant to Dartmouth Medical School: This grant outlined a comprehensive community-based Faculty Development Program designed to enhance core teaching skills in clinical care among predominantly new community internal medicine preceptors who practice in rural and underserved areas. This planned approach included four elements, one of which was to develop a core clinical teaching skills focus on several different chronic diseases, including diabetes. This project was initiated in FY 2002.

• *Division of Nursing*

Nurse Education, Practice and Retention: Brazosport Memorial Hospital has a focus on enhancing diabetes care. They intend to coordinate and provide diabetes education with all clinical partners, develop a method to identify new onset diabetics, and obtain outcome measures of effectiveness of self-care. The project period is 9/1/03–6/30/06.

Advanced Education Nursing: The University of South Alabama, College of Nursing prepares Advanced Gerontological/Diabetes Clinical Managers to provide health care for underserved and rural older adults in multiple primary care settings (nursing home, ambulatory care, acute care hospital, sub-acute/rehabilitation, and long-term care settings). The project period is 7/1/2001–6/30/2004.

• *National Health Service Corps*

Workforce Linkage Pilot Project: The majority of this pilot was carried out in FY 2003 among the National Health Service Corps (NHSC) Ready Responders (commissioned officers assigned to underserved areas and who also receive special training to respond to regional or national medical emergencies). Each Ready Responder was supplied with Personal Digital Assistants (PDAs). They use the PDAs to record health outcome data from those patients with any of the following conditions: diabetes, hypertension, asthma, obesity, breast cancer, cervical cancer, and prostate cancer. At least once per month, the clinicians "sync" their PDAs with a NHSC accessible server over the Internet (this is done in compliance with HIPAA standards). The patient outcome data is then analyzed. Ready Responders are supplied with evidence-based best practices and feedback about their patients during subsequent "sync" processes.

• *Division of State Community and Public Health*

Quentin N. Burdick Rural Program for Rural Interdisciplinary Training: Quentin N. Burdick project grantees provide education and training of health professions students in rural underserved communities and improve access to health care in rural areas. Projects supported by this grant offer interdisciplinary training, new and innovative teaching methods for healthcare professionals providing services in a rural areas, research concerning health care issues in rural areas, and increased amount of recruitment and retention of health care practitioners in rural areas.

The University of Nebraska Medical Center, School of Allied Health Professions, has a program named "Team Up for Life in Rural Tribal Communities." The primary purpose of this training grant is to contribute to the health of rural Native American communities by training caregivers and diabetic Tribal members in life-long diabetes self-care management. The training is interdisciplinary and is directed to health care professions students at an

academic health science center, to para-professional diabetes education assistants at two Tribal colleges, and to Tribal members with diabetes through Tribal diabetes centers. This project was funded in FY 2002, and it will be supported until FY 2005.

The Allied Health Project Grants (AHPG): Allied health project grantees provide training to allied health professional students and allied health professionals to become proficient in providing quality health care for the public. One of topics under the health promotion and disease prevention is type 1 and type 2 diabetes mellitus. The AHPG implemented the following three projects concerning type 1 and type 2 diabetes mellitus:

1. Southeast Alaska Regional Health Consortium in Alaska is implementing the Community Wellness Advocate (CWA) training program to train students, especially minority and disadvantaged enrollees, to provide health promotion and disease prevention services in underserved areas. One of the topics covered through this program is type 1 and type 2 diabetes mellitus. In FY 2002, the project produced 14 graduates and program completers. One hundred percent of these graduates and program completers are minority and disadvantaged students from the rural area in Alaska.

2. Ohio University in Ohio is implementing the Multidisciplinary Intervention Program for Diabetic Elderly Population in Appalachia. The purpose of the project is to meet the multiple needs of many elderly persons who have diabetes and live in poor rural communities. In FY 2003, the project produced 18 graduates and program completers.

3. College of Menominee Nation in Wisconsin is implementing the Allied Health Services Focus: Elderly Native American project. The project trains allied health and social service personnel in interdisciplinary training that emphasizes geriatric assessment and rehabilitation on the Menominee Reservation. One of the topics covered through this program is type 1 and type 2 diabetes mellitus. In FY 2003, the project produced 7 graduates and enrolled 81 students. One hundred percent of these graduates and enrollees are minority and disadvantaged students from the Menominee Reservation.

All of the above projects were funded in FY 2001 and they will be supported until FY 2003.

Geriatric Education Centers Program: Geriatric Education Centers (GECs), collaborative arrangements involving several health professions schools and health care facilities, facilitate the interdisciplinary training of health professional faculty, students, and practitioners in the diagnosis, treatment, prevention of disease, disability, and other health problems of the elderly. Projects supported by these grants must offer interdisciplinary training involving four or more health professions, one of which must be allopathic physicians, osteopathic medicine.

In FY 2003, the Geriatric Education Centers Program has 46 active GEC grants. Each grant is awarded for up to 5 years. Activities focusing primarily on diabetes include:

1. The Arkansas Geriatric Education Center at the University of Arkansas for Medical Sciences developed a video entitled, "Diabetes Management in Older Adults." This video addresses the health issues related to diabetes and recommends strategies to slow down the onset and progression of the disease. Speakers review population characteristics common in patients with diabetes and discuss the importance of early screening exams. Strategies are presented to help diabetic patients modify their lifestyles and improve their quality of life by integrating a nutritional diet and exercise regimen. Patients and health care providers learn first-hand techniques to manage food portions while preserving the nutritional value of meals.

2. The purpose of a project at the Stanford GEC at Stanford University is to develop, disseminate, and train faculty, providers and future providers, and caregivers at all levels in multiple health care disciplines to recognize and manage dementia and depressions associated with diabetes among elders from a number of ethnic and culturally diverse populations.

3. The Iowa GEC at the University of Iowa has developed PowerPoint slides, hour-long video recordings, and modules on Diabetes Management in the Elderly from its 2001 Geriatric Grand Rounds Series.

4. The Geriatric Education Center of Michigan at Michigan State University developed a one-hour video lecture on diabetes as part of its Geriatric Grand Rounds for Rural Health Providers.

5. The South, West & Panhandle Consortium GEC of Texas (SWAP–GEC) at the University of Texas Health Science Center at San Antonio has produced, demonstrated, and replicated a training program for vision station staff to screen for diabetes, counsel clients on disease prevention behaviors, and detect those behaviors.

6. The Northwest GEC at the University of Washington developed a self-study module entitled, "Health Promotion for Older Adults: Diabetes Mellitus." The module presents information on type 2 diabetes explaining the physiological mechanisms as well as emphasizing various approaches to managing the disease. It includes an expanded section on challenges faced by community providers, case studies, self-study questions, resources, and references. The module is available for free download.

Area Health Education Center (AHEC) Program

Arkansas AHEC held a 2-day program entitled "From Start to Finish" in March to prepare health professionals to sit for the Certified Diabetes Educator Exam. The review was hosted on the University of Arkansas for Medical Sciences campus. Sixteen Rural Hospital Program sites were also participating through the interactive television network. Over 235 participants took part, including 80 nurses and 33 dieticians. Thirteen hours of CEU credit were offered for nurses, pharmacists, and dieticians. The workshop was arranged to provide a broad discussion of the disease while focusing on specific areas recognized in the exam. The program included physiology and pathophysiology; acute complications, chronic complications, management in pregnancy; management in pediatrics; medical nutritional therapy; exercise and weight management; management in geriatrics; reimbursement; American Diabetes Associantion (ADA) recognition in Arkansas; and psychosocial concerns.

South Central Texas AHEC center, working with 12 Texas counties centered on San Antonio/Bexar County has provided various diabetes-related activities as requested by the communities in the area. Obesity and diabetes are significant problems in South Texas, especially among the Hispanic population. (1) In FY 2001–02, they established a "Diabetes Curriculum" at their web site. The purpose of the Diabetes Curriculum was to suggest ways in which area schools might integrate diabetes-related information into their normal coursework. They expect to maintain and update this information at the web site as long as it remains useful to their communities. (2) They have provided videoconferencing equipment and facilitated health-related programming available to remote sites in Atascosa, Gillespie, and Guadalupe Counties. Typically, these programs provide continuing education for health care providers. A number of programs have dealt with the prevention and management of diabetes. (3) For the past few summers, HCOP (Health Career Opportunity Program) activities have included a one-week Summer Biomedical Camp for high school seniors (30 or so seniors per year). A stop at the Diabetes Institute in San Antonio is an important part of the Camp. Other HCOP activities have included diabetes-related health fairs and research papers. (4) New in FY

2003–04, they are funding a project to provide ADA-certified diabetes programs as continuing education to over 500 health care providers annually in Comal County.

Georgia AHEC's Foothills Center, serving 31 counties in Northeast Georgia, has co-sponsored for the past 2 years the Athens Diabetes Wellness, a program of the American Diabetes Association. In March of 2002, they had 162 participants and in March of 2003, they had 199 participants. This program provides a full day of diabetes education for all people with type 1 and type 2 diabetes plus family and friends. They plan to continue their participation in the program for 2004 in Clarke County, the center of the service area. On October 4th–November 22, 2003, they co-sponsored along with Tri-County Health Systems Community Health Center the Warren, Greene, Taliaferro, Glascock County "Fit-For-Life Challenge." These four counties, located in rural Northeast Georgia, are all Medically Underserved Areas. This program provided educational classes on Diabetes, Cancer Prevention and Intervention, Weight Loss and Exercise, Nutrition, and High Blood Pressure. The Southwest Georgia AHEC Center reports that they are doing 28 peer to peer (MD) 2- hour night conferences on standards of care for diabetics. They are giving a toolkit to each MD who attends and are offering these programs throughout a 38-county region. They are only doing rural areas (no metro areas). Then each MDs provides academic detailing to his or her office to work with staff on reminders, jog sheets, and so forth, to help institute change within the office. It is also to help MDs follow through with complying with the standards. They give another toolkit to the nurse in the office. The academic detailing is done by a certified diabetes educator (CDE) to ensure quality of information given to staff.

AHEC/HETC Center for southern New Mexico (SoAHEC) reports two different diabetes projects going on across five of the six border counties. One is called LA VIDA (Lifestyles and Values Impacting Diabetes Awareness) and is funded by the CDC. They are a contractor in this collaborative through a community health center, Hidalgo Medical Services, Inc., and are primarily responsible for the establishment of diabetes resources centers in the three most southwestern counties of New Mexico and the provision of training and continuing education opportunities for LA VIDA Coalition staff. They are in the third fiscal year of this project and the resource centers have all been set up, stocked with culturally appropriate bilingual materials, and computer stations (several per site), and the community health workers (Promotoras) who run the resource centers have received a series of ongoing trainings ranging from accessing diabetes health information over the Internet to customer service. They are currently coordinating a series of 8 to 10 more trainings for LA VIDA coalition staff over the next 9 months. The other project began this past June 2003, and is a two-county diabetes prevention initiative (3-year) funded by a regional foundation, the Paso de Norte Health Foundation. This initiative is focusing the first year on bilingual training-of-trainers around diabetes, nutrition, and physical activity utilizing various different curricula (both local and national). The second year they intend to go into the schools and develop a group of student peer mentors utilizing our already established HCOP students. The third year, they hope to affect policy and have the vending machines either removed from the school premises, or at least offering healthier alternatives. As part of Year One activities for the latter project, they will be hosting a "Diabetes Summit" in May 2004 where they intend to bring together as many programs working in the diabetes arena from both counties to work on a strategic plan that reduces duplication of services and strengthens collaboration among providers. They will be contracting with two external facilitators and using the Future Search model for this Diabetes Summit.

Southcentral PA Area AHEC has provided several programs on diabetes: March 5, 2003, a satellite downlink–Diabetes Issues in the Home and School; and a "Living Well with Diabetes" program in conjunction with The Milton S. Hershey Medical Center, Deptartment of Family and Community Medicine, Hershey, Pennsylvania. This program is an educa-

tional seminar that includes information concerning healthy lifestyles useful to the diabetic, relatives of diabetics, and the general population with a desire for a healthy lifestyle that includes delaying or avoiding the development of diabetes. A curriculum booklet is provided to a lay coordinator who has been prepared for the role by a certified diabetes educator. The coordinator leads the discussion on the lifestyle issues and general health living. During the 2002–2003 time period in question they have provided 36 programs with over 500 attendees. They also co-sponsor a program "Annual Diabetes Update" with the Cambria-Somerset Council for Education of Health Care Professionals, Inc., on the campus of the University of Pittsburgh, Johnstown Campus. This program, which is a continuing education program for physicians, nurses, and allied health professionals, was held in April 2003, with 125 attendees. They plan to hold the above programs for the 2003–2004 fiscal year.

Gulfcoast South AHEC Center in Sarasota, Florida, provided a continued education program for health professionals entitled "Diabetes Update" and heavily promoted in their service area an educational CD-ROM entitled "Diabetes Mellitus Type Two: Clinical Practice Guidelines." Fourteen health professionals benefited from this self-study and 20 additional copies were distributed, and an interdisciplinary group of four students completed 768 hours of community service in Manatee County focused on the impact of diabetes on middle and high school students predominately from African-American and Hispanic backgrounds.

South Carolina (SC) AHEC has had a Diabetes Initiative the last 5 years. They increase awareness, offer "Best Practices" for care, and assess the State's incidence of type 1 and type 2 diabetes through the annual Diabetes Symposium with 200–250 participants. They offer day-long continuing education programs on diabetes. This past year there were numerous downlinks for programs on this topic as well. These projects have been operating at about the same funding level for the last 3 to 4 years. Many of the medical students who go out into the community have used diabetes as the focus for their community projects for the last 4 years. The Medical University of South Carolina (MUSC) Dean's students are required to address diabetes in their Community-Oriented Primary Care (COPC) projects. Upstate (SC) AHEC offered 7 diabetes-related continuing education programs to 156 health care professionals in their region. Staff work with local Diabetes Coalitions to address community issues and by supporting the Diabetes Fall Fair, an annual event held as a kick-off to Diabetes Awareness Month in November. The Fair includes pharmaceutical representatives, diabetes product representatives, and speakers on foot care, importance of exercise, and food choices, as well as the spiritual and psychological implications associated with diabetes. More than 200 health care professionals, patients, and caregivers attended this Fair in October 2002. Upstate AHEC's diabetes-related activities have remained fairly level for the last several years and, at present, they anticipate continuing efforts at approximately the same level in the near future. However, they expect to remain flexible enough to rapidly deploy resources to address emergent needs.

Illinois AHEC Program (Illinois Health Education Consortium/AHEC) Bridges to Health project reports that 955 Limited English Proficient (LEP) Latinos with diabetes have received health education from community health workers, 133 health care professionals and students have attended cultural competency workshops and/or Spanish language programs, and 5 health promoters have been trained to provide diabetes education for LEP diabetic Latinos at 5 Chicago clinics within the Cook County Bureau of Health Services system. Data indicate that health education and individual counseling provided by health promoters to LEP Latinos with diabetes has significantly reduced patient "no-show" rate within the patient group health promoters see, helped reduce the hemoglobin A1c for patients who

have received three or more visits, and increased self-monitoring of blood glucose levels. Bridges to Health has improved health care services and utilization for LEP Latino diabetic patients within the CCH Network Diabetes Program (NDP) service area. In Year 2, this initiative expanded to include diabetes prevention education and cultural competency training for providers and students in the Chicago metropolitan area. The NDP of the Cook County Bureau (the Bureau) of Health Services provides services to patients with diabetes, with priority given to those with poor metabolic control and complications. The program is a multidisciplinary team approach to the management of diabetes with a strong educational emphasis for both clients and health care professionals. The Bureau cares for approximately 30,000 diabetic patients, 40 percent of whom are LEP Latinos (12,000 patients). The NDP Team includes physicians, nurses, psychologists, registered dieticians, a pharmacist, and health promoters.

Southwest Louisiana Area Health Education Center (SWLAHEC) received a contract award from the Louisiana Office of Public Health Diabetes Control Program to implement a diabetes educational training program. The *Defeat Diabetes...through Education Program* strives to enhance diabetes training with senior-level undergraduate nursing, health education, and health promotion students from several universities in Louisiana. The Defeat Diabetes project provides development and facilitation of education and training partners, enhancement of curriculum utilized by health care professionals and educators, delivery of low literacy and culturally diverse patient education materials, and delivery of patient incentives for improved self-management of diabetes. Activities of the program included screenings, foot exams, diabetes education with diabetic patients, community assessment for diabetes resources and statistics, and the development of teaching tools. Graduate school nurse practitioner students worked to develop teaching materials to respond to the high proportion of low literacy diabetic patients in Louisiana. To date the program has enhanced the diabetes training of 364 health profession students and provided 2,607 patients with diabetes screening and education.

Southside AHEC (Virginia) region is composed of 13 underserved rural counties with large and financially deprived populations, plus three small cities where there is an emerging type 2 diabetes trend reaching down into the early teens. Despite funds precluding any dramatic inroads being made to address this progressive emerging national health care crisis, the local health care facilities do conduct diabetes clinics. In addition, the Southside AHEC in collaboration with the Piedmont Health District has a loosely knit group meeting periodically to try and develop a regional diabetes program in the Piedmont Health District. Lack of funding has precluded the program from progressing beyond review and assessment. The Southside AHEC in collaboration with the local Piedmont Health District, Southside Health District, and the Crater Health District (all within the Southside AHEC region) intends to apply for the upcoming Federal STEPS Diabetes, Obesity & Asthma proposal grant for FY 2005.

Eastern Arizona Area Health Education Center (EAHEC) has developed the Diabetes Prevention and Action Class (DPAC). It is a 25-hour curriculum designed to increase the likelihood that minority/disadvantaged students enroll in health career education programs upon graduation from high school. DPAC was delivered to 58 students in 4 freshman-year health classes at Globe High School during the 2002–2003 school year. The Arizona AHEC Program has developed a Diabetes Resource Nurse Education Program and Service Award Project. These are available to registered nurses who live in a community or area of need as identified by the regional AHECs. The registered nurse must have an interest in diabetes as well as reflect the needed individual community criteria that may apply, such as being bilingual in a border community. The Arizona AHEC Program financially supported 13 RNs for the completion of a

3-day intensive nationally accredited education program for Diabetes Educators, which was held July 22–24, 2003, in Phoenix, Arizona. This program prepared registered nurses to sit for the national Certified Diabetes Educators Exam. The participants of the July training are developing a statewide network to address their future educational needs around diabetes, as well as providing a preventive resource for alleviating professional isolation in working as the only Diabetes Resource Nurses in their communities. The Arizona AHEC Program is assisting them by providing updates and continuing education information about diabetes through the facilitation of an online diabetes education forum. This Program will be offered again in Spring 2004. Northern Arizona AHEC provides rotations for nursing and social work students at a BPHC diabetes Health Disparities Collaborative project at North Country Community Health Center in Flagstaff. It supports a wellness program at Hopi Jr./Sr. High School that provides diabetes prevention on the Hopi Reservation. It also supports a high school program at the Hopi Health Care Center called Indigenous Pride Youth Health Workers, in which high school students do community health projects on diabetes.

The Southeastern Colorado AHEC (SECAHEC) serves as a regional coordinating agency (RCA) for the Colorado Trust Healthy People 2010 Initiative. SECAHEC coordinates eight Colorado Trust grantees in the region, all of which are focused on diabetes prevention through physical activity and nutrition changes. SECAHEC was responsible for identifying this problem to the Colorado Trust resulting in financial support over a 3-year period from the Colorado Trust. In 2003, SECAHEC hosted its 2nd Annual "For the Health of It" conference where the primary focus was primary and secondary prevention of diabetes, physical activity, and nutrition. Approximately 200 physicians, nurses, dieticians, coaches, teachers, and the general public attended. The 3rd annual conference is scheduled for March 5 and 6, 2004. It too will have a strong emphasis on diabetes prevention, obesity prevention, and physical activity. SECAHEC has participated and supported the Pueblo Community Diabetes Project that brings business leaders, health care organizations and professionals, health insurance providers, and the general community together to address diabetes. Outcomes to date include collaborative educational workshops, outreach to local schools, a community-wide physical activity program called “Pueblo on the Move,” the development of a community web site, and participation in corporate educational breakfasts. SECAHEC staff members have provided technical and administrative support, assisted in grant development, served on work groups, and chaired the Board of Directors during the past year. SECAHEC partnered with the Colorado Prevention Center to launch a comprehensive medical prevention and education program for 25 local physicians who are participating in the “medical detailing” over the next year. The effort is a secondary prevention intervention for cardiovascular disease and diabetes. A second prong of the program will train 25 nurses and pharmacists from the southeast corner of the region about the latest practice guidelines. Other diabetes-related activities include participation in the local school district
consolidated school health advisory committee where the major focus for the past year-and-a-half has been obesity and physical activity in children. A variety of educational trainings specifically related to diabetes prevention and care have also been offered. For example, in October 2003, SECAHEC hosted a 2-day training for a course that provided a comprehensive overview of diabetes care, population health management strategies to increase a participant's competency about diabetes care, discussion of the latest in diabetes and prevention based on ADA standards of care, and strategies for collaborative practice and population health management.

Western Colorado AHEC sponsored a 1-day western slope Diabetes Extravaganza in September 2003 to address the increasing need for prevention and treatment-related diabetes education. There was a minimum of 300 individuals in attendance with nationally recognized speakers. There were approximately 20 RD and RN professionals in attendance representing small rural communities. This coming year Western Colorado AHEC has plans to (1) con-

duct a second day-long diabetes event for consumers and providers in another part of their 21-county region in partnership with the Mesa County Health Department and its Steps to a HealthierUS grant, and (2) conduct focus groups with consumers and providers within their Hispanic and increasing migrant and farm worker community to identify the most appropriate ways to deliver culturally appropriate education messages regarding diabetes prevention and treatment.

Maine and New Hampshire AHEC has been working with Northeast Healthcare Quality Foundation on a diabetes education project whereby records in clinics and private offices are extracted and a summary is prepared. The information is presented back to the practices in a "Lunch N' Learn" to the entire staff of the practice in an effort to improve the quality of care as reflected in real numbers from their own files. The role of the AHEC has been to identify practices that might be interested and provide logistical support to the educational presentations. They have recruited a hospital-based practice association into this effort because many members are also preceptors for students. Future plans are to expand the program to include the offices of their rural preceptors. At least one staff member is active on the ADEF Advisory Committee of a rural hospital. The Southern New Hampshire AHEC is an active partner with the New Hampshire Diabetes Education Program and has collaborated in offering the Diabetes Today conference providing continuing education to over 350 clinicians and diabetes educators. They have offered a number of diabetes trainings both in the evening and using a "Lunch and Learn" format. Some of the topics include Diabetes Medication Update; Diabetes Guidelines: Helping the Patient; Insulin Teaching; and Managing Diabetes in Your Practice: Caring for Diverse Communities. They have plans to continue education on diabetes in the coming year.

Ke Anueue (Hawaii) AHEC is providing Diabetes education through their "Ask-a-Doc" program, which is video teleconferenced through their rural communities in the State. It is a cooperative effort that involves their three AHEC offices and the community learning centers that have partnered with other rural agencies. They also have a partnership with the Diabetes Counseling and Education Center in Hilo. They provide screening and counseling services and conduct nutrition classes.

Ohio Statewide Area Health Education Centers (AHEC) program presented a statewide conference April 24, 2003: "Best Practices and Real Results Conference: Diabetes and Literacy." Over 100 nurses, dieticians, physicians, and health educators from a variety of practice settings attended the 1-day conference. The conference was co-sponsored by the Ohio Primary Care Association. Continuing education accreditation was through the Medical College of Ohio. The conference goal was to bring the latest clinical diabetes research and demonstrated diabetes management practices together with proven effective approaches for communicating with the most vulnerable populations for low literacy. Both of the AHEC-sponsored summer career camps for 9th graders use diabetes as the clinical topic since most childern know someone who has it. In addition, the Ohio AHEC provides a huge number of CME programs in rural areas including many 1-hour or grand rounds diabetes programs. In May 2003, they offered a 1-hour CME program for family physicians on "Guidelines for Diabetes Management." In September 2003, the AHEC sponsored a diabetes and hypertension screening event at a shopping mall where second-year medical students did the screenings as a Service Learning activity.

Missouri AHEC program shares with Kirksville College of Osteopathic Medicine (KCOM) the services of a Health Outreach Coordinator who provides community and professional education in 12 counties surrounding Kirksville on type 1and 2 diabetes. This registered nurse is a certified diabetes educator and since has offered Chronic Disease Self-Management training to communities throughout northeast Missouri, providing individual counseling and supports an outreach clinic allowing diabetes patients with complex needs to consult an endocrinologist. Regional AHEC centers in Missouri also offer period-

ic continuing education on diabetes. The Mid-Missouri AHEC in 2002 offered programs for health care providers on recent advances in type 1 and type 2 diabetes. In FY 2003, the East Central Missouri AHEC (affiliated with the Saint Louis University AHEC Project) provided a CME program for area professionals.

New York State AHEC System is a co-investigator in the IDEATel (Informatics for Diabetes Education and Telemedicine) project, a major joint research project of Columbia University School of Medicine and Upstate Medical University through a Federal contract with the Centers for Medicare & Medicaid Services (CMS) (formerly HCFA). The purpose of the project is to test whether the use of telemedicine and enhanced diabetes education delivered directly in the home to Medicare-eligible diabetics living in HPSAs (Health Professional Shortage Areas) will result in reduced morbidity and mortality and lower costs of care. The Institute for Urban Family Health serves as the New York Metropolitan Region Office for the New York State AHEC System. As a result, students placed at any Institute site have the opportunity to be exposed to the work of two important Federal initiatives addressing diabetes, including health promotion, nutrition and fitness interventions, and best practices in diabetes care. As a 330 Center, the Institute has participated in the HRSA Diabetes Collaborative and is in the process of replicating the collaborative goals through the use of an electronic medical record system at 12 locations. As the grantee for the REACH program, the Institute works with a community coalition of 30 community and faith-based organizations to address racial and ethnic disparities in health outcomes related to diabetes and heart disease.

North Carolina Northwest AHEC at Wake Forest University School of Medicine offers a 1-day continuing education certificate program for pharmacists designed to provide a unique educational opportunity in the area of diabetes care, focusing on the interpretation of current national guidelines, including proper diet/exercise and drug therapy. This continuing education certificate program has been offered in both 2002 and 2003 and is co-sponsored with the North Carolina Greensboro AHEC. Once pharmacists are certified, they must renew their certificate each year. The number of participants ranges from 20–30. The North Carolina Northwest AHEC at Wake Forest University School of Medicine also provides a Diabetes Management Conference co-sponsored with the Diabetes Conference Center. This continuing education program has been offered in both 2002 and 2003. The number of participants ranged from 45–75. Other North Carolina Northwest AHEC programs in the time period October 1, 2002–September 30, 2003 include The Fifth Annual Diabetes Management Conference (Pharmacy); Statewide Diabetes Conference (Public Health); Diabetes Update for Nurses (Nursing); and Diabetes Awareness, Training and Action (DATA) Program (Public Health).

Milwaukee AHEC is working with the State of Wisconsin Division of Public Health's Diabetes Prevention and Control Program to expand diabetes prevention and control in Milwaukee and southeastern Wisconsin by (1) assessing community needs for diabetes interventions, (2) developing, enhancing and maintaining partnerships with community representatives of Milwaukee and southeastern Wisconsin's major ethnic groups (African-American, Hispanic/Latino, American Indian and Asian), and (3) assisting with cooperative agreements and strategic planning to enhance identification and elimination of disparities regarding diabetes. Milwaukee AHEC has hired a Diabetes Prevention and Control Community Specialist to work with the Division of Public Health to coordinate these efforts.

Indian Health Service (IHS)
http://www.ihs.gov

Overview of the IHS National Diabetes Program

The mission of the IHS National Diabetes Program (NDP) is to develop, document, and sustain a public health effort to prevent and control diabetes in American Indian and Alaska Native (AI/AN) people. The agency promotes collaborative strategies for the prevention of diabetes and its complications in the 12 IHS Administrative Service Areas (regions) through coordination of a network of 19 Model Diabetes Programs and 12 Area Diabetes Consultants. They in turn provide resource distribution, program monitoring and evaluation activities, and technical support to 36 Federal hospitals, 63 Federal health centers, 44 Federal health stations, 13 Tribal hospitals, 158 Tribal health centers, 76 Tribal health stations, 34 urban Indian health centers, and 170 Alaska village clinics at the local level in the delivery of comprehensive health care to over 1.5 million American Indians and Alaska Natives. The NDP also continued to develop and operate the Special Diabetes Program for Indians grant program with 318 grantees in 35 States.

The IHS National Diabetes Program provides:

- *Comprehensive diabetes surveillance* (including total and age-specific prevalence rates of diabetes and diabetic complications across Indian country) at the local, regional, and national levels through collaboration with Centers for Disease Control and Prevention (CDC) epidemiologists and use of contract epidemiologists and statisticians.

- *Research translation* through training and technical assistance provided via its extensive network.

- *Promotion of quality assurance/improvement activities* in clinical and community programs through updated Standards of Care for Diabetes, the annual Diabetes Care & Outcomes Audit, and the Integrated Diabetes Care and Education Recognition Program.

- *Technical support* to IHS/Tribal/Urban (I/T/U) sites nationwide through bulletins, updates, and comprehensive website information.

- *Resource information* on a full complement of training opportunities, including specialized training related to primary outpatient treatment models of diabetes management.

- Health care provider/consumer *education resources and "best practices" information* to IHS, Tribal, and urban health programs.

- Development, field-testing, and distribution of *Native American-specific diabetes education* printed and audiovisual materials to IHS and Tribal health centers. In FY 2003, over 5700 diabetes education materials were sent to over 300 I/T/U programs nationwide.

In addition, the NDP serves as the key IHS contact and source of information for outside organizations and agencies working on diabetes and disparities related to diabetes.

Diabetes was one of the most frequently identified health problems in IHS Area Tribal consultation workshops for FY 2003 planning. Type 2 diabetes disproportionately affects AI/AN adults who are over three times more likely to have diabetes than the general U.S. population. A recent alarming trend is the increase in prevalence of type 2 diabetes in young AI/AN. Over an 11-year period, from 1990–2001, the prevalence of diabetes rose 68 percent in AI/AN adolescents and young adults. Recent data show that diabetes mortality is 4.3 times higher in the AI/AN population than in the U.S. population. There was a 24 percent increase in the American Indian age-adjusted diabetes-related death rate from 1991–1993 to 2000. There is clear evidence that for Indian people the health disparity related to diabetes is increasing.

Current Activities

Special Diabetes Program for Indians: 1997 Balanced Budget Act, 2001 Consolidated Appropriations Act, and P.L. 107-360. The IHS National Diabetes Program administered Year 6 of the *Special Diabetes Program for Indians* (SDPI) the 1997 Balanced Budget Act and the Consolidated Appropriations Act of 2001. One hundred million dollars per year have been distributed from these funds through 286 non-competitive grants administered at 318 sites throughout Indian country. Over 96 percent of these funds are distributed through grants to Tribes, IHS facilities, and urban Indian centers while 3.8 percent are withheld for administration of the grant program. Tribal entities are the direct recipients of 81 percent of the grants, while Federal and urban programs comprise the remainder. The IHS National Diabetes Program works closely with the Tribal Leaders Diabetes Committee (TLDC) to administer this program. The Request for Applications (RFA) developed by the IHS NDP this year once again included a Best Practices approach with 14 strategies identified (see below), researched and compiled for use by applicants. Sixty-seven percent of the grantees have indicated that they devote a significant portion of their funding to primary prevention of diabetes. The IHS NDP sponsored a national diabetes conference in collaboration with the TLDC in Denver, Colorado, in December 2002. The conference featured successful grant programs and results of the Diabetes Prevention Program study.

Congress stipulated that the SDPI have a strong evaluation component. To that end, the IHS NDP applied CDC's *Framework for Public Health Evaluation*, a mixed methods approach (both qualitative and quantitative methods), to the SDPI, and a preliminary analysis has been completed. A number of positive, significant short-term and intermediate term outcomes have been identified. In addition, the IHS NDP has improved the accuracy of baseline long-term measures (prevalence and mortality) and established a Diabetes Data Warehouse and "Data Mart" using RPMS (Resource and Patient Management System) data to measure accurately the long-term complications of diabetes. A Final Report to the Congress summarizing the findings from this evaluation has been prepared and is currently being printed. It will be distributed to Congress in early 2004.

The *Special Diabetes Program for Indians* grant program was reauthorized in December 2002, for 5 years (2004–2008).

IHS Used a Best Practices Approach to Sharing Lessons Learned From the Special Diabetes Program for Indians. In 2002, based upon Congressional direction, the IHS NDP developed a consensus-based Indian health "best practices" approach. This was accomplished by convening a Best Practices Workgroup, consisting of experts from IHS, the Tribes, urban Indian organizations, the IHS Model Diabetes Programs, and project coordinators from SDPI grant sites. The Workgroup developed 14 Best Practice Model approaches for successful diabetes prevention, treatment, and education practices in AI/AN communities based on findings from the latest diabetes scientific research, outcomes studies, and their own successful experiences. The Best Practice Models were used by applicants to identify strengths in diabetes resources and services in their communities, find gaps in diabetes services or programs, establish program priorities, find best practice models that could be applied within their own communities, and to begin a work plan to develop their own local best practice models.

To assess use of the consensus-based Best Practice Models for AI/AN Communities, IHS Area Chief Medical Officers and Area Diabetes Consultants completed assessments of Best Practice Model use with their review of each grant application. Data were then compiled by the NDP. In 2003, elements of the Nutrition and Physical Fitness Best Practice Model approach were used by 72 percent of grant programs, the Diabetes Screening Best Practice Model approach was used by 64 percent of grant programs, and the Basic Diabetes Care and Education Best Practice Model approach was used by 63 percent of SDPI grantees.

Clinical Standards of Care and the IHS Diabetes Care and Outcomes Audit. In 2003 the IHS National Diabetes Program updated the IHS Standards of Care for Diabetes (originally published in 1986) to reflect new science and best practices. The Annual IHS Diabetes Care and Outcomes Audit, a voluntary medical records review of 87 clinical care and public health practices and outcomes, is designed to measure and trend use of these standards and outcomes of diabetes care, including blood sugar and blood pressure control, screening for complications, and preventive health services.

The standards and audit summary results are distributed to providers IHS-wide through a network of regional Area Diabetes Consultants and local Diabetes Coordinators and are used as quality indicators at the local, regional, and national levels to identify specific problems and to determine policy and practice. In FY 2003 we reviewed over 30,000 medical records representing care to over 110,000 patients with diagnosed diabetes at 190 IHS/Tribal health facilities in the 12 IHS Areas.

This diabetes care surveillance system has been instrumental in the improvement of diabetes care practices in many Indian health settings. For example, in a special program in Alaska and in northern Minnesota from 1989–2002, lower extremity amputation rates were reduced by 60 percent in people with diabetes who received complete foot screening and protective footwear. This same system enabled IHS to measure significant improvements in blood sugar control nationwide and in blood pressure control in Montana after an intensive intervention.

Screening for Diabetes, Pre-diabetes, and Metabolic Syndrome. Diabetes has reached epidemic proportions in AI/AN communities. To address this epidemic and to proactively reduce the burden of this disease, many Tribal communities have planned or established community-based diabetes screening programs. With the publication of the DPP clinical trial results and the dissemination of these results to our communities, hope has been given to AI/AN communities that the epidemic of diabetes can be stopped.

To implement the results of these studies to prevent diabetes, communities must first find those individuals who are at highest risk. This is accomplished through widespread screening efforts. In 2002, 86 percent of the Special Diabetes Program for Indians grant programs reported that general screening for diabetes and pre-diabetes had increased and was a major emphasis in their diabetes programs, as compared with 14 percent prior to SDPI. Screening for the risks of diabetes in adults identifies people at an earlier stage and allows for intervention. In 2002, the diabetes grant programs reported that they screened adults (ages 26–54 years) for the following major risk factors:

- 78% screened for pre-diabetes.
- 91% screened for overweight and obesity.
- 39% screened for acanthosis nigricans.
- 18% screened for offspring of a diabetic pregnancy.

Elders have higher rates of diabetes. In 2002, the diabetes grant programs reported that they screened elders (age 55 years and older) for the following major risk factors:

- 76% screened for pre-diabetes.
- 88% screened for overweight and obesity.

In order to improve the development and implementation of community-based diabetes screening programs, IHS NDP is reviewing a Diabetes Screening Toolkit prepared by the Western Tribal Diabetes Project and Portland Area Indian Health Service. Plans are to disseminate the toolkit widely as it provides information on readiness assessment, preparation, implementation, and follow-up. Other resources will be included in the NDP revision to support the scientific basis for screening efforts. Technical assistance and training regarding screening program development and implementation will be provided at seven Regional Meetings being planned for SDPI grantees in the upcoming months.

A draft version of clinical guidelines for the care of individuals with pre-diabetes and metabolic syndrome has been developed and is being modified by the NDP and the IHS Area Diabetes Consultants. This will be a useful tool for improving the quality of care to individuals who will be identified in these screening efforts.

In addition, the NDP is an active partner in the Secretary's Diabetes Detection Initiative (DDI). The U.S. Department of Health and Human Services (DHHS), under the leadership of Secretary Tommy Thompson, has developed the "Diabetes Detection Initiative: Finding the Undiagnosed" to address this growing public health challenge of undiagnosed or unrecognized diabetes. Many DHHS agencies have significantly contributed to the planning, implementation, and evaluation of the DDI, including the Centers for Disease Control and Prevention, the Health Resources and Services Administration (HRSA), the Agency for Healthcare Research and Quality, the Indian Health Service, Centers for Medicare & Medicaid Services, the Food and Drug Administration, and the National Institutes of Health. The IHS NDP Director has served on the Steering Committee for this Initiative and NDP staff serve on the Evaluation Team and the Operations Team. Two AI communities have participated in the launch—Wind River of Wyoming and Choctaw Nation of Oklahoma. Tools developed in the Initiative such as the health care provider tool will be shared with the Indian health diabetes network. The purpose of this tool is to (1) help health care professionals see the steps in the screening/diagnosis process and (2) give them information on use of the finger-stick blood glucose test (capillary test) done in a health care setting as part of the algorithm for determining the need for further testing.

IHS Became a Deeming Entity for Diabetes Education Certification. In 2003 the IHS National Diabetes Program, with agency and Tribal leader support, established an Indian Health Diabetes Education Accreditation Program and received notification from the Centers for Medicare & Medicaid Services that the IHS NDP application to become a deeming entity had been approved (*Federal Register,* April 2002). This process allows Indian health diabetes education programs to become certified and thus seek Medicare reimbursement for diabetes education. Thus far 12 programs have applied for and have become certified (4 new programs in 2003), 2 sites have provisional accreditation, and 1 additional new application is under review.

Obesity Prevention. For 4 years the IHS National Diabetes Program has coordinated an obesity prevention initiative targeting Head Start children (0–5 years), families, Head Start staff, and AI communities. Four Tribal Head Start pilot sites, in collaboration with their respective community health partners, have developed obesity and diabetes prevention interventions in their local communities. Each Head Start site community action plan includes multifaceted program activities and milestones focusing on healthy eating, physical activity, healthy behavior, and community partnerships. The core component of the initiative is to develop and sustain local community partnerships in the implementation of each program's interventions.

The Initiative is presently involved in dissemination activities and sharing promising practices with other Head Start programs. In 2003 the Initiative expanded to include breastfeeding promotion for Early Head Start grantees. The first focus group was conducted and recommendations for future directions were finalized.

Medical Nutrition Therapy (MNT) and Diabetes Self-Management Training (DSMT) for Medicare Beneficiaries. IHS NDP is taking an active role in the rapid dissemination of information on the two new Medicare Part B Benefits: Medical Nutrition Therapy (MNT) and Diabetes Self-Management Training (DSMT) for Medicare Beneficiaries who have diabetes and/or kidney disease. We provide technical assistance and consultation to the I/T/U clinicians and medical records and patient billing office staff on putting systems into place for electronic billing, medical records documentation (i.e., MNT PCC+), tracking of claims and reimbursements, and imple-

menting systems to determine outcome and cost-effectiveness of these services. This provided another opportunity to promote and facilitate the implementation of the new third-party collections opportunities within the I/T/U system.

Joslin Vision Network Teleophthalmology Project. In FY 2002 Congress increased the IHS appropriation to address evaluating American Indians and Alaska Natives for diabetic retinopathy through a collaborative project with the Joslin Diabetes Center using the *Joslin Vision Network (JVN)*. The JVN is a telemedicine system that uses low-level illumination and no pupil dilation to remotely diagnose diabetic retinopathy. The acquired retinal image is sent electronically to a reading center using existing IHS networks, and an analysis of the level of diabetic retinopathy is returned to the remote site. The IHS has deployed imaging sites at the Phoenix Indian Medical Center (PIMC), Sells PHS Indian Hospital, Tuba City Indian Medical Center, Parker Indian Hospital, Hopi Health Care Center, and the Chief Andrew Isaac Health Center in Fairbanks, Alaska. Certified readers at the IHS/JVN National Reading Center in Phoenix evaluate the images acquired from these sites. Since entering its clinical phase, the program has evaluated more than 1,500 patients who had not currently met the prescribed level of care. Many of these required referral due to a dangerous level of diabetic retinopathy or other ocular pathology. Controlled study of this initial outcome indicates that this telemedicine system can markedly increase the annual diabetic retinopathy examination rate. The most mature deployment site increased its examination rate from 47 percent to more than 70 percent in less than 1 year. Ten to fifteen additional sites will be deployed during the next year at locations throughout Indian country. Primary challenges to future site development in remote locations include availability of clinical space and staffing. As of December 2003, 13 deployment sites are classified as active, 3 sites are inactive due to staffing difficulties, and 5 sites are scheduled for deployment in January 2004. Clinical effectiveness has been demonstrated in a 3 percent overall increase in eye exam rates at deployment sites from baseline measures established in 2002. In addition, a central office for all administrative, reading, and training activities was established at PIMC. New enhancements of the project include the development of an IHS/JVN Teleophthalmology website, a new software application that surveys the RPMS Patient Scheduling database to identify patients with diabetes who have an appointment for care but have not had an eye examination within the previous 400 days, and a portable IHS/JVN system for deployment at sites/areas with a diabetic population that is not practically served by a fixed IHS/JVN deployment.

In addition to the Joslin Vision Network, the IHS NDP is partnering with the Joslin Diabetes Center to develop a web-based system that is based on the case management model that tracks diabetes care and education called the Comprehensive Diabetes Management Program (CDMP). Its components include a Clinical Assessment Module, a Behavioral Assessment Module, and an Education/Reinforcement Module. Healthcare professionals on this workgroup comprise clinicians and educators who specialize in diabetes care and education and represent Joslin, IHS, the Department of Defense, and the Veterans Administraion. The CDMP will be integrated with the IHS electronic medical records system database. Beta testing of the Clinical Assessment Module and the Behavioral Assessment Module at Walter Reed Medical Center began in January 2003. The Nutrition Assessment Module is in development with planned completion by the end of calendar year 2003. The Phoenix Indian Medical Center (PIMC), IHS Information Technology Support Center, IHS/JVN, the IHS National Diabetes Program, and Joslin are collaborating to deploy CDMP at PIMC in January or early February 2004. PIMC is the pilot site. In 2004, following the pilot testing, there will be alpha testing of CDMP at an additional 3–5 sites in two IHS Areas, and then a beta testing of CDMP in an additional 3–5 sites in three IHS Areas.

NIDDK/IHS/TLDC/AIHEC Collaboration to Recruit AI/AN Students into Biomedical Science Research

and Diabetes Careers. In FY 2001, at the request of Tribal leaders serving on the Tribal Leaders Diabetes Committee (TLDC), the IHS and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) collaborated on a project to encourage young AI/AN students to consider careers in biomedical research and diabetes. This project also involves the CDC and the American Indian Higher Education Consortium (AIHEC), which represents the 34 Tribal colleges around the country. An RFA was released in spring FY 2002 on this interagency collaborative project designed to increase diabetes knowledge among American Indian/Alaska Native students through a multicultural diabetes-based science education curriculum for grades K–8 and high schools. By engaging American Indian/Alaska Native youth in the biomedical sciences at an early age in a culturally sensitive manner, a goal of increasing the number of American Indian/Alaska Native health science professionals can hopefully be achieved. Eight planning grants, have been awarded to AIHEC institutions throughout Indian Country. In 2003, Phase 2—the Curriculum Development and Pilot Testing Phase—has begun. Funded Tribal colleges are developing K–4, 5–8, and 9–12 parallel curricula. These curricula will be pilot tested in selected K–12 schools and revised for fielding in all K–12 schools in American Indian and Alaska Native communities in subsequent years.

CDC/IHS Collaboration on Redesign of the National Diabetes Prevention Center (NDPC). In FY 2001 and FY 2002, a collaborative IHS NDP/CDC NDPC strategic action planning process laid the foundation for restructure and re-orientation for the National Diabetes Prevention Center in Gallup, New Mexico. This activity has ensured consistency with the NDPC's original mission to provide diabetes outreach, information, and technical assistance to Tribes throughout the United States. The NDPC's activities for FY 2003 included gathering, connecting, and disseminating information about "what works" in diabetes care and prevention for all American Indian and Alaska Native communities. Presently, the NDPC is working in collaboration with the IHS NDP and its partners to pilot and distribute a variety of user-friendly tools such as AI/AN adaptations of the CDC's CDCynergy, Diabetes Today, and Taking Care of Your Diabetes. Data approaches to assist in diabetes care and prevention efforts such as GIS mapping of diabetes complications and a series of reports about "what works" in information technology has been packaged in a CD–ROM format for distribution to health care leaders in Tribal communities.

The Tribal Leaders Diabetes Committee continued to provided valuable advice and guidance during this past year specifically on the Diabetes Education in Tribal Schools Project, a joint project of NDPC, NDP, NIH, and the American Indian Higher Education Consortium to develop a diabetes science-based national curriculum for Tribal schools.

In addition to collaboration with IHS NDP, the NDPC has engaged in projects with American Indian Research and Education Centers at the University of Nevada at Las Vegas and the University of New Mexico on the development of data software programs for collection and analysis, and support for development of the Associate of Science curriculum in diabetes prevention.

IHS NDP continues to collaborate with NDPC on the development and printing of educational resources such as the IHS NDP *Health for Native Life* magazine. This popular publication is developed for members of Tribal communities who have diabetes and their family members. The focus is on individuals who have diabetes and the various educational topics around treatment, care, and education and community-related support systems and activities. The most recent issue has focused on individual and Tribal fitness programs, support for persons with diabetes, and self-care tips. Distribution is to I/T/U grant programs, facilities, and Tribal organizations nationwide. In addition, collaborative efforts have resulted in the development of a 90-Day Journal for Wellness for American Indian and Alaska Native individuals who wish to record a daily record of self-care activities.

Plans include completion of a video on Community Health Workers, determining feasibility of a documentary on diabetes in AI/AN communities, and developing new partnerships such as with the National Indian Youth Leadership Program.

The CDC Division of Diabetes Translation provides diabetes epidemiologic support to the IHS National Diabetes Program with one full-time position and close collaboration on projects of mutual concern.

Committee on Native American Child Health (CONACH). The IHS National Diabetes Program collaborated with the American Association of Pediatrics CONACH and Section on Endocrinology to develop a new clinical report "Prevention and Treatment of Type 2 Diabetes Mellitus in Children, With Special Emphasis on American Indian and Alaska Native Children." This article appeared in the electronic pages of the October 2003 *Pediatrics* journal. This report calls on pediatricians to aggressively work to prevent and treat type 2 diabetes in AI/AN children, as these children face a higher risk of contracting the disease than do children of other ethnicities. According to the report, prevention programs in these communities require a cooperative effort by pediatricians and other health care professionals, along with appropriate Tribal authorities, schools, communities, State and Federal agencies, and local businesses. The report also calls for more research, prevention efforts, and treatments for children with type 2 diabetes. This clinical report is an important guideline for both IHS and other health providers seeing AI/AN children.

Collaboration and Partnership With Other Federal Agencies and Organizations. Activities Include:

- IHS NDP Director serves as a member of the Translation Committee of the Diabetes Prevention Program, an NIH-sponsored study showing that type 2 diabetes can be prevented.
- IHS NDP Director serves as a member of the Steering Committee of the National Diabetes Education Committee, a joint effort of the NIH and CDC to promote national awareness about diabetes.
- IHS NDP supports the American Diabetes Association's outreach initiative program for American Indian/Alaska Native communities: Strong in Body and Spirit. Provides expert guidance related to diabetes program development and modification based on participant evaluation.
- IHS NDP participates in the American Indian subcommittee of the National Diabetes Education Program. The IHS NDP provides regular representation to the committee and helps with the formulation and distribution of program materials.
- IHS NDP participates in the Diabetes in Children and Adolescents Work Group of the National Diabetes Education Program. The IHS NDP contributed to the development of the Diabetes in Schools Guide and will assist in its dissemination to schools serving AI/AN students.
- A key partnership has been established with the American Indian Higher Education Consortium (AIHEC) Board to help build Tribal college and university capacity and infrastructure for diabetes training and program activities in AI/AN communities.
- Several IHS Area Diabetes Programs have partnered with CDC's State Diabetes Control Programs (e.g., Montana, Alaska, California, New Mexico) to share skills, resources, and training.

Future Activities

- In 2004 the IHS NDP will develop a competitive grant program within the SDPI focused on primary prevention of type 2 diabetes CVD (cardiovascular disease) risk reduction in AI/AN with diabetes. A Diabetes Collaborative approach, based on the model used by the Bureau of Primary Health Care at HRSA, will be used to implement these interventions in 40–60 AI/AN communities.

- IHS NDP will continue to conduct further in-depth evaluation and validation studies and key informant interviews of Special Diabetes Program for Indians grant program activities, as well as dissemination of successful grant program strategies.

- IHS NDP will continue to work with partners and Tribes to implement and fine-tune culturally acceptable screening approaches for AI/AN communities.

- IHS NDP will continue to develop and provide more technical assistance and training (for health professionals, Tribal leadership, administrators, paraprofessionals, and patients) and promote increased awareness regarding new diabetes prevention findings through media, booklets, Internet, and other avenues of communication.

- IHS NDP will lead the effort in partnering with the American Indian/Alaska Native Boys and Girls Clubs and the National Congress of American Indians (NCAI) to promote healthy lifestyles for children and youth aimed at reducing the risk for early onset of diabetes in youth.

- IHS NDP will continue to promote data improvement through implementation of an enhanced electronic medical record specific to diabetes to be used IHS-wide, development of an electronic medical records audit, centralized technical support for the Diabetes Management System of the IHS electronic medical record, and ongoing collaboration with and support for a Diabetes Collaboration amongst the Tribal Epidemiology Centers.

- IHS NDP will continue to focus efforts on dissemination of information on the Medicare Part B Medical Nutrition Therapy (MNT) and Diabetes Self-Management Training (DSMT) benefits to I/T/U health care facilities. Seeking reimbursement for MNT and DSMT will have far-reaching benefits for Tribes and Tribal communities by increasing access to diabetes education and nutrition services. Increased access not only benefits those with diabetes and/or pre-dialysis kidney disease, but also expands opportunities for lifestyle interventions for the primary prevention of diabetes and other chronic diseases.

National Center for Complementary and Alternative Medicine (NCCAM)

http://nccam.nih.gov

The National Center for Complementary and Alternative Medicine is dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training complementary and alternative medicine (CAM) researchers, and disseminating authoritative information to the public and professionals. To achieve its objectives, NCCAM supports basic and clinical research on CAM, awards grants to train researchers in CAM and sponsors a variety of outreach activities. The diabetes-related projects that NCCAM is currently supporting reflect its commitment to the clinical study of promising CAM substances and modalities.

Current Activities

In Fiscal Year (FY) 2001, NCCAM and its cosponsors, the NIH Office of Dietary Supplements and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) released a Program Announcement (PA), "Chromium as Adjuvant Therapy for Type 2 Diabetes and Impaired Glucose Tolerance." As a result of this PA, in FY 2003, the Center funded a project that is investigating the effects of daily chromium for 6 months at two dose levels on serum measures of glucose tolerance and on endothelial function in adults with impaired glucose tolerance. The Center continues to support a study investigating the biochemical basis for chromium enhancement of insulin action.

Other diabetes-related research includes a new pilot study of Maharishi Vedic medicine, which will determine the feasibility, acceptability, and safety of implementing a multimodality intervention for newly diagnosed type 2 diabetics while assessing efficacy on glycemic control. Another pilot study will examine the effect of yoga on cortisol levels and glucose control in diabetes. Also being studied is whether acupuncture improves impaired gastric emptying in diabetic rats. NCCAM continues to support basic studies in: (1) examining the mechanisms by which *Ginkgo biloba* may accelerate pancreatic function and reduce glucose metabolism, and (2) identifying the anti-hyperglycemic constituents of Panax ginseng berry and the synergistic effects between these constituents.

NCCAM's Division of Intramural Research established a Diabetes Unit in April 2002. Its primary research goal is to understand the molecular mechanisms of insulin action and insulin resistance and the contribution of various CAM modalities to the diagnosis, prevention, treatment, and cure of diabetes, obesity, and their vascular complications. The Diabetes Unit currently has three active clinical protocols. One protocol is developing simple methods for assessing insulin sensitivity and insulin secretion in vivo in humans. The other two protocols are investigating effects of oral vitamin C and oral glucosamine on insulin sensitivity and vascular function in diabetic, obese, and healthy subjects. The Diabetes Unit is also pursuing a number of laboratory-based projects to evaluate the role of dietary supplements DHEA and carnitine to modulate metabolic and vascular actions of insulin and adiponectin in adipose cells and endothelial cells. Other studies are evaluating cross-talk between inflammatory signaling pathways and metabolic insulin signaling to understand the molecular mechanisms of insulin resistance.

In 2003, one percent of the NCCAM clearinghouse inquiries were related to diabetes and CAM therapies. The NCCAM web site provides links to informative fact sheets on diabetes and CAM.

Future Activities

The PA "Chromium as Adjuvant Therapy for Type 2 Diabetes and Impaired Glucose Tolerance" is still posted on the NCCAM web site and continues to generate interest from the research community. Further, NCCAM encourages researchers to submit investigator-initiated applications related to diabetes.

National Center for Health Statistics (NCHS), CDC
http://www.cdc.gov/nchs

The mission of the National Center for Health Statistics, as it relates to diabetes, is to monitor and provide national diabetes statistics in the form of summary health measures, as well as, individual and healthcare encounter level data for research. This information originates from vital records, interview and examination surveys, medical records, and patient encounters.

Current Activities

During 2003, NCHS continued to improve the Nation's understanding of the impact of diabetes by collecting new data on diabetes, preparing current statistics on diabetes trends, and publishing collaborative study findings on diabetes. Examples of these accomplishments include:

- Implementing a new U.S. Standard Certificate of Live Birth that, when fully in place in all States, will provide data to distinguish pre-pregnancy diabetes from gestational diabetes and to assess the relationship of maternal weight gain to other pregnancy risk factors, such as, diabetes.

- Collecting National Health Interview Survey (NHIS) data on preventive health care among people with diabetes, with support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

- Releasing National Vital Statistics data on diabetes-related mortality.

- Collaborating with the Centers for Disease Control and Prevention (CDC) Division of Diabetes Translation (DDT) to release the first national data from the National Health and Nutrition Examination Survey (NHANES) on lower extremity disease among diabetic adults.

- Publishing a new section on diabetes in the 2003 edition of *Health, United States Chartbook on Trends in the Health of Americans.*

- Issuing a new publication, *Health Care in America: Trends in Utilization*, which presents National Health Care Survey (NHCS) data that documents the increase in use of hospital and physician services, as well as, medications for diabetes.

- Preparing jointly, across multiple public and private organizations, the 2003 National Diabetes Fact Sheet.

- Conducting and publishing a study on the relationship between glucose impairment to cancer mortality.

- Collaborating with the Agency for Healthcare Research and Quality to present National Health and Nutrition Examination Survey (NHANES) data on diabetes control and National Hospital Discharge Survey data on diabetes-related complications in two reports to Congress: The National Healthcare Quality Report and National Healthcare Disparity Report.

- Presenting a Healthy People 2010 progress report to Department of Health and Human Services (DHHS) Assistant Secretary of Health on achieving the national health objectives for diabetes.

Future Activities

National Center for Health Statistics (NCHS) will release 2003 National Health Interview Survey data on diabetes care and 2001–2002 National Health and Nutrition Examination Survey data on physical exams in persons with diabetes.

With support from CDC's Division of Diabetes Translation and NIDDK, the National Center for Health Statistics will develop the 2005 NHANES protocol to examine a sample of Americans for pre-diabetes, undiagnosed and diagnosed diabetes, and metabolic syndrome. This effort is designed to include oral glucose tolerance testing, hemoglobin A1c, and other measures of diabetes management, including blood pressure and lipid levels.

Future research will include investigations of NHANES data on lower extremity disease among diabetic persons and analysis of data from the National Survey of Family Growth to assess maternal health of women with gestational diabetes.

NCHS will continue to obtain information on diabetes-related hospitalizations, ambulatory care visits, and nursing home stays. These data characterize trends in health care utilization for diabetes; delivery of preventive care services, including counseling on diet and exercise; diagnostic screening; services provided; medications; and diabetic-related complications, including those resulting in hospitalization.

National Center for Research Resources (NCRR)
http://www.ncrr.nih.gov

NCRR develops and supports research technologies and shared resources that are critically important to the research efforts directed at maintaining and improving the health of our Nation's citizens. Selected highlights of NCRR-supported diabetes research activities and future plans that relate to diabetes are presented below.

Current Activities

Now beginning their third year, the 10 NCRR-supported Islet Cell Resource (ICR) centers:

- Provided approved transplant programs throughout the country with approximately 35 million clinical grade islets to treat 52 patients afflicted with severe type 1 diabetes.
- Established procedures through which human islets can be provided to qualified investigators engaged in approved basic research.
- Are developing islet assays predictive of clinical success via collaborative efforts between several groupings of ICRs.
- Are optimizing culture, storage, and shipping conditions to increase the likelihood of successful transplantation.
- Have enlisted the coordinating center to provide administrative, bioinformatics, and biostatistical support for laboratory studies and clinical programs that use ICR-generated islets nationwide.
- Are establishing an islet web-based processing database to share information with the NIDDK-sponsored Collaborative Islet Transplantation Registry to enable one-time data entry and decrease the reporting burden for investigators.

The 82 General Clinical Research Centers (GCRCs) and their satellites provide the infrastructure needed by diabetes investigators, who are funded by NIH, private foundations, and corporations, to:

- Study normal and abnormal glucose metabolism, diabetic complications, islet and whole pancreatic transplantation, risk factors, epidemiology, genetics, and pharmaceutical interventions.
- Investigate the pathologic consequences of diabetes using high intensity MRI (magnetic resonance imaging).
- Develop novel treatments using continuous glucose sensors and insulin pumps.
- Determine the role of race and ethnicity, gender, age, pregnancy, and patient education in diabetes prevention and treatment.

Several of NCRR's Science Education Partnership Awards focus on diabetes, providing inquiry-based educational programs for K–12 students and disseminating information about risk factors and prevention through local science centers and museums, schools, churches, and community groups.

The NIH Clinical Loan Repayment Program enables talented physicians to continue their clinical research. NCRR sponsors eight such individuals engaged in diabetes research.

The WiCell Research Institute received an NCRR Human Embryonic Stem Cell Infrastructure grant to expand and distribute human embryonic stem cells, which may lead to new methods by which islet cells can routinely be generated for subsequent transplantation into diabetic patients.

The Shared Instrumentation Grant program provided funds for mass spectrometers, flow cytometers, phosphoimagers, and DNA sequencers to support diabetes research.

Diabetes-related research is being supported at five NCRR-supported Research Centers in Minority Institutions (RCMIs). Studies include:

- Self-care interventions for Hispanic and African-American adults with diabetes.
- Use of an animal model to assess the effect of diabetes on ischemic brain damage.
- Relationship of Highly Active Anti-Retroviral Therapy (HAART), and the increasing prevalence of diabetes in AIDS patients.
- Establishment of a twin registry that allows the study of metabolic and hereditary conditions.
- Glucohomeostasis and metabolism in type 2 diabetes and obesity, and behavioral aspects of nutrient selection in human diets.
- DNA sequencing and genetic linkage computational resources for determining genetic contributions to the high incidence of diabetes in the Puerto-Rican population.

Several Research Facility Improvement Program awards for construction and renovation of research facilities will benefit diabetes research, such as:

- Establishment at the University of Missouri of a major Center for Diabetes and Cardiovascular Health and a National Swine Research and Resource Center.
- Construction of both the Maryland MedStar Research Institute of Minority and Women's Health Core Laboratory and the Drew University Life Sciences Center's Biomedical Research Unit will allow the study of the natural history and treatment of diseases that disproportionately affect minorities, such as diabetes.

Through the Institutional Development Award (IDeA) Program, research on diabetes and its complications continues through the study of:

- Hereditary, behavioral, and cultural elements that contribute to the observed increase in diabetes risk factors, such as obesity, among Alaska Natives.

- Diabetic retinopathy to aid understanding of diabetes-associated retinal degeneration.

- Whether antioxidant treatment of pregnant diabetic mothers decreases the rate of type 2 diabetes in offspring.

- The role of an enzyme, human alkaline phytoceramidase, in regulating the formation of new blood vessels from pre-existing ones, which might yield new strategies to treat angiogenesis-related diseases, such as diabetic retinopathy.

- Diabetic oral health, focusing on periodontal disease, immune function, and glycemic control and pilot testing an oral health educational program for African Americans.

- The effectiveness of physical activity intervention among African-American women with hypertension, including type 2 diabetes.

- The use of gene therapy to counter the deleterious effects of oxidative stress on major regulatory signaling pathways in vascular smooth muscle and endothelial cells in a mouse diabetic vascular disease model system.

Research model programs benefit the following diabetes research:

- Establishment of a Type 1 Diabetes (T1D) Repository at The Jackson Laboratory to serve as a distribution resource for mouse strains, to cryopreserve sperm and embryos, and to disseminate information through a web site.

- Development and characterization of rat strains that demonstrate very significant differences in aerobic capacity, adiposity, glucose metabolism, and insulin resistance.

- Investigation of the success and functionality of pancreatic islet cell allograft survival in macaques and baboons, as well as xenografts of islet cells from pigs to diabetic macaques.

- Establishment of the National Swine Research and Resource Center to serve as a central resource for depositing, maintaining, preserving, and distributing swine models.

A research group at the University of Texas Southwestern Biomedical Magnetic Resonance Facility determined glucose metabolism via three pathways: gluconeogenesis from glycerol, glycogenolysis, and gluconeogenesis from the citric acid cycle.

Future Activities

An RCMI Clinical Research Network (RCRN) will support the performance of clinical trials and other research that addresses ethnic health disparities. The RCRN will be comprised of the five RCMI clinical research centers and basic scientists at RCMI sites with expertise in genomics, proteomics, imaging, and health outcomes research.

NCRR, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Center on Minority Health and Health Disparities (NCMHD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung, and Blood Institute (NHLBI), National Eye Institute (NEI), National Institute on Aging (NIA), and National Institute on Drug Abuse (NIDA), will continue Clinical Research Education and Career Development support of diabetes-related research and training at Meharry Medical College, the University of Puerto Rico, Medical Sciences Campus, and Charles R. Drew University of Medicine and Science.

NCRR will continue efforts to develop the non-human primate model for diabetes, using molecular tools to search for naturally occurring diabetes in non-human primates and to detect genetic predisposition.

National Center on Minority Health and Health Disparities (NCMHD)
http://ncmhd.nih.gov

Statistics show that racial and ethnic minority populations constitute about 25 percent of adults with diabetes in the United States. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians and other Pacific Islanders are at particularly high risk for type 2 diabetes.

The purpose of the National Center on Minority Health and Health Disparities is to promote minority health, as well as to lead, assess, and support the National Institutes of Health's (NIH's) effort to reduce and ultimately eliminate health disparities. The NCMHD is primarily responsible for coordinating all minority health and health disparities research conducted or supported by the NIH. The NCMHD supports basic, clinical, social, and behavioral research; promotes research infrastructure development and training; fosters emerging programs; disseminates information; and reaches out to minority and other health disparity communities.

The NCMHD is addressing health disparities in racial and ethnic minorities with respect to diabetes through the support of research in three broad areas: preventing or delaying the early onset of diabetes through diabetes education and lifestyle changes; improving the management of and therapies for diabetes; and the identification of biological and genomic risk factors for diabetes. In FY 2003, the NCMHD supported over 30 diabetes-related projects. NCMHD is committed to supporting diabetes research and training in partnership with other NIH Institutes and Centers, particularly the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), as well as other Federal agencies such as the Centers for Disease Control

and Prevention. The NCMHD's programs such as the Centers of Excellence (Project EXPORT) and Loan Repayment Program also offer opportunities for institutions and individuals to assist the NCMHD in addressing diabetes.

The Centers of Excellence (Project EXPORT) program, promotes the conduct of minority health and/or health disparities research; the participation of members of health disparity populations in biomedical and behavioral research, prevention, and intervention activities through education and training; and builds research capacity in minority-serving institutions. Through Project EXPORT, the NCMHD supports approximately 33 projects that focus on diabetes among health disparity populations; 18 of those are new awards.

The Loan Repayment Program (LRP) offers two specific programs, the *Loan Repayment Program for Health Disparities Research* and the *Extramural Clinical Research Loan Repayment Program*, which are aimed at attracting a number of highly qualified health researchers with an interest in health disparities or individuals from disadvantaged backgrounds to pursue clinical research careers. Four LRP awards were to researchers focusing their work on diabetes.

Current Activities

The *Oklahoma Native American EXPORT Center* at the University of Oklahoma Health Sciences Center focuses on reducing health disparities in Native Americans, with an emphasis on diabetes prevention and health promotion strategies aimed at children and adolescents. Community outreach activities include disseminating information on the epidemiology, intervention, and prevention of diabetes and obesity to American Indian communities; encouraging and preparing communities; to participate in scientific studies of health; and providing science education opportunities to American Indian high school students.

The *Teamwork in Research and Intervention to Alleviate Disparities (TRIAD) Project* at the University of North Carolina at Greensboro is aimed at developing and enhancing research infrastructure and partnerships to address major health disparities of African Americans, Hispanics, and low-income children and adults in central North Carolina. Components of the TRIAD Project are interdisciplinary/interagency, interactive, and synergistic to ensure comprehensive efforts to address HIV/AIDS, cardiovascular disease, and diabetes and their related risk factors. The anticipated short-term outcome is an increased quality and quantity of prevention and risk avoidance research, training, and outreach efforts to eliminate health disparities. The overarching goal is to assist the community, region, and State in meeting the critical health needs of a rapidly increasing, diverse citizenry in a culturally and linguistically competent manner through research, training, and outreach.

The *Columbia Center for the Health of Urban Minorities (CHUM)* at Columbia University will build on existing research programs to develop an interdisciplinary center of research in minority health and health disparities. The research focus of CHUM will be access to care. One research core will focus on primary (financial) barriers to care, and other cores will focus on non-financial barriers in four specific areas: cardiovascular disease, mental health, diabetes, and injury and disability prevention. A Community Planning Council will be created and will work with a public health promotion specialist to facilitate collaboration between the community and the academic health center. CHUM will also support the training and research career development of minority investigators and provide the university with a unique opportunity to develop and institutionalize a cross-cultural curriculum for medical students.

National Eye Institute (NEI)
http://www.nei.nih.gov

The National Eye Institute's mission is to conduct and support research, training, health information dissemination, and other programs concerned with blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of the blind. Diabetes is responsible for diabetic retinopathy, an eye disease that is the leading cause of blindness in people between the ages of 24 and 70 years. This disease is characterized by a progressive breakdown of the normal retinal vascular system.

Current Activities

The NEI has joined other NIH institutes in issuing RFA DK-03-024, "Proteomics and Metabolomics in Type 1 Diabetes and its Complications" to encourage the scientific community to use proteomics technologies to study type 1 diabetes and its complications. The NEI has joined other NIH institutes in reissuing an RFA (DK-03-001) "Bench to Bedside Research on Type 1 Diabetes and Its Complications" with the goal of translating advances in the understanding of the molecular basis of type 1 diabetes and its complications into new therapies for the prevention, treatment, and cure of this disease. The NEI joined other NIH institutes in issuing RFA-DK-03-020, "Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) To Develop New Therapies for Type 1 Diabetes and Its Complications" to encourage the small business community to apply cutting edge technology to research to develop new approaches to prevent, treat, and cure type 1 diabetes and its complications.

NEI continues its interest along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the genetic aspects of diabetic retinopathy through PA-02-020 , "Strategies to Identify the Genetic Basis of Diabetic Retinopathy," which alerts the scientific community to this continuing interest and encourages research on the genetic basis of this disease. This Program Announcement (PA) seeks a broad range of grant applications in gene discovery, genetic epidemiology, methodological studies of phenotypic assessment of retinopathy, including possible surrogate markers, and the development and application of novel statistical methods relevant to analyzing genetic data on diabetic retinopathy.

NEI continues its collaboration with other NIH institutes and the American Diabetes Association (ADA) on PA-02-153, "Translational Research for the Prevention and Control of Diabetes." This PA seeks translation of recent advances in the prevention and treatment of type 1 and type 2 diabetes into clinical practice for individuals and communities at risk. The NEI continues to participate with other NIH institutes in a PA entitled "The Role of Antioxidants in the Prevention of Diabetic Complications." This PA focuses on the role of antioxidants in preventing, delaying, or ameliorating the micro- or macrovascular complications of diabetes as well as the mechanism(s) by which antioxidants might prevent diabetic vascular disease.

NEI continues to participate with NIDDK, the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Heart, Lung and Blood Institute (NHLBI) in a program announcement (PA–99–159) on "The Role of Growth Factors in the Development of Diabetic Complications." This PA encourages grant applications on the role of growth factors in the etiology and pathogenesis of the micro-and macrovascular complications of diabetes.

NEI continues to co-sponsor ACCORD (Action to Control Cardiovascular Disease Risk in Diabetes), a large multicenter trial supported by NHLBI and

NIDDK to assess treatments to reduce risk of cardiovascular disease in type 2 diabetes. For this trans- NIH effort, NEI is sponsoring an eye examination with fundus photography at baseline and at 4 years of follow-up to assess the effects of these treatments on diabetic retinopathy in these patients. Another initiative seeks to identify genetic associations in patients with microvascular complications of diabetes. NEI continues to supplement the FIND (Family Investigation of Nephropathy and Diabetes) study funded by NIDDK to investigate the genetics of individuals and special populations of patients with renal disease. NEI is supporting detailed eye examinations for these patients and will search for genetic associations with microvascular disease.

NEI is supporting the continuation of two NIDDK-supported clinical trials that are now follow-up studies, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) and Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS). The eye component of these two studies are important outcomes in these studies of systemic treatments for both the prevention and the treatment of diabetes and its complications such as diabetic retinopathy.

Under the National Eye Health Education Program, the NEI completed its formative research with the American Indian/Alaska Native community. This research on diabetic eye disease is being used to complete a communication plan on diabetic eye disease that will be implemented in 2004. Strategies will include working with the Indian Health Service and Tribal councils on diabetes. A series of community-based projects on diabetic eye disease were implemented as part of NEI's Healthy Vision Community Awards Program. This program provides support to communities addressing vision objectives in Healthy People 2010. The NEI joined with the National Urban League (NUL) to support five diabetic eye disease components of the NUL's Lift Every Voice Diabetes Program. Plans are underway to develop a mass media, community-based promotion on diabetic eye disease during May 2004, Healthy Vision Month. A Spanish public service campaign will be released during May. Through this effort, NEI hopes to increase awareness about the importance of
dilated eye exams for people with diabetes.

NEI continues support of the evaluation of new treatments for diabetic macular edema, a major cause of visual loss in patients with diabetes through the Diabetic Retinopathy Clinical Research Network (DRCRN). This network supports core centers to plan, implement, and conduct clinical trials on the treatment of diabetic macular edema. The overall goal of this project is to develop an infrastructure to accelerate the development and conduct of clinical trials of the treatment of diabetic macular edema. These include both medical and surgical approaches. Grant awards have been made for a coordinating center in Tampa, Florida, a reading center in Madison, Wisconsin, and a chairman's grant in Boston, Massachusetts. Over 100 clinical centers have been identified as participants in the network. A randomized clinical trial testing two different laser approaches for diabetic macular edema has been started and another randomized, phase 3 clinical trial evaluating a novel intravitreal steroid preparation for diabetic macular edema is planned to begin in the second quarter of 2004.

Future Activities

NEI will continue to incorporate the scientific priorities outlined in the Report of the Congressionally Established Diabetes Research Working Group in making funding decisions. The National Eye Health Eduction Program (NEHEP) will continue to develop and implement outreach activities for people with diabetes. NEI will continue to encourage experienced investigators from outside vision research to apply their expertise to develop novel strategies for increasing knowledge about the pathophysiology and treatment of diabetic retinopathy.

National Heart, Lung and Blood Institute (NHLBI)

http://www.nhlbi.nih.gov

The primary cause of death in patients with diabetes is cardiovascular disease (CVD). NHLBI has continued to expand its comprehensive programs of basic and clinical research to understand the pathogenesis, improve treatment, and develop effective prevention strategies to reduce or postpone the cardio-vascular complications of diabetes. Despite reductions in CVD mortality in the general population, patients with diabetes continue to have 2–4 times the CVD rates of non-diabetics of the same age, gender, and ethnic group. With increases in diabetes in the United States, diabetes will become an increasingly important cause of heart and vascular disease.

Current Activities

During the past year, NHLBI has continued work on three major clinical trials that will evaluate several therapeutic approaches designed to reduce cardiovascular complications of diabetes. The Action to Control Cardiovascular Disease Risk in Diabetes (ACCORD) trial successfully completed a 1,000 patient Vanguard phase and initiated recruitment for the main phase (9,000 additional patients). The cohort will be followed over the next 5 years to evaluate the benefits of intensified control of hyperglycemia compared to conventional glucose control and also will test the benefits of aggressive blood pressure control and intensified control of the dyslipidemias associated with diabetes upon CVD rates.

The Bypass Angioplasty Revascularization Investigations II–Diabetes (BARI 2D) trial is recruiting 2,300 patients to evaluate whether elective coronary artery revascularization plus optimal medical management of cardiovascular risk factors and symptoms is superior to optimal medical management alone. It will also evaluate the important issue of whether reducing insulin resistance provides protection against CVD complications by testing whether insulin-sensitizing drugs are superior to injected insulin or to oral drug regimens that stimulate insulin secretion at
levels of glycemic control that are attainable with current conventional treatments. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is providing partial support for both of these trials. NHLBI is also helping to fund the NIDDK-sponsored Action for Health in Diabetes (Look AHEAD) trial, which is evaluating the effect of obesity treatment on CVD complications in type 2 diabetic patients.

Taken together, these three trials should lead to new clinical approaches that reduce cardiovascular complications of both type 1 and type 2 diabetes.

NHLBI also supports basic research to identify new ways to treat and prevent the major vascular complications of diabetes. It is particularly important to develop new therapies that can reduce the macrovascular complications of diabetes without requiring intensive efforts at glucose control. NHLBI has expanded basic research related to CVD complications of diabetes including continuation of several large project grants originally cosponsored with the Juvenile Diabetes Foundation.

NHLBI has also participated, alone and in collaboration with NIDDK, in the development and initiation of a number of programs aimed at improved understanding of diabetic macrovascular complications. These programs are:

- Progression of Cardiovascular Disease in Type 1 Diabetes HL-04-013
  http://grants2.nih.gov/grants/guide/rfa-files/RFA-HL-04-013.html

- Proteomics and Metabolomics in Type 1 Diabetes and its Complications DK-03-024
  http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-03-024.html

- Innovative Partnerships in Type 1 Diabetes Research DK-03-015
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-03-015.html

- Bench to Bedside Research on Type 1 Diabetes and Its Complications DK-03-019
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-03-019.html

- Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Develop New Therapies for Type 1 Diabetes and its Complications DK-03-020
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-03-020.html

These programs have involved studies of the effects of diabetes on vascular smooth muscle and endothelial cells, effects on circulating growth factors and adhesion molecules, reactive oxygen species, advanced glycated end products, and the effect of salt restriction on insulin sensitivity. Grants have also been awarded to elucidate the etiology of diabetes-associated cardiomyopathy, an abnormality that contributes to the high rates of congestive heart failure in diabetic patients.

Other programs, through multidisciplinary research efforts, attempt to delineate the role played by hyperglycemia and insulin resistance in the genesis of cardiovascular disease in diabetes. Hypotheses to be tested include whether elevated glucose and/or insulin resistance leads to accelerated cardiovascular disease by increasing oxidative stress and inflammatory signals in the vessel wall. Progress has been made in elucidating the role of regulatory mechanisms of high glucose and fat (lipoxygenase) in initiating and accelerating atherosclerosis. The results should increase our knowledge of the factors leading to accelerated CVD in diabetes and lead to new therapeutic advances.

With the goal of elucidating biochemical, metabolic, and genetic mechanisms of macrovascular disease in insulin-dependent diabetes mellitus, NHLBI is supporting programs to define how multiple pathological processes interact at the level of the arterial wall to promote atherosclerosis. The investigators are examining changes in the composition and modifications of lipoproteins, the effects of long-term protein glycation and oxidative stress, autoimmune responses to modified lipoproteins, and changes in the kallikrein/kinin system, and testing for mechanisms and interrelationships between these factors using cell culture systems and in vivo metabolic studies.

Other investigations include the biology of nuclear receptors, as they serve as central integrators of gene regulation to a variety of physiological and pathophysiological stimuli. These studies should provide significant new insights into mechanisms by which therapy could be designed to control specific abnormalities involved in diabetes and cardiovascular disease.

Additional investigations are examining the proatherogenic effect of consumption of a high glycemic load diet on the blood vessel walls and blood clotting. Studies will provide much needed information about the cardiovascular consequences of some of the commonly used diets in order to properly advise individuals and the public at-large about the long-term consequences of dieting.

NHLBI has also participated, in collaboration with NIDDK, in the program of small, innovative grants aimed at utilizing state-of-the-art gene therapy approaches for treatment of diabetes and its complications. The information that will be gained with the completion of these experiments will be significant in the continued development of angiogenic factor gene therapies, offering new technology that will render the therapies safer for treating cardiovascular ischemic disorders of diabetes.

Finally, it is important to recognize that many of the other research efforts supported by NHLBI may help to reduce or improve treatment for cardiovascular diseases occurring in patients with either type 1 or type 2 diabetes. This is because the effect of diabetes on macrovascular disease is, at least in part, to accelerate progression of the underlying atherosclerosis that is also common in non-diabetic individuals in middle and older ages. Thus, studies on treatment of congestive heart failure, treatment of arrhythmias, including public access to defibrillation, implantation of vascular stents that contain drugs that reduce restenosis rates, regeneration of cardiac muscle, and other treatments may have major benefits for patients with diabetes.

Taken together, the clinical and basic studies described should provide better guidance for physicians to reduce cardiovascular complications of diabetes in the near future and, in later years, lead to development of easier to use, more effective therapies.

National Human Genome Research Institute (NHGRI)

http://www.nhgri.nih.gov

The National Human Genome Research Institute led the National Institutes of Health's (NIH) contribution to the International Human Genome Project (HGP), which had as its primary goal the sequencing of the human genome. This project was successfully completed in April 2003. Now, the NHGRI's mission has expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease.

To that end, NHGRI supports the development of resources and technology that will accelerate genome research and its application to human health. In the laboratories of the Division of Intramural Research (DIR), with the tools produced by the HGP, scientists are developing and using the most advanced techniques to study the fundamental mechanisms of inherited and acquired genetic disorders, including type 2 diabetes mellitus.

Current Activities

Finland–U.S. Investigation of NIDDM Genetics. Type 2 diabetes is one of the major causes of morbidity and mortality in the developed world. While environmental factors such as diet play a significant role, familial clustering indicates that there must be significant genetic susceptibility factors at work. For the past 10 years, researchers at NHGRI have been engaged in a large collaborative study known as the Finland–United States Investigation of Non-Insulin Dependent Diabetes Mellitus (FUSION), in which over 5,000 individuals with diabetes and suitable controls from Finland are being studied, using careful phenotyping of diabetes and diabetes-associated traits and genome-wide genetic linkage and association. Researchers at NHGRI have developed new approaches in the laboratory to achieve high-throughput microsatellite and SNP (single

nucleotide polymorphism) genotyping, which has allowed the collection of a massive amount of data from these Finnish diabetics and their families. This project has made significant progress, focusing on fine mapping of regions on chromosomes 6, 11, 14, 20, and 22, where prior linkage analyses have shown evidence for susceptibility genes for diabetes or related traits. In particular, researchers have identified a small region on chromosome 22 that contains a haplotype conferring an odds ratio of 1.5 for type 2 diabetes and has been confirmed and narrowed by studying a West African diabetic population. Researchers have also identified susceptibility variants in a small region of the promoter of an excellent candidate gene on the long-arm of chromosome 20, a region where a dozen groups have independently shown evidence of linkage for type 2 diabetes. These variants seem to account for most or all of the linkage signal and have just been confirmed in an independent study of Ashkenazi diabetics.

Statistical Genetic Analysis of Traits Related to Type 2 Diabetes. Researchers at NHGRI are also analyzing statistical genetic data on type 2 diabetes provided by collaborators from the Genetics of NIDDM study and GlaxoSmithKline suggesting candidate regions on chromosomes 1 and 14 in Japanese Americans. Other collaborators have provided genetic marker data from these potential candidate regions in an independent sample comprising 175 Japanese-American families with a high prevalence of diabetes from a Hawaiian population. The goal of this project is to attempt independent replication of results in these potential candidate regions, with further evaluation in the event of positive results. In FY 2003, work on this project included statistical linkage and association analyses in type 2 diabetes with DNA markers in candidate regions on chromosomes 1 and 14. Evidence of both linkage and association was obtained in the candidate region on chromosome 14, constituting independent replication of previous results in this region. These results provide additional support for the hypothesis that a susceptibility locus for type 2 diabetes may reside in this candidate region on chromosome 14. Future plans include statistical analyses of DNA markers in this candidate region using the expression level of adiponectin, a protein related to obesity and type 2 diabetes. The locus influencing adiponectin level was independently mapped to the candidate region on chromosome 14, providing a possible mechanism for genetic susceptibility in this population.

Cultural and Ethical Issues Associated with Genetic Family Studies. The institute's Ethical, Legal, and Social Implications (ELSI) Program is designed to provide a novel approach to scientific research by identifying, analyzing, and addressing the ethical, legal, and social implications of human genetics research at the same time that the basic scientific issues are studied. The ELSI Program is funding a project that aims to examine cultural and ethical issues associated with participation in genetic family studies by patients with a family history of type 2 diabetes mellitus, in order to enhance the ascertainment process and establish strategies for genetic counseling of patients and relatives with a family history of type 2 diabetes and diabetic neuropathy.

Technology Development for Natural Genetic Variation. In FY 2002, NHGRI created a program to establish new academic Centers for advanced genome research. These Centers of Excellence in Genomic Science (CEGS) will support multi-investigator, interdisciplinary teams to develop innovative genomic approaches to address biological problems. One of the CEGS aims to develop tools for studying natural genetic variation and to apply those tools to develop an improved understanding of the molecular basis of genetic susceptibilities to type 1 diabetes, progressive supranuclear palsy, and neutropenia. More broadly, the center expects, through its development of new technology and close interactions between theory and experiment, to contribute indirectly to many research projects directed at understanding the genetic contributions to human health and disease.

National Institute of Allergy and Infectious Diseases (NIAID)

http://www.niaid.nih.gov

The National Institute of Allergy and Infectious Diseases supports a broad range of research on the immunopathogenesis of autoimmune diseases, including type 1 diabetes. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. These studies provide the knowledge to develop new treatments and diagnostic tests for autoimmune diseases, including type 1 diabetes, and novel treatments for ongoing disease.

The NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC), established in FY 1998 at the request of Congress to increase collaboration and facilitate coordination of research among NIH Institutes and Centers, other Federal agencies, and private organizations. In 2002, the ADCC completed and submitted to Congress a comprehensive strategic and collaborative research plan for autoimmune diseases, which was mandated in the Children's Health Act of 2000 (P.L. 106-310). The ADCC Research Plan is a comprehensive, long-term agenda for autoimmune diseases research in epidemiology and burden of disease; etiology and pathogenesis; diagnosis, treatment, and prevention; and training, education, and information dissemination. The ADCC Research Plan highlights new programs and research areas in which future progress will benefit all autoimmune diseases and facilitate the translation of new knowledge into more effective treatments and prevention strategies. Since submitting its report to Congress, the NIH ADCC has initiated a comprehensive inventory of NIH-supported initiatives and activities in autoimmune diseases research to help identify areas of the plan that are being addressed and those areas that may need additional effort.

Current Activities

The NIAID is committed to furthering the understanding of the immunopathogenesis of autoimmune diseases, including type 1 diabetes, and to promoting the translation of basic research to clinical applications. During the past year, the NIAID has continued to expand its research program in type 1 diabetes. In FY 1999, NIAID established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel tolerance induction approaches for autoimmune diseases, asthma and allergic diseases, and prevention of graft rejection. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity to infectious agents. An important aim of the ITN is to explore the immune mechanisms underlying efficacy (or lack of efficacy) of candidate approaches. The ITN is conducting clinical trials of tolerance induction approaches for multiple autoimmune diseases, including type 1 diabetes. Examples of the ITN-supported clinical trials for type 1 diabetes include:

- The ITN is conducting the "Edmonton Protocol," an experimental islet transplantation protocol for brittle type 1 diabetes based on the approach pioneered at the University of Alberta. The ITN trial will further assess the safety and efficacy of this regimen; expand the capacity for islet preparation and clinical transplantation at nine sites in the United States, Canada, and Europe; establish the baseline success rate for islet transplantation; and facilitate the evaluation of new tolerogenic approaches for islet transplantation. In 2003, the ITN plans to initiate enrollment in two clinical studies to evaluate the potential for an antibody to CD52 or an antibody to CD3 to induce tolerance to transplanted islet cells.

- The ITN is developing therapeutic approaches for the prevention and reversal of type 1 diabetes. The ITN is currently recruiting new onset type 1 diabetics into two trials to evaluate the use of a humanized anti-CD3 monoclonal antibody, which showed promise in the Phase I trial. Another trial giving insulin B chain with adjuvant in new onset diabetics demonstrated safety and is currently expanding recruitment. If this approach proves safe without the induction of immunity to the insulin B chain, further studies to test the ability of this combination to interrupt the autoimmune process in new onset or at-risk individuals will follow.

- ITN clinical trials have integrated studies aimed at identifying the underlying mechanisms involved in disease progression and therapeutic actions of the treatment regimens. In 2003 the ITN established a contract with The Wellcome Trust Sanger Institute (U.K.) to sequence key areas of the NOD mouse genome. The data will be deposited into Genbank for use by the research community.

The ITN includes more than 80 basic and clinical scientists and physicians from over 40 institutions in the United States, Canada, and Europe, and is co-sponsored by NIDDK and the Juvenile Diabetes Research Foundation International (JDRF). More information about the ITN is available at *http://www.immunetolerance.org*.

The NIAID, in collaboration with multiple NIH Institutes and Offices, has established several large multidisciplinary research programs for autoimmune diseases, including type 1 diabetes:

- Autoimmunity Centers of Excellence (ACEs) program, co-sponsored by NIAID, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and Office of Research on Women's Health (ORWH), was renewed in 2003 and expanded to nine centers. The ACEs conduct clinical trials and basic research on immune-based therapies for autoimmune diseases, including type 1 diabetes. The program enhances interactions between scientists and clinicians to facilitate the translation of scientific research findings into medical applications. ACE investigators and NIAID representatives form the Steering Committee, which met in Bethesda in November. Protocols for clinical trials in type 1 diabetes are under development.

- The Centers for Autoimmune Disease Prevention, co-sponsored by NIAID, NIDDK, JDRF, National Institute of Child Health and Human Development (NICHD), and ORWH, focus on advancing knowledge for the prevention of type 1 diabetes and other autoimmune diseases. The Prevention Centers initiate and support pilot projects for the rapid testing of new ideas and technologies with potential application to prevention of autoimmune diseases, including a cutting-edge comprehensive longitudinal study of gene expression during the development of diabetes in the NOD mouse.

- NIAID and NIDDK will co-sponsor the Request for Applications (RFA), "Clinical Islet Transplantation Consortium: Clinical Centers" (CITC) to perform islet/beta cell transplantation studies in adult type 1 diabetes patients. The consortium of investigators and institutions will develop and implement a program of single- and/or multi-center clinical studies, accompanied by mechanistic studies, in islet transplantation (with or without accompanying kidney transplantation) for the treatment of type 1 diabetes. A complementary RFA will establish a Coordinating Center to provide statistical support, data monitoring, and core laboratory support to the CITC.

- NIAID and NIDDK reissued the RFA "Innovative Partnerships in Type 1 Diabetes Research" to provide access to specialized expertise or technologies and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. This initiative provides for collaborative research partnerships between independent principal investigators with expertise in different aspects of type 1 diabetes. Eighty-one applications have been reviewed.

- NIAID and NIDDK co-sponsored the RFA "Bench to Bedside Research on Type 1 Diabetes and its Complications" to support partnerships between clinical and basic researchers to translate advances in the understanding of the molecular basis of type 1 diabetes into new therapies for the prevention, treatment, and cure of this disease. A total of 69 applications were reviewed for this year's initiative; 2 of the 10 funded applications were assigned to NIAID. The Bench-to-Bedside initiative will be reissued in 2004.

- NIAID and NIDDK co-sponsored the RFA "Gene Transfer Approaches to Enhance Beta-Cell Transplantation" to support feasibility and pilot projects for methods to engineer beta cells or alter islets to enhance their viability. In FY 2003, NIAID supported five R21 grants to investigate various methods of genetically modifying islets or beta cells to express molecules involved in immune modulation and the effects of genetic modification on tolerance induction and survival of islets after transplantation. Successful completion of these projects could provide important insights for more efficacious treatment of type 1 diabetes.

Future Activities

NIAID will continue to support basic research and clinical trials of promising therapeutic approaches for multiple autoimmune diseases through the Autoimmunity Centers of Excellence (ACEs), the ITN, and the Centers for Autoimmune Disease Prevention.

NIAID and NIDDK will co-sponsor "Clinical Islet Transplantation Consortium: Clinical Centers" (CITC) to perform islet/beta cell transplantation studies in adult type 1 diabetes patients and a complementary RFA to establish a Coordinating Center for the CITC to provide statistical, data monitoring, and core laboratory support.

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

http://www.nibib.nih.gov

The NIBIB will lead the development and application of breakthrough technologies from science and engineering to establish a foundation to understand complex biological processes and to improve health. Consistent with its mission and vision, the NIBIB supports diabetes-related research in the areas of imaging, sensor technology, and telehealth.

Current Activities

The NIBIB, along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International, held a workshop entitled, *Imaging the Pancreatic Beta Cell*, in April 2003. The workshop was effective in providing an overview of recent advances in beta cell biology; summarizing new approaches for cellular and molecular imaging; disseminating results of research supported under previous initiatives; fostering interactions between beta cell biologists, imaging scientists, and engineers; and pointing to future applications of imaging techniques in understanding the natural progression of diabetes and monitoring clinical treatments for diabetes.

In FY 2003, the NIBIB issued three research solicitations relevant to diabetes—*Operation of Sensors In Vivo* (EB-03-001), *Research and Development of Systems and Methods for Cellular and Molecular Imaging* (EB-03-003; co-sponsored by the National Institute of General Medical Sciences (NIGMS)), and *Telehealth Technologies Development* (PA-03-030). The NIBIB also supports diabetes-related research through investigator-initiated projects.

In the area of imaging, researchers are focusing on the use of magnetic resonance imaging (MRI) as a non-invasive tool to assess encapsulated transplanted islets for viability and the ability to secrete insulin in response to changing glucose concentrations (this grant is supported under EB-03-003—Research and Development of Systems and Methods for Cellular and Molecular Imaging). NIBIB-supported scientists are also developing improved MRI probes, high-resolution imaging, and novel imaging techniques to measure responses to therapy and to monitor the development of diabetic complications.

In the area of glucose sensors, NIBIB-supported researchers are striving to improve the technology both for implanted sensors and non-invasive sensors. For example, advances in miniaturization and magnetic field technology are enabling scientists to explore the design of a sensor to measure certain compounds in saliva. In related work, researchers have developed, and are working to refine, a non-invasive glucose sensor using an iontophoretic approach to pass a low level electrical current through the skin to obtain measurements of glucose and other compounds. Investigators are also improving the technology for implantable glucose sensors to improve responsiveness and to extend their functional lifetime.

Obesity and type 2 diabetes are emerging epidemics in the United States. A modest weight loss has been proven to reduce the risk for developing diabetes and can reduce or eliminate the need for anti-diabetic medications. However, the implementation of behavioral weight loss programs in a primary care setting is challenging. While Internet-based weight loss programs are effective, access to personal computers may be limited especially in the elderly and low-income populations. Investigators supported through PA-03-030 (Telehealth Technologies Development) will develop an interactive diet and exercise program to be conducted with patients in their own home via a television set. Success in this endeavor would result in a convenient, intuitive, and inexpensive way to conduct large-scale interventions to combat obesity and type 2 diabetes.

Other investigators supported through PA-03-030 are exploring the development of various Internet- or cable television-based interactive monitoring and educational systems for chronic diseases, including diabetes.

Future Activities

During FY 2004, the NIBIB will issue a program announcement for the micro-imaging of pancreatic islets. In addition, the NIBIB will also co-sponsor a workshop in islet encapsulation along with the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International.

In summary, the NIBIB is developing a robust research program in biomedical imaging and bioengineering that will focus on developing fundamental new knowledge, fostering potent new technologies, nurturing and supporting promising researchers, and facilitating cross-cutting capabilities. Within its research mission, the NIBIB will continue to support technology-driven research to further advance all areas of diabetes-related research and to translate these discoveries to improve the health of individuals with diabetes.

National Institute of Child Health and Human Development (NICHD)

http://www.nichd.nih.gov

The mission of the National Institute of Child Health and Human Development is to promote the development of healthy children. Understanding genetic and environmental factors that contribute to the development of diabetes is consistent with this mission, given the prevalence of both type 1 and type 2 diabetes in children and the serious complications of diabetes later in life. The NICHD focuses its efforts on the earliest pathogenesis of type 1 diabetes and on optimizing insulin therapy in children with type 1 diabetes. In addition, NICHD supports research on the origins of type 2 diabetes in adolescents and on improving the outcome of pregnancy in women with gestational diabetes mellitus.

Current Activities

In efforts to prevent type 1 diabetes, the NICHD pioneered methods in stratifying levels of risk for type 1 diabetes mellitus according to genetic and immunologic markers. This work forms the basis of a collaboration with the Juvenile Diabetes Research Foundation (JDRF) to co-fund two large prospective studies of infants who have relatives with type 1 diabetes in order to ascertain the earliest immunologic changes in the pathogenesis of type 1 diabetes.

The incidence of type 1 diabetes has increased steadily over the past 30 years. It is presumed that environmental factors account for this striking increase in incidence. Epidemiologic studies and animal models implicate cow milk antigens in infant formula as an environmental agent that may trigger an autoimmune attack on the beta cells of the pancreas. In order to test this hypothesis, the NICHD is supporting an international randomized controlled clinical trial. Screening began in FY 2002 to enroll 2,000 infants at high genetic risk of type 1 diabetes, based on family history and HLA genotype. The infants are randomized to standard infant formula or to Nutramigen®, a casein hydrolysate. The investigators are documenting the development

of autoantibodies in these children. Mead-Johnson is providing the standard formula and the Nutramigen®. The study is funded by the NICHD, the JDRF, the Canadian Institutes of Health Research, the European Foundation for the Study of Diabetes, and the Netherlands Diabetes Foundation. Specially appropriated type 1 diabetes research funds are also being used to support the project. These funds are administered by the NIDDK.

The NICHD is currently supporting a 15-site, prospective, international study of hyperglycemia and adverse pregnancy outcomes. The investigators of this study of gestational diabetes mellitus are in the process of enrolling 25,000 women early in their pregnancy. These women will be followed through their gestation, delivery, and postpartum period. Their infants will be studied as well. The NIDDK is co-funding this landmark study.

Congressional Report 106-293 encourages the NICHD to work with the National Institute of Allergy and Infectious Diseases (NIAID) and NIDDK on efforts to develop a vaccine to prevent juvenile, or type 1 diabetes. In response to this Report, NICHD joined the NIDDK in co-funding TrialNet, a Network of 14 centers designed to perform clinical trials of new immunomodulatory agents to treat, delay, or prevent the onset of type 1 diabetes. The NICHD also joined the NIDDK and the NIAID in co-funding the Cooperative Study Group for Autoimmune Disease Prevention, a network of investigators who are developing new methods to induce immune tolerance to self-antigens of the beta cells of the pancreas. Ultimately, this collaborative research promises to mitigate or reverse the autoimmune process that leads to type 1 diabetes.

The NICHD supports a cooperative multicenter research network consisting of five clinical centers and a coordinating center. The mission of the Diabetes Research in Children Network (DirecNet) is to investigate the potential use of glucose monitoring technology and its impact on the management of type 1 diabetes in children. Funding, initiated in September 2001, was received from specially appropriated funds for research in type 1 diabetes. Specific goals for the network include the assessment of the accuracy of continuous monitoring devices in order to determine if these are useful in improving glycemic control and preventing hypoglycemia in diabetic children. Additional goals are to determine the optimal utilization of continuous glucose monitors in the management of diabetes in children and to assess the impact of continuous glucose monitoring on quality of life for the child and family. DirecNet has recently published glucose monitoring accuracy studies in two articles appearing in the November 2003 issue of *Diabetes Technology and Therapeutics*. Additional accuracy protocol findings, specifically studying the monitoring systems during hypoglycemia, will soon be published in *Diabetes Care*.

The Intramural Research Program of the NICHD is following children in a 15-year study designed to understand the earliest pathogensis of insulin resistance and glucose intolerance in obese children and in non-obese children of obese parents. In two randomized clinical trials, these investigators are also studying the effects of metformin and orlistat in obese insulin-resistant children. An important intramural study is now underway that is designed to develop ways to improve glycemic control in children with type 1 diatbetes.

Future Activities

DirecNet is currently recruiting subjects for an outpatient randomized controlled study examining continuous glucose monitoring systems vs. conventional care using conventional monitors in diabetic children. Furthermore, a protocol examining the use of continuous glucose monitors during exercise is currently in development. In response to a newly released RFA (Request for Applications) on establishing the precursors of the metabolic syndrome in children, the NICHD in conjunction with the NIDDK plans to fund new studies designed to ascertain the earliest origins of insulin resistance and glucose intolerance in children who are at increased risk of developing type 2 diabetes later in life.

National Institute of Dental and Craniofacial Research (NIDCR)
http://www.nidcr.nih.gov

The mission of NIDCR is to support research on the causes, prevention, diagnosis, and treatment of oral and craniofacial diseases and conditions. The oral complications of diabetes include greater prevalence and severity of periodontal diseases, increased susceptibility to oral mucosal infections, impaired wound healing, salivary gland dysfunction, and neuropathies resulting in loss or alteration of taste, smell, and mucosal sensory perception. The NIDCR supports research on the oral complications of diabetes and the effects of oral diseases and conditions on the metabolic control of blood glucose.

Current Activities

FY 2003 diabetes-related accomplishments include the following:

- lA-2 and glutamic acid decarboxylase (GAD) are major autoantigens in type 1 diabetes with between 80 and 90 percent of newly diagnosed type 1 patients showing autoantibodies to one or the other of these autoantigens. Three separate intramural collaborative clinical studies measured these autoantibodies in patients with type 2 diabetes. Approximately 5 percent of type 2 diabetes patients were found to have one of these autoantibodies. The investigators suggest that either these subjects had been misdiagnosed and actually had type 1 diabetes or that these patients' disease combined features of both type 1 and type 2 diabetes. Since there are over 16 million people in the United States with type 2 diabetes, these findings raise the possibility that an additional 1 million persons may actually have type 1 diabetes or, alternatively, that the numbers of persons with diabetes involving autoimmunity may significantly exceed levels previously estimated.

- Oral inoculation of normal and diabetic NOD mice with a periodontal diseases-causing bacterium resulted in a failure of bone formation in diabetic mice, resulting in a net loss of bone. More inflammatory genes were upregulated and a more prolonged inflammatory response occurred in diabetic mice as compared to normal mice.

- A pilot case-control study is determining the extent of periodontal disease in Asian-Pacific Islander (API) type 1, type 2, gestational diabetes, or non-diabetic women who have term and preterm deliveries. Fetal cord blood is being analyzed for markers of fetal exposure to oral pathogens of maternal origin. Ultimately, the investigators will seek to test the hypothesis that the prevalence of periodontal diseases and levels of fetal exposure to oral pathogens is higher for both diabetics and non-diabetics whose pregnancies result in preterm deliveries vs. those delivering at term.

- Another clinical study in low-income African-American and Hispanic children with type 1 or type 2 diabetes aims to (1) identify their oral disease burden, (2) determine the relationship between oral/periodontal changes and early signs of other complications (retinopathy and nephropathy), (3) test an intervention to promote awareness of the oral complications of diabetes mellitus among medical staff providing care for children and adolescents with diabetes, and (4) evaluate the intervention's impacts on early detection of oral diseases and utilization of oral health services.

- A pilot clinical trial on periodontal infection treatment and its effect on glycemic control will complete patient followup in 2004. Estimates are being obtained of changes in hemoglobin A1c and the variability of those changes over time. Results from this pilot project are expected to provide preliminary data supporting the design of a Phase III randomized clinical trial to evaluate the effect of treating periodontal infection on glycemic control in type 2 diabetes.

Future Activities

During FY 2003 NIDCR continued to participate in one Program Announcement (PA) "Enhancing Adherence to Diabetes Self-Management Behaviors." No additional initiatives are planned.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
http://www.niddk.nih.gov

The National Institute of Diabetes and Digestive and Kidney Diseases is the lead agency of the Federal Government for research efforts to combat diabetes and its complications. The Division of Diabetes, Endocrinology, and Metabolic Diseases has responsibility for extramural programs related to diabetes research and research training. The Division of Intramural Research; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases support additional diabetes-related activities. In addition to the diabetes research the NIDDK supports through its regularly appropriated funds, the Institute also leads and participates in a special U.S. Department of Health and Human Services (DHHS) program on type 1 diabetes research, described below.

Special Statutory Funding Program for Type 1 Diabetes Research

Section 330B of the Public Health Service Act provides the Secretary, DHHS, special funding for research on the prevention and cure of type 1 diabetes. The Secretary has designated the NIDDK as the lead organization for planning, implementing, and evaluating this program. The special diabetes programs were mandated for the period of FY 1998 through FY 2003 by the Balanced Budget Act of 1997 (P.L. 105–33) and by the 2001 Consolidated Appropriations Act (P.L. 106–554). The program was extended for the period of FY 2004 through FY 2008 by the Public Health Service Act Amendment for Diabetes (P.L. 107–360).

Under the leadership of the NIDDK, the Special Statutory Funding Program for Type 1 Diabetes Research has engaged in a broadly consultative process that includes the participation of multiple NIH Institutes and Centers, the Centers for Disease Control and Prevention (CDC), and other DHHS components in all aspects of program planning, imple-

mentation, and evaluation. In addition, the active involvement of external scientific and lay experts with respect to type 1 diabetes and the major diabetes voluntary organizations—the Juvenile Diabetes Research Foundation International and the American Diabetes Association—has been vital to the program's success in establishing a vigorous and productive research enterprise.

The laws that established the special diabetes funding programs also mandate interim and final evaluation reports to the Congress. The interim report on the special funding program for type 1 diabetes research was transmitted to the Congress in June 2000. The enactment of P.L. 107–360 changed the due date of the final program evaluation report from January 1, 2003, to January 1, 2007. The NIDDK has printed the evaluation report that was originally intended to meet the January 2003, statutory reporting requirement. The document, entitled, "Special Statutory Funding Program for Type 1 Diabetes Research: Report on Progress and Opportunities," was issued as an important interim assessment of the program by external scientific experts, grant recipients, and NIH and CDC staff who analyzed the associated scientific literature and other relevant data on the program. Moreover, the report contains a highly useful summary of research opportunities identified by external experts in the field. These opportunities can thus serve as a scientific guidepost in developing this trans-DHHS program in the years ahead.

The NIDDK has also launched a new website dedicated to the Special Program, which can be accessed at: *http://www.niddk.nih.gov/fund/diabetesspecialfunds/*. Investigators can use this website to find information on new and upcoming research funding opportunities, the consortia and networks supported by the program, special resources that are available, and the recently published report.

Current Activities

The NIDDK supports a vigorous program of both basic and clinical research to further understanding of the development, treatment, prevention, and cure of diabetes and its complications. To maximize research on diabetes, the Institute has fostered collaborations among the many NIH Institutes and Centers, as well as with the Centers for Disease Control and Prevention (CDC), the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA).

Capitalizing on and responding to recent advances and emerging opportunities, the NIDDK continues to foster cutting-edge research in diabetes—from the recognition and support for innovative ideas in investigator-initiated research, to the Institute-led establishment of consortia focused on important fundamental and clinical research issues. Examples of ongoing activities and new initiatives for FY 2003 follow.

Genetics of Type 1 Diabetes: Type 1 diabetes is an "autoimmune disease," in which the immune system mistakenly attacks and destroys the beta cells of the pancreatic islets—the sole producers of insulin. Without insulin, the body cannot properly regulate glucose, lipid, and protein metabolism, which results in physiologic alterations that can rapidly cause death. Researchers have yet to determine the precise factors that cause the immune system to initiate this misguided attack. However, many studies have suggested that an environmental exposure may trigger this process in individuals who have an underlying genetic susceptibility. Multiple genes are believed to be involved in an interplay with each other and with the environment to initiate the cascade that leads to disease development. Identifying genes that confer susceptibility or resistance to type 1 diabetes will propel the search for novel therapeutic targets and new assays to pinpoint those at risk who can benefit from prevention strategies.

International Type 1 Genetics Consortium. Established by the NIDDK, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the National Human Genome Research Institute (NHGRI), and the JDRF, the consortium organizes international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. Because large sample sizes are required to identify susceptibility genes, the consortium will develop a renewable source of DNA on 7,500 families with a type 1 diabetic child. A consortium database containing clinical, genetic, and medical history information will facilitate the search for susceptibility genes. The consortium also plans to develop a centralized DNA repository, which will be accessible to genetic researchers in the diabetes community.

Genetics of Type 2 Diabetes and Obesity: As with type 1 diabetes, susceptibility to type 2 diabetes and obesity is determined by both genetic and environmental factors. Environmental factors such as poor diet and inactivity are risk factors, but less is known about the genes involved. It is critically important to identify genetic variations that predispose to type 2 diabetes and obesity, given the large and increasing health burden they impose on the American people.

International Type 2 Diabetes Genetic Linkage Analysis Consortium. The NIDDK has sponsored this consortium to accelerate the search for type 2 diabetes susceptibility genes. The pooling of genetic data from the many groups in the consortium increases the probability of identifying genes that influence this genetically complex disease. This combined effort also means that more samples are available for analysis of individual ethnic groups than is possible within a single study. Members of this consortium are currently finishing genetic linkage studies.

Genetics of Obesity-Related Traits in Model Organisms. The NIDDK, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Aging (NIA), is sponsoring an initiative to take advantage of the speed and power of genetics in small model organisms—such as fruit flies and zebrafish—in order to identify obesity susceptibility genes. This information would help to identify the corresponding genes in mice and humans. This strategy might afford a quicker route to identification of genes influencing these traits in humans than attempts to identify such genes by direct genetic analysis of mice or humans.

Genetics of the Complications of Diabetes: Genes are a critical factor not only in the onset of type 1 and type 2 diabetes, but also in the onset and progression of the complications that result from both forms of the disease. Familial clustering of complications of diabetes suggests an important genetic component to their development. Finding susceptibility genes for complications has important implications for identifying and intervening in individuals at increased risk for them, as well as for developing new therapeutic approaches. Several initiatives aim to identify genes that predispose individuals with diabetes to the development of complications such as kidney and eye disease.

Epidemiology of Diabetes Interventions and Complications (EDIC). The well-characterized participants in the Diabetes Control and Complications Trial (DCCT), and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, provide an opportunity to elucidate the genetic factors that influence the risk of complications. DNA and cell lines from over 1,400 DCCT/EDIC participants and their diabetic and non-diabetic relatives are being collected and analyzed to aid in the search for susceptibility genes for diabetes complications.

Family Investigation of Nephropathy and Diabetes (FIND). Studies have shown that diabetic kidney disease is a highly heritable trait. In response to this knowledge, the NIDDK established the FIND study to uncover candidate genes associated with development of kidney complications in patients with type 1 or type 2 diabetes. FIND has also incorporated a retinopathy study. A specific objective is to search for susceptibility genes in subpopulations of Caucasians, African Americans, Hispanic Americans, and Native Americans across the United States. Three additional sites for recruitment of minority participants have recently been added.

Animal Models of Diabetic Complications Consortium (AMDCC). The NIDDK, in collaboration with the National Eye Institute (NEI), the National Institute of Dental and Craniofacial Research (NIDCR), NHLBI, and the JDRF, has expanded the "Mouse Models of Diabetic Complications Consortium" to include other animal models. Researchers in this consortium are developing animal models of diabetes complications to facilitate the study of disease prevention and treatment and the testing of candidate genes that emerge from human genetic studies. The NIDDK, with the National Institute of Environmental Health Sciences (NIEHS), NHLBI, NEI, and the JDRF, recently sponsored a meeting, "Diabetic Complications: Progress through Animal Models," which emphasized the use of animal models in discovery and translational research. The meeting included presentations on current and emerging animal models of diabetic complications, molecular and cellular mechanisms that lead to tissue damage, and the use of animal models to understand complex trait genetics and to design clinical trials. Discussion sessions regarding areas of future scientific opportunity were also included.

Translational Research for Type 1 Diabetes and Its Complications: It is critical to overcome barriers that prevent promising molecules and concepts from moving from the bench, or laboratory, to the bedside, where therapeutic agents can be tested for efficacy in treating human disease. For example, many academic scientists do not have the resources necessary for the pre-clinical development of therapeutic agents. This can cause a promising agent to be "stuck" in the laboratory, instead of moving forward for testing in human clinical trials. The Special Statutory Funding Program for Type 1 Diabetes Research has enabled the NIDDK to develop initiatives and resources to help investigators overcome these types of barriers.

Type 1 Diabetes–Rapid Access to Intervention Development (T1D–RAID). The NIDDK, in collaboration with the National Cancer Institute (NCI), has launched the T1D–RAID program to foster development of new therapeutics for type 1 diabetes. T1D–RAID is a special mechanism to make available to academic investigators the necessary resources to move novel molecules and concepts from bench-to-bedside more rapidly and effectively. T1D–RAID will assist investigators by providing preclinical development steps, the lack of which may be obstacles to clinical translation. Therapeutic agents that can be developed through the T1D–RAID program include small molecules, biologics, or vaccines for the treatment or prevention of type 1 diabetes and its complications.

Bench-to-Bedside Research. The NIDDK has reissued this initiative, which fosters interactions between basic and clinical scientists to move discoveries from a laboratory setting to preclinical or clinical testing of new therapies that could improve the health of individuals with type 1 diabetes.

Industry Participation. In collaboration with multiple other NIH Institutes, the NIDDK has sponsored a new Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Request for Applications (RFA) on type 1 diabetes and its complications. The purpose of this initiative is to propel the small business community to use cutting-edge technology in the research and development of commercial products, such as therapeutics, to prevent, treat, and cure type 1 diabetes and its complications.

Emerging Technologies To Study Type 1 Diabetes and its Complications: The recent completion of the Human Genome Project is a key example of how an emerging technology—high-throughput DNA sequencing—allowed researchers to achieve a momentous accomplishment. Other new and innovative technologies are continually being developed. Examples include technologies to describe the dynamics of protein interactions ("proteomics") and technologies to study cellular metabolites, such as lipids, amino acids, and carbohydrates ("metabolomics"). Proteomic technologies have been successfully used for studying several biological processes relevant to human health. High throughput metabolic profiling has been recently implemented for metabolomic studies. However, these technologies have only been applied in a limited way to study type 1 diabetes and its complications.

Proteomics and Metabolomics in Type 1 Diabetes and Its Complications. The NIDDK, in collaboration with the NIAID, NEI, NHLBI, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Child Health and Human Development (NICHD), has sponsored an initiative to take advantage of new and innovative technologies to enhance understanding of type 1 diabetes and its complications. These types of studies, which can be performed at different times of disease development, could lead to invaluable information for understanding the etiology and development of type 1 diabetes and its complications. Through this initiative, the NIDDK is promoting collaborative efforts between investigators with expertise in proteomics or metabolomics and investigators with expertise in type 1 diabetes. These partnerships will encourage type 1 diabetes investigators to expand their research to include use of these technologies and also provide proteomics investigators access to biological samples from type 1 diabetes patients or animal models.

Beta Cell Biology and Cell Signaling: Beta cells of the pancreatic islets sense glucose levels in the blood and respond by releasing insulin into the circulation when glucose levels exceed a physiologically-optimal range. Further understanding of cell signaling in the beta cell has been a top priority because altered function of this cell is central to the pathogenesis of both type 1 and type 2 diabetes.

Beta Cell Biology Consortium (BCBC). The NIDDK has bolstered research efforts through the BCBC, which was created to facilitate interdisciplinary approaches to advance understanding of pancreatic islet development and function. A new initiative, Seeding Collaborative Research in Beta Cell Biology (SCR–BCB), will promote collaboration among scientists working on areas such as development, systems biology, and pancreatic beta cells for the purpose of accelerating efforts towards the development of cell-based therapies for insulin delivery. A related effort is the Endocrine Pancreas Consortium, which works to apply the tools of functional genomics to the endocrine pancreas, to identify the genes expressed in mouse and human pancreas at all stages of development, and to generate DNA arrays and other tools to facilitate the identification of important signaling components. The Consortium has recently generated a research tool, called PancChip 5.0, which contains over 14,000 mouse genes that are important in the development of the pancreas. This chip can be used by the diabetes research community to study gene expression in the pancreas, which may provide insights into diabetes.

Pilot-and-Feasibility Program in Human Islet Biology. The importance of the need to obtain basic information about the general architecture and organization of human islets was underscored at a recent NIDDK-sponsored workshop, "Beta Cell Biology in the 21st Century: Engineering a Pathway to Greater Understanding," and also at an advisory meeting on islet transplantation held in May 2003. In response to the challenges identified, the NIDDK has sponsored

an initiative to increase understanding about the structure, organization, and signaling properties of human islets. The information gained from these studies should increase the ability to develop new reagents for use in in vivo imaging studies of the human islet, to develop assays for use in predicting human islet transplant success, and to further develop cellular therapies for potential use in the treatment of type 1 diabetes.

Comprehensive Programs in Beta Cell Biology. Pancreatic beta cells are in close contact with other hormone-producing cells that collectively work to regulate blood glucose levels. This initiative bolsters investigator-initiated collaborative research focused on signaling networks within the adult beta cell and the integration of signaling networks within the pancreatic islet. It seeks to characterize each step in the molecular pathway by which glucose stimulates insulin secretion, mechanisms by which other signals modify beta cell function, and the factors that regulate beta cell growth.

Obesity—Critical in Diabetes and a Major Health Problem of Its Own: The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels. Of particular concern is the increase in overweight in children and adolescents. Obesity is a major risk factor for numerous serious diseases, including type 2 diabetes, heart disease, and cancer. Overweight and obesity disproportionately affect minority populations, particularly African-American, Hispanic, and Native-American women and children. NIDDK-supported investigators are working to elucidate the molecular factors that control appetite, metabolism, and energy storage and are identifying potential targets for the development of new pharmacological agents to promote safe, long-term weight loss. As demonstrated recently by the landmark Diabetes Prevention Program (DPP) clinical trial, a five-to-seven percent sustained reduction in weight—achieved through modest improvements in diet and exercise—can delay or prevent the onset of type 2 diabetes in a high-risk population. Investigators are continuing behavioral research, such as that employed in the DPP, to help people achieve lifestyle modifications that include increased physical activity and improved diet.

The NIDDK Director has established an Office of Obesity Research to encourage multidisciplinary approaches to obesity and to coordinate all obesity-related research within the Institute. The office will coordinate the work of more than 11 programs with major obesity-related components—ranging from basic research to large clinical trials. The co-Directors of the Office of Obesity Research also lead a Trans-NIDDK Obesity Research Working Group, which synergizes efforts in this area across the Institute. The NIDDK also supports Obesity/Nutrition Research Centers and Clinical Nutrition Research Units, which conduct both basicand clinical research studies.

The NIDDK Director and the NHLBI Acting Director serve as co-chairs of the NIH Obesity Research Task Force (ORTF), which was established in April 2003, by the NIH Director to coordinate and facilitate obesity research efforts across the NIH. The ORTF membership includes numerous NIH Institutes, Centers, and Offices, as well as other NIDDK senior scientific staff. The ORTF is developing a strategic plan for obesity research, with external scientific and public input, in order to address areas of scientific promise that can benefit from collaborative efforts.

Look AHEAD (Action for Health in Diabetes) Trial. With support from other NIH Institutes and Centers, the NIDDK has launched Look AHEAD—a multicenter clinical trial that will examine the health effects of intentional weight loss in 5,000 obese diabetic patients, with particular emphasis on cardiovascular health. Enrollment, begun in June 2001, is now near completion. Trial participants, who will be followed for up to 11.5 years, are randomly assigned to one of two protocols, the Lifestyle Intervention, which is designed to help participants achieve and maintain weight loss over the long term, or Diabetes Support and Education.

Bariatric Surgery Clinical Research Consortium (BSCRC). The NIDDK has established this Consortium to facilitate research that would enhance patient evaluation and selection and may also lead to improved understanding of factors underlying the development of obesity and its associated co-morbidities, with implications for new strategies for prevention and treatment. The consortium also seeks to understand the risks and benefits of bariatric surgery as a treatment modality.

Clinical Trials and Clinical Research: The NIDDK has expanded clinical trials and clinical research directed at advancing the prevention and care of diabetes. Considerable work has been done to establish the clinical infrastructure essential for the efficient conduct of large, long-term trials by creating national, multicenter research networks or consortia. Many of these consortia provide opportunities for partnerships among the NIH, academia, and industry for collaboration, co-funding, and support of clinical research training in diabetes. This section of the report describes major new results achieved and new clinical research undertaken.

Cooperative Clinical Islet Transplantation Consortium (CCITC). The NIDDK is currently creating a major new islet transplantation network—the Cooperative Clinical Islet Transplantation Consortium (CCITC). The purpose of the CCITC is to design and implement human islet transplantation studies that may eventually result in more effective treatment of type 1 diabetes. Some of the studies may include: transplantation of islets alone, islets after kidney transplantation, and simultaneous islet-kidney transplantation; studies to better understand islet engraftment or rejection; and new approaches to minimize the toxicity of immunotherapy.

The Environmental Determinants of Diabetes in the Young (TEDDY). An international consortium has been established to provide a coordinated, multidisciplinary approach to understand the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. This information is crucial for developing prevention strategies. In this long-term effort, high-risk infants will be identified at birth and followed through adolescence. TEDDY is supported by the NIDDK, in partnership with NIAID, NICHD, NIEHS, CDC, JDRF, and ADA.

Type 1 Diabetes TrialNet. A consortium of investigators, clinical recruitment centers, and core support facilities has been established to perform intervention studies to preserve pancreatic beta cell function in patients with new-onset type 1 diabetes and to prevent type 1 diabetes in high-risk individuals. TrialNet has recently completed the DPT-1 oral insulin trial in individuals at intermediate risk for developing type 1 diabetes. Researchers found no difference in disease development between the study participants who received oral insulin and those who received placebo. TrialNet will also soon launch a "Natural History Study of the Development of Type 1 Diabetes" for the screening of first-degree relatives for the presence of autoantibodies; the assessment of risk of diabetes based on number of antibodies present, HLA type, and glucose intolerance; and the assessment of the natural history of diabetes onset in autoimmune pre-diabetes.

Continued Benefits of Improved Blood Sugar Control. The landmark Diabetes Control and Complications Trial (DCCT) previously showed that intensive control of blood glucose levels reduced the risk of damage to small blood vessels and nerves in type 1 diabetes patients. The follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continues to demonstrate long-term benefits of intensive therapy in these patients. In May 2002, EDIC investigators reported that the 6.5 year period of intensive treatment during the DCCT continued to reduce the risk of eye disease as long as 7 years after the study ended. Building on this exciting finding, a study in October 2003, showed that the former intensive treatment group had a decreased incidence of both kidney

damage and high blood pressure compared to the former conventional treatment group 8 years after the end of the DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the patients after completion of the DCCT.

While the DCCT proved that glucose control could prevent small vessel damage, which causes kidney, eye, and nerve problems, controversy remained about the effect of high glucose levels on the large vessels damaged in cardiovascular disease (CVD). In June 2003, the DCCT/EDIC research group showed that intensive control of blood glucose levels decreased progression toward atherosclerosis in type 1 diabetes. These results were achieved through use of both ultrasound to measure thickening of the wall of the carotid artery and also electron beam computed tomography (EBCT) to measure coronary calcification. This finding is significant because CVD causes death in two-thirds of patients with diabetes.

The DCCT and EDIC studies have provided conclusive evidence that patients should begin intensive therapy as early as safely possible. By maintaining intensive therapy, patients have significantly reduced development of diabetic complications, including damage to both large and small blood vessels. Researchers will continue to investigate mechanisms by which glucose exerts its devastating effects in the development of complications, with a goal of discovering therapeutic targets for treatment or prevention strategies.

Prevention of Type 2 Diabetes in People at High Risk. The Diabetes Prevention Program (DPP) demonstrated that individuals at substantial risk of developing type 2 diabetes could prevent or delay disease onset and improve their blood sugar levels through modest improvements in diet and exercise. Minority groups who are affected disproportionately from type 2 diabetes—African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and Native Americans—made up 45 percent of the over 3,200 individuals enrolled in the trial. The DPP was the first major clinical trial to show that improvements in diet and exercise can effectively reduce diabetes in a diverse American population of overweight people with pre-diabetes. Results from the DPP demonstrated a 58 percent decrease in the risk of developing diabetes with lifestyle intervention, and a 31percent decrease in risk with metformin treatment. The NIDDK is conducting follow-up studies of the DPP participants to determine the durability of the DPP interventions in preventing or delaying type 2 diabetes, as well as studying the long-term effect of the interventions on the development of complications. This research will also provide important information on the clinical course of new-onset type 2 diabetes in this diverse study population.

NIDDK Central Repositories. The NIDDK Central Repositories were established for biosamples and data collected in clinical studies. The purpose of the Repositories is to expand the usefulness of these studies by providing access to the biosamples and data to a wider research community beyond the end of a clinical study. The Repositories have three components: (1) Biosample Repository, which gathers, stores, and distributes biological samples from studies; (2) Genetics Repository, which receives and processes blood samples to allow genetic analyses; and (3) Database Repository, which gathers, stores, and distributes the incremental or finished datasets from studies. Samples and data from many diabetes clinical trials will be deposited in the NIDDK Central Repositories, which will be accessible to the greater research community for additional studies.

Understanding Hypoglycemia in Type 1 Diabetes: The potential for episodes of hypoglycemia, or low blood sugar, has limited the use of intensive insulin therapy that is known to reduce the risk of long-

term diabetic complications. Normally, the brain senses hypoglycemia and initiates a compensating cascade of signals to elevate blood glucose levels. However, in diabetic individuals who experience repeated episodes of hypoglycemia, the brain fails to respond. Because of the importance of the brain in this process, the NIDDK, in collaboration with NINDS, is sponsoring an initiative to promote research on how the brain and other critical tissues sense and respond to hypoglycemia, understand the effects of hypoglycemia on brain function, and develop more effective methodologies to prevent hypoglycemia.

Translating the Results of Clinical Research into Clinical Practice: The dramatic, positive results of large clinical trials have given insights into improved tools, treatment, and prevention strategies for both type 1 and type 2 diabetes. A key challenge is to ensure that the American people benefit from these discoveries. One approach to this challenge is to disseminate information, to those at risk and their health care providers, about measures proven effective for treating type 1 and type 2 diabetes and for preventing type 2 diabetes in individuals at high risk for this disease. It is also necessary to develop methods to take interventions that have been demonstrated to be beneficial in careful clinical investigations and extend or adapt them to larger populations or other settings. There is also increasing recognition that behavioral factors play a major role in the increased prevalence of obesity and type 2 diabetes and in the management of diabetes and its complications.

National Diabetes Education Program (NDEP). The NDEP is a partnership among the NIDDK, the CDC, and over 200 public and private organizations working together to reduce the morbidity and mortality associated with diabetes. A key feature of this program is the participation of individuals who represent communities such as African Americans, Hispanics/Latinos, Native Americans/Alaska Natives, and Asian and Pacific Islanders who are disproportionately affected by type 2 diabetes. The NDEP's "Small Steps, Big Rewards, Prevent Type 2 Diabetes" is a campaign to translate the positive results of the DPP into real health improvements for the public. The educational material contains a "Game Plan" that provides patients with information about implementing a program to prevent or delay disease onset. The NDEP's health awareness campaign, "Be Smart About Your Heart: Know the ABCs of Diabetes," is aimed at helping people with diabetes to better understand the need to control all aspects of their diabetes to help prevent heart attacks or strokes. The NDEP also has valuable resources for children with diabetes and their caregivers. "Helping the Student with Diabetes Succeed, A Guide for School Personnel" is a new comprehensive guide to empower school personnel, parents, and students to ensure a safe learning environment and promote a team approach to carry out a student's diabetes care plan. The NIDDK plans to distribute this important Guide to all schools in the country. The NDEP is also participating in the "Diabetes Detection Initiative (DDI): Finding the Undiagnosed," which is an effort to identify individuals at high risk for undiagnosed type 2 diabetes and then refer them for initial screening in a clinical setting and follow-up care, if needed. The DDI is being piloted in 10 communities in a variety of urban and rural settings, with future plans for expansion.

National Kidney Disease Education Program (NKDEP). This pilot program aims to prevent kidney disease by raising awareness about the seriousness of the problem and the importance of early diagnosis and appropriate treatment. The NKDEP is designed to close the gap between scientific evidence and medical practice by educating physicians and at-risk individuals, with the goal of identifying kidney disease in its early, treatable stages. The NKDEP pilot phase will initially target primary care providers and people at highest risk for kidney dis-

ease—particularly African Americans with diabetes, high blood pressure, or a family history of kidney disease—in four cities: Baltimore; Cleveland; Jackson, Mississippi; and Atlanta.

Behavioral Research—Key to Prevention and Treatment of Diabetes. Recent clinical trials have provided definitive evidence that type 2 diabetes can be prevented with lifestyle change and that rigorous control of blood glucose, blood pressure, and lipid levels can delay or prevent diabetes complications. Yet, this control can be arduous—requiring adherence to a complex regimen of medications, diet, and physical activity—therefore, very few Americans with this disease can attain optimal control.

An initiative is intended to further research in implementing the treatment and lifestyle changes required to prevent diabetes in high-risk groups or to improve outcomes in individuals with diabetes. Clinical or behavioral studies are encouraged on improving methods of health care delivery to patients with or at risk of diabetes, improving methods of diabetes self management, and developing cost effective community-based strategies to promote healthy lifestyles.

The NIDDK is also supporting research to study the interactive nature of diabetes and co-occurring depression. The NIDDK collaborated with the National Institute of Mental Health (NIMH) and the NIH Office of Behavioral and Social Sciences Research (OBSSR) in holding a major conference to determine the state of knowledge with regard to the co-morbid condition of depression and to propose a research agenda for the future. Based on recommendations from this conference, an initiative was developed to increase research activity on depression in relationship to diabetes, chronic renal disease, and obesity and eating disorders. As a result, research efforts and interest in this field have expanded significantly.

Advancing Research by Building Partnerships and Attracting New Research Talent: Type 1 and type 2 diabetes research spans an extraordinarily broad range of scientific disciplines including endocrinology and metabolism; immunology; cell signaling; genetics and the influence of environmental factors; obesity; the physiology of the heart, eyes, kidneys and urologic tract; and the central and peripheral nervous system. In addition, research efforts in these fields extend from basic laboratory studies to clinical trials in human patients. Understanding the underlying biological mechanisms that lead to onset of type 1 and type 2 diabetes, and developing new strategies for prevention and cure, will require a cadre of scientists with diverse research training and experience. Furthermore, it is important that scientists with diverse expertise collaborate—a multidisciplinary approach will propel greater understanding of complex diseases.

Bringing Together Basic and Clinical Researchers. An innovative "bench-to-bedside" program supports collaboration between basic research scientists, whose findings have potential direct applicability to development of new treatments or diagnostic tests, and clinical scientists, who can help translate these basic discoveries into pre-clinical or clinical trials.

Attracting New Talent to Diabetes Research. An innovative partnership program is promoting collaboration among diabetes researchers and those in areas other than diabetes who have expertise or technology that could advance diabetes research projects. The goal is to encourage diabetes researchers to act as "talent scouts" to identify other researchers who could contribute to research breakthroughs in diabetes.

Developing Clinical Researchers for Childhood Diabetes. In collaboration with the ADA and the JDRF, the NIH supports a program that fosters development of a diverse and highly trained workforce of pediatric endocrinologists to assume leadership roles related to the Nation's biomedical and behavioral research efforts in the area of pediatric diabetes. This effort supports a combination of complementary programs at institutions with particular strength in pediatric diabetes research. These combined programs will support development of new researchers by providing research training during pediatric endocrinology fellowships followed by a special career development award framed to provide research support for individuals who have completed their research training and have dedicated themselves to becoming independent clinical researchers.

National Institute of Environmental Health Sciences (NIEHS)

http://www.niehs.nih.gov

Many environmental agents have been investigated as contributing to the risk of diabetes. Environmental components have been suggested, especially for type 1 diabetes, because concordance rates between identical twins, where one twin has diabetes, remain at 30–50 percent. However, other environmental influences may also contribute to the rising incidence of type 2 diabetes as well.

The NIEHS is pursuing research in several areas relevant to environmental influences and diabetes, as summarized below.

Current Activities

Recent studies have raised the possibility that certain chemicals in the environment, such as nitrates in well water, increase the risks of type 1 diabetes. Studies in the United Kingdom, Finland, and Colorado indicate that the incidence of childhood diabetes is higher in areas with elevated levels of nitrate in the drinking water. This finding is significant for agricultural communities because well water can have elevated nitrate levels in areas where there is extensive use of fertilizers. Current and future activities in this area by NIEHS intramural scientists include:

- Initiation of a nested case-control study of environmental risk factors (e.g., pesticides, nitrates in drinking water, animal contacts) for diabetes in children of farmers enrolled in the Agricultural Health Study, a prospective cohort study involving nearly 60,000 licensed pesticide applicators and 32,000 spouses of applicators who are farmers.

- Evaluation of diabetes risk along with other health outcomes in the Agricultural Health Study. Farmers are an otherwise healthy group whose active lifestyle ought to decrease their risk for type 2 diabetes. Against this background, the role of potential environmental risk factors should be easier to detect.

In other studies, intramural investigators at NIEHS have reported an association between the body burden of a persistent organic pollutant (polychlorinated biphenyls) and type 1 diabetes. Current and future studies in this area include:

- Further studies to examine the relation between diabetes and body burden of persistent organic pollutants are either underway or being planned. For example, DNA is being collected from a cohort of men so that polymorphisms in the Ah-receptor (binds with dioxin-like polychlorinated biphenyls) can be examined in relation to body burden of persistent pollutants and risk of diabetes.

In extramural studies supported by the NIEHS, investigators are studying the possibility that arsenic in drinking water causes an increase in diabetes risk. Elevated levels of arsenicals in drinking water are common throughout the world, and oxidative forms of arsenic are known to have cytotoxic effects. These studies will:

- Investigate the effects of trivalent arsenicals and related compounds on glucose-stimulated insulin secretion in pancreatic islets and cell culture systems.

- Examine the effects of these compounds on insulin sensitivity in insulin-sensitive peripheral tissues and in intact animals.

- Examine the possibility that arsenic is exerting diabetogenic effects through direct interaction with glucocorticoid receptors.

Other extramural research efforts are examining the contributions of stress-activated protein kinases to insulin resistance and type 2 diabetes, the mechanisms of action of xenobiotic beta-cell toxins in animal models, and a potential role for glutamate-cysteine ligase gene polymorphisms in the pathogenesis of type 1 diabetes.

As noted above, the intermediate concordance rates for type 1 diabetes have stimulated the search for contributing environmental factors. Current and future activities in this area by intramural investigators include:

- In collaboration with investigators in the United Kingdom, the NIEHS is investigating the hypothesis that persistant materno-fetal michrochimerism influences the development of type 1 diabetes in a set of monozygotic twins discordant for type 1 diabetes.

- The NIEHS is investigating the possibility of establishing a discordant monozygotic twin registry in the United States for twins with type 1 diabetes, so that prospective studies of at-risk twins can be carried out.

- The NIEHS is carrying out in-depth proteomic evaluations of plasma and urine from patients with diabetes in an attempt to identify novel protein markers of diabetes control and complications.

- Intramural investigators are carrying out studies of risk factors for the development of polycystic ovary syndrome in female twins. This common syndrome of women of reproductive age is accompanied by insulin resistance, frequently leading to diabetes, and this study hopes to develop novel prevention strategies for this condition.

Future Activities

Recent findings by intramural investigators using knockout mice have identified the guanine nucleotide regulatory or G protein G0 as an important regulator of glucose tolerance and glucose-stimulated insulin secretion in mice. Future studies will involve:

- Investigations into the molecular nature of the enhanced glucose tolerance seen in the intact G0 knockout mice.

- Studies of the molecular mechanisms of the enhanced glucose-stimulated insulin secretion seen in isolated islets from the mice.

National Institute of General Medical Sciences (NIGMS)

http://www.nigms.nih.gov

The National Institute of General Medical Sciences supports research and research training in the basic biomedical sciences that provide the foundation for a better understanding of fundamental life processes. Some of this work has relevance to understanding and treating diabetes.

Current Activities

NIGMS supports the Human Genetic Cell Repository, a collection of over 8,700 cell lines from individuals with a wide variety of genetic disorders, including diabetes, and from normal individuals. Cell lines in the collection include those from individuals with both type 1 and type 2 diabetes mellitus and its complications. The repository includes an extensive collection of cell lines from members of an extended pedigree with maturity-onset diabetes of the young. This collection is of value in studies designed to map and characterize the gene(s) responsible for these disorders.

DNA is also available for many of the cell lines in the Human Genetic Cell Repository. In new initiatives, the Repository has continued to collect new, large panels of cell lines from individuals in ethnically identified, minority populations within the United States. These new collections supplement the panels of cell lines from hundreds of unrelated individuals that were acquired earlier, in order to facilitate analyses of the genetic diversity of the U.S. population. This resource has proven to be of great value to researchers for the discovery of DNA polymorphisms important in pharmacogenetic studies and in the identification of genes involved in complex genetic disorders such as diabetes. The NIGMS Human Genetic Cell Repository will continue to cooperate with the National Human Genome Research Institute in the collection of cell lines from around the world for the HapMap project.

NIGMS has an interest in understanding how genetic and environmental components interact to result in complex diseases such as diabetes. The Institute supports a portfolio of grants to develop better statistical methods for mapping and identifying genes underlying complex traits, develop mathematical models for studying gene-gene and gene-environment interactions, investigate DNA sequence variation and its evolution, examine gene activities and the consequences of abnormalities in these activities, and optimize sampling strategies. NIGMS also supports pre- and postdoctoral training that emphasizes statistical and computational skills and workshops to provide additional training in statistical methods to biologists.

NIGMS support for research on the mechanisms underlying individual variations in drug response, while not specifically targeting diabetes, has the potential to have an impact on the treatment of diabetes and its complications. Researchers are studying the structural features of a powerful peripheral vasodilator related to insulin identified as an important prospective drug for peripheral angiopathies associated with diabetes.

NIGMS, in conjunction with several other Institutes, is supporting a mouse mutagenesis and phenotyping center whose emphasis is the high-throughput generation and identification of mice with mutations in biochemical and developmental pathways that may prove useful as models for human diseases.

NIGMS is also participating in the Trans-NIH Zebrafish Initiative, whose goal is to improve the genomic resources for the zebrafish, another potentially valuable model for diabetes studies.

NIGMS is now supporting a center to model metabolic systems in cells and tissues. A multicenter effort has also been funded to produce an accounting of all of the types of lipids and lipid-associated proteins that are involved in every aspect of cell function.

NIGMS is sponsoring multiple research programs that are seeking to understand the physiologic processes involved in normal wound healing. While this support has primarily been directed toward efforts focused on trauma and burn injuries, there is now an increasing interest in investigations of infectious, inflammatory, and metabolic factors that can compromise wound repair in the context of chronic conditions such as diabetes.

Future Activities

In the future, NIGMS will continue to support basic research that focuses on underlying mechanisms and principles that are expected to shed light on both normal and disease processes and to lead to the development of new modes of treatment and prevention.

National Institute of Mental Health (NIMH)

http://www.nimh.nih.gov

The National Institute of Mental Health supports research on the processes and mechanisms underlying co-morbid mental disorders and diabetes. It also supports research to develop and test preventive, treatment, and rehabilitative interventions for mental disorders in people with diabetes. The interventions may be pharmacologic, behavioral, or psychosocial.

Current Activities

In FY 2000–2001, NIMH and the National Institute of Diabetes and Digestive and Kidney Diseases co-sponsored a major research conference, "Depression and Mental Disorders in Patients With Diabetes, Renal Disease, and Obesity/Eating Disorders," on January 29–30, 2001 at the Natcher Conference Center, National Institutes of Health. The papers resulting from the conference have been published in a 2002 special issue of the *Journal of Psychosomatic Research* (October 2002; 53(4)). The two Institutes jointly released a Request for Applications to fund new research projects in 2002. The NIMH supported two applications with its available funds.

In addition, NIMH re-issued in 2002 its program announcement calling for research applications on co-morbid mental and physical disorders, including diabetes.

National Institute of Neurological Disorders and Stroke (NINDS)

http://www.ninds.nih.gov

The National Institute of Neurological Disorders and Stroke supports investigations of the neurological complications of diabetes. Particularly important are the neuropathies found in at least 60 percent of people with diabetes with symptoms such as pain, numbness, double vision, and weakness at times to the point of paralysis. Sensory impairment even when sub-clinical, almost certainly contributes to the development of foot ulcers in diabetics and these may lead ultimately to amputations. The painful neuropathy/radiculopathy is very hard to manage and may be mistaken for pain due to a herniated disc. Symptoms of diabetic autonomic neuropathy can include heart rate abnormalities, hypertension, dizziness, digestive disturbances, and impotence. Autonomic neuropathy is an important cause of sudden cardiac death in people with diabetes. The regulation by the central nervous system to maintain euglycemia is also challenged by diabetes and insulin therapy. Altered metabolism in the form of low grade hypoglycemia (hypoglycemia unawareness) may have long-term consequences in the nervous system. Prevention and treatment of neurological complications is a central therapeutic problem in diabetes mellitus. Research supported by NINDS spans these diverse areas.

Current Activities

NINDS has participated in nine initiatives related to the special type 1 diabetes appropriations, three as the lead institute. As the result of three Requests for Applications (RFAs) published each year between FY 1998 and FY 2000, NINDS greatly expanded its research into neurological complications of diabetes. These solicitations address early detection of diabetic neuropathy, mechanisms of neuropathic pain, the neurobiology of diabetic complications, gene transfer for prevention of neuropathy, and behavioral effects of both hypoglycemia and hyperglycemia.

Several new NINDS applications were funded from two FY 2002 RFAs. Applications in response to the RFA "Surrogate Endpoints for Diabetic Microvascular Complications" are looking for ways to detect early signs of diabetic neuropathy. Applicants whose grants were in response to the RFA "Effects of Hypoglycemia on Neuronal and Glial Cell Function" are studying mechanisms by which hypoglycemia effects astrocytes and neurons in the central nervous system. In FY 2003, NINDS co-sponsored, with several other institutes, four new RFAs aimed at diabetic complications.

NINDS continues to support a large epidemiological study of neurological complications of diabetes in the Rochester, Minnesota, area in the Caucasian and Mdewakanton Dakota Native American and soon the Hispanic populations. Diabetes is characterized by large disparities in prevalence among ethnic groups, but little is known about the extent of neurological complications in these populations. This study will be the first to document the extent and progression of neurological complications in a longitudinal multiethnic cohort. Additional studies of this type have been solicited in a new jointly issued Program Announcement (PA), "Race/Ethnic Disparities in the Incidence of Diabetes Complications."

Future Activities

NINDS plans to continue investigations of diabetic neuropathy and of hypoglycemia and may seek to re-issue PAs and RFAs pertaining to these topics.

National Institute of Nursing Research (NINR)
http://ninr.nih.gov/ninr

The mission of the National Institute of Nursing Research is to support clinical and basic research to establish a scientific basis for the care of individuals across the lifespan—from management of patients during illness and recovery to the reduction of risks for disease and disability, the promotion of healthy lifestyles, the improvement of quality of life in those with chronic illness, and care for individuals at the end of life. One purpose of this research, specific to diabetes, is to understand how to promote health-sustaining behavior and to improve quality of life by relieving the effects of disease processes and their progression. Nursing research focuses on how physical and psychological responses to diabetes symptoms and treatment of the disease affect health throughout the lifespan. NINR research programs pay particular attention to the effect of diabetes in minority and underserved populations.

Current Activities

In response to Program Announcements (PAs) or Requests for Applications (RFAs) either directly or indirectly related to diabetes research, NINR had an increase in diabetes funding in FY 2003.

In FY 2003 NINR continued to encourage diabetes research through its participation in several ongoing PAs: *Race/Ethnic Disparities in the Incidence of Diabetes Complications (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)); Translational Research for the Prevention and Control of Diabetes (NIDDK); Enhancing Adherence to Diabetes Self-Management Behaviors (NINR);* and *Diabetes Self-Management in Minority Populations (NINR)*. These PAs are consistent with Diabetes Research Working Group (DRWG) recommendations (NINR was a participant in this working group).

In response to increased congressional support for type 1 diabetes research, NINR joined NIDDK to sponsor two new RFAs issued in FY 2003: *Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Develop New Therapies for Type 1 Diabetes and its Complications;* and *Innovative Partnerships in Type 1 Diabetes Research.*

NINR funded grants relating to diabetes research included career development, postdoctoral training, and investigator-initiated research. Diabetes-specific topics include ethnic variations in type 2 diabetes prevention knowledge, cardiovascular risk in adolescents with diabetes, Spanish language self-management programs, biobehavioral intervention studies in African-American, Latino, and Korean-American groups, an intervention for parents of young children with newly diagnosed diabetes, biophysical determinants of diabetes foot ulcer healing, obesity and diabetes prevention, diabetes self-management using telehealth, and exercise and oxidative stress in diabetes.

Future Activities

NINR plans to continue to support research that focuses on problems experienced by those affected by diabetes. Research efforts will be guided by the following goals:

- FY 2004: NINR will work collaboratively with other Institutes and organizations to increase and facilitate diabetes research activities. NINR will update and reissue productive Program Announcements.

- FY 2005: NINR will focus support on promising ongoing and new diabetes research opportunities, while building on recent nursing science advances.

In summary, NINR activities are designed to support research related to interventions for persons with diabetes, self-management, quality of life, special and diverse population needs, problems of defined age groups and across the lifespan, basic research, genetics, and other initiatives relevant to clinical practice and client outcomes. Translation of science advances to the practice setting is ongoing.

National Institute on Aging (NIA)

http://www.nia.nih.gov

The mission of the NIA as it relates to diabetes research and related issues is to support biomedical and behavioral research leading to improved therapies to prevent diabetes and its complications, as well as to improve quality of life of older diabetic patients.

Current Activities

An NIA-supported project has demonstrated a cause-and-effect relationship between visceral fat and major components of the metabolic syndrome. Surgical removal of visceral fat in aging (20-month-old) F344/Brown Norway (FBN) and in Zucker Diabetic Fatty (ZDF) (accounting for approximately 18 percent of their total body fat) was sufficient to restore peripheral and hepatic insulin action to the levels of young rats. While removal of visceral fat in ZDF rats prevented the progressive decrease in insulin action and delayed the onset of diabetes, it did not alter plasma free fatty acid levels. This data suggest that insulin resistance and the development of diabetes can be significantly reduced in aging rats by preventing the age-dependent accumulation of visceral fat.

The NIA Intramural Research Program has been studying compounds that might be of use for treating type 2 diabetes. They have concentrated on compounds that induce insulin release (insulin release is deficient in type 2 diabetes) and are protective of the beta cell of the pancreas. A specific gut hormone, GLP-1, that is released after eating, can lower blood sugar in type 2 diabetic subjects when given in pharmacological doses. Exendin-4 is an agonist of the GLP-1 receptor. It has all of the benefits of GLP-1 treatment and has the added advantage of having a much longer half-life—about 2 hours. Recently a study of subcutaneous exendin-4, given twice daily to type 2 diabetic subjects, for 1 month found: (1) exendin-4 is well tolerated, (2) that it retains efficacy for at least 1 month, (3) there were no unexpected side-effects, and (4) that it is at least as effective in lowering blood glucose as current treatments for type 2 diabetes. Thus, exendin-4 appears to be a viable potential candidate agent for treating type 2 diabetes and phase 3 studies to evaluate efficacy and safety in a type 2 diabetic population are warranted.

NIA-supported research is also focused on ascertaining the effects of free fatty acids (FFA) on endogenous glucose production (i.e., on gluconeogenesis (GNG) and glycogenolysis (GL)). Previous work has established that FFA may mediate hepatic insulin resistance (i.e., inhibition of insulin suppression of endogenous glucose production). Recent results showed that insulin suppressed endogenous glucose production primarily by inhibiting GL, and elevated plasma FFA levels caused hepatic insulin resistance by interfering with insulin suppression of GL. These observations may have pathophysiologic significance. In diabetic patients, partial unresponsiveness of endogenous glucose production to hyperinsulinemia is a major problem contributing to hyperglycemia. These patients commonly have elevated plasma FFA levels that may contribute to this problem by inhibiting insulin-mediated suppression of GL.

Another NIA-funded study investigated the biochemical mechanism by which FFA cause insulin resistance in skeletal muscle. This study examined the possibility that FFA-induced insulin resistance in human muscle is related to alterations in diacylglycerol (DAG)/protein kinase C (PKC) signaling. The results suggest that the insulin resistance observed in human muscle when plasma FFA levels were elevated was associated with large increases in DAG mass and membrane associated PKC activity. The data suggest that FFA cause insulin resistance by DAG-mediated activation of PKC in muscle. Based on other observations, it was suggested that FFA may stimulate pro-inflammatory and pro-atherogenic pathways. These new observations may help explain some of the increased prevalence of coronary artery disease in obese patients with type 2 diabetes, because almost all of these patients have increased plasma FFA levels and are insulin resistant.

Caloric restriction (CR, i.e., limiting caloric intake below *ad libitum* levels) in animal models, extends maximum and average lifespan by as much as 40 percent and delays age-related pathologies. Among the aging changes slowed by CR regimens are declines in glucose tolerance and insulin sensitivity and increases in body weight. To evaluate the effects of CR interventions in humans, the NIA initiated the group of U01 projects known as CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy). There are three clinical sites, testing different interventions of CR in non-obese (but mostly overweight) individuals. Locations of the clinical sites include the Washington University in St. Louis, Tufts University in Boston, and the Pennington Biomedical Research Center in Baton Rouge. The Coordinating Center is located at Duke Clinical Research Institute. The primary goals of CALERIE are to gain knowledge: (1) about CR effects in humans on physiology, metabolism, body composition, and risk factors for age-related pathologies, and (2) of similarities, differences and interactions between the effects of CR and physical activity on the physiological outcomes of interest (e.g., changes in energy metabolism, surrogate markers of oxidative stress, endocrine function). Initiated in early 2002, the CALERIE clinical sites are presently conducting pilot projects of different CR interventions involving 20–30 percent restriction of energy intake. Some of the feasibility studies also include physical activity interventions designed to achieve similar levels of negative energy balance as with CR. The results of these feasibility studies will be subsequently used to design full-scale clinical trial(s) of CR sustained for at least 2 years.

The NIA is a cosponsor of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) study, Diabetes Prevention Program-2 (DPP2).

The NIA is a cosponsor of the NIDDK Request for Applications (RFA) (DK-03-022) "Ancillary Studies to Obesity-Related Clinical Trials." This initiative has multiple receipt dates spanning FY 2004 and 2005.

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

http://www.niaaa.nih.gov

The National Institute on Alcohol Abuse and Alcoholism encourages research to understand the role of alcohol consumption as a risk factor in the development of obesity and diabetes mellitus. NIAAA also supports research to determine the effects of moderate alcohol consumption on diabetes. Several studies suggest that alcohol consumption may directly or indirectly contribute to the development of type 1 diabetes based on the following observations: (a) alcohol impairs pancreatic insulin secretion; (b) chronic alcohol intake increases plasma TNF levels which have been shown to cause pancreatic beta cell apoptosis leading to decreased beta cell number and insulin secretion; and (c) chronic alcohol consumption may impair beta cell function by eliciting immunotoxicity.

Chronic alcohol consumption also has been implicated in the development of type 2 diabetes based on the following findings: (a) chronic alcohol feeding in rats reduces the number of insulin-binding sites on isolated hepatocytes; (b) alcohol impairs insulin-mediated tyrosine phosphorylation of insulin receptors in a tumor cell line; (c) chronic alcohol exposure blunts tyrosine phosphorylation of insulin receptor substrate-1 in rat hepatocytes and a tumor cell line; and (d) chronic alcohol exposure inhibits the activity of rat hepatocyte phosphotidylinositol-3kinase which stimulates glucose transport. These effects of alcohol may lead to insulin resistance and impaired glucose transport.

Current Activities

Currently, NIAAA supports three projects that investigate the relationship between alcohol intake and diabetes.The following research areas are under investigation:

- Impact of moderate alcohol consumption on the risk of diabetes mellitus.

- Effects of fetal alcohol exposure on the biochemical and physiological changes in the insulin response and glucose homeostasis.

- Molecular mechanisms of disruption of insulin-mediated glucose transport by ethanol.

Future Activities

NIAAA will build up its portfolio on the interaction between alcohol consumption and diabetes mellitus and tissue injury. Activities planned include:

- *Workshop.* Role of Obesity in Alcoholic Liver Disease: October 2003.

- *Program Announcement.* Alcohol, Obesity and Diabetes Mellitus in FY 2004.

- *Proposed Workshop.* Alcohol and Diabetes in FY 2004.

National Institute on Deafness and Other Communication Disorders (NIDCD)

http://www.nidcd.nih.gov

Disorders of hearing, balance, smell, taste, voice, speech, and language exact a significant economic, social, and personal cost for many individuals. The mission of the National Institute on Deafness and Other Communication Disorders is to support and conduct research and research training in the normal processes and the disorders of human communication that affect many millions of Americans. NIDCD supports basic and clinical research on diabetes mellitus in the area of taste. Taste preferences for sweet-tasting substances play a crucial role in the development of insulin and non-insulin dependent diabetes.

Current Activities

NIDCD is supporting research on taste and endocrine factors in women with gestational diabetes. Gestational Diabetes Mellitus (GDM) is a common complication of pregnancy with serious consequences for maternal and child health. Diet is an integral part of the management of GDM, but current diet strategies for pregnant women with GDM are poorly defined and often fail. NIDCD-supported scientists have observed that GDM increases the preference for sweet taste and dietary intake of sweet foods, which could have important implications for the management of this disease. At the time of diagnosis (approximately 30 weeks gestational age), pregnant women with GDM showed a higher preference for sweetened dairy drinks compared to pregnant women without GDM. In addition, increased plasma glucose in women with GDM was related to higher preference for the sweet taste of glucose and higher dietary intake of simple sugars as fruit and fruit juices. Because these studies were limited to a single observation point during gestation and excluded women with severe diabetes or those treated with insulin, further studies are needed.

The specific aims of this project are: (1) to determine the relationship between hyperglycemia and increased taste preference and dietary intake of sweet foods in GDM, (2) to compare the temporal pattern of taste and dietary changes in women with GDM to those of women without GDM across pregnancy stages, and (3) to relate these taste changes to alterations in gestational hormone and metabolic profiles. A single prospective study will be conducted to measure sweet taste preferences, food cravings, dietary intake of sweet foods, and plasma indices of selected hormones and metabolites (including insulin, cortisol, and leptin) during early, middle, and late gestation and at 6-week and 20-week post-delivery. The long-term goal of this project is to obtain a better understanding of taste changes in women with GDM to develop better preventative and therapeutic dietary intervention strategies for this disease.

National Institute on Drug Abuse (NIDA)
http://www.nida.nih.gov

A study on glucose metabolism disorders in HIV-infected drug abusers was funded by NIDA in FY 2003. A brief description of the study follows prepared by Andrea Howard, M.D., Montefiore Medical Center, Bronx, New York.

Current Activities

Based on the fact that HIV-infected drug users may be at heightened risk for impaired glucose tolerance and type 2 diabetes mellitus in association with protease inhibitor (PI) therapy and co-infection with hepatitis C virus (HCV), the Principal Investigator is funded to address these issues in a 5-year prospective study of 300 individuals with or at risk for HIV infection in order to examine the associations of HIV, PI therapy, and HCV infection with impaired glucose tolerance and type 2 diabetes. The Principal Investigator will: (1) determine the prevalence of and factors associated with impaired glucose tolerance and type 2 diabetes in HIV-infected drug users, including PI therapy, HCV infection, socio-demographics, body mass index, and family history of diabetes; and (2) determine prospectively the impact of HIV infection, PI therapy, and HCV infection on the incidence of impaired glucose tolerance and type 2 diabetes. At semi-annual research visits, participants will undergo standardized interviews to assess socio-demographics, medical history, and drug use behavior; measurement of height, weight, and waist/hip ratio; and blood tests for CD4+ count, HIV viral load, HCV antibody, and HCV RNA level. In addition, fasting lipid profiles and body composition analysis using dual x-ray absorptiometry will be obtained. Oral glucose tolerance tests will be performed annually to screen for impaired glucose tolerance and diabetes. Active surveillance for clinical

disease events will also be performed. The Principal Investigator's long-term career goal is to become an independent investigator of HIV epidemiology in drug users. She will work closely with a multidisciplinary group of mentors with expertise in research related to HIV, diabetes, hepatitis C, and substance abuse and will also complete coursework in the conduct of diabetes-related clinical research, addiction medicine, and the responsible conduct of research.

The proceedings of a workshop on "Interventions for Metabolic and Endocrine Complications of HIV/AIDS and Drug Abuse," guest-edited by Jag Khalsa, Sander Genser, and Henry Francis, of the Center on AIDS and other Medical Consequences of Drug Abuse, NIDA, was published as a special supplement in the *Clinical Infectious Diseases* journal (September 1, 2003, volume 37(#2), pages s37–s153).

National Library of Medicine (NLM)
http://www.nlm.nih.gov

NLM explores the use of new information technologies to enable diabetes patients to manage their disease and avoid or delay the onset of costly and debilitating complications, especially patients from minority and medically underserved populations.

In particular, NLM seeks to learn how the use of NLM's MEDLINEplus website, and other computer-based health information resources, can be helpful to patients, their families, and members of the public to learn about and understand the latest research news on diabetes, nutritional requirements, tests, devices, and secondary prevention techniques and for obtaining answers to patient-specific questions. In the clinical setting, the principal hypothesis is that MEDLINEplus can reinforce and supplement the information provided by physicians, nurses, and health educators. A related hypothesis is that a combination of individualized training and access to publicly available computer resources at hospital libraries and elsewhere in the community can help bridge the "digital divide" experienced by minority populations that have less ready access to computers in the home, school, and workplace than the majority population.

Current Activities

NLM develops, designs, implements, and evaluates a comprehensive program of diabetes-focused outreach initiatives in collaboration with academic health science centers and libraries, clinical centers, community-based organizations, and voluntary health organizations.

Project A. Enhance the usability of MEDLINEplus for Spanish-speaking users by developing a Spanish language version of the more than 500 health topics, patient tutorials, medical encyclopedia, and drug information database and evaluate its acceptance among diabetes patients.

Project B. In collaboration with two churches serving the African-American community in Montgomery County, Maryland, experiment with the concept of "peer tutors" as a means to recruit teenagers at risk for type 2 diabetes, enhance their diabetes knowledge with the use of MEDLINEplus, and observe changes in risk behaviors by them and by their peers.

Project C. In collaboration with the University of Texas Health Science Center at San Antonio, and its regional health center and clinics in the Lower Rio Grande Valley, study how computer workstations installed in clinic waiting rooms and in information technology centers located in "colonias," can provide Hispanic patients with diabetes-related information.

Project D. In collaboration with Columbia University, conduct field usability testing of IDEATel (informatics for Diabetes Education and Telemedicine) with seniors and minority populations in New York City and State. Study and evaluate the user interface and the cognitive abilities of these patients to effectively use the interface for remote in-home diabetes monitoring and education.

Veterans Health Administration (VHA), Department of Veterans Affairs

http://www.va.gov/diabetes

The mission of the Department of Veterans Affairs Healthcare System is to serve the needs of America's veterans by providing primary care, specialized care, and related medical and social support services. To accomplish this mission, VHA needs to be a comprehensive, integrated healthcare system that provides excellence in healthcare value, excellence in service as defined by its customers, and excellence in education and research, and it needs to be an organization characterized by exceptional accountability and by being an employer of choice.

The mission of the VHA diabetes program is to improve the health of veterans with diabetes by decreasing the incidence of adverse health outcomes, especially macrovascular and microvascular disease. This will be accomplished through systems-level integration of guidelines, performance measurement, data feedback, and education to promote the increased use of evidence-based preventive and treatment processes. VHA research service supports this mission through clinical, basic science, and health services research. VHA reports the following progress in FY 2003.

Current Activities

Performance Measurement (Office of Quality and Performance). In FY 2003,VHA, through its ongoing External Peer Review Program, collected data from a random sample of veterans with diabetes from each VHA facility. A patient must have accessed VHA for any type of care some time at least once 2 years ago and at least once during the previous 12 months. The percentage of patients having chart documentation of the following measures, and the increase from FY 2002, is as follows:

- HbA1c test (94%); 81percent of HbA1c values less than 9 percent (+3%); lipid profile within 2 years (94 percent; 71 percent of LDL-C values less 120 mg/dl (+8%); Blood pressure control, 71 percent less than 140/90 (+13%).

- Dilated retinal examination, 75 percent (+3%).

- VHA adherence to diabetes and non-diabetes indicators exceeded the average in Medicare Fee for Service in FY 2000 on 12 of 13 common indicators (Effect of the Transformation of the Veterans Affairs Health Care System on the Quality of Care, *N Engl J Med*, 348: 2218-2227, 2003).

Lower Extremity Amputation Programs (Offices of Patient Care Services and Medical Inspector). In FY 2001 the Under Secretary for Health reissued the VHA Preservation, Amputation Care and Treatment Directive (PACT), which mandates multidisciplinary foot care programs, including screening, surveillance, and salvage components, at all VHA facilities. Over 92 percent of veterans have an annual visual foot examination, and about 84 percent have a sensory examination. From FY 1999–FY 2002, the age-adjusted rate of total diabetes-related amputations decreased performed in the VHA has decreased from 7.68 per 1,000 veteran clinical users to 4.84. Major amputations decreased from 3.9 per 1,000 veteran clinical users to 2.3, and minor amputations decreased from 3.78 per 1,000 veteran clinical users to 2.54.

Guideline Development (Offices of Quality and Performance and Patient Care Services). VHA, in partnership with the Department of Defense, updated its Diabetes Clinical Practice Guidelines (May 2003). The guidelines, covering outpatient management of glycemia, blood pressure, hyperlipidemia, diabetic retinopathy, foot care, and renal disease, emphasize transparency of the evidence underlying clinical recommendations as well as principles of absolute risk reduction and patient-clinician decision-making.

Research Service. There are three VHA Research Enhancement Award Programs (REAPs) on diabetes research funded by Medical Research Service. The REAPs focus on investigating the effects of diabetes upon the vascular system; the regulation of gene transcription by insulin and by glucose and its metabolites in order to improve insulin responsiveness; and the mechanism linking decreased islet beta-cell function to the abnormal glucagon secretion that occurs during hypoglycemia in patients with diabetes.

Ongoing programs include the 5-year cooperative study (VA Diabetes Trial, CSP #465) to evaluate the effect of near-normal glycemic control upon cardiovascular outcomes in type 2 diabetes.

The VHA Quality Enhancement Research Initiative (QUERI) has been cited by the Institute of Medicine as a model for translational research. Diabetes Mellitus-QUERI program continues to focus upon more aggressive treatment of modifiable risk factors and the prevention of progressive complications among veterans with diabetes and continues to work with partners outside VHA, including the Centers for Disease Control and Prevention (Translating Research Into Action for Diabetes).

Education. Over thirty VHA facilities have obtained American Diabetes Association Recognition of their patient education programs—more than any other national system of health care. VHA hosted the annual VA Diabetes Educators Conference for over 200 VHA clinician educators. This represents an institutional commitment to translating agency priorities and research findings into results at the field level.

Future Activities

VHA remains committed to leveraging performance measurement, its medical informatics system, research, and patient and clinician education to improve interim metabolic outcomes (A1c, blood pressure, and cholesterol), as well as to improve cardiovascular, chronic kidney disease, eye, and foot care outcomes.

THE NATIONAL DIABETES EDUCATION PROGRAM

THE NATIONAL DIABETES EDUCATION PROGRAM

http://www.ndep.nih.gov

Fiscal Year 2003 Accomplishments

The National Diabetes Education Program (NDEP) is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health and the Centers for Disease Control and Prevention (CDC) and is a subcommittee of the Federal Government's Diabetes Mellitus Interagency Coordinating Committee (DMICC). The program develops information and education messages and materials for people with diabetes and their families, health care providers, payers and purchasers of health care, health care system policymakers, and the general public, including people with undiagnosed diabetes and those at risk for the disease.

The NDEP's efforts are aided by a Steering Committee comprised of representatives from diabetes-related, health care, racial/ethnic, and voluntary service organizations. Federal liaisons to the NDEP Steering Committee include several representatives from the DMICC. Members of the Steering Committee serve on NDEP work groups that provide direction and help implement NDEP initiatives.

The NDEP also has developed a Partnership Network of over 200 organizations to help disseminate program messages to the mass media, community groups, and health systems serving people with diabetes. The website, "Team Diabetes," provides an interactive, online site for NDEP partners to exchange resources and information.

Fiscal Year 2003 Highlights

During FY 2003, NDEP supported a variety of activities to promote the importance of comprehensive diabetes care and diabetes prevention. Highlights of NDEP's activities during the past year are summarized below.

Media Campaigns

From June 1998, when NDEP launched its first Public Service Advertisements (PSA) campaign, through September 30, 2003, the NDEP's diabetes control and prevention television PSAs have obtained well over $17 million in free advertising time, and print PSAs have reached over 36 million readers. NDEP carried out extensive market research before initiating its PSA campaigns and has developed the messages in conjunction with NDEP work groups. The program also has provided ongoing support for continuing campaigns targeted to African Americans, Hispanic and Latino Americans, American Indians and Alaska Natives, and Asian Americans and Pacific Islanders.

The "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign is based on the results of the Diabetes Prevention Program (DPP) clinical trial that proved diabetes could be prevented or delayed in an overweight population with pre-diabetes. The "Small Steps" campaign encourages people at high risk to lose a small amount of weight by eating healthy and getting 150 minutes of physical activity a week.

In November 2002, HHS Secretary Tommy G. Thompson launched the "Small Steps" campaign and the "Get Real" TV PSA. To date, "Get Real" TV PSAs have generated nearly $1.5 million in free advertising, and the print PSAs have reached almost 1 million readers.

In February 2003, the NDEP held the first national "Partners in Diabetes Prevention" meeting to encourage NDEP partners, businesses, and community-based programs to promote NDEP's diabetes prevention messages and materials. NDEP unveiled and distributed the "Small Steps GAME PLAN" toolkit at this meeting. The toolkit contains information and education materials for health care providers to help their patients take steps to lower

their risk for diabetes. In less than 6 months, 3,000 GAME PLAN toolkits and 3,000 packets for patients have been distributed.

The "Be Smart About Your Heart: Control the ABCs of Diabetes" campaign creates awareness about the link between diabetes and heart disease and promotes comprehensive diabetes care to control blood glucose (A1c), blood pressure, and cholesterol—the ABCs of diabetes.

In November 2002, the NDEP continued partnering with the American Diabetes Association (ADA) to promote the ABCs message by distributing the ADA's "Broken Heart" campaign materials, including print and radio PSAs with the NDEP logo, to over 200 NDEP partners.

The NDEP has adapted the "Control the ABCs" message into Spanish for reaching Hispanic and Latino Americans and created the "Si Tiene Diabetes, Cuide su Corazon" (If you have diabetes, take care of your heart) campaign. To reinforce the campaign message, NDEP developed a bilingual flipchart for health educators to explain the link between diabetes and heart disease, using easy-to-understand illustrations accompanied by a scripted presentation and copier-ready handouts (in Spanish and English).

Also in FY 2003, the "Take Care of Your Heart. Manage Your Diabetes" educational handout was adapted into 15 Asian and Pacific Islander languages. The handout explains the link between diabetes and heart disease and the importance of managing blood glucose, blood pressure, and cholesterol and is available in English and the following languages: Cambodian, Chamorro, Chinese, Chuukese, Gugarati, Hindi, Hmong, Japanese, Korean, Laotian, Samoan, Tagalog, Thai, Tongan, and Vietnamese.

Media Outreach

In conjunction with these awareness campaigns, NDEP continued to conduct media outreach to obtain coverage about diabetes in the print and broadcast media. Program messages were featured in a number of national media outlets, including *The New York Times*, *Time*, *Newsweek*, *Ladies Home Journal*, *Essence*, *Prevention*, and *Woman's Day*, and generated almost 64 million media impressions.

NDEP Conference Participation

Program spokespersons gave presentations and represented NDEP at numerous professional meetings in FY 2003, including the American Public Health Association (APHA) (November 2002); the CDC's Diabetes Translation Conference (May 2003); American Diabetes Association and National Association of School Nurses (June 2003); National Association of La Raza (July 2003); and Administration on Aging and the Food Marketing Institute (September 2003).

Diabetes at the Worksite

NDEP's Business and Managed Care Work Group has designed a web-based resource that employers, human resource, and health professionals can use to assess the scope of the diabetes problem in their workforces and to conduct diabetes education at the worksite. Hosted by the Washington Business Group on Health, this resource is available at *www.diabetesatwork.org*. In November 2002, during the APHA meeting in Philadelphia, NDEP conducted a workshop for local businesses on how to use the resources on this website. NDEP is planning to conduct additional workshops during FY 2004.

Diabetes in Children and Adolescents

In June 2003, the NDEP launched *Helping the Student with Diabetes Succeed: A Guide for School Personnel*. This manual helps school personnel ensure a safe learning environment for children with diabetes and equal access to all educational opportunities. Also released in FY 2003 are four tip sheets for children with type 2 diabetes and their families. Topics covered include: what is diabetes, staying at a healthy weight, eating healthy, and being more physically active.

Systems Changes for Better Diabetes Care

NDEP's Health Care Provider work group provided guidance for *BetterDiabetesCare.nih.gov,* a new website. This practical resource is designed to help health care providers make a difference in the way diabetes is prevented and treated. The work group undertook this task to help address the steps outlined by the Committee on the Quality of Health Care in America in its 2001 report to the Institute of Medicine. The NDEP believes that systems change is essential to provide the type of evidence-based, patient-centered care needed to manage diabetes effectively and to prevent its serious complications. The website provides models, links, resources, and tools to help the professional assess needs, plan strategies, implement actions, and evaluate results.

The Pharmacy, Podiatry, Optometry, and Dentistry (PPOD) work group is finalizing a diabetes primer to expand PPOD professionals' understanding of their role in caring for people with diabetes beyond their own specialty and to include education about the need for glycemic, blood pressure, and cholesterol control for people with diabetes. A poster aimed at people with diabetes is being developed based on the principles outlined in the primer.

The Older Adults work group is finalizing materials to promote the Medical Nutrition Therapy and diabetes self-management benefits for people with diabetes who are enrolled in Medicare.

Future Activities

During FY 2004, NDEP will continue to promote comprehensive diabetes control and diabetes prevention. The NDEP is tailoring the messages and materials from the "Small Steps" prevention campaign for high-risk population groups, including older adults, African Americans, Hispanic and Latino Americans, American Indians and Alaska Natives, and Asian Americans and Pacific Islanders.

The program also will promote the U.S. Department of Health and Human Service's "Diabetes Detection Initiative," designed to reach people with diabetes who are undiagnosed. A component of "Steps to a HealthierUS," this initiative focuses on helping Americans better understand their diabetes risks and what actions they need to take.

These new and important NDEP prevention and control messages and initiatives will add a new dimension to the NDEP and its goal of "changing the way diabetes is treated." For more information about the National Diabetes Education Program, please visit our websites at *www.ndep.nih.gov* and *www.cdc.gov/team-ndep* on the Internet.

MEETING SUMMARIES

MEETING SUMMARIES

DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE MEETING

National Institutes of Health Campus
Natcher Conference Center, Conference Room A
Bethesda, Maryland
February 25, 2003

THE METABOLIC SYNDROME SUMMARY MINUTES

Dr. Saul Malozowski, Executive Director of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), convened the meeting and presented Dr. Allen Spiegel, DMICC Chair and Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). Dr. Spiegel welcomed the speakers, committee members, and guests. He stated that they were an important body of persons with the opportunity to coordinate manifold activities as representatives of agencies of the U.S. Department of Health and Human Services (DHHS), along with important stakeholders such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE).

Dr. Spiegel noted that there are critical issues to be addressed regarding the metabolic syndrome. These include definition issues, the etiology of the metabolic syndrome, risk factors represented by the syndrome, and implications for prevention and treatment of the syndrome. Since a major definition was developed by the National Heart, Blood and Lung Institute's (NHLBI's) National Cholesterol Education Program's (NCEP's) Adult Treatment Panel III (ATP III), the group was fortunate to have Dr. Peter Savage present today representing NHLBI's membership on the DMICC. Dr. Claude Lenfant, NHLBI Director, regretted not being able to attend but was looking forward to hearing the results of the meeting.

Dr. Savage, Director, NHLBI Division of Epidemiology and Clinical Applications, joined Dr. Spiegel in emphasizing that today's meeting provided the group with a major opportunity to discuss the metabolic syndrome and its relationship to diabetes and to cardiovascular complications in non-diabetes. He agreed that there were many questions to be answered regarding the definitions and the magnitude of the problem. An overview of these issues would be presented by three speakers very active in the field—Dr. James Meigs, Dr. Steven Haffner, and Dr. Scott Grundy. Following these overviews, DMICC agency representatives and members of ADA and AACE would present their groups' perspective on the metabolic syndrome. (Dr. Haffner's and Dr. Grundy's slide presentations are available at http://www.niddk.nih.gov/federal/dmicc/Haffner.ppt and http://www.niddk.nih.gov/federal/dmicc/grundy.ppt. For informational purposes and due to the need of further analyses only part of these presentations are available. (Dr. Meigs slides could not be posted because they contained data that has not been published yet.)

James B. Meigs, MD, MPH, Assistant Professor of Medicine, General Medicine Division, Harvard Medical School, and Massachusetts General Hospital, Boston.

Definitions of the Metabolic Syndrome and Related Risk of Heart Disease and Type 2 Diabetes

Dr. Meigs introduced the NCEP ATP III definition, developed in 2001, and the World Health Organization (WHO) definition of 1999 (see box), which differ in trait thresholds and inclusion crite-

ria. Regardless of the definition used, the metabolic syndrome is very common, according to Dr. Meigs. Those with the syndrome, again regardless of the definition, are more insulin resistant and at greater predicted risk for coronary heart disease (CHD) and diabetes. Presence of the metabolic syndrome doubles the risk for CHD events and dramatically increases by as much as 10-fold the risk for type 2 diabetes. Specific clustering of traits may better predict the risk or burden of CHD or type 2 diabetes than the presence of any three individual traits. According to data from the Framingham Heart Study, in which Dr. Meigs has been a key participant, prevalence of the NCEP-defined metabolic syndrome increased from about 15-20 percent in men and 7-16 percent in women from the late 1980s to the mid-1990s.

NCEP ATP III (2001) 3 or more of:	WHO (1999) (IFG or IGT, or DM) and/or IR* plus 2 or more of:
Waist circ >40" (M) or 35" (W)	BP ≥140/90
TG≥150	TG ≥150 and/or HDL <35 (M) 39 (W)
HDL <40 (M) or 50 (W)	WHR >0.9 (M) or 0.85 (W) and/or BMI >30
BP ≥130/85	UACR ≥30/
FPG ≥110/	

BP: blood pressure
DM: diabetes mellitus
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
IR: insulin resistance
FPG: fasting plasma glucose
TG: triglycerides
UACR: urinary albumin creatinine ratio
Waist circ: waist circumference
WHR: waist:hip ratio
IR*: clamp-assessed glucose uptake <25 percentile

Source: NCEP ATP III JAMA 2001:285:2486-97

Prevalence by Definition. Based on the National Health and Nutrition Examination Survey of 1999-2000 (NHANES III), the metabolic syndrome as defined by NCEP tends to be heterogeneous across racial/ethnic populations, is more common in men than in women, and prevalence increases with age. Population-based comparisons of the data from NHANES III, the San Antonio Heart Study, and the Framingham Offspring Study indicate that, of the components of the NCEP definition, hyperglycemia was the least common trait. Components varied across populations and tended to be most prevalent in Mexican Americans. It was interesting that both whites and Mexican Americans had a higher prevalence of the syndrome than white Finnish males in the Kuopio IHDRF Study, possibly because the Kuopio men are relatively slender. Comparing the prevalence of the WHO metabolic syndrome traits in populations from the Framingham Offspring Study, the San Antonio Heart Study, the Botnia Study, and the Kuopio IHDRF Study, hyperglycemia with or without insulin resistance (IR) was nearly as common in white Finns from Botnia as it was in the San Antonio Mexican Americans as was the prevalence of the syndrome, with 46 percent of the Botnia subjects and 49 percent of the Mexican Americans having the syndrome.

Issues in Defining the Syndrome. Dr. Meigs listed several uncertainties that arise in considering any definition of the metabolic syndrome. Should simple trait counting be used or empiric weights or clusters? Are insulin levels being measured or insulin resistance? Should high glucose or diagnosed diabetes be included as part of the definition or as an outcome? Which is a better indicator, BMI or waist circumference? What about microalbuminuria or C-reactive protein (CRP) and other inflammatory markers? Finally, which thresholds should be used—NCEP or WHO? Comparison of waist circumference versus waist:hip ratio is not the same measure and NCEP does not include BMI, fasting glucose, or diabetes.

In counting traits, rather than clusters, Dr. Meigs said it is important to note that the individual syndrome traits do not have equal predictive power. On the other hand, factor analyses show that certain

traits tend to cluster, suggesting physiological trait clusters exist, and that the most common clusters include from two to four factors. This may indicate a need to define the syndrome by requiring selection of traits based on their specificity for insulin resistance. For instance, requiring that a large waist circumference and low HDL/high triglyceride dyslipidemia be present may increase the specificity of the diagnosis of metabolic syndrome. Comparisons were made of Framingham Offspring and San Antonio Heart Study subjects with factors added, such as BMI and empiric clusters to the NCEP and microabluminuria to WHO. Dr. Meigs pointed out that overall prevalence and the degree of HOMA-IR (homeostasis model assessment of IR) between whites and Mexican Americans is highly similar regardless of the alternative definition used, except for slightly higher rates according to the WHO definition, especially for Mexican Americans. Also, the prevalence drops dramatically when the NCEP definition is applied with empiric clusters, although subjects remain quite insulin resistant and at elevated predicted CHD risk even by this definition.

Metabolic Syndrome and Risk for CHD and Diabetes. The risk for coronary heart disease (CHD) based on the Framingham Heart Study Risk Score is also similar, regardless of alternative definitions used, with both whites and Mexican Americans who have the metabolic syndrome being at much higher risk. The 11-year adjusted relative risk for CHD and all-cause mortality associated with the metabolic syndrome, regardless of definition, was also true for Finnish men in the Kuopio IHDRF Study. The relative risk for CHD and cardiovascular disease (CVD) in the Framingham Offspring Study participants showed slight differences between those who had two versus three traits of the metabolic syndrome, but with three traits certainly increasing the risk. Dr. Meigs emphasized that, on the other hand, the presence of any two or three traits was a powerful indicator of risk for diabetes.

Dr. Meigs next described the population-attributable risk percent (PAR%) formula, or the burden of disease that can be attributed to a given condition, as a clinically useful indicator for public health. He stated that, in the Framingham Offspring Study, the 8-year age-adjusted relative risk and PAR% for CHD was always highest for those with a three-way combination that included lipid and waist traits. For type 2 diabetes. the PAR% was very high for any three-way combinations, with those including fasting glucose and waist traits being the highest for both relative risk and PAR%.

The risk of CHD was higher in those with the fasting plasma glucose and waist combination and increased in those who had any three-way combination, any two-way combination, or the HDL-blood pressure combination. The burden of CHD increased as persons had any two-way combination of traits and increased with any three-way combination or HDL-blood pressure combination.

For diabetes, the risk increased beginning with the fasting plasma glucose trait in combination with any other one or two traits and the risk increased or was equal to this with any two- or three-way combination of traits. The public health burden for diabetes was predictable given any three-way or two-way combination of traits and increased with the presence of the HDL-waist combination.

Steven M. Haffner, MD, MPH, Professor of Medicine, Department of Medicine/Clinical Epidemiology, University of Texas Health Science Center, San Antonio.

Etiology(ies) of the Metabolic Syndrome and Variations Across Racial/Ethnic Groups

Dr. Haffner presented the risk of CHD and/or of diabetes as one criteria for comparing the NCEP and WHO definitions of the metabolic syndrome. A second possible criteria is the relation of the syndrome to IR, and a third is the prevalence of the syndrome in the community and by different racial/ethnic groups. The metabolic syndrome is associated with increased risk of heart disease, although the increased risk may not be entirely due to increased IR. On the other hand, most subjects

with the metabolic syndrome do not have type 2 diabetes. African Americans tend to have low triglycerides and high HDL; therefore, the prevalence of the metabolic syndrome in this population is lower according to the NCEP definition and is higher according to the WHO definition, a peculiarity that Dr. Haffner felt deserves consideration. He stated that another thing to consider is the simplicity or understandability of the definition in order to apply it in the general population not just discuss it as a theoretical aspect.

Dr. Haffner addressed the prediabetic state as a model for the metabolic syndrome; insulin resistance, insulin secretion, and subclinical inflammation as predictors of the metabolic syndrome; the relation of inflammation to increased insulin resistance and decreased insulin secretion; factor analyses from the Framingham and the Insulin Resistance Atheroscerlosis Study (IRAS); the metabolic syndrome, diabetes, and coronary heart disease prevalence in the NHANES and other database populations; and identification of persons with insulin resistance and beta-cell dysfunction using alternate definitions of the metabolic syndrome. Dr. Haffner's presentation was based on data from five studies: the San Antonio Heart Study (SAHS), IRAS, the Mexico City Diabetes Study, the Framingham Study, and NHANES

Literature on the Eiology of the Metabolic Syndrome. Dr. Haffner said the question of clustering of cardiovascular risk factors has been talked about for at least 35 years. The concept was developed by an Italian group in the late 1960s, and in the 1970s there were a variety of papers on the subject. A group in East Germany led by Hanefeld talked about clustering of cardiovascular risk factors and about insulin but because the literature was in German and the wall was still up, this received little publicity.

Reaven began the discussion about an insulin resistant syndrome, calling it syndrome X (*Diabetes*, 1987), and Ferrannini (*Diabetologia*, 1991), and Haffner (*Diabetes*, 1992) added to this. Reaven's discussion was based on non-obese persons with insulin resistance. Some people objected to this because in the United States and other western countries, the syndrome occurred primarily in obese persons. John Despres referred to the hypertriglyceridemic waist (triglycerides at 176 mg/dL and a 90 centimeter waist in men), and Peter Wilson discussed the presence of weight gain in multiple metabolic disorders (*Arch Int Med*, 2000) from the Framingham Study, while not referring to the metabolic syndrome. Glycemia in the non-diabetic range was given as the primary cause by Gerstein, who called it the dysglycaemic syndrome, and glycemia was also presented in the DECODE data. There remains an issue that needs further study about whether the syndrome is related only to the risk factors within itself or to cardiovascular risk factors. Subclinical inflammation has also been presented as a factor.

Prediabetic State as Model of Metabolic Syndrome. A prediabetic syndrome was an early attempt at looking at the metabolic syndrome. Basically, the suggestion was that increased cardiovascular risk factors preceded the onset of type 2 diabetes. An issue was whether it was glucose or insulin that increased the CVD risk. In nondiabetic subjects, people who are insulin resistant always have slightly elevated glucose levels. United Kingdom Prospective Diabetes Study (UKPDS) data suggest that the relationship between glucose concentrations, while clearly significant related to myocardial infarction (MI) is a lot more modest than its relationship to microvascular disease. Dr. Frank Hu reported (*Diabetes Care* 2002:25(7):1129-1134) that in the Nurses Health Study, not only those who were diabetic at the beginning of the 20-year followup had a five-fold increased risk of cardiovascular disease, but those who were prediabetics had a three-fold risk prior to diagnosis. In each of the populations cited in the literature, cardiovascular risk factors were all higher in prediabetic subjects. Dr. Haffner explained this is important as part of the intellectual basis for prevention of type 2 diabetes as an important strategy as opposed to screening for diabetes and then managing it with tight control.

Insulin as a Predictor of the Metabolic Syndrome and CHD. Dr. Haffner next addressed insulin resistance, insulin secretion, and subclinical inflammation as predictors of the metabolic syndrome and noted that there is some controversy about insulin levels as a predictor of CHD, although most of the data indicates a positive correlation. He stated that it is known that insulin concentrations predict the metabolic disorders and also predict multiple metabolic disorders. High absolute concentrations of LDL are not related to baseline insulin levels, but high insulin concentrations predict the development of small dense LDL.

In the San Antionio Heart Study, people with normal glucose tolerance were followed to see whether they developed type 2 diabetes. At baseline, they had higher tryglycerides, higher HDL, higher systolic blood pressure (BP) than prediabetics, slightly higher glucose levels but the differences were really very small, although significant, and much higher insulin concentration. The argument was that it was hyperinsulinemia and IR that drove this pre-diabetic issue. After Gerstein's data came out, the San Antonio data was reviewed and an attempt made to develop a model for IR versus glucose. From a San Antonio cohort, where there was information on surrogates of IR and low insulin secretion, and from earlier studies of the Pima Indians and data from Joslin, it was shown that low insulin secretion and IR do predict the onset of type 2 diabetes. Furthermore, when these factors were combined, there was about a 20-fold excess of incidence of type 2 diabetes.

Next the SAHS investigators looked at 105 individuals before they became diabetic and compared them according to IR and insulin secretion and traditional cardiovascular risk factors—triglycerides, HDL cholesterol, and systolic blood pressure. Fifty-four percent were IR, 29 percent were IR but had fairly good stimulated insulin secretion based on the change in insulin and in glucose over 30 minutes of a glucose tolerance test, about 16 percent had low insulin secretion, and a little less than 2 percent had neither defect, although the latter data has some difficulties. These subjects were Mexican Americans and non-Hispanic whites in four groups with identical glucose tolerance, which allowed matching for glucose control and comparison of those who developed type 2 diabetes. The data is very similar across the ethnic groups. Analysis of the data strongly suggests that among prediabetics as a model, it is IR, not small changes in glucose levels, that predicts type 2 diabetes.

The two groups with matched glucose and with high IR had higher rates of conversion to diabetes and much higher tryglycerides than those with low insulin secretion who converted, even when stratified and controlled for weight differences. Those with low insulin secretion who converted to diabetes had tryglycerides similar to non-converters. There was a similar pattern with HDL cholesterol and systolic blood pressure, in that those with low secretion tended to have similar blood pressure and HDL levels to those who did not convert. These low secretion converters and the nonconverters had lower blood pressure and higher HDL levels than those with IR who converted. LDL data on these groups also was similar. Dr. Haffner also presented data from a 25-year followup study reported by Pyorala et al. (Circulation, 1998; 98:398-404) that showed that nondiabetic men with the highest IR are at greatest risk for a major CHD event.

Subclinical Inflammation as a Predictor of the Metabolic Syndrome and CHD. With regard to CRP, Dr. Haffner referred to a 1992 consensus conference sponsored by the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC). The participants discussed the relative risk of CVD as predicted by markers of inflammation. Their recommendations (see Pearson et al., *Circulation*, 2003; 107:499-511) adopted the following CRP cut-points: high-sensitivity as 3 m/L or higher (in mg/dL this would be 0.3 mg/dL), low as less than 1 mg/L, and average as 1 to 3 m/L.

In the IRAS study with nondiabetics, data adjusted for demographics (age, sex, clinic, ethnicity) and smoking (because smoking is related to high CRP

levels and some people think it is related to IR as well), showed a strong correlation of CRP with obesity and waist circumference, a positive association with fasting insulin levels, a significant but weaker relationship with systolic blood pressure and fasting glucose, and an inverse relationship with insulin sensitivity directly measured by frequently sampled intravenous glucose tolerance tests. The original comparison was made prior to the NCEP definition, but was redone using the NCEP definition and the WHO definition, with similar results—the higher the CRP level, the greater the number of metabolic disorders.

Dr. Haffner also referred to six studies on the 5-year incidence of type 2 diabetes stratified by quartiles of three inflammatory proteins—fibrinogen, CRP, and PAI-1—that showed that high CRPs predict type 2 diabetes, in some circumstances independent of fasting insulin, although not significantly when adjusted for IR. PAI-1 (plasminogen activator inhibitor-1) levels were a stronger predictor, but Dr. Haffner said PAI-1 is unlikely to be used for clinical purposes because of collection and measurement issues.

Effect of Insulin-Sensitizing Interventions on Reducing CRP Levels. Dr. Haffner cited Diabetes Prevention Program (DPP) unpublished data presented at an AHA meeting in 2002 that showed that two insulin-sensitizing interventions, modest lifestyle changes and metformin, reduced CRP levels by 58 percent and 31 percent, respectively, in this impaired glucose tolerance cohort. Lifestyle changes caused the most lowering of CRP levels in both genders, but were most significant in women who tend to have higher levels than men. The lowering of CRP by lifestyle and metformin continued to increase for women over the 12-month period. Dr. Haffner indicated that, although the data covers only 1 year, it suggests that lifestyle changes that produce greater changes in type 2 diabetes may also have greater effects on CVD. The use of rosiglitazone, a TZD (thiazolidinedione), with diabetics, a different population than that of the DPP, showed a 25 percent reduction in triglycerides, similar to most statin studies (see *Circulation* 2002;106:679-684).

Elevated CRP Levels as Predictors of the NCEP Metabolic Syndrome. Data from the Mexico City Diabetes Study indicates basically no relationship in men between CRP levels and development of the metabolic syndrome and a very limited relationship to development of type 2 diabetes. In women, those in the lowest quartile of CRP levels have about a 7 percent chance of developing the syndrome over a 6-year period, whereas those in the higher quartile have about a 3.5-fold increase in risk. CRPs predict the metabolic syndrome in both lean and obese women, indicating that obesity, whether determined by BMI or waist circumference, plays a strong role as a predictor aside from CRPs. Dr. Haffner recommended that additional studies with other populations be conducted to examine whether testing for CRP would be helpful in determining risk of developing the metabolic syndrome in women, independent of BMI and HOMA-IR.

Relationship of Inflammation to Increased IR vs. Decreased Insulin Secretion in the Pre-Diabetic State . Dr. Haffner noted again that in the IRAS, those with high IRs who converted to type 2 diabetes had high CRP levels The high IR/high CRP group was also more overweight than the other two groups. There was basically no difference in CRP levels in those with low secretion but no IR who developed diabetes regardless of their BMI. However, the non-converters with high BMI also tended to have higher CRP levels, though not as high as the converters with high IR. Because glucose levels were similar in all the groups, Dr. Haffner said this strongly suggests that IR is the major factor in predicting type 2 diabetes, but this is a complicated area because most people think that among the principal determinants of subclinical inflammation (CRP is produced by the liver) are cytokines pro-

duced in adipocytes such as IL6 and TNF-alpha but many of the interventions that lower CRP do not actually decrease IL6 in studies, possibly for measurement reasons.

Factor Analyses From the Framingham Study and IRAS. The basic conclusion from factor analyses of the Framingham study reported by Dr. Meigs in *Diabetes* in 1997 and the IRAS analyses described by Dr. Anthony Hanley in *Diabetes* in 2001 is that hypertension is a separate factor not associated with IR. Framingham also included a glucose factor. In IRAS, there was a metabolic factor that included adiposity, triglycerides, and glucose levels. IRAS also concluded that, along with hypertension, there was PAI-1 that entered into the metabolic factor and a separate inflammatory factor with CRP and fibrinogen. According to Dr. Haffner, it does not look like IR is responsible for all of these factors, such as hypertension.

Prevalence of Metabolic Syndrome, Diabetes, and CHD Based on NHANES III and Other Study Data. Dr. Haffner said that according to a paper by Charles M. Alexander et al. to be published in *Diabetes*, of which Dr. Haffner is an author, 85 percent of diabetics have the metabolic syndrome based on NHANES III. The overall risk for CHD appears to be intermediate between diabetes with and without the metabolic syndrome. In the NHANES population, the risk of CHD in those with metabolic syndrome but no diagnosed diabetes is approximately 14 percent and approximately 19 percent in those with both the syndrome and diabetes. The risk without the syndrome or diabetes is 8.7 percent and without the syndrome, but with diabetes, the risk is 7.5 percent. Of interest to Dr. Haffner was the relatively small number of diabetics who do not have the metabolic syndrome and whose risk of CHD is very close to that of nondiabetics without the syndrome. This is probably not a surprise, since hypertension is a well-known risk factor for CHD among diabetics.

Four other databases, including data from a large European and American pharmaceutical study in new diabetics called ADOPT (A Diabetes Outcome Progression Trial), whether one uses the NCEP or the WHO definition, indicate that somewhere between 75 and 80 percent of diabetics have metabolic syndrome. These numbers appear to be equally true in populations where obesity is less common than in the United States, as in some areas in Europe.

Prediction of CHD based on multivariate logistic regression analysis of NHANES data do not show that the metabolic syndrome predicts CHD independently of its individual components. However, the individual components that have a higher correlation as risk predictors are low HDL, high blood pressure, and diabetes, which is similar to the information provided by Dr. Meigs' Framingham data. Therefore, some of the components of the metabolic syndrome may be more related to CHD than are other components.

Comparison of characteristics among the U.S. population age 20 and older with and without the metabolic syndrome are similar whether the WHO or NCEP definition is used and the IR is similar to Framingham data. Although the 1998 WHO definition includes HOMA-IR data and the 1999 definition involves IR as clamp-assessed glucose uptake, the comparisons are based on HOMA-IR because no one had clamp data. When a different measure of insulin sensitivity is used, there is a different answer, as discussed below.

Identification of Subjects With IR and Beta-Cell Dysfunction Using Alternate Definitions of the Metabolic Syndrome. In IRAS, Dr. Haffner said data on the lowest quartile for insulin sensitivity in three different population groups of nondiabetics—African Americans and non-Hispanic whites and Hispanics, all of whom were actually Mexican Americans—were examined to determine how well the metabolic syndrome identified persons with IR

but without diabetes as a criteria for comparing the NCEP and WHO definitions. Unlike the Framingham and NHANES data that look at surrogate measures, direct measurement of insulin sensitivity presented a different study. The group with the lowest sensitivity met neither definition. About half the population with insulin sensitivity met both definitions, and about one-quarter with sensitivity met one or the other definition. Combining the criteria of the definitions made no difference. The WHO definition was better than the NCEP in identifying persons with IR. Overall, the direct measurement of insulin sensitivity was better than HOMA-IR or any of the NCEP or WHO surrogate measures in identifying those with IR.

In looking at the measure of insulin secretion in IRAS nondiabetics, the metabolic syndrome did predict people with low insulin secretion, with NCEP being a better predictor than WHO. Dr. Haffner pointed out that of special interest in this data is that the NCEP definition identified a group of nondiabetic African Americans with insulin secretory defects, and there is literature that indicates that not only does this population have IR as a cause for their increased rate of developing type 2 diabetes, but there may be lower glucose effectiveness and lower insulin responses in African Americans. Dr. Haffner suggested further analysis is needed in this area.

In conclusion, Dr. Haffner remarked that the characteristics of the metabolic syndrome need to be reexamined based on the data from the IRAS. Using directly measured IR across three different ethnic groups, the WHO definition was better than the NCEP as a predictor of IR, but whether this is significant enough is another matter. Obesity is a significant factor in the United States, IR has data that suggests it is and is not important, and subclinical inflammation appears to be important according to experimental work in epidemiology. IR is certainly not the cause of the entire syndrome, but it does seem to be a contributing factor, according to Dr. Haffner.

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Issues for Prevention and Treatment of the Metabolic Syndrome

Dr. Grundy served as Chair of the NHLBI's National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of Blood Cholesterol in Adults (Adult Treatment Panel III). He opened his presentation by explaining that the NCEP ATP II committee and panel members involved in developing LDL cholesterol guidelines to prevent and treat coronary heart disease (CHD) were concerned about a nutritional approach along with the drug treatment approach that clinical trials had shown could reduce the risk for CHD. ATP II thus addressed obesity and physical inactivity, but this was not really noticed. The increasing evidence that obesity and physical inactivity leads to CHD prompted the ATP III members to take a new approach. Concerned that the NCEP guidelines would be seen as only drug treatment guidelines for LDL, they decided to define a set of medical conditions related to obesity, physical inactivity, and nutrition and define these conditions as a metabolic syndrome. Based on the prevalence of CHD and its mortality rate in those with type 2 diabetes, the panel also elevated type 2 diabetes to a CHD risk equivalent or high-risk condition. The intention was to get physicians to pay more attention to their patients at risk for both CHD and diabetes because of lifestyle-related problems. Therefore, the guidelines addressed high LDL, the cluster of medical conditions termed metabolic syndrome, and type 2 diabetes that tends to result from or accompany the syndrome, as being high-risk factors for CHD. Dr. Grundy stated that by defining a syndrome, rather than merely further emphasizing obesity and physical inactivity as CHD and diabetes risk factors, ATP III has successfully moved forward in acquiring attention about these risk factors.

Dr. Grundy stated that it is known through the literature reports of clinical studies that therapeutic lifestyle changes do correct or at least modify all of the metabolic syndrome risk factors (excess fat in adipose tissue and abdominal fat, high blood pressure, high triglycerides, low HDL, insulin resistance, high PAI-1, and high CRP). These reports also show that drug treatment is a potential approach to managing the individual components such as using aspirin and hypertensive drugs for the prothrombotic state, the insulin-sensitizing drugs such as metformin and the TZDs for insulin resistance, the lipid-lowering drugs to reduce the proinflammatory state , and drugs besides statins for patients with atherogenic dyslipidemia. Factors in favor of drug therapy for the metabolic syndrome would be high-risk individuals such as those with established CVD and/or type 2 diabetes, persons with multiple risk factors, and also moderately high-risk patients who have a 10-year risk in this range according to ATP III guidelines.

Issues for Prevention and Treatment of the Metabolic Syndrome. Dr. Grundy listed public health and clinical strategies as key issues for the prevention and treatment of the metabolic syndrome. In clinical strategies, it is important to know about risk assessment in patients with the syndrome, selection of patients for interventions, both lifestyle, which was made the major part of the ATP III guidelines related to metabolic syndrome, and pharmacological intervention. Prevention and therapy issues include defining the syndrome, determining its prevalence, identifying the metabolic components or risk factors and potential treatment targets, assessing the health consequences of these components, and understanding the pathophysiology of the syndrome.

What Is the Metabolic Syndrome? Dr. Grundy noted that definitions of the metabolic syndrome have come from several areas, each of which has particular implications for prevention and treatment of the metabolic syndrome.. The syndrome has been defined according to clinical outcomes (CHD and diabetes), in relation to underlying causes such as insulin resistance or obesity; by its metabolic components as in the ATP III clustering of metabolic cardiovascular risk factors, and according to clinical criteria as in the NCEP definition based on cardiovascular disease (CVD) risk factors and the WHO definition based on insulin resistance as an underlying cause.

Implications for Therapy and Intervention Based on Definitions of the Metabolic Syndrome. Dr. Grundy stated that how the metabolic syndrome is defined has implications for therapy and intervention in patients identified with the syndrome. When defined by insulin resistance as the underlying cause, the metabolic syndrome is often called the insulin resistant syndrome. When lifestyle, especially obesity, is considered the major underlying cause, the concept is known as the metabolic syndrome. Each viewpoint results in different treatments.

Implications Based on Clinical Outcomes. The cardiovascular area sees the metabolic syndrome as primarily a precursor or risk factor for cardiovascular disease and treats it to prevent CHD. Those in the diabetes field view it as mainly a precursor or predisposing factor for type 2 diabetes and look on it and treat it as pre-diabetes. (Dr. Grundy acknowledged that this is not the ADA definition for pre-diabetes.) For lifestyle interventions, each viewpoint's therapeutic implications are much the same, but for pharmacological interventions, there is generally divergence of these two pathways.

Implications Based on Components or Risk Factors. A variety of components have been identified as being associated with metabolic syndrome, such as those in the ATP III definition: atherogenic dyslipidemia (high triglycerides, perhaps increased apoliprotein B (apo B), small LDL, and low HDL); raised blood pressure; insulin resistance with or without hyperglycemia; a proinflammatory state; and, increasingly, the prothrombotic state, which many people see as the dominant component, whereas from the cardiovascular point of view, these other factors are equally important. Therapeutic implications according to this definition see all

these components as potential targets of treatment and management, independent of the underlying causes. For instance, in addition to treating high triglycerides, low HDL, and blood pressure, there is a great deal of current interest in directly targeting the proinflammatory state as a separate approach to reducing cardiovascular risk. It is also known that through aspirin or any platelet therapy, the prothrombotic state can be reduced.

Implications Based on Underlying Causes and Clinical Criteria. The NCEP ATP III definition was based on obesity, especially abdominal obesity, as the primary factor that gives rise to the other four components as a CVD risk, whereas the WHO definition emphasized insulin resistance as the underlying cause. Although not specifically requiring abdominal obesity as a requirement, the ATP III definition's clinical criteria and therapeutic strategy was meant to focus on obesity and its treatment, and the public health strategy was to prevent obesity in the general population, which is the approach of the NHLBI/NIDDK Obesity Education Initiative. However, there has been a developing interest in the field in focusing on treating the individual metabolic components, which has implications for the use of drug therapies. The WHO definition's clinical criteria places more emphasis on the genetic basis of the syndrome, rather than obesity. The WHO requirement of IR or one of the glucose abnormalites (IFG, IGT, diabetes) for the diagnosis places the therapeutic focus on the use of drugs to treat patients with the metabolic syndrome. Dr. Grundy noted that this use of drug therapy concerns many people in discussing the value of the metabolic syndrome as a means of identifying CVD metabolic risk factors and of recommending interventions to prevent development of the disease.

Implications of Including Type 2 Diabetes in the Definition. Dr. Grundy noted that inclusion of type 2 diabetes in the definition of the metabolic syndrome also has important therapeutic implications. The NCEP and WHO include it. The American Academy of Clinical Endocrinologists (AACE) and Framingham analysis do not. If included, clinical intervention will be emphasized more, including greater emphasis on drug therapy for the CVD risk factor components once the patient has developed type 2 diabetes. Clinical trials have provided evidence of the benefits of such drug therapy. This also raises the question of when should drug therapy for the individual risk factors be introduced in the pre-diabetic state.

Prevalence of the Metabolic Syndrome and Implications for Therapy and Intervention. NHANES III data reported by Dr. Earl Ford of the Centers for Disease Control and Prevention (CDC) in the *Journal of the American Medical Association (JAMA)* (Ford et al. *JAMA* 2002;287:356-359) shows the rising prevalence of the metabolic syndrome by age regardless of gender. Dr. Grundy pointed out that, although the prevalence of individual components varies, the magnitude of the problem and the relevant issues for clinical management and public health are evidenced by the fact that approximately 24 percent of 47 million U.S. citizens have at least three of the abnormalities defined by the metabolic syndrome. Some populations, such as Hispanics, Mexican Americans, Asians, particularly South Asians, and African-American women, have even higher prevalences. In the NHANES III period between 1990 and 1999, diabetes rates as an outgrowth of the metabolic syndrome increased at an alarming rate, particularly in young adults. Dr. Grundy stated that there are as many people with diabetes in the United States as with established CHD, making these two diseases basically equal for development of metabolic and cardiovascular complications in the U.S. population.

Implications for Intervention. The fact that 47 million people have the metabolic syndrome and 18 million have type 2 diabetes appears to indicate that one-third or more of persons with the metabolic syndrome will develop diabetes, which has serious public health and therapeutic implications. This is true for young adults, older adults, ethnic populations, and women.

There is a relatively high prevalence of the metabolic syndrome among *young adults* and, in the decade of 1990-1999, there was a 76 percent increase in type 2 diabetes in adults between the ages of 30 to 39. Dr. Grundy directed the audiences' attention to the CARDIA study that points out the dangers of early development of the metabolic syndrome and its risk factors. He stated that the current 35-45 percent prevalence of the metabolic syndrome in *middle-age and older people* indicates the need to focus attention on public health strategies that target adolescents and young adults to reduce the burden of the syndrome in the future. It also means clinical strategies are needed to identify and provide interventions for the substantial number of persons already affected by the syndrome, and it may possibly indicate the need for public health strategies for this group.

Dr. Grundy urged that more attention be paid to the health consequences of the metabolic syndrome in the *ethnic populations* who appear to be prone to the syndrome and that additional research be conducted on interventions for these high-prevalence groups. With regard to CVD, Dr. Grundy said he suspects that the metabolic syndrome may be a dominant cause of cardiovascular disease in *women* in all ethnic groups. The Framingham Heart Study indicated that although women are at lower risk for CVD, the metabolic syndrome is very common among women who develop CVD. NHANES indicates that the metabolic syndrome is equally prevalent in men and women, and the risk for type 2 diabetes in those with metabolic syndrome is also about equal.

Components of Metabolic Syndrome and Relationship to CVD. From accepted guidelines, it is known that the intensity of any therapy should be proportionate to the level of risk. Therefore, it is extremely important to know the risk of the metabolic syndrome for both development of CVD and diabetes. Each of the components of the metabolic syndrome are connected in some way but vary in their relative risk for developing CHD and work through different mechanisms. Dr. Grundy noted that there is increasing evidence that each of the metabolic syndrome components are in some ways a separate risk factor for either atherogenesis or acute coronary syndromes. If that is the case, then each of the components as a metabolic risk factor is a potential target for a lifestyle or drug therapy intervention.

According to Dr. Grundy, this is an area that needs a lot more investigation. The data may already be contained in the Framingham study and other studies, but it needs to be mined, analyzed, and studied to better understand the absolute risk associated with the metabolic syndrome for these two conditions. Framingham suggests that people with the metabolic syndrome are perhaps at 2 to 3 times higher risk for CHD, although this needs to be analyzed in more detail. The results of the Finnish study also indicate that coronary mortality is much higher in patients with the syndrome than in those without it (Laska et al., *JAMA* 2002; 288:2709-2726). In a study reported by Norhammar et al. (*Lancet*, 2002; 359:3140-2144), the majority of acute myocardial infarctions (MIs) occur in people with unrecognized abnormal glucose tolerance. Dr. Grundy says this needs to be confirmed but is of great interest. In the Norhammer study, among 200 patients admitted to a Swedish hospital with acute MI, 20 percent had established diabetes, another 33 percent without known diabetes actually had diabetes according to an oral glucose tolerance test (OGTT), and another 31 percent had impaired glucose tolerance. Only 35 percent of the so-called normals (those without known diabetes) actually had normal OGTTs. Dr. Grundy pointed out that this report indicates there is a high prevalence of metabolic disorders in patients who have acute coronary syndromes or MI, and it illustrates the importance of glucose and insulin abnormalities in patients with CVD, factors that should certainly help bring the two fields together.

Metabolic Syndrome and Risk for CVD. Dr. Grundy spoke of the confusion that exists about the ATP III guidelines and the metabolic syndrome as a risk for CVD. He said it is important to clarify this because of the possible pharmaceutical versus lifestyle interventions that would result based on a miscon-

ception. Some people mistakenly believe that the ATP III defined the metabolic syndrome as a CHD risk equivalent, which it did not do. ATP III did identify type 2 diabetes, or diabetes in general, as a high-risk condition for CHD. Dr. Grundy recommended further study of Framingham and other databases to determine the absolute risk of CHD among patients with the metabolic syndrome.

Type 2 Diabetes and Risk for CHD. One of the reasons ATP III identified type 2 diabetes as a high risk condition for CHD is that CVD is the number one cause of death in type 2 diabetes and probably in type 1 diabetes also. Furthermore, there is a high 10-year risk in diabetics for developing CHD, a high lifetime risk, and nearly twice the risk of mortality after MI compared to nondiabetics after MI.

Relationship of Diabetes to Obesity. NHANES III showed that as the body mass index (BMI) increases in U.S. adults ages 20-49, so does the prevalence of diagnosed diabetes, especially when the BMI is 35 or more. In adults over the age of 50, 23 percent of those with a BMI equal to or greater than 35 have diabetes. There is also a very high incidence of IR in those with obesity, somewhere in the range of 85-90 percent. Not all of these persons will develop the beta cell dysfunction that leads to hyperglycemia and type 2 diabetes, perhaps only 15 to 20 percent. The relationship between obesity and type 2 diabetes is certainly not universal, as it appears to be with IR, because it requires a second factor. This has implications for intervention. Dr. Grundy stressed that although the majority of people with obesity and IR do not develop type 2 diabetes, nonetheless prevention of obesity in the general population will reduce the prevalence of type 2 diabetes and this is a worthy goal. He added that the relationship of diabetes to obesity perhaps also indicates the need for early detection of glucose intolerance to aid in the selection of patients for prevention of type 2 diabetes beyond just the identification of the obese individual.

Pathophysiology of the Metabolic Syndrome and Implications for Intervention. Dr. Grundy divided the pathophysiology of the metabolic syndrome into two major areas—upstream abnormalities such as underlying causes, particularly adipose-tissue disorders, and downstream abnormalities such as the responses in the risk factors to the underlying causes, possible risk factors specific to genetic abnormalities, and ethnic characteristics that determine the expression of the metabolic syndrome in the presence of these upstream underlying causes.

Adipose tissue disorders include (1) excess fat in adipose tissue (obesity), (2) lipodystrophies where there is a deficiency of adipose tissue, (3) abdominal fat distribution (abdominal obesity), and (4) primary IR of adipose tissue, which is a separate and perhaps genetic factor that may or may not be present in people with these other disorders. There is a public health approach for the general population dealing with excess fat or obesity and clinical therapeutic guidelines for lifestyle changes in the NHLBI/NIDDK Obesity Education Initiative, which did not have as a primary focus the subsequent risk factors associated with obesity, although there was more emphasis on clinical intervention in overweight people when risk factors were present. Since a third of overweight/obese Americans have the metabolic syndrome according to NHANES III, Dr. Grundy believes these patients need special attention for clinical detection and probably more intensive intervention.

Dr. Grundy said that *lipodystrophy*, which comes in several forms, is an interesting model for the metabolic syndrome. When there is a deficiency of adipose tissue, there is a redistribution of fat between adipose tissue that in many ways serves as a storage or even protective organ and fat distributed into muscle and liver, which gives rise to the syndrome. Patients with lipodystrophy usually manifest the metabolic syndrome. The congenital, rare lipodystrophies have been studied at NIDDK and by Dr.

Abhimanyu Garg at the University of Texas Southwestern Medical Center. There are also partial lipodystrophies (lamin A/C mutations, PPAR (peroxisome proliferative-activated receptor) gamma mutations, HIV lipodystrophy) that are associated with the metabolic syndrome. The HIV lipodsytrophy associated with the metabolic syndrome is quite common and presents a therapeutic dilemma for physicians taking care of HIV patients. Dr. Grundy said that research is needed in this area from a clinical viewpoint and also may provide important information about how to approach the metabolic syndrome in other situations.

In speaking of *fat distribution* patterns, Dr. Grundy said there is a lot of clinical evidence that patients with lower body (gluteofemoral) obesity have a lower prevalence of the metabolic syndrome than those with upper body obesity. Different kinds of upper body obesity is perhaps related to different metabolic syndrome components and different implications for therapy. Some people who have upper body obesity and predominantly subcutaneous fat are at increased risk for diabetes. Those with predominantly visceral fat also are at increased risk and more prone to develop dyslipidemia. Dr. Grundy stressed that if abdominal obesity as a risk factor for the metabolic syndrome is important, then there is a need to encourage waist measurement in the clinical setting to help identify these high risk patients. He added that perhaps there also is a need for intensive testing for the presence of the metabolic syndrome with abdominal obesity and, if present, then more aggressive intervention for weight reduction and treatment of risk factors.

Next Dr. Grundy addressed *primary IR of adipose tissue* and generalized IR that extends to adipose tissue. When this occurs, often on a genetic basis, there is an excessive release of NEFA (non-esterified fatty acids) in circulation and other adipocyte products associated with mild obesity, which gives rise to this syndrome. Certain populations are at high risk for this type of abnormality, particularly South Asians, who are very insulin resistant on a genetic or racial basis and who have the metabolic syndrome, premature CHD, and diabetes at exceptional rates. Studies also show that offspring of diabetic parents tend to be insulin resistant and manifest the syndrome even with mild obesity and patients with primary hypertriglyceridemia probably also have an underlying IR and adipose tissue that leads to this hypertriglyceridemia. So there is a high prevalence of the metabolic syndrome even in the presence of mild obesity, which illustrates the problem of using obesity as the only factor in identifying the metabolic syndrome in some individuals. Dr. Grundy stated that it remains to be seen how far to stress this in the clinical area. Perhaps there is a need to identify IR with minimal abdominal obesity in a subpopulation of people or perhaps in certain population groups because even mild obesity in persons who have IR by this mechanism accentuates their risks and should be a target for treatment by weight reduction and possibly even TZDs, although he did not advocate the latter.

According to Dr. Grundy , genetic factors contribute to all the metabolic syndrome components—atherogenic dyslipidemia (high triglycerides, high apo B, small LDL, low HDL), hypertension, hyperglycemia, the proinflammatory state, and the prothrombotic state.

General Discussion of the Morning Presentations

The general discussion that followed the presentations addressed the definitions of the metabolic syndrome and its etiology, prevalence of the syndrome, the relationship of the syndrome to risk for CVD and diabetes, and implications for prevention and therapy. An overall major issue was the heuristic value of the syndrome.

Definition of the Metabolic Syndrome and Its Etiology. Dr. Peter Savage, NHLBI, remarked that it was likely that there are multiple causes of the metabolic syndrome, which may be difficult to identify, and even the possibility of the chance concurrence of common risk factors in a given individual. On the other hand, data from the CARDIA study indicates that people who have multiple risk factors

tend to persist in having multiple risk factors over time. So from a pragmatic point of view, regardless of the etiology, the metabolic syndrome has significance by defining the development of risk later on in life. Dr. Savage said that a pragmatic definition is therefore important and useful, even without universal agreement on what the exact criteria of the metabolic syndrome should be.

Dr. Judith Fradkin, NIDDK, suggested that perhaps rather than defining the cluster of risk factors as the metabolic syndrome, the same purpose of achieving recognition and attention for the clustering might be accomplished by using the data to develop a continuous and individualized risk engine. Persons could then view their personal risk engine and learn what losing 10 pounds by walking could do in reducing their own risk of developing diabetes or heart disease. This might motivate people as much as presenting them with a syndrome.

Dr. Grundy replied that NCEP tried very hard to get physicians interested in using Framingham risk scoring and even made it the core of their guidelines. However, his impression is that the metabolic syndrome has generated a lot more interest. He is now hoping that Framingham will include the risk factors from the metabolic syndrome. He believes there is something about the simplicity of the idea of the metabolic syndrome that seems to appeal to many people who have not yet accepted the Framingham risk scoring, even though it is a very powerful tool in defining cost-effective and appropriate therapies.

Dr. Grundy added that another possible component of the metabolic syndrome might be stone disease. It is related to obesity and insulin resistance and there is a lot of data on the mechanisms. He felt that if an expanded view was to be developed, then it would fit in as one of the complications like fatty liver.

Dr. Vinicor commented that viewing the metabolic syndrome as a concept or a vehicle to increase attention by the practitioner was one thing, but the use of the word "syndrome" or "disease" creates a different issue. What is required to move from a concept to a statement that something is a syndrome or a disease is determined by experts in nosology who classify diseases. While he agreed that consensus on a definition was worthwhile, he felt that it was also important to consider what is necessary to identify this cluster of conditions as a syndrome because this has huge policy and financial implications that go beyond a conceptual or methodological viewpoint. He urged the group not to move too easily or quickly from an area that may be intellectually important or may become clinically important to an area that is practically, financially, and public policymaking important without a clear understanding of the implications. He referred to conversations he has had with persons from the Centers for Medicaid & Medicare Services about why hypertension is a disease and high cholesterol is not. However, whether a condition is a risk factor, a syndrome, or a disease does have very important implications.

Dr. Grundy said that the NCEP panel had similar issues in defining individual risk factors. Is hypertension a symptom or a sign or a disease? Is diabetes a syndrome or a disease? He agreed that defining this concept does present problems but thinks they are built on top of existing underlying problems.

Dr. Haffner added that an interesting implication in establishing guidelines is that if hypertension is a disease then treatment is not based on the global risk over the short-term, whereas if cholesterol is a symptom, then global risk is calculated and considered in treating it.

Dr. Jay Everhart, NIDDK, asked if there was data on serum leptin in regard to the metabolic syndrome, particularly since leptin is both a marker of adiposity and a marker of inflammation. Dr. Haffner replied that there must be, but he could not actually remember seeing it.

Prevalence of Metabolic Syndrome. Dr. Frank Vinicor, CDC, asked what was the role of the aging U.S. population in the increased prevalence of the metabolic syndrome based on the Framingham and NHANES III data. Dr. Haffner answered that it would be necessary to use broad cohorts to actually look at that, but it would be interesting to do an analysis by different age groups to acquire an idea of the magnitude of this increasing problem.

The Metabolic Syndrome and Risk for CVD and Diabetes. Asked why people who have MI, both acute and long-term, and diabetes have a mortality rate that is double that of nondiabetics with MI, Dr. Grundy replied that it was probably due to the presence of multiple factors such as more hypertension, advanced atherosclerotic disease because of their diabetes, and diabetic caridionmiopathy, which is a complex condition. One reason it is important to prevent heart disease in the first place in patients with diabetes is that they are at higher risk for heart failure once they develop established CHD and have a very high risk of dying from the CHD.

Dr. Richard Kahn, American Diabetes Association (ADA), asked if anyone had studied the metabolic syndrome in a population, such as the Framingham cohort, by adding CRP to the other components and identifying which of the components had a greater effect on development of CVD. Dr. Haffner replied that a report by Dr. Paul Ridker's group based on the Women's Health Study, which is a very low-risk population, only about 0.2 percent per year, indicated that CRP was basically independent of the metabolic syndrome as a risk factor. This may indicate that CRP is not caused by the metabolic syndrome as stated in many papers. Dr. Haffner's data suggests that CRP is a fairly good risk factor for diabetes, not as good as glucose levels, but probably as good as waist circumference. He added that, ironically, some people think CRP is easier to measure than the waist.

Dr. Meigs explained that the Framingham risk score is calculated as points for the presence of incrementally elevated risk factors even within the normal range, so that a blood pressure that is mildly elevated gives a little bit of extra risk. Age is a major driver of the Framingham risk score, and what happens with the metabolic syndrome and age is unknown, other than that the prevalence increases considerably. Framingham only considers total cholesterol or LDL cholesterol, but not high triglycerides. Also the main published use of the Framingham risk score only considers established diabetes, not impaired fasting glucose or post-challenge glucose.

Dr. Meigs said that Framingham is working on the question of what is added by including the metabolic syndrome criteria to the Framingham risk score. They should have an answer in another month or two. Dr. Meigs does not consider the current Framingham risk score as the right tool to measure whether the metabolic syndrome increases risk because the metabolic syndrome captures a different set of risk factors than the Framingham risk score. He thought it entirely plausible that adding the metabolic syndrome criteria to the Framingham risk score would increase the predictive capacity fractionally because of these additional components.

Dr. Haffner stated that the Framingham risk score handles HDL and blood pressure very well as CVD risk factors, better than the metabolic syndrome, because they are separate categories. Although Framingham does not include any individual glucose information, just the presence of diabetes, that data and low HDL may be unimportant in calculating CHD risk. Framingham does include waist circumference but not BMI. Dr. Haffner wondered if including BMI or weight would have served as a tool to teach people about the importance of lifestyle changes. Dr. Haffner agreed with Dr. Meigs that, to his knowledge, there was no data that tested any population adding the metabolic syndrome to the global risk within strata to determine increase in risk, which would be key to determining implications for therapy.

In response to a question from Dr. Kahn about the integrity of risk levels associated with the metabolic syndrome based on the different components and

the levels of the individual components, Dr. Grundy pointed out that there is a consensual similarity between the metabolic syndrome and the Framingham risk score in that they are both mult-risk factor concepts. Framingham risk scoring includes one set of risk factors; the metabolic syndrome has an overlapping relationship to Framingham scoring, but goes beyond it by including obesity and triglycerides. These additional factors are increasingly common in the population, and many people believe they are truly independent risk factors. The *PROCAM (Prospective Cardiovascular Münster Heart Study)* algorithm being used in Europe includes weight and triglycerides as independent risk factors. Using the PROCAM algorithm for patients with the metabolic syndrome results in an absolute risk somewhat different from that of the Framingham score. Incorporating weight and triglycerides into Framingham would be a big service in Dr. Grundy's opinion.

Dr. Meigs addressed Dr. Kahn's question by saying that different trait combinations do confer risk for different endpoints in Framingham. For example, people with normal blood pressure but a larger waist may have a different risk than people with elevated blood pressure and a normal waist. Another issue is that measurement of thresholds are quite variable; an individual would certainly require at least two glucose measurements for the establishment of diabetes. However, a fasting glucose of 127 mg/dL twice would be clinically diagnosed as diabetes even though it is likely that the patient has a normal hemoglobin A1c. The situation is still taken seriously because it is known that eventually the patient is going to have more hyperglycemia and resultant complications. It is just the timeframe that is longer than for a person with a higher threshold. When thinking about metabolic risk factors, this diabetes analogy is helpful to consider. The CARDIA study also shows that even a person who is very, very mildly abnormal, when tracked over time, is identified as a person in the early stages of cardiovascular risk.

Dr. Kahn stated that ADA is looking at another kind of modeling of the various risk factors and examining the effect caused by reducing one or the other. For example, instead of looking at a continuum, the model will examine a group of people who have blood pressure or fasting glucose levels that are borderline but not severe, such as 130 to 140 or 110 to 125, respectively, and evaluate risk. The model will also evaluate risk based on whether an individual has one or more risk factors that are at high levels versus one or more risk factors that are at low levels.

Dr. David Orloff, FDA, had a question about prevalence data of the metabolic syndrome, the risk of CVD prior to clinical diagnosis of type 2 diabetes, and prevention versus screening and aggressive treatment of diabetes: Dr. Haffner answered that slides have limitations in presenting data: The Nurses Health Study was a very large study but diabetes was self-reported so the actual onset was probably earlier. Also, the data were only for women. The lifetime risk was approximately a 20-year risk. About 25 percent of the risk of CVD might actually occur prior to clinical diagnosis. That is not trivial and could be an impetus for prevention, especially if it is believed that lifestyle interventions have an effect on decreasing CVD even in people who do not develop diabetes. NHANES and Framingham data might also be calculated to determine the population-attributable risk of people who eventually develop type 2 diabetes. Economic analyses could also be done. The data needs to come from populations of both genders to decide on an optimal strategy between early screening and aggressive treatment versus prevention strategies.

Dr. Spiegel commented that the followup to the Diabetes Prevention Program (DPP) will look at data on this well-characterized population in which the exact onset of overt diabetes is known and will also look at the CVD influence. Dr. Haffner agreed that the DPP data is very important and that hopefully within a year there will also be atherosclerosis data based on carotid artery intima-media thickness (IMTs), which may provide a hint of what is happening in this area.

In response to a question from Dr. Spiegel regarding type 1 diabetes, macrovascular complications, and inflammation, Dr. Haffner said that there would be an NIH workshop on this subject in a couple of months. He stated that the ideal way to study this, and possibly NIDDK is funding this, is to look at type 1 diabetes in adults in Scandinavia where there is a relatively high rate of type 1 diabetes in adults, and using registry data, match persons who develop type 1 and type 2 diabetes at the same age and then follow them prospectively. The problem with studying this issue in children is that it takes a long time to develop and the risk is very low. It could be done with atherosclerosis studies, since there is so much type 2 diabetes starting to occur in adolescence in the United States and the progression of atherosclerosis is known. Dr. Haffner assumed that those with type 2 diabetes would have more disease because they are much more obese than persons with type 1 diabetes when matched for age. In the Diabetes Control and Complications Trial (DCCT), the early data on IMTs did not show a difference between those with type 1 diabetes and normal controls. The progression data may now be showing an acceleration, but Dr. Haffner is not on that review panel and so does not have that data. Dr. Fradkin added that surrogate measures from DCCT do indicate clear differences between the treatment groups in terms of progression.

Implications for Therapy. Dr. Malozowski noted that even in patients with established diabetes, long-term compliance with lifestyle changes is difficult to achieve. For persons who have the metabolic syndrome but have not been diagnosed with diabetes or CVD, he asked what interventions are necessary and practical. Even though lifestyle changes have been shown to be an excellent approach, the potential of using different medications has also been discussed. Among these are the TZDs, which provide improvements in some of the metabolic aspects but are known to increase weight gain, sometimes substantial weight gain.

Dr. Haffner replied that the TZD issue is two issues: the diabetic issue and the non-diabetic issue. The diabetic issue is less problematic to some degree because the TZD does lower glucose. While all diabetes drugs have their own limitations, if you use conventional definitions of the metabolic syndrome, whether WHO or NCEP, TZD, in spite of the weight gain, will improve the metabolic syndrome. They raise HDL, are slightly beneficial or neutral for triglycerides, claim to lower blood pressure, and clearly improve insulin sensitivity. Several studies, some of which are NIH-funded and some that are pharmaceutical studies, are looking at the long-term effects of TZDs on diabetes. BARI2-DM (Bypass Angioplasty Revascularization Investigation and Diabetes Mellitus) will presumably collect information on weight gain and will compare sensitizing versus insulin providing drugs. ADOPT (A Diabetes Outcome Progression Trial) is probably the clearest in terms of weight gain and waist circumference and will resolve some of the issues that measure lipids in the components. However, this does not mean that these agents are better for CVD, according to Dr. Haffner, which is a real limitation for their use. There are very few trials, here or abroad, competently looking at this issue of paying to take a medication that may or may not be more effective than lifestyle modification for diabetes and may not be effective for CVD. Dr. Haffner said that he thought the Food and Drug Administration (FDA) should require companies to do endpoint studies if they want to treat non-diabetics with insulin sensitizers rather than rely on a "leap of faith."

Dr. Jay Everhart, NIDDK, inquired whether the DPP has looked at changes in the metabolic syndrome constellation following the lifestyle intervention. In terms of the public health aspect, it would be very attractive to show an effect of lifestyle intervention on this constellation. Dr. Haffner referred to a paper submitted to ADA by Dr. Robert Ratner that presents statistically significant blood pressure, triglyceride, and HDL changes but does not calculate the metabolic syndrome at the beginning and end of the

study. The prevalence of the syndrome in the DPP cohort was about 60 percent. The study subjects had to have impaired glucose tolerance (IGT) and a fasting glucose of 95 mg/DL or higher. Dr. Haffner assumed that the numbers went down with the lifestyle intervention. Dr. Kahn said the biggest change was in triglycerides; blood pressure went down a fair amount in the first year but less at the end of the 3 years when the subjects regained some weight.

Heuristic Value of the Metabolic Syndrome. Dr. Spiegel remarked that the metabolic syndrome is basically a concept involving a very heterogeneous set of disorders with undoubtedly many underlying genetic sequence variations and environmental interactions. He noted that much of this will become clearer after Dr. Francis Collins of the National Human Genome Project provides the sequence on a chip. Meanwhile, based on the current definitions of the syndrome, Dr. Spiegel asked what is the real heuristic and practical value of the metabolic syndrome. The syndrome presents a constellation of treatable abnormalities, whether they be lipid abnormalities, hypertension, or glucose abnormalities. Is this an issue of defining different cutpoints that would then lead to treatment with drugs? What is being learned? What is the practical significance of this concept of a metabolic syndrome?

Dr. Grundy responded that one of the reasons the metabolic syndrome was introduced or emphasized in the ATP III guidelines was to get physicians to pay more attention to the medical aspects of obesity and its complications, which were being ignored. Obesity had tended to be considered as something one could do little about in a clinical setting. If the metabolic syndrome could draw attention to people who have risk factors that converge and emerge from the presence of obesity, then physicians might begin to internalize this idea, pay more attention to it, and make it more meaningful in their practice.

Dr. Haffner spoke of the many databases that include the components of the metabolic syndrome or the modified metabolic syndrome, but few papers that discuss the interrelationship of these components. He added that people pay little attention to behavioral aspects, but if they become convinced that this is an important syndrome whatever their actual risk, and if lifestyle interventions are relatively more effective for this syndrome than are drugs, which he thinks is likely to be true, then they just they might do the right things, even if not exactly for the right reasons, which would make this a useful concept. The concern Dr. Haffner sees people struggling with is whether this is this going to lead to a huge explosion of drug therapy and the use of new drugs in non-diabetic patients because they have the metabolic syndrome.

Dr. Meigs, as a primary care doctor and researcher, said he thinks the value is two-fold. First, defining the metabolic syndrome helps to focus attention on the importance of mildly elevated risk factors in combination as being important targets for some form of intervention, rather than ignoring mildly elevated blood pressure or mildly abnormal lipid levels. Defining the syndrome also crystallizes the concept of multiple risk factors occurring together as being worthy of some form of intervention. It provides a handle on obesity as a target for intervention in terms of treating the related risk factors as defined by the metabolic syndrome. Historically, obesity is difficult to deal with and clinically doctors tend to view it as not their problem. For these reasons, Dr. Meigs felt it was valuable to move toward a consensus definition. on how to actually define it. Secondly, the etiology of the syndrome seems to derive largely from lifestyle issues that arise in childhood and adolescence. It is, therefore, important to address these issues early. The issue of treating basically asymptomatic, otherwise healthy people with drugs to prevent development of a disease 10 or 20 years in the future requires serious evaluation, especially in the setting of emerging data that lifestyle changes are so effective in preventing at least diabetes.

Agency Presentations

National Institute of Diabetes and Digestive and Kidney Diseases
Judith Fradkin, MD, Director of Division of Diabetes, Endocrinology, and Metabolic Diseases

Dr. Fradkin stated that NIDDK is not specifically investigating the metabolic syndrome, but the Institute is conducting programs indirectly related to it such as the Diabetes Prevention Program (DPP). In February 2003, the National Diabetes Education Program (NDEP), funded by NIDDK and CDC, launched the Small Steps, Big Rewards campaign based on DPP results. DPP showed that a modest weight loss and 30 minutes of exercise 5 days a week reduced the risk of developing type 2 diabetes and the complication of CVD in subjects who were overweight, had impaired fasting glucose, and a family history of diabetes. NDEP is working with its partners to develop materials for physicians and patients based on the DPP lifestyle intervention. As part of their campaign to put these tools to physicians and patients, they have established a Web site (http://ndep.nih.gov). The Web site has links to and now we will talking with partners in trying to get those materials into the hands physicians and patients. The website has inks to NHLBI and to the Obesity Education Initiative that NHLBI helped develop. NIDDK is also increasing its efforts with regard to obesity research from trying to identify new potential targets for therapy from molecular research to clinical research related to prevention and intervention.

NIDDK also is developing a school-based prevention study for type 2 diabetes. Currently in its pilot phase, the study will collect baseline data on height, weight, waist circumference, blood pressure, glucose tolerance testing, and lipids from students in middle schools with at least 50 percent minority populations. Investigators will use the baseline data to define metabolic outcome measures for the intervention, not just a weight loss outcome, for the clinical trial. Dr. Fradkin said these pilot studies will provide a lot of population-based information about the prevalence of the components of the metabolic syndrome in early adolescent children. She added that she would be very interested to hear from other groups about the metabolic syndrome in children, including what definitions are being used, in order to coordinate the outcome measures NIDDK is developing. This would likely make the results of the trial more relevant to the syndrome as defined and used by others.

Finally, NIDDK is talking with the National Center on Health Statistics about potentially restoring the oral glucose tolerance test (OGTT) to NHANES. She explained that it was done this way in NHANES III but when the yearly NHANES began, it was dropped, largely to tie in with the ADA recommendations for using fasting blood glucose to diagnose diabetes. With the increasing prevalence of type 2 diabetes and the DPP and other data related to the risk factors for CVD, the decision to use the 2-hour OGTT is being reconsidered. Dr. Fradkin said the earliest the change could happen would be in 2005, but she was interested in the group's opinion on how useful this would be. Drs. Grundy and Haffner agreed this was an interesting idea.

National Heart, Lung, and Blood Institute
Peter Savage, MD, Director, Division of Epidemiology and Clinical Applications

Dr. Savage announced that NHLBI in collaboration with the American Heart Association will conduct two conferences on the metabolic syndrome, one in April on the definitions and one in September on treatment issues. Dr. Grundy will chair both meetings.

Dr. Savage presented opportunities for investigating the metabolic syndrome through NHLBI-funded cohort studies including the Framingham Original Cohort and Framingham Offspring studies, the Honolulu Heart Program, Atherosclerosis Risk in Communities (ARIC),Cardiovascular Health Study (CHS), and the and the Coronary Artery Risk Development in Young Adults (CARDIA). Like NIDDK, his Institute is not directly studying the metabolic

syndrome but NHLBI does have studies related to it and data sets that provide an opportunity to look at questions, some of which had been discussed today.

CARDIA is a study of approximately 5,000 (5,115) 18- to 30-year-old African American and white young adults initially examined in 1985-86. Metabolic syndrome defined by ATP III was rare, about 4 percent. Therefore, the investigators defined a pre-metabolic syndrome to look at those who were above the gender-specific 90th percentile at the baseline exam for three or more of the risk factors used by ATP III and below the 10th percentile for HDL cholesterol.

The group was relatively unique in its balance by race, sex, education, and age within centers. There were five examinations over time with a substantial followup. Seventy-four percent (74%) returned for the Year 15 examination. What we found was that the frequency of risk factors increased fairly strikingly over the 15-year period in these young adults. The prevalence of the syndrome rose from 4 percent at baseline to 21 percent. It was highest in those at year 15 who were already overweight at baseline versus those who were normal at baseline, 41 percent versus 11 percent. Although all the group gained some weight, the prevalence was higher in those who gained 15 kilograms or more versus those with little weight gain, 44 percent versus 25 percent. Young adults with the pre-metabolic syndrome at baseline were much more likely to have the full-blown ATP III syndrome at the end of 15 years. Now the young adult years between ages 20 and 40 are relatively silent years. Disease progresses during that time, but the individuals tend to feel well and do not have much in the way of symptomatic disease. These are people who are still healthy in young adulthood and yet they are well on their way to developing the abnormalities that are likely to lead to clinical disease sometime in middle age or early older years.

Dr. Savage next offered data sets available through NHLBI to address some of the questions about the metabolic syndrome. In addition to the cohort studies he listed at the beginning of this presentation, Dr. Savage noted there is also data from current clinical trials (Asymptomatic Cardiac Ischemia Pilot (ACIP); Intermittent Positive Pressure Breathing (IPPB), Post-Coronary Artery Bypass Graft Study (Post CABG), Thrombolysis in Myocardial Infarction Study (TIMI II), Lung Health Study (LHS), Digitalis Investigation Group (DIG), Beta Agonist in Mild Asthma (BAGS), Antiarrthymics Versus Implantable Defibrillators (AVID), and Colchicine in Moderate Asthma (CIMA)). There is data on almost 50,000 people who have had longitudinal exams, multiple racial/ethnic groups, men and women, ages ranging from about 18 to 100. Dr. Savage explained that NHLBI is planning to gradually make more and more data from the large studies available.

Researchers may collaborate with existing study investigators or request a public access data tape to work on at their own pace. He pointed out that collaborating with the primary study investigators on an issue as complex the metabolic syndrome has many advantages such as the knowledge of the investigator, the assistance in doing complex analyses provided by the statisticians of the coordinating center, and access to the most recent data. The rights of the primary investigators are protected by giving those doing epidemiology studies a 5-year period after the close of an examination and a 3-year period after publication of the primary paper and the clinical trial. So for access to the most recent, complex longitudinal data sets, it is important to try and work with the study group. There are also a set of rules to protect participant privacy and procedures about what can and cannot be done with the data. To obtain data sets directly from NHLBI, researchers must agree to follow certain rules and procedures to protect both the rights of the investigators and the participants.

NHLBI's Web site (www.nhlbi.nih.gov/resources/deca/default.htm) provides data documentation, distribution agreement forms, information about Institutional Review Board (IRB) approval, and the overall policies that NHLBI has developed. The data is provided at no cost to the applicant.

Centers for Disease Control and Prevention
Frank Vinicor, MD, Director, Division of Diabetes Translation

Dr. Vinicor stressed the importance of having science-based evidence before launching a public health program as opposed to a clinical program related to a disease or a syndrome. There is general consensus that the 17 million persons diagnosed with diabetes deserve treatment, not only for the their glucose problem but for all the components included in the metabolic syndrome definitions. In NDEP and in other public health efforts, obesity, cardiovascular risk factors, and so forth are addressed. In taking a broad view of diabetes, however, CDC's Division of Diabetes Translation is asking: When does the diabetes clock start ticking? There is some question whether CDC should be looking for the missing roughly 6 million people with present but undiagnosed diabetes, an issue that will have to be decided at the policymaking level more than at the scientific level. Next, there is a cohort of about 16 million persons who presumably have what is now called pre-diabetes. That group is reasonably defined by IFG and/or IGT based on several randomized controlled trials indicating that primary prevention should work and the question is how to make it work. The fact that there is good science underlying this gives us the moral, ethical, and programmatic responsibility to take a public health program forward. Those we call pre-diabetic presumably emanate out of the cohort of 45 million people identified in Dr. Earl Ford's study as having the metabolic syndrome as defined by ATP III. Dr. Grundy indicated today that there are a lot of people with metabolic syndrome who do develop pre-diabetes and then diabetes. Finally, there is the issue of the fetal programming mentioned by Dr. Grave that may precede development or contribute to the development of the metabolic syndrome.

Dr. Vinicor listed CDC's public health activities as involving basically three areas—surveillance activities, epidemiology and translation research, and pubic health programs. As evidenced by Dr. Ford's surveillance work, CDC is using national data sets to examine the prevalence and associated factors of the cluster of conditions called the metabolic syndrome. The nature of the utility of these national surveys varies. For example, the Behavioral Risk Factor Surveillance Survey (BRFSS) is a self-report so to the degree to which people do not know about the syndrome, they cannot be asked "Have you ever been told you have the metabolic syndrome?" There is slightly better reliability in administrative data, such as discharge data. Finally, NHANES, where the components are actually measured, actually provides a sense of the prevalence of the factors associated with the metabolic syndrome. Surveillance is typically not hypothesis driven.

Epidemiological and translation research is more hypothesis generated. For example, the SEASRCH study with CDC's colleagues at NIDDK will hopefully identify people with type 2 diabetes and might be an opportunity in a prospective way of looking at whether or not elements of the metabolic syndrome exist in this group. Similarly, Dr. Rodolfo Valdez who was involved with the Bugalosa Heart Study in Louisiana and Dr. Henry Kahn of CDC are looking at ways to more easily define the metabolic syndrome from a public health standpoint.

As a framework for public health programs, Dr. Vinicor listed six progressive, interrelated steps delineated by Dr. Detsky of Canada and his colleagues in 1990. The initial step is fundamental research. Next is an efficacy trial, such as the DCCT, followed by determining the intervention's effectiveness, efficiency, availability, and distribution in the real world—it works but at what financial cost, is it affordable, are policies such as reimbursement in place to allow to happen, and can it be distributed in Small Town, Indiana, as well as in Bethesda, Maryland. Dr. Savage reiterated that all these steps are involved in thinking about what can be done from a public health perspective to help people. He said that, in his opinion, the field is at the fundamental research stage with regard to the metabolic syndrome and cautioned against leaping over the intervening steps between research and availability. He felt it important to determine if it will make a

real difference to identify persons with the syndrome rather than simply treating the individual components, which no one would argue with as being reasonable and necessary.

CDC is interested in participating in the fundamental research and through surveillance to understand the syndrome better. The agency is not ready to develop public health programs and policies based on the metabolic syndrome. First, the case definition needs to be clarified and examined by the nosology experts to officially identify is as a syndrome. Second, there needs to be more science-based evidence comparable to that from DCCT or DPP upon which to build a public health perspective. Thirdly, public health policy can not be determined by the tails of the distribution curve; it appears to be a heterogeneous condition, it is not clear how common it is, and whereas unusual cases can determine a clinical viewpoint, they cannot determine public health policy. Finally, currently, CDC has many competing priorities. The Division's mission is to help people who have diabetes and now, for those with pre-diabetes, to prevent diabetes. While the group is interested intellectually, conceptually, and scientifically, there simply are no resources to deal with the metabolic syndrome as a public health program.

Dr. Vinicor's opinion was that "there is real gold out there" but the definition needs to be clarified and a consensus reached on just what the metabolic syndrome is. He saw value in finding a way to identify people at a younger age who might have or develop the components and go on to develop diabetes or cardiovascular diseases, but the science is not yet there from a CDC public health perspective. Dr. Vinicor emphasized once again that CDC is interested from an investigative or scientific stance, but his viewpoint is that it is a mistake to launch public health programs unless there is solid science behind them.

In the discussion that followed, Dr. Vinicor agreed with Dr. Grundy that obesity is a public health concern. However, in studies with different racial/ethnic populations, the sequence of events regarding obesity and hyperinsulinemia varies greatly. Therefore, he believed it premature at this time to view obesity together with the metabolic syndrome from a public health point of view. NDEP is focusing its efforts on that portion of the total obesity population that is pre-diabetic, not a small group, some 16 to 18 million persons. Other programs at CDC and at NIH are focusing on the broader obesity issues for the entire population. The CDC Division of Diabetes Translation is part of that team but not taking the lead. That is the role of a sister division.

American Association of Clinical Endocrinologists (AACE)
Helena Rodbard, MD

Dr. Rodbard discussed the results of the American College of Endocrinology (ACE) conference held in the summer of 2002 and convened to address the growing epidemic of the metabolic or insulin resistance syndrome. The conference's consensus statement will be published in the March issue of *Endocrine Practice*. The previous year, ACE had developed guidelines for treatment of type 2 diabetes with emphasis on the prevention of macrovascular disease and its comorbidities. The ACE Task Force on the Insulin Resistance Syndrome was co-chaired by Dr. Daniel Einhorn and Dr. Gerald Reaven. Dr. Earl Ford of CDC was also a member. Dr. Rodbard said that ACE also championed development of the CPT code (277.7) for the metabolic syndrome, which helped to put the syndrome on the map, particularly for third-party payers and to legitimize the syndrome as a real clinical concern.

The first issue at the conference was what to call the syndrome. Different names were proposed, such as the metabolic syndrome, the dysmetabolic syndrome, and syndrome X. Finally, insulin resistance syndrome was agreed on based on the rationale that it was a more encompassing name and addressed the pathophysiology of the disease. Diabetes, as Dr. Grundy pointed out, previously was not part of this syndrome, but was considered as another risk factor for CHD. At the center of the equation as the main concerns were heart disease and stroke. Although

the vast majority of the people did not have diabetes, some of them actually would develop diabetes, as well as the other complications associated with CVD.

The components of the insulin resistance syndrome as defined by ACE are a constellation of factors including some degree of glucose intolerance, although not overt diabetes; abnormal uric acid metabolism; dyslipidemia, particularly with elevated triglyceride levels, low HDL, high concentrations of the small dense LDL, and the high lipidogenic particles; hemodynamic changes, with hypertension being at the core of those; prothrombotic factors, PAI-1 being one of them, and fibrinogen; markers of inflammation, such as CRP, endothelial dysfunction, and other markers of inflammation; polycystic ovary syndrome (PCOS), a frequent concomitant of this syndrome, and non-alcoholic fatty liver disease (NASH). The concept is very emperic, but the main concern is to decrease the incidence of CAD in the population, primarily through lifestyle modifications rather than pharmacological therapy.

Screening of people most likely to develop the insulin resistance syndrome and be at high risk would include those who have coronary heart disease, hypertension, PCOS, or acanthosis nigricans. Dr. Rodbard said this latter symptom is particularly important to clinicians as an indication of the syndrome that can be easily seen when the patient walks into the room. Other indications are a family history of type 2 diabetes, hypertension, or CVD; women with a history of gestational diabetes or individuals with glucose intolerance; ethnic minorities; people with sedentary lifestyles; a BMI greater than 25 kg/m2; and age, particularly people over the age of 40.

Particular hallmarks, the clinician would be looking for as a definite for the diagnosis, would be triglyceride levels greater than 150 mg/dL, HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, blood pressure greater than 130/85 mm/Hg, and fasting glucose between 110 and 126 mg/dL, people who would be candidates then for a OGTT. A lesser factor, but one of the components, would be increased microalbumin or urinary albumin excretion. Dr. Rodbard remarked that in Renoir's time, abdominal obesity might have been a mark of beauty, but today concepts have changed. We know that it is not healthy. She said it is incumbent on the leaders of medicine in the United States to join forces and fight this growing epidemic..

In the discussion that followed, Dr. Rodbard explained that the CPT code for the metabolic syndrome is a combination of mostly clinical criteria, a combination of phenotypes, and some laboratory tests as well. The CPT panel were not too specific. The existence of a code was to make it implicit that there is such a syndrome and there should be some type of reimbursement for diagnosing and treating it, because there is no reimbursement for obesity, per se, unfortunately. Obviously, not everyone who is obese has this syndrome, but if they have obesity and they have some of the components of the syndrome, this code would be applicable.

Dr. Rodbard agreed with Dr. Vinicor that establishment of a code by the American Medical Association CPT Editorial Panel does not guarantee reimbursement for screening or for treating something as a syndrome by, for instance, the Centers for Medicaid & Medicare Services (CMS).

Dr. Grundy suggested that when this metabolic condition is called the insulin resistance syndrome and requires a glucose abnormality, it is likely to lead to a focus on drug treatment of insulin resistance and treating persons with insulin-sensitizing drugs prior to their developing diabetes. Also, it would almost have to require glucose tolerance testing on a large number of people to make the diagnosis. Who those people would be is another issue—would it be just overweight people, or since overweight is not a factor, would every patient be tested as is commonly done now for cholesterol and blood pressure?

Dr. Rodbard replied that therapeutical approaches will be the subject of a future conference. At this time ACE was simply trying to identify people with the syndrome because of concern for the coronary risk factors and comorbidities associated with it. The primary approach will probably be educating the patients and encouraging them to be less sedentary, lose weight, do lifestyle modification, rather than medical therapy. She said they did not have much data to justify pharmacological therapy. It would not make sense to putting everybody on TZDs or another form of insulin-sensitizer without having the data to show that would be effective.

American Diabetes Association
Richard Kahn, PhD

Dr. Kahn announced that ADA is in the midst, along with some collaborators, in developing a paper on the metabolic syndrome for publication in and ADA journal and across,at least two or three other journals that reach different disciplines. The purpose of the paper is to provide a perspective and address questions such as "To what extent is the definition of the metabolic syndrome based on data?" A number of components have been named by ATP III and WHO and Dr. Rodbard added a few more from the ACE definition. The issue, he said, is what is the basis for choosing these components,. On what basis are the cutpoints chosen? Are there data to suggest that one cutpoint is better or worse than another cutpoint for any of the components? How does a risk factor become a part of the definition? Why, for example, is not LDL or age a risk factor? Age is as metabolic as blood pressure.

The second issue the paper will address is do all combinations of the factors imbue the same risk? Are the risks of adverse outcomes the same between all ages, all races, and at all levels of any of the risk factors? Dr. Kahn said this is important before screening and treating a population based on the syndrome.

The third major topic in the paper will be the etiology of the metabolic syndrome. Is it really all insulin resistance or to what extent is it insulin resistance versus something else. As Dr. Grundy pointed out, there are different therapeutic ramifications depending on what the underlying etiology is? Is enough known yet to even say what the underlying etiology is?

Last and most importantly, in Dr. Kahn's opinion, is what is the appropriate therapy for someone with the metabolic syndrome? Is there any clinical evidence to support any therapy for the syndrome itself—not hypertension, not diabetes, not dyslipidemia, but the general metabolic syndrome? Are there any clinical studies that show CVD or diabetes can be reduced by identifying someone with the metabolic syndrome? The closest there is to that is the results of the lifestyle interventions in the DPP and the Finnish study, but they are not definitive for the metabolic syndrome as defined.

Dr. Kahn stated that these questions important for three reasons. First, the concept of a metabolic syndrome has grown from a very interesting, probably important, epidemiological finding of clustering into a disease in and of itself. As Dr. Rodbard pointed, it has a treatment code and potentially could cost billions of dollars in health care costs. Instead of turning into a strategy to reduce obesity, it has become a disease to be treated. Patients are not only receiving pharmacological therapy , it has become a gold mine of insulin assays for laboratories and referrals for specialists. The practitioner is unaware of the uncertainties and problems regarding the syndrome that are being discussed in this meeting.

Second, definitions tend to become cemented and are very difficult to change even when new data arrives, as ADA has experienced in the area of diabetes. It is critical not to define anything in a relatively arbitrary manner.

The third factor is the adding on of layer after layer of things for physicians to do and for consumers to do, which may divert attention from what may be the most important things to do. For example, a recent article in *Diabetes Care*, reported that only 3

percent of diabetic patients treated by endocrinologists in an academic medical center were reaching their hypertension, LDL , and hyperglycemia goals. If additional items are added on, clinicians and consumers are likely to become more and more frustrated. Dr. Kahn's recommendation was to "try to hold the train back a little bit," while continuing with additional research.

Dr. Kahn's comments elicited considerable discussion. Dr. Savage commented that there is not evidence that the metabolic syndrome is a disease or that it should be treated in any specific way. On the other hand, there is an epidemic of obesity in the United States; millions of people are becoming overweight, and data from the last 25 to 30 years shows an alarming growth of obesity-related problems in children and young adults. There are many questions to be examined. However, one relatively clear message is that obese people are at markedly increased risk of developing diabetes and at an increased risk of developing heart disease. Therefore, the public and those delivering health care need guidance to deal with the problem and prevent the full-blown metabolic syndrome from developing in large numbers of people.

Dr. Kahn responded that the conclusion that obesity is a predominant, if not the most predominant, risk factor, could have been reached 3 or 4 years ago. He went on to say that organized medicine as it exists today is not going to help the obesity problem, because physicians by and large have no training and no time to do what it takes and there are no interventions that work in the long-term from the medical perspective. In addition, there are billions of dollars of marketing money favoring obesity. It is possible to draw attention to obesity as a public health problem, and this must be done, but what is going to change the situation in the absence of a pharmaceutical agent is really mass social reengineering.

Dr. Savage agreed that a cultural change was needed before physicians could intervene in a way that would change the problem in millions of people. He added that people who gain a lot of weight, particularly during the years from 20 to 50, tend to be the people who also have a much higher risk of developing multiple risk factors and the complications that follow. This means that an attempt needs to be made to promote a cultural change in the public that will result in behavior changes. On the other hand, if someone has full-blown risk factors, they need conventional medical therapy.

Dr. Spiegel said that one of the most compelling presentations he had heard was by Lawrence Green in speaking of the smoking problem at a translation session. Although the obesity challenge is even more daunting, there are applicable comparisons to smoking, including the billions of marketing dollars targeted at the U.S. population and the fact that physicians alone cannot be the sole solution to the problem. A possible lesson can be learned from the Surgeon General's report on smoking and cancer that was the impetus; it was clear cut. And even though, the country is not "home free" and everything is not all solved and perfect—young women are lighting up at increasing frequency—nonetheless, there has been a tremendous shift culturally. Today's stigma associated with smoking needs to be avoided where obesity is concerned. Still, once there is scientifically based data comparable to that of the Surgeon General's on smoking, then the public message can be that obesity is not a moral problem, it is not a cosmetic problem, it is a health problem. Dr. Spiegel stated that getting to the dimensions of it as a health problem in the most rigorous, precise way is what this discussion was really about.

Dr. Kahn agreed but drew attention to the fact that, in spite of the intention to focus the issue on the clusters of risk factors, or obesity's relation to them, the unintended consequence has been the rise of a whole medical industry focusing on laboratory tests and drugs at a time when the definitions are not firm and the interventions are unclear. Although there is a huge problem with obesity, the most telling aspect is that if one looks at attendees at

annual scientific sessions or any group of people who should know about obesity, are they really any different from the population at large?

Dr. Spiegel replied that there is a difference. If you look at the behavioral risk factor surveys, there is a totally inverse correlation between education and diabetes, particularly type 2 diabetes, and obesity. There is a whole segment of the population that has access to health clubs and so forth. The other thing is that only a few decades ago, a significant number of those present at a scientific gathering such as this meeting would have been smoking. That no longer happens. Eventually if the science is there and the public health message is presented appropriately, substantial differences will be seen in overweight and obesity. That is not a Pollyanna point of view.

Dr. Grundy added that when cardiovascular guidelines were being developed, similar criticisms were voiced about definitions and other imperfections. The same was true with cholesterol and blood pressure. His other point was that although there are separate guidelines dealing with blood pressure and cholesterol, patients tend to have the same cluster of conditions—hypertension, dyslipidemia, and obesity. In fact, there has been criticism for not unifying the guidelines. The metabolic syndrome is a first attempt to look at the whole patient and to recognize all the different components that make up the constellation. It is a step in the direction of bringing together and synthesizing a total risk package for the patient.

Dr. Kahn raised another issue taken from the world of diabetes. People have suggested that the 1997 definition for diabetes based on the so-called "gold standard" of the OGTT as being 140 for IGT and 200 for diabetes should be changed based on current data. The problem with doing that is that too many papers have been written based on the old definition. As more and more people relate to the definition of the metabolic syndrome and base their research and analyses on, for instance, the NCEP definition, if data comes along demonstrating that a cutpoint should be higher or lower or that a component should be added or subtracted, there will be a point where people will say, "We can't do that. It would be too disruptive even if the data shows this is not right or should be modified." This is what happened with the OGTT.

Dr. Haffner stated that changing from doing OGTTs had some beneficial effects in identifying more undiagnosed diabetic subjects. The use of the metabolic syndrome has not suggested new pharmacological therapy. It has suggested that there be a focus on those risk factors for which there are already guidelines. It also has focused on behavior. The NCEP ATP II also recommended behavior modification, but the problem was that the behavioral effects on LDL cholesterol were not that much, so people wrote off the suggestion. The ATP III is being taken more seriously. The definitions are probably not perfect. More research is needed. There continues to be a need for standardization of insulin concentrations, which was agreed to 5 or 6 years ago but has not happened. Interest in the metabolic syndrome may stimulate that. One of the reasons that people dislike the WHO definition is because they do not know what insulin concentrations mean.

Dr. Kahn told the group that ADA has a committee that will meet soon on standardizing the insulin assay. He also pointed out that although the intentions of the ATP III definition were clear, the consequence has been a growing number of pharmaceutical companies approaching ADA and fundamentally saying they want their drug, no matter what it is, to be associated with the metabolic syndrome. Some companies have said they even do not want their drug associated with lowering a particular parameter such as blood pressure or glucose or weight; they want it positioned as affecting the metabolic syndrome.

Dr. Vinicor spoke of the power of science that was experienced though the experience of DCCT. DCCT created not just a medical change but a cultural change in thinking about the importance of glucose control. This power facilitated social-cultural

change beyond the doctor's office; it affected policy-making, Congressional appropriations, third-party reimbursements, and the CMS. This is also true for the DPP and the Finnish study. He urged that the power of good science not be underestimated. If a good study showed that addressing weight in 20-year-olds in a rigorous way improved even intermediate outcomes in lipids and blood pressure after 5 years, that study could then change society.

Dr. Savage said that treating individual endpoints would probably yield a slight incremental benefit, but he felt that treating the metabolic syndrome abnormalities as a whole would result in the most benefit. It would be important to do an intervention study in healthy young adults to see whether or not there was a relatively cost-effective way of changing the pattern of development of obesity and risk factors before they are clearly established, rather than just continuing to document their prevalence in more and more populations.

National Institute of Child Health and Human Development (NICHD)
Gilman Grave, MD, Chief, Endocrinology, Nutrition, and Growth Branch

Dr. Grave referred to the growing numbers of adolescents with type 2 diabetes, obesity, and high blood pressure. NICHD is very interested in the early origins of the clustering of these factors of the metabolic syndrome and the heuristic value of looking at these in childhood, especially the fetal origins of the syndrome. The NICHD National Children's Study will look at fetal origins of adult disease to learn when it is first possible to detect the appearance of the cluster, to closely track it into adulthood, and to assess its implications. Referring to a study by Dr. Boyd Metzger and the late Dr. Norbert Freinkel, both of Northwestern University, Dr. Grave noted that it will be interesting to see if study subjects who are now in their 20s and are the offspring of women who had gestational diabetes show evidence of the clustering since the study showed earlier that the level of amniotic fluid insulin in their mothers highly correlated with the incidence of the children's obesity at 10 years of age. NICHD also is very interested in the genotype-phenotype correlations and what the environmental interactions are because so many women with obesity do not have this clustering.. He invited those present to participate in an NICHD workshop on June 30-July 1 that will address the same questions presented here: What is the etiology? What are the definitional issues? What are the cutout points, especially by age in children? How does puberty affect insulin resistance?

Food and Drug Administration
David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products

In his presentation of FDA's perspective on drug development in the metabolic syndrome, Dr. Orloff noted that the idea of the metabolic syndrome as a target for therapy in and of itself has great appeal to the pharmaceutical industry. He also stressed that if the syndrome is to have public health implications, a consensus definition must first be established. While FDA shares the public health goals of the other DMICC members, their mandate is sometimes incongruous in their duel role of protecting the public health and also regulating and even promoting commerce in presumably safe and effective drugs. FDA challenges sponsors to develop safe and effective treatment and preventive agents, conducts a guidance and review process and regulatory actions to bring new drugs to market, and then partners in the public health arena to label the drugs or treatment and preventive agents appropriately with regard to expected risks and benefits. Dr. Orloff said that expected risks and benefits is a very important concept in drug labeling and to ensure "balanced promotion."

The agency's current position on what would be required for a "treatment for metabolic syndrome" and a drug label is that diagnostic criteria is needed that identifies a population in which negative outcomes attributable to the syndrome can be reliably predicted. There would need to be a central pathogenetic mechanism or combination of mechanisms, a

drug or combination of drugs impacting this mechanism that predictably ameliorates the spectrum of metabolic and physiologic abnormalities of the syndrome, and finally evidence based on hard outcomes of a role for drugs in the management of CVD or another potentially mortal risk. Short of meeting these criteria, FDA would say treat the components of the syndrome, or without a consensus definition of the syndrome, treat the known established cardiovascular risk factors for which there are effective interventions as demonstrated by the impact on intermediate or surrogate measures or evidence of impact on overall hard outcomes. FDA agrees that the metabolic syndrome comprises a constellation of cardiovascular risk factors and that there is plentiful evidence suggesting these should be addressed therapeutically. However, absent a unifying pathogenetic mechanism and evidence of a salutary effect on outcomes of the intervention on that mechanism, drug target(s) remain the components of the syndrome not the syndrome itself. Obesity interventions, such as lifestyle modification, that do not involve drugs do not come under the purview of the FDA.

Dr. Grundy commented that one of his concerns has been that in treating the components physicians sometimes concentrate on one component and ignore others. This is highlighted in patients with diabetes where physicians may focus on treating glucose because the patient has diabetes but fail to treat the hypertension that almost all patients with type 2 diabetes have, do not treat lipids appropriately, and do not recommend aspirin and things like that. An advantage of looking at the syndrome is that it considers all the components and points to the need for each one requiring the appropriate intervention, either drugs or not drugs.

Dr. Orloff agreed but said there is not universal agreement on this at FDA. However, for a long time, the agency has included in the labels for the lipid-altering drugs, the National Cholesterol Education Program guidelines and information on multiple risk factor intervention. Dr. Orloff proposed that similar information could be provided on labels that would be appropriate and applicable to patients who have a constellation of cardiovascular risk factors, such as the components of the metabolic syndrome. To include such directions in labeling, the expected benefits of the intervention must be specific and have been shown to impact a particular outcome. Once that is well-established and a consensus reached on how to predict risk in patients with a constellation of risk factors and how to guide them therapeutically, then such information could be included on labels.

Indian Health Service
Kelly Moore, MD, Clinical Specialty Consultant, National Indian Health Service Diabetes Program

Dr. Moore reported that as a clinical care system, IHS plans to provide training to its clinicians and administrators on the metabolic syndrome and in applying the additional funding received under the special diabetes grant program for prevention and treatment of diabetes in its patient population, the agency will be looking at screening for diabetes and for the metabolic syndrome. She said there is a sense of the metabolic syndrome among IHS clinicians, and there have been a number of training sessions on the diagnostic criteria and on interventions related to some of the components. Patients do not have much knowledge of it.

Dr. Moore's presentation focused on the risk factors for the metabolic syndrome in the American Indian and Alaska Native (AI/AN) population based on the epidemiology of diabetes and obesity in this group, particularly those who have diabetes but also AI/AN youth at risk. IHS has developed state-by-state maps, similar to CDC's obesity maps, to show an increasing age-adjusted prevalence of diagnosed diabetes among AI/AN persons age 20 years and older. Clearly there is an epidemic. The rate of high prevalence in 1991 that existed in only four states—Florida, Nebraska, Maine, and Mississippi—in 2001 existed in 18 states, Arizona, Colorado, Iowa, Kansas, Maine, Michigan, Minnesota, Mississippi, Montana, Nebraska, New Mexico, North Carolina, North and South Dakota, Texas, Utah, Wisconsin,

and Wyoming. Comparing prevalence in 1991 versus 2001 by age group shows alarming increases in the younger age groups. There has been a 106 percent increase in diagnosed diabetes in the 15- to 19-year-old adolescent population. There was also an increase in prevalence of overweight and obesity from 1994 through 2001 in the patient population with diabetes. In a study of overweight AI youth from a large tribe in the Southwest, children of 6 years of age are already well along the trajectory towards developing diabetes (Elsenmann, 2000).

IHS does not have good data on the metabolic syndrome in AI/AN groups; their best data is from the annual audit of the patient population with diabetes. The 2001 diabetes audit showed that nearly 40 percent of men and 30 percent of women under the age of 45 who have diabetes were taking lipid-lowering drugs. Over the age of 45, the percentage increased to nearly 50 percent for men and a little over 40 percent for women. There has been significant improvement in blood pressure control. However, IHS is limited in data collection to patients voluntarily seeking care so there is not any national aggregate data on the general population. For example, there is very little data about men from age 20 to mid-40s because they do not often access the health care system..

An intertribal heart project was reported by Kurt Greenland et al. in *Diabetes Care* in 1999 that looked at a cluster of risk factors associated with insulin resistance including hypertension, diabetes, high triglycerides, and low HDL, among three communities in Wisconsin and Minnesota. Prevalence estimates based on the study were approximately 10 percent for AI men and 6 percent for AI women. Generally, the percentage of individuals with each trait increased as the number of other syndrome traits increased. In both men and women, the number of syndrome traits was related positively with age and inversely with education level and unrelated to their Native American ancestry.

A small study was conduced in the state of Montana that screened youth from seven schools on two reservations from 1999 through 2000. Fifty-five percent were from 6 to 11 years of age and 43 percent were 12 to 19 years of age. The majority of children were AI youth. In terms of risk factors for diabetes among this population, 31 percent were overweight, 33 percent had acanthosis nigricans, and 61 percent had a family history of diabetes. Compared to NHANES III data for youth in the same age groups in the general U.S. population, the AI youth had a 30-31 prevalence of overweight compared to the 13-14 percent of their U.S. counterparts.

Veterans Health Administration (VHA)
Thakor Patel, MD

Dr. Patel was unable to attend the meeting as planned, but he submitted a set of slides that were included in the participants' program package. The slides presented VHA clinical user demographics and implications for the metabolic syndrome. Key points were that the prevalence of the syndrome in VHA is unknown, but data suggests that the prevalence is likely very high given the age of the clinical population, which is increasing along with the increasing number of minority groups. Diabetes prevalence is increasing at younger ages in both women and African Americans of both genders. In fiscal year 1999, there was an overall prevalence of diabetes of 16 percent, a 40.4 percent prevalence of hypertension in the VA population as a whole, and a 65.6 percent rate of hypertension among patients with diabetes. Veterans with diabetes also tend to have numerous comorbidities and disabilities that may limit lifestyle interventions.

Closing Remarks

Dr. Malozowski summarized the meeting by saying that a consensus on a definition of the metabolic syndrome was needed, there are many opportunities to find answers to the questions raised at the meeting, some through mechanisms available at NIH, and opportunities to pursue additional research in the metabolic area. He thanked the participants and the three speakers, and he thanked Dr. Savage for being active in organizing the meeting.

Dr. Spiegel also thanked the attendees and added that there exists today an underlying vision of prevention and of change in the health care system from being reactive to being proactive. This is a major reason why groups are grappling with issues like those discussed at this meeting, why more research is needed, and why ultimately understanding of the genotype-phenotype correlation and gene-environment interaction will be forthcoming.

Dr. Fradkin noted that all the major groups—NIDDK, NHLBI, CDC, ADA, ACE, NCEP, NDEP—are presenting basically the same message with regard to hypertension, hyperlipidemia, and hyperglycemia and the prevention of cardiovascular disease and the complications of diabetes based on evidence from a large number of clinical trials. In discussing the metabolic syndrome, the consensus heard around the table today was that the public is receiving a very confusing picture. Each group has different names for the syndrome and defines it differently. Most importantly, there is not a research base to know specifically what to do about the syndrome. The most productive course of action at this point, according to Dr. Fradkin, would be for the group to define a research agenda related to the metabolic syndrome and not get too far ahead of itself in terms of a public health message. She emphasized that it certainly had been very helpful for those present to come together and share their perspectives.

The meeting was adjourned at 12:52 p.m.

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DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE MEETING

Lister Hill Auditorium, NIH Campus
Bethesda, Maryland
April 11, 2003

SUMMARY MINUTES

Dr. Judith E. Fradkin, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), opened the session by thanking the speakers and attendees for their participation in the 20th anniversary symposium of the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) Study to which the DMICC meeting was appended. Dr. Fradkin then reiterated the conference goals of the DCCT/EDIC symposium, held April 10–11 and entitled "Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back":

- To celebrate and commemorate the accomplishments of the DCCT/EDIC on its 20th anniversary;
- To explore the possible mechanistic basis for what has been tentatively termed "metabolic memory" or "imprinting"; and
- To generate plans for the fostering of research in developing new therapies for the complications of type 1 diabetes.

Dr. Fradkin explained to the guests present that the DMICC is a forum for the coordination of diabetes research and healthcare aspects across multiple institutes and centers at the National Institutes of Health (NIH), other agencies within the U.S. Department of Health and Human Services (DHHS), and beyond.

Special funding for type 1 diabetes research began in 1998, with a $30 million annual budget, and has increased to five times that amount, $150 million per year, for FY 2004-2008, providing a total funding of $1.14 billion over the course of its legislative history (Balanced Budget Act of 1997, P.L. 105–33, amended by FY 2001 Consolidated Appropriations Act, P.L. 106–554). Since its inception, this funding has been the source of a number of initiatives, such as the establishment of genetic consortia including a genetic collection being carried out by the EDIC study group. DCCT/EDIC has provided a very well-characterized group of patients in terms of meta bolic control for examination of the potential genetic factors that might influence the risk of complications. Other initiatives relevant to complications pursued with the special funds include the Animal Models of Diabetic Complications Consortium (AMDCC), the macular edema clinical research consortia, initiatives for the development of surrogate markers for diabetes complications, and pilot studies for the development of new therapies.

Of particular emphasis has been the funding of studies fostering bench-to-bedside research. Dr. Fradkin stressed that development of partnerships between individuals working in type 1 diabetes with experts from outside the field, such as some of those who were very much a part of the current DCCT/EDIC conference, is an area that will aid in the exploration and examination of new directions for diabetes research.

In May 2002, an Advisory Panel recommended expanding the areas of opportunity for type 1

diabetes research to include research in inflammation and vascular disease complications, development of improved animal models, expanded clinical research, and the application of new technologies. They further recognized that available resources and infrastructure can be enhanced by the development of consortia to examine multiple complications and the fostering of partnerships between researchers in academia, Government, and industry. Preclinical development of therapeutic applications and a central knowledge base of complications-related initiatives were also recommended. Dr. Fradkin said a Web site will be developed to identify opportunities using type 1 funds in response to these recommendations and to announce the availability of resources resulting from such initiatives.

To capitalize on what was presented during the DCCT/EDIC conference and to focus future fundamental research on potential opportunities and initiatives recommended by conference participants, Dr. Fradkin outlined several key questions concerning the pathogenesis, prevention, and therapy of complications and invited speakers to respond with specific recommendations. The following sections summarize their presentations and the attendees' comments.

What Are the Major Gaps in Our Knowledge of the Pathogenesis and Therapy of Vascular Complications?

Dr. David M. Nathan, Professor of Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, summarized the following lessons learned from DCCT/EDIC that were presented during the symposium and outlined opportunities for future research:

- Glycemia is clearly the predominant mediator of the effects of intensive versus conventional therapy, explaining more than 95 percent of the effect of intensive therapy.
- Despite the subsequent narrowing of glycemia levels, the differences in outcomes between the original intensive and conventional therapy groups persist.
- The persistent difference in diabetic complications, potentially mediated by long-term beneficial effects of lower glycemia and/or persistent adverse effects of hyperglycemia, appears to be maintained for as long as 8 years after the separation in glycemia has dissipated, a phenomenon currently termed "imprinting" or "metabolic memory.
- One of the major and most interesting observations from DCCT was the demonstration that it is the original separation in glycemia level that accounts for most of the original effect.
- Glycemic levels and the changes mediated by intensive therapy may play a role in the development of macrovascular disease, as well as microvascular disease.
- Recent data with regard to calcification in the heart appear to demonstrate a difference between intensive and conventional groups.

During the DCCT/EDIC conference, several pathophysiologic mechanisms were presented to explain the effects of glycemic control and other currently used interventions on diabetic micro- and macrovascular complications, including glycation, inflammation, glycoxidation, apoptosis, lipoxidation, cellular issues, oxidation, and genetics/epigenetics. Investigators from diverse backgrounds explored several of these potential mechanisms that might explain the imprinting effects or metabolic memory from the early intensive glycemic control on long-term complications, including glycation/receptors for advanced glycation endproducts (RAGE), genetics/epigenetics, cellular/vascular/angiogenesis issues, and immunologic factors. Topics addressed during the conference included:

- Imprinting in DCCT/EDIC.
- Pathophysiology of diabetic complications.
- Potential mechanisms for long-term effects.
- Animal models and data regarding micro- and macrovascular disease.
- New methods of detecting and tracking complications that may be useful in clinical trials.
- Results of clinical trials directed at a number of factors that may be operant in diabetic complications.

Dr. Nathan also mentioned several topics that were not discussed, but which might have been considered within the scope of the conference, such as the limitations in achieving long-term control of hyperglycemia with currently available therapy; the ways of improving glucose control in type 1 diabetes, either by biological or mechanical approaches to maintain normal glycemia; and the prevention or cure of type 1 diabetes.

A significant outcome of the symposium was the identification of several areas for additional research. First, a consensus must be reached regarding reliable, practical biomarkers or surrogates for cardiovascular disease, so that meaningful comparisons can be made in clinical trials between the effects of different interventions. Doing so will ultimately result in clarification of what sometimes appear to be contradictory results in studies and will allow for greater efficiency in the performance of interventional studies. Second, a better understanding is needed of the differences and similarities in the effects of glycemic and other interventions on different end organs, as well as the influence of genetic factors in this regard.

Dr. Nathan emphasized that the DCCT/EDIC group is the most vigorously and thoroughly studied population of type 1 diabetic patients in history, with 95 percent retention of subjects over a span of 20 years (n=1385/1441), and with an average follow-up of approximately 16 years. The population has been extensively characterized and phenotyped over time with regard to complications, diabetes therapy and chronic glycemia, and established and potential risk factors, and it has provided researchers with an incredibly valuable resource of stored biological specimens, including DNA, which can be well utilized for the validation of biomarkers.

Dr. Nathan suggested that the DCCT/EDIC group continue to examine the relationship between the panoply of risk factors and macrovascular disease and the more severe stages of microvascular disease. As the DCCT/EDIC population evolves and develops more advanced eye, kidney, and macrovascular disease, investigators will be able to study the effects of established and putative risk factors on these clinically onerous complications. Diabetes researchers should also continue to study and to define the imprinting phenomenon described during the DCCT/EDIC symposium, including expanding epidemiologic approaches currently in use and through case-control studies.

DCCT/EDIC data can be used to identify and define clinically relevant biomarkers of complications that may be used in future studies, using phenotypic data and stored samples, which may also be used to identify biochemical steps in the pathogenesis of complications. Finally, the current DCCT/EDIC genetic initiative that is looking at the genetic contribution to susceptibility for developing complications ought to be continued.

Dr. Saul Genuth, Professor of Medicine, Division of Clinical and Molecular Endocrinology, Case Western Reserve University, added that the DCCT/EDIC cohort is not only the most vigorously and consistently studied group of type 1 diabetics, but that it is also the most accurately studied group, producing high quality data as a result of good quality control measures. Dr. Genuth stressed the importance of and opportunity for lifelong follow-up by NIH, given the high level of commitment of the patient participants in the cohort, due in part to the research mindset of

the patients and to the personal bonding between patients and study investigators. He recommended that researchers capitalize on the strong research motivation of the cohort patients in their consideration of future studies and initiatives.

During the discussion following Dr. Nathan's presentation, Dr. Michael Brownlee, Anita and Jack Saltz Professor of Diabetes Research, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, pointed out a further knowledge gap with regard to the adverse effects of acute hyperglycemia or stress hyperglycemia. Data suggest that coronary disease is largely a metabolic disease; in treatment of individuals with stress hyperglycemia, the outcome in the area of infarction in the brain is proportional to the level of hyperglycemia on admission. Seventy percent of those who have myocardial infarctions are either diagnosed diabetics or people with impaired glucose tolerance. A better understanding of the mechanisms of the disease will aid in the prevention of damaging effects on outcomes, especially since the events typically measured in the diabetic population are ultimately fatal.

During the discussion following Dr. Nathan's presentation, Dr. Michael Brownlee, Anita and Jack Saltz Professor of Diabetes Research, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, pointed out a further knowledge gap with regard to the adverse effects of acute hyperglycemia or stress hyperglycemia. In addition to recent data showing that the majority of patients with coronary artery disease are either diabetic or have impaired glucose tolerance, acute hyperglycemia has been shown to adversely affect the outcome of myocardial infarction and stroke. The area of infarction in the brain is proportional to the level of hyperglycemia on admission. Seventy percent of those who have myocardial infarctions are either diagnosed diabetics or people with impaired glucose tolerance.

Dr. Mark E. Cooper, Director, Baker Heart Research Institute, Melbourne, Australia, stressed that the development of macrovascular complications from diabetes will prove to be especially important over the next 10 years for the DCCT/EDIC population. Why some diabetic individuals are less able to withstand a given load of macrovascular disease than their non-diabetic counterparts is an area of research that may be further examined with data from the DCCT/EDIC cohort, since baseline data such as echocardiography is available for these patients. Advanced echocardiography allows diastolic dysfunction—which may be linked to the mechanisms reviewed during the DCCT/EDIC symposium—to be more easily discernible and more accurately diagnosed. Dr. Genuth added that the DCCT/EDIC patient population is exceptionally receptive to further testing or exams, especially where heart function is concerned, stating that 85 percent have already had coronary calcium scans performed.

Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI), offered three points that bear closer scrutiny: (1) the subclinical cardiac dysfunction known to occur in diabetics; (2) the amount of vascular disease prior to and following the onset of renal disease and the association of renal disease with the exacerbation or progression of atherosclerosis; and (3) the importance of more efficient clinical trials to examine the means for and to document the correlate between subclinical disease measures and events, particularly in light of the new and multiple interventions available. As an example, Dr. Savage suggested that abnormalities in the system might add substantially to the subclinical disease; if not, then the subclinical disease could be used as a predictor.

Dr. David R. Matthews, Professor of Diabetic Medicine, Oxford Centre for Diabetes Endocrinology and Metabolism, England, observed that perhaps part of the "imprinting" in the DCCT/EDIC cohort is due to the education of and attention given to the patient participants.

Dr. John W. Baynes, Carolina Distinguished Professor, Department of Chemistry and

Biochemistry, University of South Carolina, Columbia, cautioned that the group not become too glucocentric. While glucose might turn out to be a statistically important mediator, understanding the downstream effects is also critical. Dr. Baynes suggested that a greater emphasis be placed on insulin resistance in pre-diabetic states, which often precede the development of type 2 diabetes, during which time substantial damage can occur. Dr. Helen Vlassara, Director, Division of Experimental Diabetes and Aging, Mount Sinai School of Medicine, New York, added that researchers ought not to ignore derivatives of glucose metabolism.

The area of implementation and dissemination research, also termed translational research, was an area not covered by the symposium, but one which Dr. Denise Simons-Morton, Acting Director, Clinical Applications and Prevention, Division of Epidemiology and Clinical Applications, NHLBI, brought to the attention of the group. It was suggested by Dr. Daniel Stryer, Acting Director, Center for Quality Improvement and Patient Safety, Agency for Healthcare Research and Quality (AHRQ), that banked clinical data studies could also be supported by R03 or hyper-accelerated grant applications, and that these data could provide information on general markers of inflammation.

Dr. John M. Lachin, Professor of Biostatistics and Epidemiology, The Biostatistics Center, George Washington University, Rockville, Maryland, offered the idea that a future challenge for researchers will be the characterization of lesions at the cellular level, which would represent the true factors that are determining the risk of further disease progression or the risk of complications.

How Can We Foster Development of Animal Models in Which Potential New Therapies Can be Explored?

Dr. Timothy S. Kern, Director, Center for Diabetes Research, Case Western Reserve University, Cleveland, addressed the issues of animal models in type 1 diabetes research. Although most purely diabetic animal models do not progress to advanced stages, they nonetheless provide valuable information, including biochemical abnormalities that seem to play a role in the development of various forms of pathology.

Areas that warrant further attention and research include:

- Establishment of the validity of animal models, given that they largely tend to develop the early lesions, but fail to progress.
- Use of animal models in the development and validation of surrogate markers.
- Examination of genetic contributions to complications, since animal models offer a unique opportunity in terms of cross-breeding.
- Understanding the clonal basis or "imprinting" basis of "metabolic memory."

Considering how long complications take to develop in humans, barriers exist in the use of animal models in diabetes research on complications because the animals have relatively short lifespans. A further obstacle is the lack of macular edema models and the inability of researchers to make specialized measurements. However, the latter difficulty might be overcome through the use of core facilities to provide measurement services.

Dr. Kern encouraged the establishment of a group that would evaluate therapies and decide methods for moving therapies into the clinical setting. He also suggested expansion of the consortium on animal models to provide an arena for discussion beyond the grant recipients and broaden the scope of researchers, a suggestion echoed by several participants at the symposium.

Dr. Cooper expressed concern that appropriate animal models be used. Since the consortium is trying to generate new animal models, they might consider starting with animals such as the db/db mice, which have fewer complications that will affect study

results. Drs. Kern and Vlassara agreed with this comment, and Dr. Vlassara further challenged the definition of what constitutes a normal animal model or normal baseline. She suggested a new "hyperglycotoxemic" model be developed.

Dr. Eva L. Feldman, Professor of Neurology, University of Michigan, Ann Arbor, shared information from the AMDCC. The consortium has moved from having 2 animal models to 12 models and is now gathering interesting data on atherosclerotic and nephropathic models. The large bioinformation component of the consortium has allowed for a generous amount of shared data.

Dr. Fradkin suggested that further comments regarding expansion of the consortium be directed to Dr. Robert Star, Senior Scientific Advisor, NIDDK, at Robert_Star@nih.gov.

How Can We Foster Development of Surrogate Markers Useful for Clinical Trials of Potential New Therapies?

Dr. Ann Marie Schmidt, Associate Professor and Chief, Division of Surgical Science, College of Physicians and Surgeons, Columbia University, New York, categorized cardiovascular disease and diabetes into three parts: (1) the innate cardiac dysfunction; (2) surrogate endpoints for long-term vascular disease, including stenting and the amount of neointimal expansion as a potential surrogate endpoint, given that diabetic individuals undergoing angioplasty and revascularization procedures do very poorly; and (3) macrovascular disease and atherosclerosis itself. (Dr. Schmidt served on the May 16, 2002, Advisory Panel.)

Dr. Schmidt proposed that intravascular ultrasonography (IVUS) might also be used as an endpoint. Since the increase in IVUS quantification of macrovascular disease has been demonstrated, it appears that the Food and Drug Administration (FDA) might be softening with respect to endpoints other than death and clinical events.

With regard to plaque and instability, examination of the inflammatory mediators and inflammatory markers produced by peripheral monocytes in humans following intervention may provide a useful surrogate marker. MMP9, antigen activity, and procoagulant response are also being investigated, as well as impaired endothelial independent relaxation, although the last is not an FDA-approved endpoint. The response to acetylcholine is very abnormal in diabetic individuals and can in and of itself be a surrogate marker.

Clearly, a very important surrogate marker is C-reactive protein (CRP), which might prove useful not only with regard to defining response to therapy, but also when examining quartiles of elevated CRP levels at baseline and their application to relative risk.

Dr. Schmidt identified the following methods for development of surrogate markers:

- Functional MRI is a promising study method, particularly because of its wide availability, but one which may require incentives to encourage study participation.

- Urine protocytes may be a potential marker of early injury, although albuminuria is not an FDA-approved endpoint.

- Degree of alveolar bone loss and periodontal disease are potential surrogate markers for inflammatory baseline and response, since epidemiological data suggest that periodontal disease, regardless of the presence or absence of diabetes, is a risk factor for the development of atherosclerosis.

- Erectile dysfunction, because it involves not only neurology but also vasculature, is a possible surrogate marker.

- Skin biopsies could be surrogate markers for levels of collagen abnormalities.

- Live oxidation products are possible surrogate markers for measurement.

Information presented during the DCCT/EDIC symposium suggested proteomics and genomics as possible surrogate markers, an idea Dr. Schmidt found attractive not only because of the availability of DCCT/EDIC samples, but also because research in these areas encourages basic researchers and clinical trialists to partner with biotech companies, thereby increasing the sample pool and fostering further multidisciplinary action.

Following Dr. Schmidt's presentation, Dr. Bruce Berkowitz, Professor, Department of Cell Biology and Opthalmology, Wayne State University School of Medicine, Detroit, cautioned researchers to use the most finely honed tools available, and as the MRI community possesses an extremely powerful set of tools for diabetic research, they ought to be enticed to form partnerships.

Dr. Matthews commented that better data would become available if researchers could get repeat measures where some specific change or threshold could be predefined. Surrogate markers for the process as an endpoint would reduce regulators' dependency on hard endpoints such as myocardial infarction and death.

Dr. Josephine Briggs, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, offered a follow-up to Dr. Matthew's remarks on working with regulators, saying that she and Dr. Thomas Hostetter, Director, National Kidney Disease Education Program, NIDDK, have been in contact with FDA regarding the development of a research agenda that would lead to clarity in proteinuria as a process marker.

How Can We Foster Identification of New Therapeutic Targets and Agents?

Dr. Lloyd Paul Aiello, Assistant Director, Beetham Eye Institute and Associate Professor of Ophthalmology, Harvard Medical School, Joslin Diabetes Center, suggested that increased consortium or network approaches would prove useful in moving research findings into clinical trials more rapidly. Excellent characterization and uniformly standardized evaluation of consortia resources would speed evaluation, provide larger sample numbers, and improve comparability between studies. These repositories could also provide some fundamental analyses that are helpful or commonly utilized for this transition, either within the collected samples or perhaps within the repositories. Benefits would include improved comparability between studies, more efficient and consistent evaluation, and services for investigators who are in possession of samples but are unfamiliar with a particular evaluation technique.

Dr. Aiello pointed out the need to rapidly identify, evaluate, characterize, and implement new technologies that may become increasingly important both in the identification of new targets and the evaluation of potential surrogate markers. Such approaches, in addition to providing novel targets may provide cross-fertilization among different complication disciplines and characterize new mechanisms by which researchers could evaluate markers in clinical trials in an efficient and rigorous manner.

During subsequent discussion, Dr. Aiello emphasized that a functional genomics/proteomics approach, conducted with homogenous patients or animal models and identifying different targets, would aid in fostering identification of new therapeutic targets.

Dr. Feldman proposed that some type 1 funds might be directed toward discovery studies, which could lead to new mechanisms, particularly in the proteomics field. Dr. Brownlee commented that discussion seemed to center on two general topics: (1) a focus on optimizing what is currently available, and

(2) the concept of discovery. Dr. Vlassara remarked that the DCCT was basically an era of intervention, focusing on the control and modification of blood sugar; perhaps now it was time to add another dimension to the DCCT.

How Can We Move Promising Therapeutic Agents From Bench to Bedside?

Dr. Nigel Calcutt, Associate Professor, Department of Pathology, University of California San Diego, used his experience with moving a molecule (prosaptide) from discovery to phase 2 clinical trials over a relatively short time as an analysis of the bench-to-bedside procedure. According to Dr. Calcutt, doing so involves correctly targeted funding. He identified several factors which contributed to the successful process:

- Personal drive and focus of the Principal Investigators, which included discovery of the molecule and raising money through private funds and venture capital.

- Availability of the STAR program, a fast-moving funding mechanism, where funding was provided in part by the State of California, part by the company of interest. A most important aspect of this funding program is the recognition of the academic as Principal Investigator. The funding is therapy-oriented and results-driven, protects company intellectual property, and provides for initial proof-of-concept studies, allowing investigators to produce the preliminary data necessary to qualify for NIH funding.

- Availability of an NIH Request for Application (RFA), an important aspect because it targeted money at therapy-driven research, rather than purely mechanistic-driven studies.

- Luck and opportunity for collaboration between researchers.

Dr. Calcutt noted that, while these conditions are admittedly unlikely to reoccur in the near future, there are steps NIH can take to create a similarly helpful environment. For example, NIH could fund exploratory research programs that provide money for 1-year rolling, results-driven projects, such as those provided by the Juvenile Diabetes Research Foundation (JDRF) International. An incentive for academics to participate could be initiated through the creation of modified STAR/SBIR (Small Business Innovation Research) funding to include both industry and academia, where both parties would receive recognition for participation. RFAs for R01s to support therapy-driven research should be made available, not to the exclusion of mechanistic-driven research, but to allow for quicker progression. Support systems, both informational banks and funding sources, to connect Principal Investigators having potential therapeutics with those skilled in phase 1 and 2 trials, might be made available through the use of paired grants. Further, NIH could provide assistance through both funding and information to small biotechnology companies to aid them in moving potential therapeutic agents through phase 1 and 2 trials.

During discussion, the point was made that using surrogate markers and non-regulatory approved endpoints may speed up the process. Dr. Calcutt suggested the formation of a body to negotiate a compromise between NIH's scientific position and FDA's required position from a safety point of view.

Dr. Spiegel, Director, NIDDK, recommended Rapid Access to Interventional Development (RAID), a program used at the National Cancer Institute that provides, on a contract basis, some functions such as producing a sufficient quantity or quality of a product, by means that ordinarily would not be available to an investigator who has a patented therapeutic agent. Production issues might also be expanded through this program.

Dr. Fradkin pointed out the availability of the innovative partnerships RFA that pairs researchers working in diabetes with scientists who have expertise relative to diabetes but who are working in other fields, and proposed the notion that rather than a

single grant, two paired grants might be a more attractive option for investigators, a suggestion that was met with general agreement.

Dr. Spiegel concluded with the observation that future research teams ought to embody the concept of a multidisciplinary approach, acknowledging that equal credit for more than a single Principal Investigator is a crucial aspect of team research.

What Are the Most Promising Opportunities To Advance Research To Develop New Therapies for Complications?

Dr. Brownlee posed several possible research questions for consideration by those in attendance:

- What are the mechanisms responsible for microvascular complications?
- What are the mechanisms responsible for macrovascular complications?
- What genetic issues determine the development and progression of diabetic complications?

He expressed the opinion that further investigation and definition of the issue of metabolic memory is certainly necessary, including expansion of the concept to include other areas such as insulin-resistance and fatty acid memory.

Dr. Brownlee recognized the importance of drugs with regard to the prevention of diabetic complications, but remarked that perhaps a greater focus ought to be placed on secondary prevention, since the mechanisms responsible for initiation may not be the same mechanisms responsible for progression of complications. Surrogate markers and a new clinical study paradigm are also areas that he believed warrant additional study, because current paradigms are too costly and require too many years to effectively screen treatments that show promise in animal models.

It is generally accepted that, when considering genetic susceptibility to complications, animal models such as those provided by the AMDCC provide investigators with the advantage of using animals with known genetic backgrounds. These models ought to be further utilized.

As researchers focus design attempts on drugs aimed at specific targets, Dr. Brownlee identified high throughput screening for new therapeutic targets and agents as the new wave of the future.

Dr. Brownlee noted that the DCCT/EDIC symposium's emphasis on multidisciplinary research and collaboration between areas of expertise strongly suggests that dual Principal Investigator grants and exploratory research programs that promote discovery and innovative research should be a priority. In conclusion, he listed the following areas as the most important and most promising research opportunities:

- Development of a mechanism for real discovery and innovation.
- Multidisciplinary efforts fostered through dual investigator grants between researchers in complementary fields to produce innovative work.
- Funding for non-patented therapeutic agent trials.

Dr. Fradkin closed the session with the comment that the meeting produced not only intriguing ideas in the area of diabetes research, but identified available resources for carrying them to fruition.

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DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE MEETING: USE OF SPECIAL FUNDS FOR TYPE 1 DIABETES RESEARCH

April 14, 2003
Building 31, Conference Room 6C
National Institutes of Health (NIH)
Bethesda, Maryland

SUMMARY MINUTES

Dr. Saul Malozowski, Executive Secretary of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) and Senior Advisor for Clinical Trials and Diabetes Translation, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), opened the meeting, welcomed the Committee members and their guests from the Juvenile Diabetes Research Foundation International (JDRF), and introduced Dr. Allen Spiegel, Director, NIDDK.

Dr. Spiegel welcomed the attendees and explained that DMICC is the venue for coordination of a number of diabetes functions. DMICC includes members from the major NIH institutes and centers (ICs), the Centers for Disease Control and Prevention (CDC), and other U.S. Department of Health and Human Services (DHHS) agencies. Dr. Spiegel acknowledged the phenomenal support from Congress for type 1 diabetes research. The 107th Congress not only extended the initial special statutory funding program for type 1 diabetes research from FY 2004 to FY 2008 but also increased the funds to $150 million per year. This poses both an opportunity and a challenge.

Dr. Spiegel announced that an evaluation report on the original funding will be published in April or May. The original January 2003 due date for this report was changed by the latest bill to January 2007; however, NIDDK felt the report was of such value and interest that it will issue it. In addition to presenting the results accomplished from projects supported from FY 1998–2002, the report includes an Office of Management and Budget (OMB) approved survey of all the investigators supported through these funds. This survey, as well as an analysis of the grants funded, documents that the special statutory funds were instrumental in bringing new investigators into type 1 diabetes research efforts as well as established investigators who had not previously worked in this area. Dr. Spiegel stressed that with this new stream of funding, it is critical to examine carefully each of the commitments made for initiatives, consortia, and networks that have been so productive and define milestones and criteria for how they should be renewed. At the same time, the best possible new initiatives need to be identified to move forward. Dr. Spiegel then turned the meeting over to Dr. Judith Fradkin, Director of NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases, who has spearheaded the management of this special statutory funding program and crafted an ambitious program to respond to this dual obligation for use of the new funds.

Dr. Fradkin summarized the legislative history of the type 1 special statutory funds, which have grown from the original $30 million a year in 1998 to $150 million a year for FY 2004–2008, for a total of $1.14 billion for FY 1998–2008. This funding is intended for use in trans-DHHS research efforts. Flexibility to provide for a rapid response to emerging scientific

opportunities will be preserved through use of pilot and feasibility grants and short-term commitments that could roll over to subsequent initiatives. Research and voluntary communities are actively involved in the planning and evaluation of the use of the funds. Most importantly the funds are not to supplant research funded by regular NIH appropriations, but rather to augment and go beyond these efforts to fund opportunities that would not ordinarily be addressed with regular funds. Based on these principles, six major goals have been defined (see box). To date the funds have established a large-scale, collaborative, infrastructure of intensive initiatives that could not be pursued through R01s (i.e., investigator-initiated research); promoted innovative, high-risk, high-impact research, particularly through pilot feasibility grants; brought in new talent; and fostered state-of-the-art technologies.

Six Major Goals
1 Identify Genetic and Environmental Causes of Type 1 Diabetes
2 Prevent or Reverse Type 1 Diabetes
3 Develop Cell Replacement Therapy
4 Prevent or Reduce Hypoglycemia
5 Prevent or Reduce Complications
6 Attract New Talent

On May 16, 2002, an Advisory Panel of scientific and lay experts met and evaluated the research efforts funded to date. The panel strongly endorsed the six major goals noted above and the initiatives resulting from them. They were also asked to identify new and highly promising opportunities for research on type 1 diabetes. At the time the advisors met, it was not known that Congress would be providing additional funding to support these opportunities. Their recommendations will form the foundation for use of the newly appropriated funds. These recommendations included:

- Continue support for investigator-initiated projects.
- Continue support of the consortia and the resources that have been developed.
- Pursue development and application of new technologies.
- Encourage coordinated trans-DHHS and multidisciplinary approaches.
- Re-issue targeted Requests for Applications (RFAs) to create ongoing research opportunities.
- Continue to attract new research talent to type 1 diabetes research.

In addition there were specific recommendations for each of the six major goals that will be presented in more detail. These recommendations from the May meeting will be supplemented by focused meetings on the major goals or subcomponents of the goals.

Dr. Fradkin elaborated on the May 2002 Advisory Panel's recommendations based on the six major goals and sought the opinions and comments of today's participants.

Goals 1 and 2: Identify Genetic and Environmental Causes and Prevent or Reverse Type 1 Diabetes

To date, substantial resources have been used to develop strong consortia. The Advisory Panel recommended promoting interactions, data sharing, and coordination among these groups. They wanted to see common bioinformatics platforms; ability to integrate data; common consent forms, particularly as samples are being put into repositories for use by future scientists; and standardized assays, for instance for measuring HLA genotypes, antibodies, and C-peptides as outcomes. The panel encouraged support and interaction within the consortia for ancillary studies such as the immune response studies from the Immune Tolerance Network (ITN) in

conjunction with TrialNet clinical trials, as well as partnerships with industry and academia. It was felt that fast-track mechanisms were needed to facilitate preclinical development and mechanisms for bench-to-bedside support (e.g., production of biologics when there is good preclinical data to suggest these would be efficacious in a clinical trial, access to GMP (good manufacturing practice) facilities to make materials for use in humans, and support and access to animal tests for safety, toxicology, immunoactivity, and efficacy).

Dr. Fradkin emphasized that close coordination is essential, given the number of consortia and the fact that they will be recruiting from the same population, as well as to promote the panel's recommendations for common bioinformatics platforms, standardization of assays, and partnerships. This will mean coordinating recruitment and enrollment. Particularly where multiple studies are recruiting in a common geographic area, information exchange and joint approaches to referring physicians will maximize access to patients. Cross-identification of families is needed to avoid duplication in submitting specimens to repositories. Standardization of assays, phenotyping, and consent forms will also be needed. Dr. Fradkin said that NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID) have already identified an individual who will be asked take the lead in developing a coordination mechanism. Other DHHS components responsible for consortia will be asked to participate in this effort.

At Dr. Spiegel's suggestion, the attendees described the various consortia. TrialNet is a joint effort of NIDDK, NIAID, the National Institute of Child Health and Human Development (NICHD), and JDRF to test methods to delay or prevent type 1 diabetes in patients with new onset diabetes or at high risk for diabetes. It also has a natural history component allied with NIAID's Immune Tolerance Network for mechanistic assays to understand the ongoing pathogenesis of type 1 diabetes. ITN is a joint effort of NIAID, NIDDK, and JDRF. Its mission includes conduct of clinical trials to test therapies and to develop assays to monitor the induction, maintenance, and loss of tolerance. The areas covered are kidney and islet transplantation, liver transplantation, and asthma, allergies, and autoimmune diseases among which type 1 diabetes is the major focus of proposals to the ITN. To date, about 28 percent of ITN funds have been directed to type 1 diabetes activities.

Dr. Fradkin said that ITN, TrialNet, and the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1), which was the precursor of TrialNet, are good examples of efforts, originally undertaken by the Institutes with regular funds, where type 1 funds allowed expansion of the research in ways that would not have been permissible under regular funds.

The Autoimmunity Centers of Excellent (ACE), also an NIAID initiative co-sponsored by NIDDK, is a basic or preclinical research program, with clinical components, in four centers that conduct trials with the major focus on diabetes, although they work with potentially more than 80 autoimmune diseases. NICHD's Trial to Reduce the Incidence of Type 1 Diabetes in the Genetically at Risk (TRIGR) is an international clinical trial in which children at high genetic risk for type 1 diabetes are randomized at time of weaning to regular formula or Nutramigen®, a partial hydrolysate of casein produced by Mead Johnson. The outcome is the development of autoimmune antibodies to pancreatic antigens and eventually, if the children are followed long enough, onset of type 1 diabetes. A preliminary trial about 5 years ago with approximately 200 children indicated that those who were put on Nutramigen® versus regular formula had a slightly smaller incidence of diabetes, although the data are not stable or statistically significant. The goal of the Triggers and Environmental Determinants of Diabetes in the Young (TEDDY) initiative is to organize international efforts to identify infectious agents, dietary factors, or other environmental factors that trigger type 1 diabetes in genetically susceptible individuals. The TRIGR and TEDDY studies will have overlap in the sense that they are both recruiting neonates at high genetic risk at birth.

The Centers for Disease Control and Prevention's SEARCH is an effort to look at childhood diabetes, particularly type 1, but also type 2, to acquire more accurate knowledge of the incidence and prevalence of the diseases and to identify characteristics that might clinically and epidemiologically distinguish between traditional type 1 and so-called type 2 diabetes in children. SEARCH will also follow these children to examine quality of care. SEARCH's six centers are jointly funded by CDC and by type 1 special statutory funds.

CDC's Genetics of Kidneys in Diabetes (GoKinD) is an international effort to study the genetic risk factors for renal disease of type 1 diabetes and is complementary to NIDDK's Family Investigation of Nephropathy and Diabetes (FIND). GoKinD is a joint effort by CDC and, JDRF. FIND is a large consortia of seven clinical centers and a genetics coordinating center that is undertaking two studies on the susceptibility to diabetic nephropathy. About 85 percent of the patients being recruited have type 2 diabetes and about 15 percent have type 1. One strategy is to look at concordant and discordant sibling pairs. The other strategy, called mapping by admixture linkage disequilibrium, is recruiting case controls to look at genetic loci with regard to racial admixture. FIND has been working closely with GoKinD in the informatics aspects, with the long-term goal of integrating the two databases so the identified susceptibility loci can be looked at in both databases. The original goal was to look only at nephropathy susceptibility, but with the support of the National Eye Institute and some type 1 money, retinal photographs have been added and analysis will be done of retinopathy susceptibility as well. NIDDK's Epidemiology of Diabetes Interventions and Complications (EDIC) study is also collecting genetic samples from subjects and their family members for analyzing susceptibility to complications in a particularly well characterized clinical cohort. It will complement FIND and GoKinD.

The International Type 1 Diabetes Genetic Consortium (T1DGC), composed of three clinical networks and a data coordinating center, is studying genes that influence the pathogenesis of type 1 diabetes. It will generate a large standardized family collection of genetic and phenotypic data. The NIAID's International Histocompatibility Working Group (IHWG) is a multi-institute sponsored activity that includes the Office of the Director. IHWG is looking at genetic components of a number of diseases, including the genetics of transplantation. It includes more than 100 international programs and has received some type 1 statutory funds for SNP (single nucleotide polymorphism) identification in 100 genes presumed to be possibly related to type 1 diabetes.

The Diabetes Research on Children Network (DirecNet) is conducting studies of new glucose monitoring devices to determine their accuracy and utility in improving diabetes control and avoiding hypoglycemia in children with type 1 diabetes. It is led by NICHD with NIDDK participation.

Discussion

Dr. Fradkin asked everyone to be thinking about who from their consortia should represent them on the consortia coordinating committee. There may be multiple representatives so that subcommittees can be formed on specific issues, such as standardization of consent forms, phenotyping, assays, and so forth.

Dr. Fradkin explained that a Web site dedicated to the type 1 special statutory funds program will include information from each of the consortia on their resources that will become available and when they will be available. Type 1 funding will include a requirement for public access by the general scientific community to these resources. The NIDDK is creating a repository that will store and distribute samples from clinical studies for use by the broader

community. A requirement to deposit specimens into this repository is written into TrialNet and the TEDDY grant awards. The Diabetes Control and Complications Trial (DCCT) has developed a process for access to samples from that study. DPT-1 will soon have finished its second randomized trial and plans are being made to share available samples from their studies with the larger scientific community.

Dr. Daniel Rotrosen, Director, Division of Allergy, Immunology, and Transplantation, NIAID, explained that if ITN has sufficient material, samples will be in the public domain along with data and protocols. He pointed out that one problem, which also may be true of other trials, is the availability of sufficient materials from young children due to mechanistic studies already planned within the ITN protocols. Material such as DNA that is readily available and can be amplified is not a problem, but serum is quite limited. This is also true of ACE. NIAID has not yet established a mechanism for soliciting requests for samples or distributing them. He suggested the consortia would benefit from a central repository with a standard mechanism to receive requests and to distribute materials.

Dr. Gilman Grave, Chief, Endocrinology, Nutrition, and Growth Branch, NICHD, said that since TRIGR is looking at neonates, there are not many specimens available, although a predecessor study has been collecting samples in Finland for 10 years. They have also not addressed a distribution mechanism yet, but will probably ask other consortia members for submission of specific information on what they have in place for distribution.

Dr. Patricia Mueller, Chief, Diabetes and Molecular Risk Assessment, CDC, explained that GoKinD was designed to be a collection of samples that will be in a CDC repository, so the collaborating investigators can do additional studies. Then they will be made available to the broader research community, probably through a modified Framingham model. Proposals will be reviewed by a JDRF-appointed committee of independent investigators.

SEARCH, according to Dr. Frank Vinicor, Director, Division of Diabetes Translation, CDC, has established a repository and is willing to share data with other investigators but does not have a mechanism in place yet. Currently, CDC's standard approach is that investigators must submit a proposal that is then reviewed by the SEARCH Executive Committee. The SEARCH Executive Committee will be looking at the challenge of how to strike a balance between making the samples publicly available for studies that have an appropriate scientific base without using them up.

Dr. Fradkin said that peer review can be very useful in that regard. EDIC has two peer-reviewed program project (P01) grants that will use EDIC samples and are funded with separate NIH funds. One is an NHLBI-supported P01 at the University of South Carolina and the other is an NIDDK-supported P01 at the University of Washington.

Dr. Fradkin recommended that in making samples available to the broader community, it is better if those who collect the samples are not the sole determinants of who may use them. If the collection of the samples has been supported by substantial type 1 diabetes special statutory funding resources, there is a real obligation to share them, not just by making them available among the collaborating investigators, but by placing them in the public domain. What is needed is an in-place mechanism to provide support to those who will do ancillary studies with the samples, independent of the control of the investigators. She urged everyone to be aware of the importance of this. In EDIC, for example, some of the review committee members are from EDIC, but it is not an EDIC committee. This provides insights into the use of the samples that derive from the knowledge of EDIC investigators who know the study design in detail, but does not give the study group exclusive use of the samples. Ideally, the terms and conditions of the notice of grant award or the RFA should include this understanding to prevent any difficulty in acquiring access to the samples or data. Under contracts or U01s (cooperative agreements), there is more ability to influence

the process than under an R01. Dr. Fradkin explained that agreeing to share the samples and associated de-identified information will be a factor in deciding support for type 1 activities.

Dr. Vinicor brought up the related issue of the HIPPA (Health Insurance Portability and Accountability Act of 1996) rules and regulations regarding patient privacy of personal health information that will also affect the sharing of samples and data. The administrative and legal processes affected by the HIPPA rules do not have to be a major barrier but it is important to be aware of them as a potential impediment. Dr. Fradkin agreed that the consortia coordinating group needs to look at HIPPA, particularly with regard to consent forms. While these investigations are ongoing and there is regular contact with the subjects is the best time to get proper consents for sharing of data and samples.

Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI) remarked that NHLBI, through its considerable recent experience in sharing data and samples, has noticed people interpret fairly clear statements in a wide variety of ways. He urged the group to have a standardized procedure for securing data or samples and one that certainly includes the legal implications of the HIPPA regulations. He also stressed the importance of the agreement's not being so broad that later, because of commercial interest or some other consideration, there is a lot of opposition to it. Dr. Fradkin added that it would also be important to proactively talk with people about the language in the Notice of Grant Award, since there is a tendency among investigators not to read the detailed award provisions. The meaning of the terms and conditions should be discussed and clarified to ensure they are agreed to and clearly understood. Dr. Mueller also expressed support for a consistent mechanism for making the samples available. The consensus was that this would be advantageous to everyone.

Dr. Robert Goldstein, Chief Scientific Officer, JDRF, agreed with the type 1 Advisory Panel's recommendation that coordination among the consortia (and he included the DCCT/EDIC) was extremely important and offered untold opportunities for the future, especially regarding the data centers and sample repositories. He said the international community would welcome a standard procedure for sharing these resources across borders. In all JDRF grant awards where sample collection takes place and has value, JDRF has made ultimate sharing mandatory and the notion of a public resource preeminent, despite variations in international rules and guidelines. The lack of a standard consent form and standardization of sample collecting and measurement across international borders is a barrier to providing resources from these studies to U.S. researchers. Dr. Goldstein added that once rules and guidelines are established, the clinical trials funded by JDRF could contribute to a centralized effort other populations and materials that do not duplicate those from NIH. Dr. Fradkin remarked that many of the type 1 diabetes consortia are international in scope. Making funding contingent on willingness to supply the samples has been an issue with the type 1 genetic consortia because of the lack of standardization of consent processes internationally.

Dr. Goldstein also urged that industry be granted access at some point in time to some of the resources from this phenotypically valuable patient population, which is too small in number compared to those populations with other diseases to be assessed in this way by industry. However, if industry is presented with a well-documented population, regardless of size, it is then commercially attractive for them to study that group.

Dr. Goldstein commented that it would be extremely helpful to his organization, and surely to others, including Congress, to have a summary of the amount of money the NIH ICs spend on type 1 research as a whole, since this will not be included in the type 1 special statutory funds' evaluation

report. Dr. Spiegel replied that to do what Dr. Goldstein requested would require a special mechanism to collect the information across all ICs, which is being done for the special statutory funding program for type 1 diabetes research. He explained that Dr. Elias A. Zerhouni, NIH Director, in his addresses to Congress presents overarching themes for all the diseases within the ICs areas of responsibility, rather than specific diseases. However, NIDDK and the other institutes publish many documents each year covering their advances and opportunities in intramural and extramural research.

Dr. Rotrosen said that due to the strong interactions he has had with NIDDK over the years, he is confident that NIAID and NIDDK have good mechanisms for addressing overlap. He suggested that CDC, the other ICs, and multiple partners meet more frequently to ensure the same level of communication. Dr. Fradkin assured him that CDC's funded research, for instance, is very discrete from what is happening at NIH. GoKinD and FIND are complementary, but recruiting different populations. SEARCH is not duplicated by any NIH projects she is aware of. She agreed that meetings facilitated communication and added that a coordination mechanism for the consortia will also provide DHHS staff with a forum to obtain progress reports and hear about events in which they are not directly involved.

Goal 3: Develop Cell Replacement Therapy

Dr. Fradkin noted that the May 2002 Advisory Panel was very enthusiastic about the Beta Cell Biology Consortium (BCBC). The panel strongly recommended expanding the BCBC, involving new researchers, and integrating the research with other consortia's efforts to identify markers for imaging beta cells and for assessing the quality of islets for transplantation. This is ongoing.

In transplantation, there are several coordinated efforts, including the ITN, that are looking at immunomodulation and tolerance. There is also a primate consortia that is looking at a number of transplantation-related issues. The Advisory Panel felt that in addition to these, there were other areas that needed to be developed. These included:

- Improving harvesting, isolation, assessment, and preservation.
- Improving engraftment (insights from angiogenesis) and function.
- Conducting clinical trials other than for tolerance (i.e., site and method of transplant, less toxic immunosuppression).
- Looking at xenotransplantation (islets, reagents).
- Expanding animal and pre-clinical research.

NIDDK is planning an advisory meeting on May 30, 2003, with the National Center for Research Resources (NCRR), NIAID, and JDRF to discuss transplantation initiatives such as expanding the primate consortia. The date for the meeting was selected to coincide with a meeting in the metropolitan Washington, D.C. area, of the American Society of Transplantation.

Discussion

The discussion on transplantation included the following points:

- Multiple groups are discussing the issues, including a trans-NIH coordinating committee and an Executive Committee from Secretary Tommy Thompson's office at DHHS. Close coordination among these groups is needed.
- The trans-NIH committee has largely focused on major organ transplantation but will include islets, but not the full pancreas, in its FY 2004 initiatives. It will be FY 2005 or beyond before they address xenotransplantation.

- The Secretary's office is aware of some high profile advances in transplantation, including islet transplantation, and of third-party payer issues for kidney transplantation.

- Key issues in islet transplantation are new approaches to genomic assessment of the quality of the islets; possibly the use of xeno islets or islets derived from stem cells; and development of better tolerance or immunosuppressive approaches.

- The Secretary's office also has an advisory committee on xenotransplantation, largely taking a very broad view and focusing on scientific feasibility and industry interaction with the Food and Drug Administration.

- Although xenotransplantation research goes back about 20 years, it has not had the success anticipated. Now that transgenic pigs engineered to prevent hyperacute rejection are available, funding may attract new investigators and encourage research in this area as an alternative approach to treat type 1 diabetes.

- Encapsulation is an area that also has not had significant success so far, but if it is de-coupled from xenotransplantation, small businesses might be interested in the two fields separately. Currently, there is confusion about their relationship.

- NIDDK provided additional funding through its diabetes centers in 2002 to promote research in encapsulation and attract new talent in this area of research.

- To propel the technology forward, Small Business Innovation Research (SBIR) programs were recommended as a possible approach, subject to peer review, to getting small businesses, possibly in the bioengineering community, interested in encapsulation and in xenotransplantation as separate endeavors. In addition non-SBIR funds still may be needed to involve the right people in investigating the xenotransplantation and encapsulation issues.

- Prior to FY 2001, there was no set-aside for small business from the type 1 special statutory funds. Currently the NIDDK funds the small business commitments generated by the special statutory type 1 diabetes funding from its appropriated funds. Beginning in 2004 special statutory type 1 funds will be used for this set-aside.

Goal 4: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Dr. Fradkin noted that hypoglycemia is a major problem for those living with type 1 diabetes. The May 2002 Advisory Panel identified several new opportunities for research, particularly to bring in some of the latest technologies from neuroscience and neuro-imaging to prevent or reduce hypoglycemia. Their recommendations included the following:

- Study the mechanism of restoration of hypoglycemia unawareness and counter-regulation in new transplant recipients.

- Recruit neuroscientists and brain-imaging specialists to study glucose-sensing mechanisms in the brain, islets, and other glucose-sensing tissues (e.g., muscle, liver).

- Understand the brain effects of recurrent hypoglycemia (especially in young children) using brain imaging technology (PET) and assessment of glucose metabolism.

- Foster application of discovery of sensors for brain substrates and neurotransmitters to type 1 diabetes.

- Identify transporters that may be involved in hypoglycemia.

• Understand how sleep promotes hypoglycemia.

Dr. Fradkin complimented Dr. Grave for how quickly DirecNet became established. It has already initiated and completed studies on the GlucoWatch and the Minimed Medtronic continuous sensor. Dr. Grave credited the data coordinating center and DirecNet's five clinical centers. Investigators at the centers have already issued about eight abstracts and some papers.

Recommendations To Prevent/Reduce Complications DMICC – April 11, 2003	
Animal models:	• Knockout (KO) and transgenics to define pathophysiology • Explore genetic differences among strains re development of complications after prolonged hyperglycemia • Need models that fully develop complications (e.g., no models of macular edema) • Cores for standardized assessment
Identify cell types important in specific complications	
Multiple potential mechanisms of complications (e.g., glycation, lipoxidation, inflammation, apoptosis, angiogenesis) require multidisciplinary teams	
More Efficient Trials:	• Reliable, practical biomarkers • Correlate subclinical disease with events • New technology (e.g., MRI, proteomics) • Discovery-based studies (as opposed to mechanistic)
Bench to Bedside:	• Exploratory results-driven projects • Assays to determine which agents to carry forward to clinical trials

Goal 5: Prevent or Reduce Complications in Type 1 Diabetes

An overall recommendation from the May 2002 Advisory Panel that Dr. Fradkin noted was the need to bring together those working on different complications in order to share information and ensure maximum use of the information acquired, for instance from existing animal models. While the Animal Models of Diabetic Complications Consortium (AMDCC) has been helpful in doing this, there are potential expansions of this effort to advance the understanding of complications. The Advisory Panel recommended facilitating animal research that addresses multiple complications and evaluates multiple tissues. They also suggested developing resources for distributing animals with prolonged hyperglycemia and developing a mechanism for preclinical pharmaceutical testing of animal models. Development of animal models provides a means of testing concepts from basic research to identify the best places to invest funds for clinical research.

In addition to those from the May 2002 Advisory Panel, Dr. Fradkin brought recommendations from the April 10–11, 2003, DCCT/EDIC 20th anniversary meeting. The participants at this meeting had focused on the concept of a possible "metabolic memory" resulting from early intensive glycemic control. In the tight control group, the onset of complications tended to be delayed long after the tight control was ended, even though the subjects' glycemic levels became approxi-mately the same as those of subjects in the standard treatment group. Following the main meeting, the group met with DMICC to contri-bute suggestions for further research on complications in type 1 diabetes (see box). Animal models were a major subject of discussion. It was suggested that the animal model consortium be a venue for bringing researchers of different disciplines together through regular confer-ences and symposia. It was con-sidered important to bring the trans-NIH and trans-DHHS groups together with the consortium to ensure that all of the complications are being considered and to develop strategies to coordinate, expand, and broaden the joint efforts. Currently NIDDK provides coordination for the consortium, and NHLBI administers a number of the awards.

Dr. Fradkin briefly spoke of the other recommendations, including expanding the cores as a resource so that those with expertise in one organ could send their animals to be characterized in terms of other organs. Standardized characterization would help to not only find genes but to identify animals that have a higher innate susceptibility, which is important in deciding which animals to use to create knockouts that are potentially susceptible to complications.

Other key areas are to learn which cell types are involved in the development of complications and to take advantage of the progress in integrating the potential mechanisms of complications by expanding multidisciplinary approaches that involve inflammatory expertise and so forth. Clinical trials still need reliable biomarkers to make them more efficient. Finally, the goal of moving from bench to bedside requires exploratory results-driven projects and assays to determine which agents should be carried forward to clinical trials so funds are not spent pursuing ultimately unfruitful things.

Discussion

Dr. Josephine Briggs, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, spoke of the value of NIDDK's partnership with NHLBI. The current animal model consortium includes three projects on large animal models and a group of investigators who are coordinating efforts on the mouse. The mouse group is focusing on genetically engineering target genes to identify cell types specific for complications and on other genetic strategies to make the mouse more susceptible. The consortium has made substantial progress in developing agreement on assessment protocols for the mouse and overcoming the sizable technical problems in doing this assessment in the mouse. The nephropathic and neuropathic groups within the consortium are reasonably well advanced; there was no retinopathy proposal originally, but a group of investigators who will be looking at retinopathy is being brought in. This is an area where the consortium would like to see substantially more effort.

Dr. Briggs explained that some things in the broad area of animal models are not being addressed yet. The group has not undertaken extensive investment in the genetics susceptibility of loci to be able to translate them into the mouse to see if they have impact. It also does not include any rat studies. People in the field report that since the rat is being used and the protocols for identifying diabetic complications vary wildly from laboratory to laboratory, more standardization of protocols is needed. What needs to be understood is that the genetic manipulation to develop animal models is not an enormously rapid process. It takes about a year to make a knockout, and this group is just reaching the point where they have models that it makes sense to talk about distributing. The consortium meets every 2 to 3 months, but these have not been meetings open to others. Dr. Briggs heard a strong message at the April 11 meeting that to open these meetings and expand their dialog would be valuable both to those within the consortium and to the broader community.

Dr. Goldstein agreed that it would be valuable to use such a venue to bring together in one place people concerned about eye disease and nerve disease and kidney disease. To date, there has been no common forum or place to have such discussions. If this can be done around animal model discussions, it would help everybody. Dr. Spiegel added that it is important to involve the National Eye Institute (NEI) and the National Institute of Neurological Disorders and Stroke (NINDS).

Dr. Savage said that a NHLBI working group is going to be exploring opportunities to better understand the causes of macrovascular disease in type 1 diabetes. Dr. Paul Nichols, Program Director, Systems and Cognitive Neuroscience Program, NINDS, added that there is an interest in his group to study various aspects related to diabetes such as pain mechanisms, stroke, cognitive deficits in type 1 diabetes, and sleep research, particularly its relationship to hypoglycemia. They are interested in doing a diabetes initiative or preclinical trial involving neurological complications, which they feel would not require a great deal of money.

Dr. Goldstein commented on the compelling discussion at the April 11 DMICC meeting about providing funds for a program to encourage high-risk, innovative studies of novel therapeutics for complications and immunomodulation. Such a program would require a different review process. It might also attract researchers who are not currently involved in diabetes, but who have expertise to contribute.

Dr. Fradkin replied that the bench-to-bedside RFA, supported across multiple institutes, addressed that type of focused preliminary studies. The RFA, which encourages collaboration between basic research scientists and clinical scientists, has been successful and probably will be issued annually as an impetus and path for innovative studies. However, additional mechanisms are needed to move new agents forward into trials. A mechanism similar to that of the National Cancer Institute's (NCI's) Rapid Access to Intervention Development (RAID) is also being considered. (RAID is a mechanism to provide investi-gators with access to drug development resources in order to bring therapeutic applications that originate in an academic laboratory through preclinical development.)

Dr. Fradkin agreed with Dr. Goldstein that a special peer review process for applications for use of the RAID mechanism will be essential, both to foster a rapid response and because such efforts tend to be very expensive. It is important to invest the type 1 funds in development of the most promising agents. In addition to proposals for new therapeutics for complications, there are some proposals coming out of ITN and TrialNet that need preclinical development, mouse studies, toxicological studies, and such that the individual consortia members are not equipped to do; the consortia could benefit from such a mechanism. In addition, availability of an impartial review for access to this type of preclinical development mechanism might challenge the broader community to develop new therapeutics.

Goal 6: Attract New Talent to Research in Type 1 Diabetes

In introducing Goal 6, Dr. Fradkin said that the Advisory Panel clearly recommended major bold new initiatives with these funds. Complications may be a good area to pilot these since relatively fewer resources have been directed to them in the previous funding years and, even though there are excellent investigators in the area, it is a fairly small field and one that needs new talent. This might be a place for a mechanism to attract those who would not be typically attracted by an R01 award. The Panel recommended encouraging multidisciplinary teams and novel technologies, supporting high-impact goals, and, most importantly, making continued funding contingent on milestones.

A DARPA (Defense Advanced Research Projects Administration)-like review was also recommended. Such a review was discussed at a recent JDRF scientific advisory board meeting. It assesses a researcher's capabilities, track record, and the novelty of the proposal being offered, rather than focusing on the technical aspects that are central to an R01 review. For example, it does not require the level of preliminary data required for an R01. The idea is for the review to be flexible and examine where opportunities lie in the applications. Because acceptance is based primarily on potential, it is essential to have specific milestones and ongoing evaluations. DARPA projects are intended to develop a specified application driven by a pre-defined outcome. They usually have a lifetime of 3-5 years and a large budget of $5-10 million.)

Challenging topics might include new animal models focused on complications, surrogate markers, angiogenesis, and endothelial biology. The challenge will be to take on a difficult problem such as developing surrogate markers or a high throughput assay that could be used to move things from the bench to the bedside. Hopefully this will bring in people, such as endothelial developmental biologists, cell biologists, or those with expertise in angiogenesis, who are not currently focused on diabetes and its

complications. This has worked well for cancer research. If this is successful in attracting the right people to the field, then it could be expanded in subsequent years to other goals.

Discussion

Dr. Rotrosen cautioned that the challenge opportunities be well-defined, since most investigators believe their project is innovative and challenging. Also, a useful technique that NIAID had for their challenge grant initiatives was to not require matching funds from industry and to provide multiyear funding in one year, which is atypical, but got the attention of companies and academic investigators who otherwise might not have been interested.

Dr. Spiegel was impressed at the April 10–11, 2003, DCCT/EDIC meeting by the amount of important talent that has largely focused on the cancer area, but not on diabetes. Angiogenesis, for instance, has burgeoned dramatically in the cancer field. He said it will be important to find an inducement for these researchers to shift their focus and apply their abilities in the diabetes field. He urged the group to seize the opportunity this year to tap into the tremendous talent pool that is available—to attract those who have successfully solved problems in one area and have them focus now on diabetes—both with regular appropriations and the special statutory type 1 funds. Integrating industry also is an issue for which an appropriate program is needed.

Dr. Fradkin asked if there was interest in a pilot program to identify one or two areas of focus regarding fundamental biology related to complications. Understanding the biology might then provide the opportunity to develop biomarkers, surrogate outcomes, and other measures to move novel therapeutics forward. Before looking for therapies, it is necessary to have a reliable assay that will accurately measure the outcome of the intervention process; this is not presently available for complications. That could be the focus of the challenge.

Dr. Charles Queenan, Chair of Research, JDRF, suggested that, rather than an all-or-nothing approach, portions of innovative proposals could be approved or applications could be combined, particularly with a DARPA-like review mechanism.

Dr. Savage thought that seed funding might be the best approach to take at the present time rather than soliciting large multidisciplinary projects since many areas related to diabetes complications are still relatively primitive. For instance, there are some very specific things to be defined in the area of biomarkers, which are needed for clinical trials. Another area of interest would be to try to identify those who are at risk, and those who appear to be protected, by studying people who have diabetes for 20 or 30 years and do not develop complications versus others who develop them very early.

Seeding Collaborative Research Supplements for Shared Resources

Dr. Fradkin proposed providing supplements to regular NIH grants in a new mechanism to seed multidisciplinary collaborative research. The supplements would enable a person in one area to seek out others whose expertise, along with core or shared resources, would benefit collaborative research funded through a peer-reviewed mechanism. There would be very clear definitions on how the supplements could be used. They could not be used for merely continuing the investigator's ongoing research projects. The seed money would be expected to "jump start" important collaborative research efforts, bring in new talent, and lead to other beneficial consortia. Potentially, it would foster the following types of initiatives:

- Establishment of research consortia among researchers in complementary fields to investigate:

- Multiple issues affected by vascular disease.

- Inflammation, immunology, and endothelial biology.

- Sharing of unique reagents, technology, or complementary expertise.

- Funding two to five researchers, each with independent peer-reviewed support.

- Supporting a collaborative project within the scope of individual grants.

Projects would be peer-reviewed by senior NIH staff, both initially and through ongoing evaluations. The projects would be assessed on their novelty or uniqueness, the added value they will bring to underlying research, and their potential benefit to type 1 diabetes research.

Report on Consortia and Resources

The current consortia will be reporting in May 2003 on the special statutory type 1 funds they have been awarded to date. Their reports will include the following topics:

- Goals and structure (i.e., steering committee, sites, Web sites).

- Accomplishments to date.

- Milestones for future accomplishments.

- Evaluations (e.g., by External Advisory Committee, reports, recommendations).

•Coordination efforts with other consortia.

- Materials, products, and samples that will be made available to the scientific community.

- Future support requested.

With the exception of the budgets, the reports will be posted on the type 1 diabetes special statutory funds Web site that is in the process of being created. The Web site will describe the consortia and the resources available through the consortia. It will provide a central resource for people seeking information on type 1 diabetes research, including links to non-special statutory funded research as well as links to the individual consortia Web sites. Opportunities for funding will also be listed.

Dr. Fradkin said that the recommendations by the May 2002 Advisory Panel have been carefully reviewed and mechanisms are being put into place to fund these in the FY 2004 budget.

New or Re-Issued Solicitations

Goals that the Advisory Panel members were enthusiastic about will be supported by re-issued and new solicitations, including the following:

- Innovative Grants Immune Tolerance

- Bench-to-Bedside Research

- Innovative Partnerships for Type 1 Diabetes

- Ancillary Studies to Type 1 Diabetes Consortia

- Expand Beta Cell Biology Consortium

- Expand Non-Human Primate Consortium

- Hypoglycemia.

It is also likely that additional solicitations may be issued based on recommendations from upcoming meetings on the role of inflammation in CVD complications, beta cell imaging, and proteomics and islet transplantation.

Dr. Fradkin explained that these will be similar to previously issued solicitations in these areas of opportunity but will be amended based on the May 2002 Advisory Panel and other advisory committee and scientific meetings. The innovative partnerships RFA serves as a "talent scout" by fostering collaboration between researchers with expertise in type 1

diabetes and researchers whose expertise, while not in type 1 diabetes, is relevant to it. A draft of the innovative partnerships RFA has been circulated to the ICs, and NIDDK has received suggestions from individual ICs on topics that are within the mission of the IC. This is not what the Institute is looking for with this RFA. It is intended to focus on opportunities identified by the external Advisory Panel, including cross-cutting topics that would involve multiple ICs, particularly with regard to complications and studies looking at various tissues and organs. The RFA will be re-circulated based on the recommendation from the April 11, 2003, meeting to create a mechanism for paired grants in order to attract new talent. All ICs were invited to contact Dr. James Hyde, NIDDK, if they wished to participate.

SBIR and STTR Potential Program Announcement Topics

NIDDK is required to set-aside a portion of the type 1 special statutory funds for small business. For FY 2004, the following areas will be available for development through SBIR or Small Business Technology Transfer (STTR) programs:

- Drugs or protocols to induce tolerance or reduce autoimmunity.
- Methods to assess progression and immune modulation in type 1 diabetes such as:
- Imaging/tracking of autoimmune cells
- Proteomic approaches
- Genetic, proteomic, or other improved tests for identifying individuals at risk.
- Islet transplantation:
    - Enhance islet survival, engraftment, in vivo regeneration
    - Improve islet isolation methodologies: media, collagenase
    - Islet encapsulation
    - Development of a closed-loop artificial pancreas.
- Application of new technology to complications research, such as:
- Chips for assessment of tissues and organs involved in complications
- Biomarkers
- Improved animal models of type 1 diabetes and complications for testing new therapies such as embryonic stem cells from a NOD (non-obese diabetic) mouse.

NIDDK will be putting together an SBIR solicitation that will be a multi-IC solicitation. Dr. Fradkin invited those present to send her other suggestions for discrete areas where small businesses could make a contribution and to indicate their interest in participating in this solicitation.

Asked if companies working with human embryonic stem cells would be eligible, Dr. Spiegel answered that the funds could only be used to support those with cell lines already on the registry, which is the same restriction that applies to academic investigators. For SBIRs/STTRs, the companies must be U.S. owned and there is a limitation on the number of employees and on gross revenues. Dr. Goldstein added that the ones with approved cell lines are already being heavily solicited by NIH. The majority are not eligible for SBIR funds. Dr. Goldstein urged that new therapies be sought for the complications of type 1 diabetes.

Schedule of Advisory Meetings To Inform the Planning Process

Dr. Fradkin concluded her presentation with a slide listing the advisory meetings that would be contributing to the type 1 special statutory funds planning process. These include:

- DMICC Meeting on Complications of Type 1 Diabetes, April 11, appended to the DCCT/EDIC 20th Anniversary Meeting, April 10–11, 2003
- Inflammation and Cardiovascular Disease, April 27–28 (with NHLBI and JDRF)
- Beta Cell Imaging, April 21–22
- Proteomics and Diabetes, April 24–25
- Transplantation, May 30 (with NIAID, NCRR, and JDRF)
- Integration of Clinical Consortia, June 2003
- External Advisory Committee (EAC) Meetings of Ongoing Consortia
- Beta Cell Biology Consortium, May 4–6
- International Type 1 Diabetes Genetics Consortium, July 15
- TEDDY, October 2003

Dr. Fradkin welcomed all those present to attend these meetings and urged those who are leading other consortia to notify the other members of the EAC meetings coming up for their groups and where they are being held. Dr. Goldstein announced that an NIH stem cell meeting is being held June 12, that some might be interested in. Dr. Spiegel added that there would be a symposium in the morning and workshops in the afternoon. There are a number of related activities taking place that week. The NIH event will be preceded by a meeting of the new Stem Cell Society that will be held in Washington, D.C., and it will be followed on June 13 by a joint NCRR–NIDDK meeting of the infrastructure board.

Dr. Fradkin thanked those present for their participation. She emphasized that she is looking forward to working in partnership with them in these exciting times to carry out the responsibilities and challenges to use the type 1 special statutory funds in promising ways and to do so wisely.

The meeting was adjourned at 11:05 a.m.

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APPENDICES

APPENDIX A

NATIONAL DIABETES MELLITUS RESEARCH AND EDUCATION ACT, SECTION 429: Interagency Coordinating Committees

Sec.429. [285c—3]

(a) For the purpose of—

(1) better coordination of the research activities of all the national research institutes relating to diabetes mellitus, digestive diseases, and kidney, urologic, and hematologic diseases; and

(2) coordinating those aspects of all Federal health programs and activities relating to such diseases to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities;

the secretary shall establish a Diabetes Mellitus Interagency Coordinating Committee, a Digestive Diseases Interagency Coordinating Committee, and a Kidney, Urologic, and Hematologic Diseases Coordinating Committee (hereafter in this section individually referred to as a "Committee").

(b) Each committee shall be composed of the Directors of each of the national research institutes and divisions involved in research with respect to the diseases for which the Committee is established, the Division Director of the Institute for the diseases for which the Committee is established, the Chief Medical Director of the Veterans' Administration,[1] and the Assistant Secretary of Defense for Health Affairs (or the designees of such officers) and shall include representation from all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to such diseases, as determined by the Secretary. Each Committee shall be chaired by the Director of NIH (or the designee of the Director). Each committee shall meet at the call of the chairman, but not less often than four times a year.

(c) each Committee shall prepare an annual report for—

(1) the Secretary;

(2) the Director of NIH; and

(3) the Advisory Board established under section 430 for the diseases for which the Committee was established, detailing the work of the Committee in carrying out paragraphs (1) and (2) of subsection (a) in the fiscal year for which the report was prepared. Such report shall be submitted not later than 120 days after the end of each fiscal year.

[1] The reference is deemed to be a reference to the Under Secretary for Health of the Department of Veteran Affairs. See section 302 (e)(1) of Public Law 102-405(106) Stat. 1985 and section 10(4) of Public Law 100-527 (102 Stat.2641).

APPENDIX B

DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE

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