NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
COMPREHENSIVE STRATEGIC PLAN AND BUDGET
TO REDUCE AND ULTIMATELY ELIMINATE HEALTH DISPARITIES

RESEARCH AREA OF FOCUS: AIDS

RESEARCH AREA OF FOCUS: DISEASES OF THE PROSTATE

INFRASTRUCTURE AND CROSS-CUTTING ISSUES

PUBLIC INFORMATION AND OUTREACH

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NIDDK's Mission/Vision Statement

The **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)** conducts and supports research on many chronic and costly diseases affecting public health. Several diseases studied by the NIDDK are among the leading causes of disability and death in the Nation; all seriously affect the quality of life of those suffering from them.

Many diseases and disorders that disproportionately impact the health of minority populations in the United States receive high priority in NIDDK research areas. These include diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder disease, *H. pylori* infection, sickle cell disease, kidney diseases, diseases of the prostate, and complications from infection with the human immunodeficiency virus. The NIDDK gives increased priority to support research and to encourage specific efforts in these areas of health disparity in order to advance the foundation of knowledge in the biomedical sciences. The strategic vision that guides NIDDK is improved health and quality of life for all Americans, through basic, clinical, and behavioral research to address the diseases and disorders within the Institute's statutory research mandate.

A focus on basic research has traditionally guided the Institute's programs. It is grounded in the belief that a fundamental understanding of biological systems will ultimately explain the abnormalities underlying each disease and is therefore imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, however, the Institute has a strong commitment to apply advances in the understanding of disease processes to appropriate clinical studies and ultimately to efforts to transmit knowledge and effective technologies to practicing physicians, as well as those affected, and their families.

Shared interests in the biochemical and genetic processes underlying disease provide a linkage mechanism for the programs and divisions of the Institute, and serve to foster integration of fundamental knowledge with clinical research. The same is true for the close communication between NIDDK and other NIH programs' vital areas of investigation.

National Institute of Diabetes and Digestive and Kidney Diseases Areas of Emphasis in Health Disparities Research for Minorities and Underserved Populations.

The ability of NIDDK to implement these proposed initiatives is contingent upon the availability of funds.

Research Area of Focus: Diabetes Mellitus, Type 2

THE DIABETES PREVENTION PROGRAM OUTCOMES STUDY (DPPOS)

Background
The DPP was a large NIDDK supported, randomized clinical trial designed to determine whether individuals at high risk for developing type 2 diabetes could have their risk for developing diabetes prevented or delayed. The interventions tested were lifestyle or the drug metformin. 3,234 individuals with IGT were randomly assigned to metformin, placebo or a lifestyle program. The lifestyle program was aimed at a weight loss of 7% or greater and 150 minutes or greater physical activity per week. Participants mean age was 51 years, 68% were women, and 45% were from minority groups. The study results indicated that metformin reduced diabetes incidence rates by 31% and lifestyle by 58% over an average intervention of 2.8 years.

The DPP was designed with the expectation that prevention or delay of diabetes would in the end prevent or delay the development of long-term, duration dependent diabetes-specific complications. Also, preventing or delaying cardiovascular disease (CVD) and/or CVD risk factors resulting from diabetes prevention or delay would be of major benefit to individuals with IGT and contribute to long-term health.

Research Goals and Scope
The DPP follow-up study or DPPOS is a 5-year study that will take advantage of the unique cohort of volunteers that participated in the conduct of the DPP. The DPPOS will permit, 1) examination of the long-term effects and durability of the prior DPP interventions on DPP outcomes that include diabetes onset, CVD, atherosclerosis through measurement of IMT, quality of life and cost-benefit; 2) determination of the clinical course of new onset type 2 diabetes, not possible in any other existing cohort of individuals; 3) examination of 1 and 2 in minority populations, men vs. women, and in older and aging subjects of the DPP.

Timeline: FY 2003 - FY 2008

Outcome measures: Of the 3,234 subjects randomized to the 3 arms of the DPP, it is estimated that 2,300 participants will remain in the long-term follow-up of the DPP cohort that have not converted to type 2 diabetes and agree to participate. Participant retention will remain a focus of the follow-up study. The study, based on the numbers projected, will have sufficient power to continue to follow the conversion to diabetes. The study will also be powered to detect differences in the development of retinopathy between the originally randomized groups including the converters to diabetes. For the first time it will be possible, using the DPP cohort, to follow the development of retinopathy from its initiation and the effects of the DPP treatments

on this process. In addition, the cohort will be followed using surrogate measures of cardiovascular risk and clinical CVD events. Although poorly powered to examine the latter over this 5-year phase of the DPPOS, it is hoped that participants will be followed over the long-term to permit sufficient power to compare the intervention groups for clinical CVD events.

Performance Measures: The DPPOS Data Safety Monitoring Board (DSMB) has been charged by the NIDDK to oversee study performance both in terms of study conduct and in terms of participant safety. The DSMB will make recommendations to the NIDDK as to study performance and study continuation. In addition DPPOS subcommittees will be created with the responsibility of overseeing ongoing protocol adherence and participant retention.

RACE/ETHNIC DISPARITIES IN THE INCIDENCE OF DIABETES COMPLICATIONS

Background

Epidemiologic studies have generally found a striking and large excess of diabetic microvascular disease in minority racial and ethnic groups, including Native Americans, African Americans, Hispanic Americans, and Asian and Pacific Islanders. However, the reasons for these differences are not well understood.

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKDPS), for type 2 diabetes, established the importance of intensive diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensive glucose control in reducing the risk for the microvascular complications of diabetes, such as retinopathy, neuropathy, and nephropathy. In addition, numerous studies have recently demonstrated that intensive blood pressure control is essential in preventing both micro- and macrovascular complications of diabetes. Aggressive management of dyslipidemia has also been shown to decrease macrovascular complications. Some of the racial differences in diabetic complications may be explained by differences in availability and quality of health services. There may be differences by race/ethnicity and socioeconomic status in self-care practices, health care provider practices, and/or access to quality health care and prevention services that directly impinge on the frequency and magnitude of risk factors for diabetes complications and the intensity of medical care for early stages of complications to prevent progression to end-stage disease.

In addition to differences in blood glucose, lipid and blood pressure control, which may be modified by improved medical care; genetic susceptibility and other biological risk factors may contribute in unknown ways that lead to complications. This is suggested by the clustering of complications (especially nephropathy) within families and by the excess risk of retinopathy in Hispanics versus non-Hispanics that remains when the degree of hyperglycemic exposure is taken into account.

Finally, lifestyle, psychosocial factors, stress, family structure, social support, diet and culture, and socioeconomic status vary among racial and ethnic minorities and may contribute to differential risk of developing diabetes complications and progression of complications. Little is

known about how these behavioral factors influence the risk of complications and the effectiveness of interventions designed to prevent or reduce diabetes complications in racial and ethnic minority groups.

Identification of these divergent etiologies and quantification of their correlation to risk have important implications for prevention and amelioration of microvascular complications. Such information might improve the effectiveness of treatment to reduce the disparities in the incidence in diabetes complications among racial and ethnic groups.

In contrast to microvascular complications, racial and ethnic minorities with diabetes often have lower rates of macrovascular disease than Caucasian population groups. Angina, myocardial infarction, and other forms of coronary heart disease appear to be less common in African Americans, Mexican Americans and Native Americans than in non-Hispanic whites. This difference is particularly striking given the higher incidence of diabetes in these populations. The factors that account for the differing macrovascular disease rates are unknown. For example, the relative contribution of glycemia (versus other risk factors) to cardiovascular risk in these minority populations has not been studied.

Research Goals and Scope

The overall objective of this Program Announcement is to understand racial/ethnic disparities in the development of the micro- and macrovascular complications of diabetes. It is recognized that both biologic and non-biologic factors may be operating in these populations.

Approaches may include metabolic, genetic and/or epidemiologic studies in representative populations. Advantage might be taken of extant cohort studies that have been established for investigation of diabetes or other diseases. Collaboration among investigators of these established cohorts would be desirable, so that these studies might jointly develop protocols and evaluate findings. Alternatively, investigators may propose to start a new cohort, appropriately powered, to capture the current risks and outcomes in the era of new medications for glucose, blood pressure and lipid control. Such studies of current risks might appropriately be based in large HMOs or clinical practices with structure and data management practices conducive to efficient and cost-effective analyses.

Investigators are encouraged to incorporate appropriate surrogate markers for complications into study design to shorten the duration of studies. Such surrogate markers might include early indicators of end-stage complications (background retinopathy, albuminuria, serum creatinine, basement membrane thickening, EKG, carotid ultrasound).

Appropriate topics for investigation would include but are not limited to:

- Epidemiologic studies to determine the rates of micro- and macrovascular diabetic complications in appropriate representative samples of contemporary populations.

- Studies to identify genes that might affect the development and progression of micro- and macrovascular complications in different populations.

- State-of-the-art, hypothesis-driven metabolic studies to determine whether there are differences in metabolism, insulin sensitivity, energy expenditure, beta cell function, and body composition that might influence glycemic control and risk of complications in different populations.

- Studies to compare the contribution of glycemia versus other risk factors (e.g., smoking, hyperlipidemia, body composition, blood pressure) in the development of micro- and macrovascular disease in patients with diabetes, and to study how treatment of these factors may influence rates of development of complications in different racial/ethnic groups.

- Studies to investigate environmental factors, such as medical care, behavior and lifestyle, and socioeconomic status that may contribute to risk for development and progression of complications. Such studies could incorporate culturally specific lifestyle factors into treatment and prevention strategies to reduce risk across racial and ethnic groups.

- Studies to determine whether different pathophysiologic mechanisms or risk factors are operative among subgroups within racial/ethnic minorities (e.g., different subgroups of Hispanic Americans, such as Mexican Americans, Puerto Ricans, Caribbean Hispanics, Cuban Americans).

Understanding the basis for differing susceptibilities could provide information that would lead to specific therapies likely to be useful in various subpopulations at high risk for the development of diabetes complications.

Timeline: FY 2000 - FY 2006 and beyond

Performance Measures: The performance measures that the institute will utilize to demonstrate that the objectives have been met will include the number of grants funded, the quality of proposals, the number of patients enrolled in the study, and the funding level.

Outcome Measures: The outcome measures will include the extent to which the results accurately define the rates of diabetic complications, differences in the genes, metabolic differences, and the effect of social economic and behavioral factors, in the different racial and ethnic populations.

RACIAL AND ETHNIC DIFFERENCES IN THE ETIOLOGY OF TYPE 2 DIABETES IN THE UNITED STATES

Background

It is well recognized that there are major differences in the prevalence of type 2 diabetes among race-ethnic groups in the United States. Substantial progress has been made toward identifying population-based risk factors for the development of type 2 diabetes that might lead to these race-ethnic disparities. Such established risk factors include, for example, genetic predisposition, total and central obesity, duration of obesity, high caloric intake, and physical inactivity. Factors such as socioeconomic status, acculturation, and stress may also be important.

Individuals who have progressed along the pathogenic course toward diabetes are at higher risk of developing overt disease, and these individuals include those with insulin resistance, impaired glucose tolerance, gestational diabetes, and reduced beta cell function.

Although these diabetes risk factors appear to operate in all race-ethnic groups, it is not known whether specific groups are inherently different in the ways they respond to risk factors, which may lead to their differential susceptibility to diabetes. Environmental, genetic, and metabolic differences may underlie the disparity in diabetes rates, and physiological outcomes of risk factors may arise from a complex interplay of genetic and nongenetic (behavioral, lifestyle, and environmental) factors.

Epidemiologic studies have documented the differing risk for diabetes among race-ethnic groups and have established the identity of diabetes risk factors. However, with few exceptions, these studies have not been designed to examine in depth the metabolic and physiologic effects of diabetes risk factors in specific race-ethnic populations. Consequently, there is an important need for carefully designed clinical studies to investigate these issues in representative samples of the various U.S. race-ethnic groups.

Research Goals and Scope

The overall objective of this Program Announcement is to determine the metabolic and physiologic reasons for disparities in the incidence of type 2 diabetes in minority race-ethnic populations. Such information could lead to new prevention and treatment strategies, especially for high risk groups. Additionally, information from these studies would be important for devising cost-effective approaches to phenotyping patients with type 2 diabetes and individuals at risk for developing diabetes. The ability to characterize and identify discrete subgroups of type 2 diabetes would be essential in genetic studies of this disease.

Studies to investigate the behavioral, socioeconomic, psychosocial, cultural, family, and community factors that influence the individual's risk for developing type 2 diabetes and how these factors can lead to racial and ethnic disparities in incidence rates are clearly of importance. Understanding these issues is vital to the development of culturally appropriate prevention strategies to reduce risk across racial and ethnic groups. However, studies to investigate non-biologic factors should not be submitted under this Program Announcement, which will focus on biologic factors responsible for race/ethnic disparities in the incidence of type 2 diabetes.

Appropriate topics for investigation would include but are not limited to:

- State-of-the-art, hypothesis-driven metabolic studies in which fat metabolism, glucose levels, insulin secretion, energy expenditure, etc., are measured in individuals from U.S. race-ethnic groups. Such studies might determine, for example, whether some groups are at greater risk for type 2 diabetes from insulin resistance or from reduced beta-cell reserve; whether fat content and distribution differ among race-ethnic groups, and what metabolic or physiologic processes are responsible in the pathogenetic pathway leading to type 2 diabetes.

- The temporal relationship of changes in body weight and body composition, glucose tolerance, and insulin resistance in the etiology of type 2 diabetes. Clinical studies could unravel the sequence of events leading to type 2 diabetes, especially the timing of weight gain with regard to glucose tolerance and insulin resistance. A critical question is whether individuals who will develop diabetes first gain weight and then develop diabetes, with the same genes leading to both conditions; or whether individuals gain weight and then proceed to diabetes because of beta cell defects.

- Beta-cell function. There is growing appreciation that substantial beta-cell defects occur prior to the onset of type 2 diabetes. Very little is known about the types of defects that actually predict or attend diabetes. Most studies that have examined complex aspects of beta-cell function in vivo have been cross-sectional comparisons of high- vs. low-risk individuals. A combination of detailed beta-cell assessments with longitudinal follow-up would likely yield important information about the pathogenesis of the beta cell defects. Other phenotypic traits may also be useful in such studies, such as beta-cell responses to fatty acids, hyperglycemia, amino acids, and insulin resistance. Studies are needed to better understand whether there are racial/ethnic differences in the incidence and prevalence of impaired fasting glucose and impaired glucose tolerance, and whether there are differences among groups in the rates of progression to type 2 diabetes.

- Fat metabolism and insulin resistance. There is mounting evidence that altered fat metabolism in the whole body and, possibly, in skeletal muscle or adipocytes in muscle are important determinants of insulin resistance. Longitudinal studies employing detailed assessments of fatty acid turnover and/or muscle fat metabolism could yield important information about the relation between fat metabolism and insulin resistance as people change their physical activity, weight, etc.

- The temporal relationships among the components of the metabolic syndrome (Syndrome X). The clustering of hypertension, hyperglycemia, obesity and insulin resistance is well documented; however, the temporal development of the individual components of the metabolic syndrome remain to be determined. In particular, the etiologic relationship among these components, and their relationship to type 2 diabetes, need further investigation. Studies should examine the racial/ethnic differences in the constellation of metabolic abnormalities in this syndrome.

- The role of the in utero environment on the subsequent development of impaired glucose tolerance or type 2 diabetes. Extensive epidemiologic evidence suggests that intrauterine growth retardation is associated with numerous metabolic abnormalities in adults, including hypertension, cardiovascular disease, impaired glucose tolerance, hyperinsulinemia, and type 2 diabetes. However, little is known about the pathophysiologic mechanisms by which the intrauterine environment programs fetal metabolism to predispose individuals to chronic disease later in life. Studies are needed to assess whether abnormalities in the uterine environment contribute to ethnic/racial disparities in the incidence of type 2 diabetes, and, conversely, whether there are racial/ethnic differences in the response to a given in utero milieu.

Advantage might be taken of extant cohort studies that may have been established for investigation of diabetes or investigation of other diseases. Collaboration among investigators of these established cohorts would be desirable, so that these studies might jointly develop protocols and evaluate findings. Alternatively, investigators may propose to start new cohorts, appropriately powered, to capture the current risks for development of type 2 diabetes.

Timeline: FY 1999 - FY 2006 and beyond.

Performance Measures: The performance measures that the institute will include the number of grants funded, the quality of proposals, the number of patients enrolled in the study, and the level of funding.

Outcome Measures: The outcome measures will include definition of the incident rate of type 2 diabetes, difference in the genes, metabolic differences, and the effect of social economic and behavioral factors, in the different racial and ethnic populations.

PREVENTION AND TREATMENT OF TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS--CLINICAL CENTERS AND COORDINATING CENTER

Background

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, although its precise etiology and pathogenesis are only incompletely understood. The public health impact of type 2 diabetes is enormous.

Clearly associated with aging and obesity, type 2 diabetes has traditionally been considered a disease of adults. Children are assumed to have type 1 diabetes, an autoimmune disease. However, recent epidemiologic data reveal an increasing number of cases of type 2 diabetes in the pediatric population, especially among adolescents and in certain minority populations. In general, population-based screening data are not available. Data culled from diabetes clinics in several locations suggest that the percentage of children diagnosed with diabetes who are classified as having type 2 diabetes has risen from less than 5 percent (prior to 1994) to 20 to 30 percent (after 1994). The increase in type 2 diabetes in children is presumed to be a consequence of widespread obesity and decreased physical activity.

Data from NHANES III suggest that up to one-third of adults who have type 2 diabetes may go undiagnosed. A similar situation may exist with children. In fact, the diagnosis of type 2 diabetes in children is often made because of routine laboratory screening being conducted as part of a school physical and not because the child presents to a health care provider with specific complaints. Thus, many children who do not receive such screening may go undiagnosed until they become symptomatic, at which time they may have been hyperglycemic for many years and are at high risk of developing diabetic micro- and macrovascular complications. In addition, significant numbers of children may not have frank diabetes, but may be at high risk of developing diabetes based on the presence of insulin resistance, impaired fasting glucose or impaired glucose tolerance. It is, therefore, imperative to establish appropriate screening criteria and effective primary prevention programs to avoid a potential major public health burden.

The majority of children with type 2 diabetes are in the pre-adolescent or adolescent age range. The adolescent period presents special challenges to health care providers and families when attempting to promote behavior and life style changes. Prevention and treatment programs must also consider cultural differences among racial and ethnic groups that may influence acceptance of medical regimens. This is especially important for type 2 diabetes in children, which disproportionately affects minority groups.

When children do develop diabetes, efficacious therapy is needed to maintain euglycemia in order to prevent the development of complications. Diabetes is currently estimated to cost the U.S. health care system approximately $98 billion annually. Much of the cost is related to the micro- and macrovascular complications of diabetes. Since the development of complications is related, in part, to the duration of diabetes, children represent a population at high risk. Unfortunately, the drugs currently approved for use in adults with type 2 diabetes have not been systematically studied in children. Thus, treatment options for those children diagnosed with type 2 diabetes are restricted by the lack of data on the use of such pharmacological agents. Optimal treatment of type 2 diabetes in children, as well as in adults, should go beyond merely achieving euglycemia. Preserving beta cell function in children with impaired glucose tolerance or type 2 diabetes is of critical importance. Thus, clinical trials are needed to establish appropriate and effective treatment regimens for children with type 2 diabetes.

Research Goals and Scope
NIDDK has funded a cooperative agreement to plan and conduct trials for the prevention and treatment of type 2 diabetes in the pediatric population. Previously two cooperative agreement RFAs were issued—one to solicit applications from potential study sites to perform clinical trials for the prevention and treatment of type 2 diabetes in children, and the second to solicit applications for a coordinating center to provide clinical center coordination, and analytical and statistical support for the clinical trials. Based on peer review, awards were made to 7 clinical sites and the Coordinating Center.

The cooperative agreement is funded for 7 years, anticipating three phases: 1) planning, 2) recruitment and study, and 3) analysis. Currently, a Steering Committee, composed of the Principal Investigator from the clinical sites, the Principal Investigator from the Coordinating Center, an NIDDK representative, and several outside experts, is beginning protocol development for these trials. The treatment trial will likely include lifestyle changes, as well as pharmacologic therapy, and will assess beta cell function, as well as glucose control. The primary prevention trial will focus on a cost-effective, school-based intervention with the potential for broad population-wide study. The trials will be carried out at multiple sites, to insure an adequate sample size, as well as geographic and racial/ethnic diversity.

Timeline: FY 2001 - FY 2008

Performance Measures: The performance measures will include the number of centers funded, and the quality of research proposals.

Outcome Measures: The outcome measures will include the extent to which the results will alter clinical practice, including the diagnosis, prevention, and treatment of type 2 diabetes in children and adolescents.

INTERNATIONAL TYPE 2 DIABETES LINKAGE ANALYSIS CONSORTIUM

Background

In 1997, a group of investigators studying type 2 diabetes, decided to form the International Type 2 Genetic Linkage Analysis Consortium to combine the data from multiple genome scans. The group started with an analysis of chromosome 20. This analysis suggested that there was more than one locus on chromosome 20 linked to type 2 diabetes in the Caucasian population. This study was used as the preliminary data for an R01 application that was submitted in 1998 to study the remaining chromosomes. The grant consisted of 11 research groups, with three of these groups from Europe. In addition, Glaxo and the NIDDK Phoenix Epidemiology and Clinical Research Branch continues to participate, but does not receive compensation from the grant. The application was converted to a U01 to allow for staff involvement and more flexibility in funding. The grant was awarded in August 1999.

Research Goals and Scope

The transmission of complex phenotypes such as type 2 diabetes is likely to reflect the actions and interactions of multiple genetic and environmental factors. Linkage studies designed to localize genes for type 2 diabetes have yield few regions with highly significant evidence for linkage and fewer still that have been replicated in additional studies. While it is widely recognized that increasing the size of the sample included in linkage studies will provide the power to detect and localize susceptibility loci with modesty or moderate effects, collection of family data is the most expensive and time-consuming aspect of linkage studies. In an effort to maximize the utility of data that already have been collected to map genes for type 2 diabetes, The International Type 2 Diabetes Linkage Analysis Consortium has been formed to combine existing data sets for linkage analysis. In addition, the availability of a large number of samples allows for analysis of individual ethnic groups for predominant diabetes susceptibility genes. Although the Consortium data sets provide data to analyze most ethnic groups, there is a deficiency of African American samples. Two additional sets of DNA samples from African Americans with diabetes have been genotyped by CIDR. These data will be combined with the GENNID sample and analyzed to identify diabetes genes in the African American population.

Combining data from 26 groups have shown that several datasets demonstrate evidence for a diabetes susceptibility gene on chromosome 1q. The populations that showed evidence for linkage are the Pima Indians, Utah Caucasians, Amish, U.K. Caucasians and French Caucasians. In order to further study this region, a subcommittee consisting of these groups has been formed. The goal of this subcommittee is to fine map the putative type 2 diabetes susceptibility gene on chromosome 1q by linkage disequilibrium mapping using SNPs. Linkage disequilibrium would provide further evidence of a diabetes susceptibility gene.

Timeline: FY 2002

Performance Measures: The performance measures will include the number of African Americans enrolled, and the success in obtaining appropriate samples for genetic linkage studies.

Outcome Measures: The extent to which the results of the research from the consortium will aid in the diagnosis of genetic diseases in minority populations, and the number and quality of publications resulting from these studies.

DIABETES-FOCUSED SCIENCE EDUCATION IN TRIBAL MIDDLE AND HIGH SCHOOLS (RFA DK-02-030)

Background

It is the overall objective of this trans-NIDDK initiative to support faculty at Tribal Colleges and Universities (TCUs) to develop science education programs working with tribal community middle and high schools. It is the intention of this initiative to increase the presence of American Indians in the biomedical sciences by exposing and motivating American Indian students to biomedical science through the prism of diabetes.

The 33 existing TCUs are fully engaged in serving and strengthening local communities. They routinely provide assistance to Indian communities on various programs and projects and are deeply integrated into tribal culture and institutional life. The colleges serve as culturally supportive role models for future success in communities of historically low levels of educational attainment. An association between Tribal Colleges and local schools already exists through the Tribal College Rural Systemic Initiative. This program is part of the Rural Systemic Initiatives in Science, Mathematics and Technology Education Program funded by the National Science Foundation and designed to promote excellence in the teaching of the sciences. The Diabetes-Focused Science Education in Tribal Middle and High Schools program would utilize these existing collaborations to design, test and implement a biomedical science education program around diabetes. The outcome would be increased awareness of diabetes and its risk factors and the role of science in the attainment of health and a healthy lifestyle in a population overburdened with diabetes and its devastating health outcomes. This awareness would be used as the motivational focus for students selecting their future career paths.

Research Goals and Scope

This trans-NIDDK initiative aims to increase the interest and competitiveness of American Indian students in elementary, middle and high schools in the pursuit of biomedical careers.

Timeline: The planning grant is for one year, FY2002. The subsequent initiative timeline is for FY 2003 - FY 2008.

Performance Measures: The performance measures include the number of centers funded, the quality of proposals, and level of funding.

Outcome Measures: The extent to which the results of this initiative alters health behavior, increase recruitment of Native American youth to biomedical research career, and increase awareness of diabetes in the Native American youth population.

TRANSLATIONAL RESEARCH FOR THE PREVENTION AND CONTROL OF DIABETES (PA-01-069)

Background

The Diabetes Control and Complications Trial (DCCT), for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), for type 2 diabetes, established the importance of intensified diabetes control in dramatically reducing the devastating complications that result from poorly controlled diabetes. Both the DCCT and the UKPDS demonstrated the efficacy of intensified glucose control in reducing the risk for the microvascular complications of diabetes, such as retinopathy, neuropathy, and nephropathy. In addition, results from the UKPDS suggested that strokes may be reduced in patients with type 2 diabetes through a combined regimen of intensive blood pressure and glycemic control. Unfortunately, the advances of these studies have not been successfully incorporated into general health care practice. This underutilization of current knowledge was highlighted in a recent study of diabetic individuals that demonstrated a low frequency of self-monitoring of blood glucose, good glycemic control, regular foot care, and ophthalmic examinations, all of which markedly reduce the incidence and progression of diabetic complications. Alarmingly, less than 2 percent of adults with diabetes receive the level of care that has been recommended by the American Diabetes Association (ADA), with self-monitoring of blood glucose following the ADA guidelines performed by only one in five adults with diabetes. Thus, it is clear that effective mechanisms for diabetes treatment, shown by the DCCT and the UKPDS to reduce the burden of diabetes, are not being implemented.

Ongoing clinical trials are underway that address the prevention of type 1 or type 2 diabetes (e.g., DPT-1 and DPP). The DPP has concluded its randomized intervention phase early, and the results demonstrate that both lifestyle and pharmacologic treatments can significantly reduce the onset of type 2 diabetes in a high-risk population. This important finding will make it even more crucial that effective translation strategies be developed and adopted to improve adherence to accepted standards of diabetes care, and to overcome barriers to the translation of scientific advances into clinical practice.

This Program Announcement (PA) solicits research in the translation of recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk. This PA establishes a diabetes prevention and control program, and seeks applications for clinical and behavioral studies to develop and test strategies for: (1) achieving objectives that have already been proven beneficial, such as control of glycemia and other risk factors for diabetic complications; or (2) enhancing behaviors that are expected to improve health outcomes for individuals with type 1 or type 2 diabetes. Of particular interest are interventions that focus on translating new advances into practice in underserved and minority populations.

Research Goals and Scope

This PA solicits applications furthering research in diabetes translation research. Trials proposed under this program should test: (1) improved methods of health care delivery to patients with or at risk of diabetes; (2) improved methods of diabetes self-management; and (3) cost effective community-based strategies to promote healthy lifestyles that will reduce the risk of diabetes and

obesity. Generally, these studies will take interventions that have been demonstrated to be beneficial by controlled laboratory or clinical investigations (e.g., intensive glycemic control), and extend or adapt these interventions to larger populations or other settings. Alternatively, trials may focus on enhancing behaviors (e.g., increased physical activity in individuals at risk for diabetes) generally accepted as likely to improve health outcomes for patients with or at risk of diabetes.

Timeline: FY 2001 - FY 2006

Performance Measures: The performance measures will include the number of grants funded, the quality of proposals, and the level of funding.

Outcome Measures: The outcome measures will include success in the translation of the results into policy regarding diagnosis, prevention and treatment of type 1 and type 2 diabetics.

Research Area of Focus: Obesity

LOOK AHEAD: ACTION FOR HEALTH IN DIABETES (formerly SHOW-LOSS ANCILLARY STUDIES (RFA DK-00-017)

Background

Numerous studies have demonstrated the beneficial impact of short-term weight loss on risk factors such as dyslipidemia, hyperinsulinemia, hypertension, and elevated plasma glucose. Based on long-term epidemiological evidence of the health hazards of overweight and obesity and on shorter term clinical trial evidence, public health policy recommends weight loss for obese individuals (body mass index [BMI] 30 or above) or overweight individuals (BMI 25.0 to 29.9) with one or more additional co-morbidities.

Currently in the U.S., 40 percent of women and 25 percent of men are attempting to lose weight, using a variety of means. Despite this fact, few studies have examined the health effects of intentional weight loss over a period greater than one year and very few beyond four years. Moreover, several major observational studies show a significant association between weight loss and mortality that persists even after attempts to correct for confounding factors (e.g., smoking or pre-existing illness). However, most of these observational studies are unable to distinguish between voluntary and involuntary weight loss.

The Look AHEAD trial is a multi-center clinical trial to investigate the benefits and risks of interventions designed to sustain weight loss over the long term. The Look AHEAD trial is currently in the design phase, and is expected to begin enrollment in spring of 2001. The study will enroll 6,000 overweight patients with type 2 diabetes over a period of three years, randomizing them to either standard medical (community) care or intensive life-style modification that may include pharmacological therapy. Long-term health benefits will be monitored; with the primary endpoint being combined cardiovascular deaths (including fatal myocardial infarction and stroke), non-fatal myocardial infarction, and non-fatal stroke.

A Request for Applications (RFA) for "Ancillary Studies in Conjunction with Look AHEAD" was released on August 2, 2000 for funding in FY 2001. This RFA solicits R01 grants to take advantage of the availability of such a well-described and diverse population of obese individuals with type 2 diabetes undergoing long-term weight loss interventions. The National Heart, Lung and Blood Institute, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Nursing Research, and National Institute of Dental and Craniofacial Research cosponsor the RFA. Applicants are encouraged to propose studies that investigate health disparities in subpopulations defined by variables such as ethnicity/race, gender, or socioeconomic status.

Research Goals and Scope
The purpose of this initiative is to solicit applications for a range of basic, clinical, and behavioral ancillary research studies that are consistent with the aims of Look AHEAD. These ancillary studies can enhance investigation of the response of the various participants' characteristics to weight loss interventions, the impact of weight loss interventions on obesity-related comorbid conditions, the relationship of genetic factors to these responses, and the psychosocial correlates or determinants of behavior change. In addition, the Look AHEAD cohort may offer the opportunity for ancillary studies to examine the incidence or progression of obesity-related pathological conditions in populations in which additional study is needed, to identify biomarkers for disease risk, and to investigate relatively rare or understudied obesity-related conditions in this large sample.

Examples of research topics considered responsive to this RFA include, but are not limited to:

A. Genetic Studies, such as: mutation and polymorphism detection and genotype/phenotype association studies.

B. Metabolic/Physiological studies, such as: substrate utilization as a function of treatment/weight loss; lipid metabolism and kinetics; insulin action and glucose disposal; modulation of inflammatory markers/mediators; left ventricular mass or function; and effects of hormonal status on response to intervention.

C. Natural History of Co-morbid Conditions or Impact of Interventions on Conditions such as: sleep apnea; diabetic eye disease; urologic and renal disease; non-alcoholic steatohepatitis; osteoporosis/bone density; osteoarthritis; periodontal disease; and sub clinical cardiovascular disease measures.

D. Psychosocial, Behavioral, and Economic Correlates or Predictors in research areas such as: health and/or physiological outcomes; long term weight maintenance; eating behaviors; psychopathology; diet and physical activity; and changes and adherence to medications.

E. Measures and Methodology Studies such as: body composition measures other than total fat and fat free mass; objective measures of diet or physical activity complementary to those proposed for SHOW; measures of sub clinical disease; and measures of medication adherence.

Timeline: FY 2002 - FY2012

Performance Measures: The performance measures will include the number of participants screened and randomized.

Outcome Measures: The outcome measures will include success in alteration of clinical practice regarding prevention and treatment of obesity and type 2 diabetes.

ENVIRONMENTAL APPROACHES TO THE PREVENTION OF OBESITY

Background

Obesity is the most common nutritional disorder in the U.S., and its prevalence is increasing in both children and adults. Minority populations, particularly African American, Hispanic, and Native American women, are disproportionately affected. Although genetic factors are believed to contribute substantially to the predisposition towards obesity, environmental factors play an important role. The dramatic increase in obesity prevalence over the past two decades is believed to be a consequence of environmental factors that favor increased energy intake along with decreased energy expenditure. It has been suggested that while genetic factors may account for a significant proportion of within-population variability in body weight, environmental factors may account for most variability in body weight between populations or over time. Genetic approaches will undoubtedly provide important insights into the control of body weight, which may eventually lead to improved efforts in prevention and treatment. However, it is unlikely that addressing genetic factors alone will overcome the substantial environmental pressures for over-consumption and sedentary behavior that currently affects Americans.

Environmental factors believed to play a role in the development of obesity include those that increase energy intake, such as advertisements for and low price of high-energy density foods, consumption of larger portion sizes, greater frequency of restaurant meals, and the use of more fast-foods and convenience foods. For infants, bottle-feeding may also increase energy intake relative to breastfeeding. Numerous environmental factors also lead to decreased energy expenditure. Work is more likely to be sedentary than in the past, with near universal use of automated equipment and electronic communications. At home, wireless phones, remote controls, and various labor saving devices for household chores also decrease physical activity. More time is spent using the computer, watching television, and playing video games, particularly among children and adolescents. At the same time, the number of schools requiring daily physical education has declined. Suburban communities often lack sidewalks, and lack of neighborhood resources make it difficult to walk even short distances to stores and recreation. Many individuals report difficulties going out to exercise because their neighborhoods are perceived as unsafe. In addition, children in day care or before and after school care often lack facilities to engage in, or adequate supervision for, active play.

Prevention of obesity is frequently attempted through educational approaches aimed at improving knowledge and motivation, with consequent presumed impact on individual lifestyle choices. Such approaches have been largely ineffective at preventing weight gain. Other prevention strategies have focused on changing individual behaviors related to dieting and physical activity, but have limited applicability to large populations. In contrast, environmental and policy approaches attempt to modify the environment in which such choices are made, rather

than relying on individual will. Policy approaches are environmental interventions that involve establishing social, economic, or legal structures within a formal governmental or non-governmental organization.

Environmental changes that reinforce factors supporting healthy lifestyles and reduce barriers to healthy lifestyles may also serve to diminish health disparities, as barriers may be more prevalent in disadvantaged and ethnic minority communities. Environmental approaches that modify the environment to promote healthful eating, increase physical activity, and decrease sedentary behaviors, offer the potential for safe and effective programs for obesity prevention that could be widely disseminated. The NIDDK will invite applications to study promising interventions that would target environmental factors that contribute to inappropriate weight gain in children, adolescents and adults. Investigators should collaborate with organizations/institutions such as schools, supermarkets, restaurants, religious organizations, recreation facilities, industry, governmental or community groups, worksites, and so forth, to develop approaches that, if successful, could potentially be translated into larger-scale interventions.

The need for an obesity prevention initiative has been recognized by a number of NIH advisory groups. In 1994, the National Task Force on Prevention and Treatment of Obesity developed a long-range plan focused on prevention of obesity and recently reaffirmed obesity prevention as a priority area for clinical research. The recently issued NHLBI/NIDDK Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults include a discussion of the importance of preventing obesity and suggestions for strategies to be attempted. This review includes recommendations for research on obesity prevention. The February 1998, NHLBI Report of the Task Force on Behavioral Research in Cardiovascular, Lung and Blood Health and Disease also has recommended development of obesity prevention research efforts. In December 2000, the Surgeon General held a listening session in an effort to develop a national action plan to combat overweight and obesity. The session identified obesity prevention as a critical target, and suggested that efforts focus on environmental factors, including the family and community, schools, work sites, the health care delivery system, and the media.

Research Goals and Scope

This RFA responds to the need for systematic studies of environmental approaches to the prevention of obesity. Although many environmental factors have been cited as contributing to obesity, there have been few controlled studies showing that changes in these environmental factors will prevent weight gain. The sponsoring organizations will encourage submission of grants for innovative studies with a goal of modifying the individual, family, group, or community environment such that inappropriate weight gain is prevented by improvements in diet, increases in physical activity, and/or decreases in sedentary behaviors. For purposes of this RFA, prevention of obesity includes the primary prevention of overweight and/or obesity, the prevention of additional weight gain or increase in body fat in those already overweight and/or obese, and prevention of weight regain following weight loss. However, studies of weight management programs or use of medications or dietary supplements to prevent weight gain are not appropriate. Applications should address: the content of the intervention (e.g., relative focus on aspects of diet, physical activity, sedentary behaviors, combinations of these, or other factors), the setting of the intervention (e.g., in health care settings, community groups, recreation facilities, home, school), and the method of intervention delivery (e.g., individual, family, group,

community). Applications targeting groups or populations at high risk for the development of obesity will be encouraged.

Timeline: FY 2002 - FY 2007

Performance Measures: The performance measures will include the number of grants funded, the quality of proposals, and the level of funding.

Outcome Measures: The outcome measures include successful modification of the environment to promote healthful eating, increased physical activity, and decrease sedentary behaviors, and the potential for safe and effective programs for obesity prevention.

PATHOPHYSIOLOGIC MECHANISMS OF OBESITY-ASSOCIATED CARDIOVASCULAR DISEASE

Background

The adult U.S. population, whose prevalence of overweight and obesity now exceeds 50 percent, is experiencing a mass exposure to obesity-related cardiovascular risk factors and will suffer the inevitable clinical consequences in years to come. Also alarming are the ever-rising rates of overweight and obesity in children and adolescents. Increased rates of non-insulin dependent diabetes mellitus (type 2 diabetes) and evidence of increased risk of hepatic damage in overweight adolescents make it clear that children are not protected from the metabolic perturbations that accompany excess adipose tissue stores; we do not know what the consequences might be for a still-developing cardiovascular system if obesity is present during growth and maturation.

Overweight or obese individuals experience greatly elevated morbidity and mortality from nearly all of the common cardiovascular diseases (stroke, coronary heart disease, congestive heart failure, cardiomyopathy, and possibly arrhythmia/sudden death). This is partly attributable to co-morbidities (type 2 diabetes, insulin resistance, hypertension, dyslipidemias, and sleep apnea). The residual independent effects of obesity on cardiovascular risk, however, also suggest a role for less well-characterized mediators such as sleep-disordered breathing and other causes of chronic sleep loss. Because primary treatment and prevention of obesity often fail or are only partially successful, there will be increasing demands to treat the cardiovascular conditions attributable to obesity. In order to develop rational therapeutic approaches, it is necessary to understand the basic biology of obesity-related cardiovascular disease.

Emphasis will be placed on linking current knowledge of adipocyte and adipose tissue metabolism and function with cardiac and vascular biology or sleep regulation. Major areas needing further research and clarification include: (1) the role of adipose tissue as a pro-inflammatory secretory organ affecting multiple components of the cardiovascular system (e.g., blood pressure, lipid metabolism, vascular reactivity, myocardial metabolism, and clotting and inflammatory pathways) at every level of biological organization; (2) lipid infiltration (i.e., lipotoxicity) as a novel pathophysiologic mechanism; (3) cardiovascular, respiratory, and sleep neurobiology during obesity; (4) the impact of excessive adipose tissue burden on the final maturation of the cardiovascular system in young animals; (5) the specific pathophysiology of

obesity cardiomyopathy; and (6) complex interactions between chronic sleep loss, hypertension, insulin resistance, and other endocrine dysregulation syndromes.

In addition, important knowledge gaps continue to exist for many "classical" risk factors, as well. For example, the exact mechanism by which hyperinsulinemia contributes to cardiovascular disease is not well understood, but it cannot simply be explained by an association between insulin resistance and other known risk factors (e.g., dyslipidemia). Innovative approaches to understanding the molecular mechanisms by which insulin resistance and hyperinsulinemia cause endothelial dysfunction will contribute to understanding the pathophysiology of obesity-associated cardiovascular disease.

The purpose of this initiative is to stimulate new research approaches to clarify the biologic basis of various obesity-related cardiovascular diseases, including atherosclerosis, cardiomyopathies, heart failure, arrhythmia/sudden death, and sleep-disordered breathing (sleep apnea). Funds would support basic and clinical mechanistic studies and the development of needed research resources.

Research Goals and Scope
Novel experimental approaches taking advantage of the cardiovascular and respiratory dimensions of genetic and experimental models of obesity would be encouraged. New animal models are needed, including immature and growing animals. Distinct lean and obese phenotypes, and other well-defined intermediate phenotypes, in humans and large animals also may have high utility for mechanistic studies. In addition, new methodologies such as microarray technology and targeted gene expression may help speed the search for markers that predict disease, track its development, or influence treatment outcomes.

The budget for this program is structured to provide funds primarily for regular research project grants. In addition, it is envisioned that several projects could encompass the development of resources needed to advance the field; these resources would be supported with the provision that they be made readily available to other researchers. Costs for such approved research resource components would be provided on a scale up to that of the main project.

Timeline: FY2003 - FY 2006

Performance Measures: The performance measures will include the number of grants, the quality of proposals, and the funding level of this initiative.

Outcome Measures: The outcome measures include the number and quality of publications resulting from the studies, and successful development of new diagnostic, preventive, and therapeutic measures.

Research Area of Focus: End-Stage Renal Disease

FAMILY INVESTIGATION OF NEPHROPATHY AND DIABETES: INCREASE MINORITY RECRUITMENT

Background

Kidney disease has a disproportionate impact on minority populations, especially African Americans and Native Americans. In 1996, the point prevalence rates of ESRD per million population, (adjusted for age and sex) were 3,404 in African Americans and 2,761 in Native Americans/Alaska Natives, compared to 754 in Caucasians, differences of 4.5 and 3.7 fold, respectively. African Americans develop end-stage renal failure at an earlier age than Caucasians; their mean age at ESRD incidence was 55.8 years compared with 62.2 in Caucasians. African Americans constitute almost 30 percent of prevalent ESRD patients, yet constitute only 12.6 percent of the U.S. population.

The FIND study was funded as a Cooperative Agreement (UO1) as the result of RFA DK-99-005. The aims of the FIND consortium are to identify genetic loci and ultimately genes that influence susceptibility and severity of diabetic nephropathy in Caucasian, African American, Hispanic, and Native American populations across the U.S. The Study Consortium consists of eight Participating Investigative Centers (PICs) and a Genetic Analysis and Data Coordinating Center. The External Advisory Committee for FIND has expressed concern that the susceptibility genes may differ in these sub-population groups, and that the sample size projected for African Americans may not offer adequate power to address analyses in this group. Given the high susceptibility of African Americans to kidney disease and the substantial health burden on this population, increased emphasis on this population was felt to be appropriate.

Research Goals and Scope

Several of the FIND participating investigative centers are able to expand minority recruitment by developing affiliations with minority institutions or inner city dialysis clinics. Complementary studies in the AASK clinical trial population are also proposed. This population is comprised of approximately 1,000 African American patients with renal insufficiency, most subjects with hypertensive nephrosclerosis. In this population, phenotypic parameters such as rates of progression of nephropathy and response to treatment are well characterized. Genetic analyses in this population will provide a comparison sample for analyses on diabetic nephropathy in patient populations of different ethnic backgrounds. Both family-based and mapping by admixture linkage disequilibrium approaches are planned.

Timeline: FY2001

Performance Measures: The performance measures will include the total number of African Americans recruited into the FIND study.

Outcome Measures: The outcome measures will include successful recruitment of African Americans into the FIND study.

PROSPECTIVE COHORT STUDY OF CHRONIC RENAL INSUFFICIENCY

Background

End-stage renal disease (ESRD) is an important medical and public health problem in the U.S. that disproportionately affects racial and ethnic minority groups. The increase in the number of ESRD patients is due mainly to an increase in the number of patients with renal disease caused by diabetes. In patients with ESRD, cardiovascular disease is the leading cause of death, and a better understanding of the risk factors for this disease burden is required before interventions can be evaluated and implemented. While numerous epidemiological studies have been conducted in patients with ESRD leading to improved care and better quality of life, few studies have been performed in patients with chronic renal disease prior to reaching ESRD, during a period of chronic renal insufficiency. Of the small number of studies conducted, all of them have significant methodological shortcomings. Thus, our knowledge about the factors that influence decline in renal function and development of cardiovascular disease in patients with chronic renal insufficiency is rudimentary.

Prospective cohort studies have played an important role in defining risk factors for a wide range of diseases and it is envisioned that data and patient specimens obtained from this cohort study will serve as a national resource for investigations of chronic renal disease and cardiovascular disease.

Research Goals and Scope

The objective of this RFA is to establish a prospective, multi-ethnic, and racial cohort study of approximately 3,000 patients with chronic renal insufficiency to determine the risk factors for rapid decline in renal function and development of cardiovascular disease. Establishing a cohort of patients with chronic renal insufficiency, with cause of renal disease similar to that observed in the U.S. ESRD patient population, and following them prospectively will also provide an opportunity to examine genetic, environmental, behavioral, nutritional, quality of life, and health resource utilization factors in this patient population.

Timeline: FY2001 - FY 2006

Performance Measures: The performance measures will include the total number of grants awarded, the quality of centers funded, the number of patients successfully recruited, and the funding level.

Outcome Measures: The outcome measures include the extent to which the results from the study alter clinical practice, including the diagnosis, prevention and treatment of renal diseases.

AASK COHORT STUDY

Background

African Americans are disproportionately afflicted with end-stage renal disease (ESRD). They constitute approximately 12 percent of the U.S. population but comprise 32 percent of the prevalent ESRD population. Diabetes mellitus is the predominant cause of ESRD in the U.S. population. In African Americans, especially, hypertension is a major cause of ESRD. In 1990,

the NIDDK launched an initiative to investigate the underlying cause of hypertensive kidney disease and to study mechanisms that could slow its progression in African Americans. The clinical trial, "African American Study of Kidney Disease and Hypertension" (AASK), was initiated to investigate whether a specific class of antihypertensive agents (beta-adrenergic blockers, calcium channel blockers, or angiotensin converting enzyme inhibitors), and/or the level of blood pressure (mean arterial pressure [MAP] of 102-107 mm Hg or MAP of 92 mm Hg) would influence progression of hypertensive kidney disease in African Americans.

After a brief pilot study (1992-1994), 20 clinical centers and a data coordinating center were funded to carry out the full-scale clinical trial in 1994. The 21st clinical center was added in June 1996. As in the pilot clinical trial, all four historically black medical schools are funded to participate in the full-scale trial. The centers required nine months to revise the protocol for the full-scale trial, and participant recruitment and randomization began in April 1995. The intervention component is scheduled to end in March 2002, and the primary analysis of the study results to conclude in June 2002. The cohort study will commence at the conclusion of the intervention study. The investigators at the clinical and data coordinating centers and the program staff at the NIDDK have been meeting and discussing the format of the "After-AASK" Cohort Study during the past three months. The team will complete design of the study within the next four months.

Research Goals and Scope

The AASK cohort will continue to be followed at the clinical centers; however, some patients at centers with a small number of participants will be followed at a nearby larger participating center. In some instances, some of the smaller centers may be asked to recruit additional African Americans with hypertensive kidney disease to augment the patient population at the center. The patients will be provided with the usual clinical care given to all such patients at the respective centers. Baseline demographic information, selected laboratory tests, and other studies will be obtained at the initiation of the Cohort Study. Patients will be seen quarterly at the centers, and some selected studies will be done at these visits. Samples will be obtained and stored for additional studies and analyses at a later date. The protocol used in the AASK Cohort Study will be similar to that proposed for the new Chronic Renal Insufficiency Cohort (CRIC) study to be initiated by mid- to late 2002 to permit ultimate integration and comparison of the two data sets.

Timeline: FY2002 - FY 2007

Performance Measures: The performance measures will include the total number of patients successfully recruited into the cohort study, a successful cohort protocol, and the funding level.

Outcome Measures: The outcome measures will include the extent of which the results from the cohort study strengthen clinical practice in the diagnosis, prevention and treatment of hypertensive renal disease in African Americans.

MINORITY ORGAN AND TISSUE DONATION PROGRAM (RFA DK-02-019)

Background

Racial and ethnic minorities, particularly African Americans, American Indians, Alaskan Natives, and Hispanic Americans, are disproportionately afflicted with end-stage renal disease (ESRD). Although transplantation is the preferred renal replacement therapy because it improves survival and quality of life for successful transplant recipients, these racial and ethnic minority groups are less often transplanted. A frequently cited reason is that the organ donation rate for minority groups is much lower than their representation in the ESRD patient population. With an increased number of organs from minority groups in the pool, there would be a better match, and ultimately, better graft survival for minority patients.

Over the past five to eight years, several programs have been initiated to increase organ and tissue donation in minority groups. The NCMHD/NIDDK-funded MOTTEP program was established, in which intensive educational and information activities have occurred in 15 cities across the U.S. During the same period, the Department of Health and Human Services intensified educational and information programs throughout the U.S. through the Organ and Tissue Donation initiative. Perhaps as the result of these combined efforts, organ and tissue donation has increased, especially in the minority communities. However, the rate of organ and tissue donation from minorities is lower than their representation in the population with organ failure, especially ESRD. By increasing the educational activities in other minority communities, this will enhance minority organs in the pool, and hence increase the chances of a better match and improved graft survival.

Several potential grantees have been in contact with NIDDK program directors and have expressed their wishes to participate in the educational process, especially in minority communities.

Research Goals and Scope

The purpose of this initiative is to create an environment supportive of organ donation by

- Increasing exposure to donation messages and to opportunities to express donation commitments. This could be accomplished through increasing exposure in national and local media; increasing community interventions (at schools, churches, etc.); increasing promotion of organ donation through health promotion and disease prevention efforts; and disseminating and replicating best practices identified through research and evaluation.
- Evaluating the impact of increased support for living organ donation (e.g., provisions to cover child care, travel, and other expenses for living donors).
- Increasing minority cadaveric and living organ donation.
- Increasing donation from non-traditional donors (e.g., older donors and living donors).

Timeline: FY2002 - FY 2007

Performance Measures: The performance measures will include the total number of centers funded, the quality of proposals, and the level of funding.

Outcome Measures: The outcome measures will include the successful increase in the number of organs and tissues donated by the racial/ethnic minority groups.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) IN CHILDREN AND YOUNG ADULTS INTERVENTIONAL STUDY

Background

FSGS is a common, irreversible process that results in steroid-resistant nephrotic syndrome. It often appears as a primary condition, with a propensity for an unfavorable outcome—risk of progression to end-stage renal disease (ESRD). FSGS is one of the most common recurrent diseases post transplant in children, resulting in allograft injury (20 to 30 percent), or graft loss (40 to 50 percent). The peak incidence is in pre-school age children, with males more often affected (2:1). The worst prognosis is observed in African American children. Steroid therapy (i.e., prednisolone or, lately, deflazacort) has been used to treat children with FSGS; the response is unpredictable. Limited data suggest that alternative therapy with alkylating agents (i.e., cyclophosphamide or chlorambucil) or with immunosuppressive agents (i.e., levamisole or CsA) may be beneficial in reducing relapses, reducing proteinuria, and perhaps arresting disease progression.

Non-selective proteinuria, ascribed as contributing to tubulo-interstitial damage and progression of renal disease, is considered both a marker of glomerular injury and a risk factor for progression. The localization of the gene for the rare inherited type of FSGS to *1q25-q31* has helped to define one distinct subset of the disease.

A task force to gather information on the criteria for, and nature of, interventions for a clinical trial was convened jointly by the NIDDK and the American Society of Pediatric Nephrology in November 2000. This initiative is based on the recommendations of this group.

Research Goals and Scope

A prospective, randomized, multi-center clinical trial examining the impact of immuno-modulatory therapy on proteinuria is proposed. The needed sample size is estimated at approximately 300 patients enrolled over a three-year period and followed for approximately 24 months. If successful, the results of the clinical trial will guide physicians in providing the safest and most efficient care for children with FSGS.

Timeline: FY2002 - FY 2007

Performance Measures: The performance measures will include the total number of grants awarded, the quality of centers funded, the number of patients successfully recruited, and the funding level.

Outcome Measures: The outcome measures will include the improvement in clinical practice in the diagnosis, prevention and treatment of FSGS, especially in minority children and young adults.

CHRONIC HEPATITIS C IN AFRICAN AMERICANS: STUDY OF RESISTANCE TO ANTIVIRAL THERAPY IN CHRONIC HEPATITIS C (VIRAHEP-C)

Background

The hepatitis C virus (HCV) is probably the major cause of cirrhosis and end-stage liver disease in the U.S.--accounting for 8,000 to10,000 deaths per year and at least 30 percent of all liver transplants done in adults in the U.S. Hepatitis C is two- to three-fold more common among African Americans than non-Hispanic Caucasians. The current optimal therapy of chronic hepatitis C is a combination of alpha interferon and ribavirin given for 24 to 48 weeks. Retrospective analyses of studies of antiviral therapy have shown that response rates are two- to three-fold less among African American patients than among non-Hispanic Caucasians with hepatitis C. The reasons for this difference are not clear, but may be due to viral strain or genotype, immunological factors, or genetic differences in interferon signaling and response pathways. Unfortunately, studies of antiviral therapy have included too few African American patients to provide reliable estimates of the response rate to current therapies or to analyze factors responsible for a lack of effect of therapy. Better information is needed, to help improve response rates among African Americans as well as to provide valid clinical recommendations for treatment.

A Request for Applications (RFA) was released in September 2000 for an interlocking set of cooperative agreements to design and implement a study of the frequency, pattern, nature and cause of antiviral resistance in chronic hepatitis C, focusing upon a cohort of African Americans among whom such resistance is common.

Research Goals and Scope

The proposed study includes a cooperative agreement will call for applications for eight clinical centers, four ancillary research studies, and a data coordinating center. The investigators will develop a detailed clinical protocol and strategies for analysis of the mechanism of antiviral effect and resistance to alpha interferon in chronic hepatitis C. During the study itself, each clinical center will enroll and treat 50 patients (25 African Americans and 25 non-Hispanic Caucasians) with chronic hepatitis C using the optimal regimen of therapy. Samples will be collected for the ancillary investigations of virological, cell signaling, immunological and genetic factors that may play a role in antiviral resistance in hepatitis C. The research goals will be to address five research questions: (1) Are there differences in sustained virological response rates among African Americans and non-Hispanic Caucasians? (2) What factors predict a response in both groups and are they different? (3) Do the early viral kinetics predict ultimate outcome of therapy? (4) Can a simple, clinically useful algorithm be developed to guide clinical decision-making in therapy for both African American and non-Hispanic Caucasians? (5) What are the virological, immunological, genetic and pharmacokinetic causes of viral resistance to combination therapy in chronic hepatitis C?

Timeline: FY2001 - FY 2006

Performance Measures: The performance measures to demonstrate that the objectives have been met will include the total number of grants awarded, the quality of proposals funded, the number of patients successfully recruited, and the funding level.

Outcome Measures: The outcome measures will include the extent to which the results alter clinical practice, including the diagnosis and treatment of Hepatitis C in African Americans.

HEPATITIS C ANTIVIRAL LONG-TERM TREATMENT AGAINST CIRRHOSIS (HALT-C) TRIAL, ENHANCE MINORITY RECRUITMENT (40% MINORITY ENROLLMENT)

Background

Therapy for hepatitis C, although improving, is ineffective in "curing" the infection (eradicating hepatitis C virus) in about 70% of treated individuals. Among African-Americans, response to treatment is even more dismal, since 90%-95% fail to respond. The reason(s) for the poor response rate among African-Americans is presently unclear. Recent treatment studies suggest that interferon may have both an antiviral and anti-fibrotic action. Studies from both Japan and the United States have suggested that interferon treatment reduces progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma even if it does not eradicate the virus.

NIDDK plans to enhance the minority recruitment of HALT-C clinical trial, a seven year study of therapy for hepatitis C focusing on patients with advanced disease (with severe fibrosis or cirrhosis) who have not responded to conventional therapy and for whom there are no other practical options available. Patients are randomly assigned to receive long-term treatment with pegylated interferon (a once weekly injection) or no therapy. Patients will be intensively studied for both beneficial and adverse effects, supplemented by ten separately funded ancillary studies. This trial is designed to enroll over 1200 patients, with enrollment scheduled to be completed by December 2002.

Research Goals and Scope

The purpose of this project is to determine the following: 1) if 4 years of interferon therapy will prevent progression of advanced fibrosis to cirrhosis in patients with chronic hepatitis C who failed previous interferon therapy; 2) if 4 years of interferon therapy in patients with cirrhosis secondary to chronic hepatitis C who failed previous interferon therapy will: a) reduce the risk of developing hepatic decompensation; b) reduce the need for hepatic transplantation; c) reduce the risk of developing hepatocellular carcinoma; and 3) if 4 years of interferon therapy will improve the quality of life in patients with advanced fibrosis secondary to chronic hepatitis C who failed previous interferon therapy.

Timeline: FY 2002 - FY 2006

Performance Measure: The performance measures to demonstrate that the objectives have been met will include the total number of grants awarded, the quality of proposals funded, the number of minority enrollment, and the funding level.

Outcome Measure: The outcome measures will include the extent to which the results alter clinical practice, including the diagnosis and treatment of Hepatitis C in African Americans.

CLINICAL RESEARCH NETWORK IN NON-ALCOHOLIC STEATOHEPATITIS (RFA DK-01-025)

Background

NASH is a common but poorly understood liver disease that is characterized by accumulation of fat in the liver (steatosis), accompanied by inflammation, cell injury and fibrosis (hepatitis) that closely resembles alcoholic liver disease but occurs in patients who drink little or no alcohol. NASH is most common in adults above the age of 40 who are overweight or have diabetes, insulin resistance or hyperlipidemia. However, the disease also occurs in children and in persons who are not obese or diabetic. Currently, there are no effective therapies for NASH and its natural history and prognosis are not well understood.

A Request for Applications (RFA) was released on February 12, 2001, to form an interlocking network of cooperative agreements to design and implement a database and clinical research network to study the etiology, contributing factors, natural history, complications, and therapy of non-alcoholic steatohepatitis (NASH). Cooperative agreements will be awarded to six clinical centers and a data coordinating center to establish a large clinical cohort of patients with NASH to be followed in a natural history study and undergo clinical investigations as to the etiology and contributing factors for development and worsening of this disease. The network is intended to provide a mechanism that will facilitate and perform clinical, epidemiological and therapeutic research in NASH.

Research Goals and Scope

Six clinical centers and a data-coordinating center will form the NASH Clinical Research Network. The initial focus will be the development of a clinical database of patients with NASH and the development of common definitions, nomenclature and terms for the clinical diagnosis and staging of NASH. The database will be designed to address specific questions and to provide appropriate reagents or patient populations for clinical or laboratory investigation. The NASH Clinical Network is intended to provide the preliminary data and background for further investigator-initiated research and is expected to interact with basic and laboratory research investigators with interest in these diseases by providing reagents, specimens or opportunities to assess hypotheses on the pathogenesis, prevention or treatment of the disease. The Clinical Research Network will also establish pilot studies of promising therapeutic approaches and when appropriate, full scale clinical trials of therapies for NASH.

Timeline: FY2002 - FY 2005 and beyond.

Performance Measures: The performance measures will include the total number of grants awarded, the quality of the proposals, the number of patients successfully recruited, and the funding level.

Outcome Measures: The outcome measures will include the extent to which the results alter clinical practice, including diagnosis, prevention and treatment of non-alcoholic steatohepatitis.

Research Area of Focus: AIDS

LIVER AND PANCREATIC DISEASE IN HIV INFECTION (PA-01-117)

Background
The current initiative specifically targets hepatic and pancreatic comorbidities in the context of HIV infection, and metabolic complications of antiretroviral treatment in support of basic and clinical research that addresses the significant emerging clinical issues of disease progression in patients with HIV infection.

Highly active antiretroviral therapy (HAART) has slowed the progression of HIV disease and decreased the rate of HIV-associated mortality. In the context of enhanced longevity for HIV patients, other co-morbidities, such as chronic liver disease and pancreatitis, can assume greater importance in the medical management of patients. Based on shared routes of transmission, HBV and HCV infection are common in HIV-infected patients. HIV infection has a significant effect on the natural history of HBV infection with co-infected individuals more likely to experience severe liver disease. Individuals treated with lamivudine as part of their antiretroviral treatment more frequently fail treatment, resulting in the emergence of drug resistant strains of HBV. Several studies have also documented that HIV modifies the natural history of chronic HCV infection leading to an accelerated course of progression to end-stage liver disease and death. The accelerated course to end-stage liver disease has been suggested to be reduced from the two to four decade time-frame for HCV mono-infection to as little as five to six years in HCV/HIV co-infected patients. The result of the common occurrence of hepatitis and HIV co-infection and accelerated disease progression is the report that end-stage liver disease is now the leading cause of death in hospitalized HIV-infected patients.

The etiology and pathogenesis of enhanced progression to end-stage liver disease in HIV co-infected patients is unknown. Recent data have shown that hepatitis co-infection results in enhanced liver disease in individuals infected with HIV through enhanced severity of fibrosis, a higher frequency of cirrhosis and end-stage liver disease as well as increased deaths due to liver disease. The role of HCV quasi species, the effects of immune deficiency on the course of hepatitis C, hepatotoxicity due to antiretroviral treatment, chronic HBV infection, immune restoration and HBV infection, and development of nonalcoholic steatohepatitis (NASH) as a result of lipodystrophy have all been hypothesized to play a role in the enhanced liver disease seen in co-infected individuals. Additional research is needed to identify the mechanism(s) of pathogenesis and to identify therapeutic targets for treatment.

This Program Announcement (PA) was published on July 17, 2001, and invites clinical and basic research applications that focus on the pathogenesis and therapeutics of the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. The co-infections targeted by this PA specifically include hepatitis B (HBV) and hepatitis C (HCV), which are frequent causes of end-stage liver disease, a leading cause of death in HIV infected patients. Metabolic complications,

involving the liver and pancreas, associated with the treatment of HIV infection include: hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis (NASH) and pancreatitis, which are all important causes of morbidity in patients with HIV infection. The proposed studies should advance our understanding of the pathogenesis of liver and pancreatic disease in patients with HIV and/or metabolic complications of therapy. These advances should lead to enhanced medical management of individuals infected with HIV.

Research Goals and Scope
This initiative will support basic and clinical research in HIV co-infection and metabolic disease related to antiretroviral treatment. Areas of interest include but are not limited to:

- The elucidation of biological mechanism(s) that promote enhanced progression of liver disease in HIV-infected patients.
- A further elucidation of drug-induced hepatotoxicity associated with anti-retroviral treatment regimens.
- The identification of therapeutic targets and/or novel therapies for the treatment of liver disease in HIV-infected patients.
- The elucidation of synergy between HIV and HCV, resulting in enhanced liver disease.
- The enhanced knowledge of antiviral treatment failures of HBV/HIV co-infection and the emergence of HBV drug-resistant strains.
- The identification of underlying liver disease, such as NASH, in combination with HIV infection and antiretroviral treatment, that progresses to end-stage liver disease.
- Therapeutics development for the enhanced medical management of patients with HBV/HIV or HCV/HIV co-infection or metabolic abnormalities due to antiretroviral treatment.
- Altered hepatic lipid metabolism due to antiretroviral treatment.
- HIV-associated pancreatitis and risk factors, including hypertriglyceridemia, obesity and gallstones.
- The impact of liver transplantation on disease progression in select patients with co-infection with Hepatitis B or Hepatitis C.

Timeline: FY2002 - FY 2007

Performance Measure: The performance measures will include the total number of grants awarded, the number of patients successfully recruited, and the funding level.

Outcome Measure: The Outcome Measures will include the extent to which the results alter clinical practice, including diagnosis, prevention and management of HIV patients with liver and pancreatic disease.

TREATMENT OF HAART-ASSOCIATED METABOLIC CHANGES IN PATIENTS WITH HIV INFECTION

Background
In recent years, the advent of highly active anti-retroviral therapy (HAART) has dramatically improved the survival of patients with HIV infection. Despite the clear benefits of the new anti-

retroviral therapies, HAART has been associated with a variety of metabolic complications—including dyslipidemia, insulin resistance and abnormal distribution of body fat (lipodystrophy). These metabolic abnormalities represent major risk factors for the development of other serious diseases, such as diabetes and cardiovascular disease. Even more recently, reports of clinically significant osteopenia have been emerging in HAART-treated patients.

Lipodystrophy, characterized by increased deposition of fat (lipohypertophy) in the abdomen and trunk, and/or loss of fat (lipoatrophy) in the face and extremities, appears to occur commonly in patients on HAART. Currently, it is not clear whether abdominal lipohypertophy is simply accompanied by peripheral lipoatrophy, or whether these changes constitute two separate entities. The lipodystrophic changes have been a particular issue for many affected individuals. In addition to concerns over potential long-term health implications of these body composition changes, distress over these often disfiguring changes has caused some patients to stop taking anti-viral medications.

HAART has also been increasingly associated with hyperinsulinemia and impaired glucose tolerance; to date, frank diabetes has been reportedly less frequently. However, concern about eventual progression to diabetes is real, particularly in those patients who also have accumulation of abdominal (particularly visceral) fat.

Patients receiving HAART frequently develop hypertriglyceridemia, which can be extreme, as well as hypercholesterolemia. Elevated total and LDL-cholesterol levels, which occur following the institution of HAART, may be superimposed on low HDL-cholesterol levels, which have been described in HIV-infected patients prior to initiating any therapy. In non-HIV-infected individuals, co-existence of dyslipidemia and insulin resistance/diabetes confers additive risk for the development of atherosclerotic heart disease, making these HAART-associated side effects a serious potential public health concern.

Large epidemiologic studies are currently ongoing to better describe the metabolic changes associated with HAART and understand whether particular drugs, or classes of drugs, are the etiologic agent(s) of these changes. In addition, a large research effort is aimed at understanding the molecular mechanism(s) by which anti-retroviral drugs might lead to these metabolic abnormalities. A long-term goal of such research might be the development of new, highly-active anti-HIV drugs that lack these adverse metabolic consequences.

In the meantime, it is essential to develop strategies to normalize lipid levels, insulin sensitivity and body fat distribution, and to minimize bone loss in order to enhance patient compliance and decrease the risk for future disease. The safety and efficacy of lipid lowering drugs or diabetes medications have not been extensively studied in patients infected with HIV and/or receiving HAART. It is not known whether adverse drug interactions might affect efficacy and safety, or whether the underlying infection with HIV (or other opportunistic infections), might affect treatment success. For example, the metabolism and clearance of some statins may be affected by concomitant use of protease inhibitors. Some available drugs (e.g., metformin, thiazolidinediones) will be contraindicated because of co-existing renal or liver disease in patients with AIDS. In addition, attention must be paid to other risk factors for diabetes and cardiovascular disease, such as smoking, physical inactivity, diet and hypertension.

An RFA will be issued in collaboration with the National Heart, Lung and Blood Institute to encourage applications to develop and test strategies for treating the metabolic complications associated with anti-retroviral drug therapy in patients with HIV infection.

Research Goals and Scope
This RFA solicits clinical studies to: (1) test the efficacy, in patients infected with HIV, of agents currently approved for the treatment of dyslipidemia, insulin resistance or diabetes, and Osteoporosis/osteopenia; and (2) develop and test novel treatment approaches to the metabolic consequences of anti-HIV therapy, including lipodystrophy.

Appropriate topics for investigation under this RFA would include: (1) studies to examine the effects of currently available pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia in the metabolic syndromes associated with HAART; (2) studies to identify potential drug interactions between HAART and current pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia; (3) studies to identify and test new therapies to prevent or reverse the metabolic complications associated with HAART; (4) studies to evaluate the efficacy of diet and exercise alone, or in combination with medication, in reversing dyslipidemia and insulin resistance/diabetes in patients on HAART; (5) studies to evaluate whether switching anti-HIV drugs is an effective approach to the treatment of metabolic changes; and (6) studies to test agents that affect fat deposition and/or metabolism for the treatment of HAART-associated lipodystrophy.

Timeline: FY2003 - FY2007

Performance Measure: The performance measures will include the number of grants awarded, the quality of proposals, and the level of funding.

Outcome Measures: The outcome measures will include successful improvement in clinical practice, including treatment approaches to the metabolic consequences of anti-HIV therapy.

SEMEN IN TRANSMISSION OF HIV

Background
HIV in semen is one the major factors in the development of the AIDS epidemic. Sexual contact with HIV seropositive men is a major route for transmission of HIV. Sources of HIV transmission in semen have been identified as both the free virus particles and infected cells. Confounding factors in the study of the biology of HIV in semen are the limited knowledge of the relationship among systemic host factors, the levels of potentially infectious HIV in the semen, and the immunology of the male urogenital tract. The anatomical origins and sources of HIV in the male genital tract have not been positively identified; neither have the effects of therapeutic interventions on HIV infectivity. This initiative is the outcome of a planning meeting convened in spring 2000 to review the state of knowledge and to develop a research plan.

Research Goals and Scope
The purpose of this initiative is to develop studies that will elucidate factors determining HIV transmission and shedding in the male genital tract. Other important research areas include: (1) elucidation of HIV infectivity in semen fractions; (2) relationship between the immunobiology of the male genital tract and HIV replication and infectivity; and (3) factors that influence HIV transmission through semen, such as genital tract inflammation.

Timeline: FY2002 - FY2006

Performance Measure: The performance measures will include the number of grants, the quality of proposals, and the level of funding.

Outcome Measures: The outcome measures will include utility of the results in alteration in clinical practice, including prevention of transmission of HIV.

Research Area of Focus: Diseases of the Prostate

MINORITY RECRUITMENT IN CHRONIC PROSTATITIS COHORT STUDY

Background
Diseases of the prostate are a major health care burden for men. There is strong documentation that cancer of the prostate has a higher incidence in African American men. Although it has been suggested that the other two diseases of the prostate, benign prostatic hyperplasia (BPH) and chronic prostatitis (CP), are also more prevalent in African American men, these data are controversial and not well documented. Finally, it is unclear whether prostatitis increases the risk of malignancy in African Americans. Accurate determination of the incidence and natural history of the three main diseases of the prostate in various racial and ethnic populations is essential if insights into etiology, genetic susceptibility, and even treatment strategies are to be effectively developed.

In 1997, the NIDDK established and funded the CPCRN. The purpose of this network was two-fold: (1) to develop and follow a cohort of patients, who meet the NIDDK definition of CP, which can be utilized to characterize the clinical and epidemiological characteristics of this disorder, and (2) to start innovative therapeutic interventions in persons who meet the criteria for CP.

The CPCRN consists of six clinical centers and a data-coordinating center. Currently the CPCRN is addressing the first aim of the network--to develop and follow longitudinally a cohort of patients who meet defined clinical criteria. Patient recruitment into the centers has been excellent and has met or exceeded the established goals. However, the percentage of non-Caucasian, minority patients into the cohort has been less than five percent. This small percentage will not allow valid statistical determination of characteristics of chronic prostatitis in minority males. The initial selection of centers was based on ability to recruit patients with CP, and not on ability to access minority populations. In order to significantly increase enrollment of minority men into the cohort, it will be necessary to add an additional clinical center that has a demonstrated large population of minority men.

The Chronic Prostatitis Collaborative Research Network (CPCRN) will be expanded by addition of new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis.

Research Goals and Scope
A clinical center located at the University of Mississippi in Jackson will be added to the CPCRN. This center has a large minority population and the principal investigator has a long-standing interest in the study of prostate diseases, including CP. Additional support will be provided to other centers with access to minority populations to provide support for personnel trained at minority recruitment. Patient recruitment at these clinical centers will significantly increase the enrollment of minority patients in the CPCRN cohort and allow for statistically significant data analyses.

Timeline: FY 1997 - 2005

Performance Measures: The performance measures will include the quality of proposals, the level of funding, and the total number of minority patients enrolled in this study.

Outcome Measures: The outcome measures will include the successful increase in the number of minority patients enrolled in the CPCRN cohort.

Infrastructure and Cross-Cutting Issues

CLINICAL RESEARCH TRAINING IN MINORITY SERVING INSTITUTION

Background
As part of the effort of the Department of Health and Human Services to eliminate racial and ethnic disparities in health, a need has been identified to expand the training of clinical research at Minority Servicing Institutions (MSIs) as one approach to fostering careers in clinical research addressing health disparities. MSIs conduct high quality programs for educating ethnic minorities, and they represent a rich resource of talent with the appropriate cultural sensitivity and perspectives needed in clinical research. However, MSIs have had difficulties developing and sustaining independent clinical research programs, and there is a paucity of ethnic minority clinical researchers who are pursuing successful clinical research careers. The NIDDK, ORMH, and NIAMS have teamed to promote the first step in fostering the development of curricula in clinical research leading to a masters degree in Clinical Research at MSIs through this one-year planning grant. This planning grant is seen as the first phase. The second phase, to be announced through an RFA in FY 2001, will provide support to assist in the actual development of the clinical research curriculum. The awards are planned for FY 2002.

Research Goals and Scope
The planning grant provided funds to enable MSIs to assess the resources; both at the home institution and potential affiliate institutions, for development of a masters degree curriculum in clinical research. The curriculum is to focus on clinical--patient or population-based--research. For the purpose of this award, clinical research includes:

Patient-oriented research, epidemiological and behavioral studies, and outcomes or health services research. Patient-oriented research is defined as research conducted with human subjects (or on material of human origin, such as tissues and specimens), as well as research on cognitive phenomena, that requires direct interactions with human subjects. Patient-oriented research also includes the development of new technologies, understanding mechanisms of human disease, therapeutic interventions and clinical trials.

The core curriculum is to include an array of clinical research-related topics of general interest, such as biostatistics, bioethics, clinical trials design, and observational study design. Other topics may include human genetics, pharmacology, patenting and material transfer agreements, as well as legal and social issues. The scope of the core curriculum can be flexible to meet the perceived needs of the institution.

Timeline: 2001 - 2006 and beyond

Performance Measure: The performance measures will include development of effective curriculum in each of the participating minority serving institutions, and the number of trainees enrolled in the programs.

Outcome Measure: Successful increase in the number of racial and ethnic minorities pursuing careers in clinical research.

NIDDK SMALL GRANTS FOR UNDERREPRESENTED INVESTIGATORS

Background

The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) recognizes the need to increase the racial and ethnic diversity of the pool of scientists in research areas important to the NIDDK. This program is aimed primarily at recently trained M.D. and/or Ph.D. investigators. The program will enable the applicant to accept a tenure earning position, gain additional research experience while transitioning to independence, and obtain preliminary data on which to base a subsequent research grant application in an area of diabetes, endocrinology, metabolism, digestive diseases, obesity, nutrition, kidney, urology, or hematology research.

Research Goals and Scope

The primary purpose of this PA is to foster the research careers of underrepresented minority investigators conducting research in areas of interest to the NIDDK. Individuals who have received training through individual postdoctoral fellowships or institutional training grants still require a transition period to demonstrate independence and to generate the preliminary data necessary for obtaining independent funding. This small grant program is meant to provide this transitional support and to encourage minority investigators to pursue research careers and become independent scientists.

Timeline: FY2001 - FY 2006 and beyond.

Performance Measures: The performance measures will include the number of underrepresented investigators funded.

Outcome Measures: Increase in the number of underrepresented investigators funded.

MEDICAL STUDENT RESEARCH SCHOLARS (MSRS) PROGRAM (RFA DK-02-003)

Background
Available data indicate that there is a serious shortage of racial and ethnic minority physicians. There is an even greater shortage of health researchers from these groups. These physicians from racial/ethnic minority communities provide an invaluable service to patients who are minorities, poor and are Medicaid beneficiaries. It is essential that there be adequate numbers of physician researchers trained to focus on problems related to health disparities and bring incisive research to these areas.

This program is designed to attract students in the early stages of their medical careers; provide research training and mentoring with outstanding investigators actively engaged in biomedical research; and encourage the students to continue in a research career path once their medical school and clinical training has been completed. It is critical for the success of this program that the members of the training faculty, the administration of the medical school, and the training program director work together to identify, recruit and encourage those minority medical students demonstrating an interest in a research career to participate in the program. This will include outreach efforts, with the assistance of the staff of the recently created NIDDK Office of Minority Health Research Coordination (OMHRC), to interested students at minority-serving institutions where currently there are no NIDDK-supported centers.

Research Goals and Scope
This announcement invites applications for a National Research Service Award (NRSA) Program developed to address the shortage of minority investigators trained in biomedical research. This program provides the opportunity for members of underrepresented minority groups who have completed at least two years of medical school and are currently enrolled, to gain research experience by contributing to or completing a research project in conjunction with one of the NIDDK-supported research centers.

The NIDDK supports P30, P50 and P60 Centers at 28 locations. To ensure that the medical students supported by the MSRS program are exposed to the highest quality research using the most-up-to-date equipment and cutting edge technologies, the NIDDK encourages the use of already funded, ongoing core facilities at the applicant institution. The training faculty recruited for the program should have access to these core facilities and most often will be members of one or more NIDDK-supported Centers. In addition, the trainees should be exposed to all of the enrichment activities organized and funded by the Centers.

Timeline: FY2002 - FY2007

Performance Measures: The performance measures will include the number of racial and ethnic minority medical students recruited and funded at NIDDK-supported centers.

Outcome Measures: Increase in the number of minority medical students trained at the centers, and subsequently taking up careers in biomedical research.

Public Information and Outreach

EXPAND NDEP MEDIA CAMPAIGN AND OTHER NDEP MESSAGES AND DEVELOP RESOURCES AND TRAINING MATERIALS FOR HEALTH CARE PROVIDERS

Background

The NDEP takes a multi-component approach to address its goal to improve the treatment and outcomes for people with diabetes. These components include public awareness and education campaigns, special population approaches, community-based interventions, health systems changes, and an inclusive partnership network. Strategies and activities are being implemented in each of these component areas through established partner-based work groups that provide guidance, direction, and resources. Specific work groups representing each targeted minority population have been created to assist the NDEP in developing strategies, activities and products that are culturally and linguistically appropriate and to disseminate the materials to their communities. NDEP is an initiative in the NIDDK Strategic Plan on Minority Health Disparities.

The NDEP is currently conducting a series of diabetes awareness campaigns using the theme, "Control Your Diabetes For Life," to encourage people with diabetes to manage their diabetes to live healthier lives. The campaigns target general audiences and the populations disproportionately affected by diabetes, namely, African Americans, Hispanic/Latinos, Asian Americans and Pacific Islanders, Native Americans, and senior citizens. The campaigns include television, radio and print public service announcements, educational materials, and information kits for the media and communities. The NDEP is currently developing campaigns for health care providers to encourage them to work with their patients to improve glucose control, and to identify, diagnose, and treat children with type 1 and type 2 diabetes.

For diabetes messages to reach communities, the NDEP has developed a Partnership Network of over 200 organizations from the national, state and local levels. These partners are valued and trusted community channels and serve as a dissemination vehicle for NDEP information and messages. The NDEP has created a Community Partnership guide, and a video and training module that provide tools, resources and information to assist individuals and organizations to implement diabetes activities in their communities. Interventions for minority populations using nontraditional partners to promote healthy lifestyle behaviors and help improve diabetes care in communities are currently being developed.

Research Goals and Scope

The purpose of the NDEP is to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. The NDEP's objectives are: (1) to increase public awareness of the seriousness of diabetes, its risk factors, and potential strategies for preventing diabetes and its complications; (2) to improve understanding about diabetes and its control and to promote better self-management behaviors among people

with diabetes; (3) to improve health care providers' understanding of diabetes and its control and to promote an integrated approach to care; and (4) to promote health care policies that improve the quality of and access to diabetes care. The NDEP will continue to develop and promote diabetes messages that reflect the newest scientific evidence about diabetes control, treatment and prevention. The NDEP may expand its target audiences to include those people who can benefit from the scientific results. The NDEP will continue to foster relationships with new partners, especially non-traditional partners such as the faith community, to increase NDEP's reach to its target audiences. Furthermore, the NDEP will develop innovative community interventions for minority populations that promote healthy lifestyle behaviors and help improve diabetes care in communities.

Timeline: Ongoing

Performance Measures: The performance measures will include the development of educational materials that are culturally sensitive and appropriate for racial and ethnic minority communities.

Outcome Measures: Increase in the awareness and preventive measures of type 2 diabetes in African American, Hispanic/Latino, Native American/Alaska Native, and Asian and Pacific Islander communities.

NATIONAL KIDNEY DISEASE EDUCATION PROGRAM

Background

The Council of American Kidney Societies--representing all major voluntary and professional organizations for kidney disease--has urged NIDDK to launch an education program to reduce the morbidity and mortality of kidney disease.

The health problems driving this interest include: (1) a striking, steady increase in the incidence of renal failure over the past two decades; (2) markedly higher rates of cardiovascular disease in people with renal insufficiency and renal failure; (3) high rates of "late diagnosis" of renal failure and consequently poor implementation of strategies to slow progression and prepare for renal replacement therapy; and (4) striking racial disparities in both the incidence of renal disease and the provision of optimum care. The current cost of treating people for kidney failure is an estimated $16 billion.

On July 18, 2000, NIDDK convened an ad hoc Kidney Disease Education Task Force to obtain advice from a cadre of individuals with substantial expertise in health policy, education, and preventive medicine. The group identified areas of consensus that are ideal starting points for an education or outreach program, areas that may be ripe for consensus, and areas needing further research. The group placed high priority on developing outreach programs targeting high-risk minority populations, especially African Americans, Native Americans, and Hispanic Americans, using treatments for which scientific consensus already exist.

In FY2001, NIDDK began planning a National Kidney Disease Education Program by sponsoring one or more planning conferences involving researchers, voluntary and professional organizations, health care providers and public health practitioners from academia, government,

industry and groups representing diverse racial and ethnic populations. NIDDK established an executive committee to focus the program's overall vision, goal, objectives, and direction, and to document the science base for an education program, including incidence and prevalence and the current environment for the diagnosis, prevention, and treatment of kidney disease. This program is part of NIDDK's initiatives to reduce health disparities in ethnic and racial minority populations.

Research Goals and Scope
NIDDK will need to (1) further refine the science and organization of the education program; (2) seek broad public comment and establish partnerships; (3) prepare a strategic plan identifying baseline data, target audiences and plans to reach audiences; (4) establish a steering committee to extend the reach of the Executive Committee to ensure broad representation in planning and organizing the National Kidney Disease Education Program; and (5) implement strategies.

Timeline: 2001 - 2006 and beyond

Performance Measure: The performance measures will include the development of educational materials culturally sensitive for all minority communities.

Outcome Measure: The outcome measures will include successful increase in the awareness of kidney disease and preventive measures in racial and ethnic minority communities.

ORGAN DONATION VIDEO FOR PIMA INDIANS

Background
The NIDDK began working with Pima Indian volunteers in Phoenix, Arizona in the mid 1960s, after a health survey revealed an astonishing rate of type 2 diabetes in the tribe. Half of Pima Indians who are 35 and older have type 2 diabetes, the highest prevalence in the world. Pimas also develop diabetes at a much younger age than other populations, and the numbers of Pima children with the disease are increasing.

With the support of hundreds of Pima volunteers and the Indian Health Service, NIDDK's Phoenix Epidemiology and Clinical Research Branch has studied the origin, development and natural history of diabetes, its complications, and obesity for over 35 years. In addition to a clinical research center in Phoenix, NIDDK runs a diabetes clinic at Hu Hu Kam Memorial Hospital at Sacaton, Arizona, and has established dialysis centers on the Gila River Indian Reservation to treat kidney failure.

Research conducted in Phoenix and Sacaton established that the Pima Indians have10 times the prevalence of type 2 diabetes found in Caucasian populations. These studies have also shown that diabetes, obesity, and kidney failure run in families, developing from genetic, prenatal, and environmental influences. In addition, doctors now recognize that high blood pressure predicts the complications of diabetes, and that lowering blood pressure may slow their onset and the progress of already existing diabetic kidney disease.

In spite of ongoing efforts to curb the incidence of kidney failure, prevalence remains high. The Hopi Indians have successfully raised awareness with a video and pamphlet encouraging organ donation. NIDDK staff and the Gila River Tribal Council hope to increase organ donation among the Pima Indians with a similar video and pamphlet.

NIDDK supported the development and production of a video that included interviews with appropriate tribal members and Native American medical staff. The video was to (1) educate tribal members about the fact that transplantation is a viable alternative to dialysis therapy; (2) raise awareness among the Gila River Community of the need for organs to alleviate the distress of patients on dialysis and to improve their quality of life; (3) address the cultural beliefs that may prohibit some American Indians from donating organs; and (4) demonstrate that Western and traditional methods of healing can complement each other to improve and extend life. A pamphlet that includes an organ donor card will provide a take-home message and an appropriate reminder to those who have seen the video.

Research Goals and Scope

There are striking racial and ethnic differences in the incidence and prevalence rates for kidney failure particularly among Native Americans, who are disproportionately affected by both diabetes and diabetic kidney disease. In Native Americans--as in the general U.S. population--diabetic nephropathy is the predominant cause of kidney failure. Greater access to kidney transplants for this population will substantially reduce the cost of medical care incurred with either hemodialysis or peritoneal dialysis and greatly improve their quality of life. Therefore, the goal of this initiative is to increase awareness of the need to donate organs and to encourage organ donation for transplantation in this population.

Timeline: FY2001 - FY 2002

Performance Measures: Successful development of educational materials, including video tapes explaining the utility of organ and tissue donation in the Pima Indian communities.

*Outcome Measure*s: Increased awareness of the need for organ donation in the Native American, especially the Pima Indian population, and the increase in the number of organs and tissues donated for transplantation.

NIDDK STUDY TO DEVELOP OUTREACH TO SPANISH LANGUAGE NEWS MEDIA

Background

NIDDK's research mission includes diseases and disorders that disproportionately affect Hispanic Americans. NIDDK publishes an extensive inventory of publications for this audience including the following topics: diabetes, kidney failure, chronic hepatitis C, peptic ulcer disease and *H. pylori*, and urinary incontinence in women (seven part series). Materials that will be published in the future include obesity and weight control and gallbladder disease. Currently, the National Diabetes Education Program of NIDDK supports a public service media campaign about type 2 diabetes for the Hispanic population. The success of the campaign with Hispanic media suggests the potential for greater access for other NIDDK materials and the need to

capitalize on relationships initiated through this national program. Efforts will be coordinated with other NIH Institutes through the NIH Hispanic Communications Coordinator.

Research Goals and Scope
The goal of the study is to develop a report and recommendations for future activities to increase the coverage of NIDDK health and research topics in the Spanish-language and Hispanic oriented communications media. This goal will be supported by objectives such as the following: (1) describing the media habits of Hispanic audiences especially in regard to health information; (2) performing content analysis of health coverage in national Hispanic print and broadcast media; (3) determining the views and opinions of relevant gatekeepers in the Hispanic media about the use of NIDDK information; (4) surveying other NIH Institutes about relevant experiences with Hispanic media; and (5) seeking input from representatives of Hispanic organizations on appropriate approaches to Hispanic media representatives and journalists.

Timeline: Ongoing

Performance Measures: The performance measures will include the successful development of culturally sensitive Spanish or Latino oriented educational materials.

Outcome Measures: Increased awareness and prevention of diseases and disorders that disproportionately impact Hispanic/Latino American audiences such as type 2 diabetes, obesity, kidney failure and gallbladder disease.

EXPAND WEIGHT-CONTROL INFORMATION NETWORK'S SISTERS TOGETHER

Background
NIDDK's Weight-control Information Network (WIN) provides culturally appropriate, evidence-based information about obesity, physical activity, weight control, and adolescent and childhood obesity to people who are overweight and/or obese, the general public, health care providers, the media, and the Congress. In addition to creating and distributing materials, WIN developed the "Sisters Together: Move More, Eat Better" pilot program for African American women because data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that they have the highest rates of obesity and overweight among all racial and ethnic groups in the U.S. WIN plans to implement a nation-wide, media-based "Sisters Together: Move More, Eat Better" program for African American women ages 18 and over. WIN will also develop partnerships with agencies and organizations that encourage and promote healthy lifestyle behaviors for many audiences, particularly African American audiences. The "Sisters Together: Move More, Eat Better" program is a part of NIDDK's Strategic Plan on Minority Health Disparities.

Strategies being considered are publicizing the availability of current "Sisters Together" materials and plans to expand outreach to churches, community organizations, state and local health departments, black media outlets, and black organizations such as the National Black Women's Health Project and the National Caucus and Center on Black Aged.

As WIN plans to expand the "Sisters Together: Move More, Eat Better" program to a national audience, it will also sponsor local activities for African American women living in the Washington metropolitan area. For the "Sisters Together: Move More, Eat Better" messages and activities to resonate with African American women nationally, WIN will nurture and facilitate partnerships with national, state, and local groups and individuals. WIN is currently developing relationships with nontraditional partners such as hair and nail salons.

The "Sisters Together: Move More, Eat Better" program was piloted from 1995 to1998 in the three Boston-based, predominantly black communities of Dorchester, Mattapan, and Roxbury. The program activities consisted of community outreach activities such as walking groups and cooking demonstrations, distribution of materials promoting healthy eating and regular exercise, and media outreach.

To increase awareness among African American women about the health benefits of regular exercise and healthy eating, WIN, through its "Sisters Together: Move More, Eat Better" program, created a planning guide that details the steps used to develop the Boston-based "Sisters Together" program. The guide helps individuals and organizations plan, promote, implement, and evaluate health awareness programs designed for African American women. The guide is distributed to churches, community organizations, and black media outlets.

Research Goals and Scope
The purpose of the "Sisters Together: Move More, Eat Better" program is to raise awareness about how moving more and eating better improve health, reduce risks for certain diseases, and, ultimately, enhance quality of life. A national "Sisters Together" program will also aim to develop and disseminate new, culturally relevant messages based on recent scientific findings about lifestyle interventions, obesity, and physical activity. Partnerships with new organizations and individuals will also be pursued during the expansion of the "Sisters Together" program.

Timeline: Ongoing

Performance Measures: The performance measures will include the increase in the awareness among African American women of health benefits of regular exercise and healthy eating.

Outcome Measures: The extend to which the results of this media outreach alters health behavior of African American women regarding exercise and healthy eating.

NATIONAL MINORITY RESEARCH INVESTIGATOR COMMUNICATION NETWORK

Background
NIDDK's research mission includes many diseases and disorders that disproportionately affect African Americans, Hispanic Americans, American Indians, and Asian American and Pacific Islanders. Diabetes, obesity, hepatitis and kidney failure adversely impact the health, longevity, and quality of life of minority populations in the U.S. NIDDK's commitment to reducing the impact of health disparities among the majority and minority populations in the U.S. has been strengthened by two events at the start of the new millennium. In March 2000 the Institute

completed its initial Strategic Plan on Minority Health Disparities. This trans-NIDDK effort to focus initiatives directed at diseases and disorders that affect minority populations was quickly followed by the establishment in July 2000 of the NIDDK Office of Minority Health Research Coordination in the Office of the Director, NIDDK. Central to the mission of this office is communication with the communities that will be affected by its actions in the biomedical research arena.

Research Goals and Scope
The goal of the study is to provide specific data to support the establishment of the first NIDDK communications network aimed at individuals and institutions in the biomedical research enterprise that serve and represent minority populations in the U.S. The goal of the study will be supported by the following objectives: (1) surveying the existing environment surrounding participation of minority investigators in basic and clinical research and (2) using that information to develop a strategy to establish and strengthen two-way communication between NIDDK leadership and minority investigators.

Timeline: FY 2002 - FY 2005

Performance Measures: Successful development of a cadre of under represented minority investigators interacting with the NIDDK to receive relevant information to help them succeed in careers in biomedical research, and providing the Institute with pertinent information in order to improve service to their respective communities

Outcome Measures: Increased number of underserved populations entering into biomedical research.

URINARY INCONTINENCE AWARENESS CAMPAIGN

Background
An estimated 13 million people in the U.S. experience incontinence, but women are affected twice as often as men. Pregnancy and childbirth, menopause, and the structure of the female urinary tract account for this difference, but nerve damage from diabetes—a disease that affects 16 million Americans and disproportionately affects African American and Hispanic populations compared to Caucasians—is also a factor. Women who have diabetes and damage to bladder nerves may not know when the bladder is full, and may have problems controlling the urge to empty the bladder and problems emptying it completely, allowing urine to leak and bacteria to grow more easily in the bladder and kidneys.

Research Goals and Scope
The NIDDK's National Kidney and Urologic Diseases Information Clearinghouse will launch a coordinated information program to reach African American and Hispanic and Latino American women, especially those with diabetes. Easy-to-read and culturally-sensitive publications on bladder control that will be translated into Spanish include *Bladder Control for Women; Exercising Your Pelvic Muscles; Menopause and Bladder Control; Pregnancy, Childbirth, and Bladder Control; Talking to Your Health Care Team About Bladder Control; Your Body's Design for Bladder Control*; and *Your Medicines and Bladder Control*. The NIDDK will also

plan and develop additional culturally sensitive messages and materials, working with public and private partners representing African Americans and Hispanic and Latino Americans to identify additional information needs of patients, families, and physicians. This program is one of NIDDK's initiatives to reduce health disparities in ethnic and racial minority populations.

NIDDK will: (1) extend its reach to public and private partners to develop culturally-sensitive materials about approaches to bladder control; (2) attend additional professional meetings at which incontinence publications may be promoted; and (3) will promote the availability of free bladder control information in publications for minority audiences.

Timeline: Ongoing

Performance Measures: The performance measures will include the development of effective educational materials to increase awareness in the minority communities of the problems of urinary incontinence.

Outcome Measures: Increased awareness of bladder control problems, and preventive measures in African American and Hispanic and Latino American women, especially those with diabetes.

NIDDK Health Disparities Budget
(Dollars in Millions)

	FY 2002			FY 2003		
Institute / Center	Research	Infrastructure	Outreach	Research	Infrastructure	Outreach
NIDDK	$130.00	$11.00	$4.00	$141.00	$12.00	$4.00