DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2004 Budget Request

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Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for FY 2004, a sum of $1,670,007,000, which reflects an increase of $66,846,000 over the comparable Fiscal Year 2003 appropriation. The fiscal year (FY) 2004 budget comprises $1,820 million which includes $150 million ($100 million in FY 2003) for the Special Appropriation for Research on Type 1 Diabetes through P.L. 107-360. The NIDDK transfers some of these to other institutes of the NIH and to the CDC. Adjusted for these mandatory funds, this is an increase of $48 million over the FY 2003 enacted level of $1,622 million comparable for transfers proposed in the President's request. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second annual performance report, which compared our FY 2002 results to the goals in our FY 2002 performance plan.

OBESITY RESEARCH

I appreciate the opportunity to testify on behalf of the NIDDK, which supports research on a wide range of chronic, debilitating diseases. Many of these diseases, including type 2 diabetes, nonalcoholic fatty liver disease, gallstones, end-stage kidney disease, and urinary incontinence, are caused, directly or indirectly, by obesity. Data from the Centers for Disease Control and Prevention documents that obesity is growing at an alarming rate in both adults and children, and that it disproportionately affects minorities. Recent results from the Framingham Heart Study indicate that obesity cuts six to seven years off of life, comparable to the effects of smoking. The 2001 *Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity* reports that

each year, it costs this country an estimated $117 billion in health care related expenditures.

We must approach obesity, not as a cosmetic or moral problem, but rather as a health problem. To address this problem, research is vital, and the NIDDK and the National Institutes of Health are formulating a bold and coordinated research plan. Obesity and its associated diseases result from complex interactions of biologic and environmental factors. The environmental factors include social, demographic, and economic changes that encourage people to eat more food than necessary to meet their energy requirements, and discourage physical activity that would increase their energy expenditure. These environmental factors disproportionately affect individuals who are biologically more susceptible to becoming obese and to develop obesity-associated diseases.

Tremendous progress has been made recently in understanding the biologic basis of obesity, and I will cite just a few examples. We now understand better how appetite is controlled through newly discovered hormones such as ghrelin and PYY. They are produced by the stomach and small intestine, and signal the brain, respectively, to increase and decrease appetite. Blood levels of ghrelin peak just before meals, and peaks are significantly higher in obese individuals who have lost weight by dieting, perhaps explaining why sustaining weight loss is so difficult. Bariatric, or gastric bypass, surgery is being increasingly performed in the U.S., and part of its effectiveness in achieving sustained weight loss may be explained by the recent finding that ghrelin levels are suppressed by some forms of the surgery. Blocking the action of ghrelin is

thus a potentially attractive target for drug development

Similar advances are being made in understanding how the body decides whether and where to metabolize or store fat. Discovery of hormones such as leptin and adiponectin secreted by fat have shown that fat signals to brain, liver, and muscle to regulate fuel metabolism and response to insulin. Such discoveries help explain how obesity leads to insulin resistance and type 2 diabetes, and offer new ways of treating or preventing obesity-associated disorders. Epidemiologic results and clinical studies show that differences in distribution of body fat may also be important in determining which individuals develop obesity-associated disorders.

Progress in behavioral research provided the basis for the lifestyle intervention of our Diabetes Prevention Program (DPP), which revealed that participants who lost 5 to 7 percent or more of their body weight and who performed at least 150 minutes of physical activity per week reduced their risk of developing type 2 diabetes by 58 percent. We are conducting a follow-up DPP Outcomes Study to assess the durability of the DPP interventions in preventing diabetes, and to determine whether the interventions reduce cardiovascular disease. Our Look AHEAD: Action for Health in Diabetes clinical trial is testing the effect of sustained weight loss on prevention of cardiovascular disease in obese individuals who already have type 2 diabetes.

To further sharpen the NIDDK's obesity research efforts, I recently announced creation of a new Office of Obesity Research within the NIDDK that is bringing together expertise in our Division of Diabetes, Endocrinology, and Metabolic Diseases, and our Division of Digestive Diseases and Nutrition, both of which have

important input to obesity research. This new group is framing initiatives across a wide range of obesity research areas to address the epidemic of obesity, from the fundamental biologic aspects to the behavioral and environmental. Examples include a study of the life cycle of the fat cell directed at discovery of novel targets for treatment of obesity and associated metabolic disorders. In order to address obesity-associated diseases such as type 2 diabetes, we will expand our Diabetes Genome Anatomy Project to include genetic analysis of all the major organ systems affected by diabetes and its complications . We are helping re-engineer the clinical research enterprise by creating a new Bariatric Surgery Clinical Research Consortium (BSCRSC). The BSCRC will develop a common data collection protocol to accelerate clinical research and progress in understanding the development of severe obesity and its complications, as well as understanding the risks and benefits of bariatric surgery as a treatment method.

In behavioral research, we have begun a clinical trial to develop effective strategies to prevent type 2 diabetes in children. This initiative focuses on school-based primary prevention programs to decrease risk factors for type 2 diabetes and lower the incidence of the disorder. We are supporting research to translate the results of the highly successful Diabetes Prevention Program, into clinical practice for prevention of type 2 diabetes in individuals and communities at risk. Of particular interest will be interventions that focus on underserved and minority populations disproportionately affected by the disease. Given the environmental influences fueling the obesity epidemic, we are encouraging research to study promising interventions that would

target environmental factors contributing to inappropriate weight gain in children, adolescents and adults. We are asking investigators to partner with community organizations or businesses, such as schools, supermarkets, restaurants, churches, community groups, and worksites to develop interventions that could potentially be translated into larger-scale interventions.

These are just some of the ways we are encouraging research to combat obesity and its co-morbid conditions. We believe NIDDK and NIH research is our best hope for stemming the tide of this epidemic. Why? Because we stand poised, given new information about the human genome and the advent of new research tools to determine the biologic and genetic factors that make one person more (or less) susceptible to obesity than another. Why is this important? Because it should allow targeted obesity prevention and allow the development of new kinds of drugs and therapies that should be more successful in preventing weight gain and in helping people lose weight and to sustain weight loss. Tied to this is improved research-based behavioral approaches to weight loss and maintenance. In addition, NIH research ultimately will provide the scientific basis for policy decisions on needed changes in environmental factors that affect diet, nutrition, and physical activity. Obesity is a complex problem requiring a multi-disciplinary research approach if we are to reverse this ominous threat to our nation's health.

DIABETES

Approximately one million Americans suffer from a type of diabetes that is not obesity-related. Rather, type 1 diabetes involves immune destruction of the insulin-

producing beta cells of the pancreas. We are vigorously pursuing cutting-edge research opportunities for prevention of type 1 diabetes through our TrialNet, and for treatment and cure of type 1 diabetes through support of the field of regenerative medicine. One example of the latter is our Beta Cell Biology Consortium, which brings together multi-disciplinary teams of investigators with expertise in pancreatic development, beta cell biology, stem cell biology, and bioinformatics. Through such collaborative research programs, we are laying a solid foundation for the future development of innovative, cell and regenerative growth factor therapies for diabetes and other debilitating diseases. Increased understanding of beta cell biology should also improve our ability to develop noninvasive, functional imaging technology that would, for example, help monitor type 1 diabetes prevention trials.

HEPATITIS C

The hepatitis C virus is the cause of the most common form of end-stage liver disease in the U.S. We recently held a Consensus Development Conference on the management of hepatitis C that recommended directions for future research, and led to development of initiatives that are encouraging further basic and clinical research on hepatitis C, research on management of hepatitis C in people with chronic kidney disease, and research on new therapies for children with hepatitis C. From such research should emerge more effective forms of treatment and prevention.

GASTROINTESTINAL DISEASES

We are bolstering our research activities across the full spectrum of gastrointestinal (GI) diseases, ranging from celiac disease, in which a known dietary

factor triggers intestinal damage in genetically susceptible individuals, to functional GI disorders such as irritable bowel syndrome. Our strong research portfolio in inflammatory bowel disease (IBD) is paying dividends. A recent clinical trial reported that a recombinant monoclonal antibody that blocked the action of certain cell adhesion molecules could be used to reduce the symptoms and improve quality of life of patients with Crohn's disease, an inflammatory bowel disease. The NIDDK supported the basic research underpinning this exciting work, providing another example of the critical role of NIH research in the development of therapies for human disease. Our IBD Genetics Research Consortium aims to identify genes associated with increased risk of developing Crohn's disease and ulcerative colitis. The long-term goal is to increase molecular understanding of IBD so as to facilitate development of novel therapies and new diagnostic methods.

KIDNEY DISEASE

We are addressing the sharp rise in end-stage renal disease (ESRD) by supporting research on the causes, treatment, and prevention of the major forms of kidney disease leading to ESRD. The discovery that the proteins encoded by the polycystic kidney disease (PKD) genes are localized to cilia (hair-like projections) in kidney tubular cells demonstrates the rapid progress in understanding the pathogenesis of the major cause of inherited ESRD. Results from some of our major kidney disease trials have significant implications for clinical practice. Our African American Study of Kidney Disease and Hypertension (AASK) showed that angiotenson-converting enzyme inhibitors, compared with calcium channel blockers, slowed kidney disease progression

by 36 percent, and drastically reduced the risk of ESRD by 48 percent in patients who had at least one gram of protein in the urine, a sign of kidney failure.

The Institute's HEMO clinical trial recently showed that the standard recommended hemodialysis dosage and filters are adequate for reducing morbidity and mortality in ESRD patients, and that increasing dialysis dose using a conventional three times per week regimen does not provide greater benefit to patients. However, the important question now is the duration and frequency of dialysis. We therefore have planned clinical trials to compare conventional dialysis with more frequent dialysis in patients with ESRD. We also have launched a prospective epidemiological study of children with chronic kidney disease to determine the risk factors for decline in kidney function, and associated morbidities such as impaired neurocognitive development, cardiovascular disease, and growth failure.

UROLOGIC DISEASES

Our major clinical trial on Medical Therapy of Prostate Symptoms (MTOPS) recently demonstrated that two drugs commonly used to treat benign prostatic hyperplasia (BPH), finasteride and doxasozin, are significantly more effective at preventing symptomatic BPH incidence and progression when given in combination. Samples collected during the MTOPS trial will be used by our new MTOPS Prostate Samples Analysis Consortium to discover and validate biologic markers for detection and risk assessment of BPH.

Our Bladder Progress Review Group report provides a strategic plan for future bladder research. We are already implementing the report's recommendations on

interstitial cystitis (IC), a debilitating, chronic syndrome of urinary urgency, frequency, and pelvic pain, by encouraging basic research pertinent to IC, the ultimate goal being the development of reliable diagnostic tools, and new and effective disease treatments and prevention.

Mr. Chairman and Members of the Committee, these are just a few examples of our many research advances and initiatives. I would be pleased to answer any questions.