DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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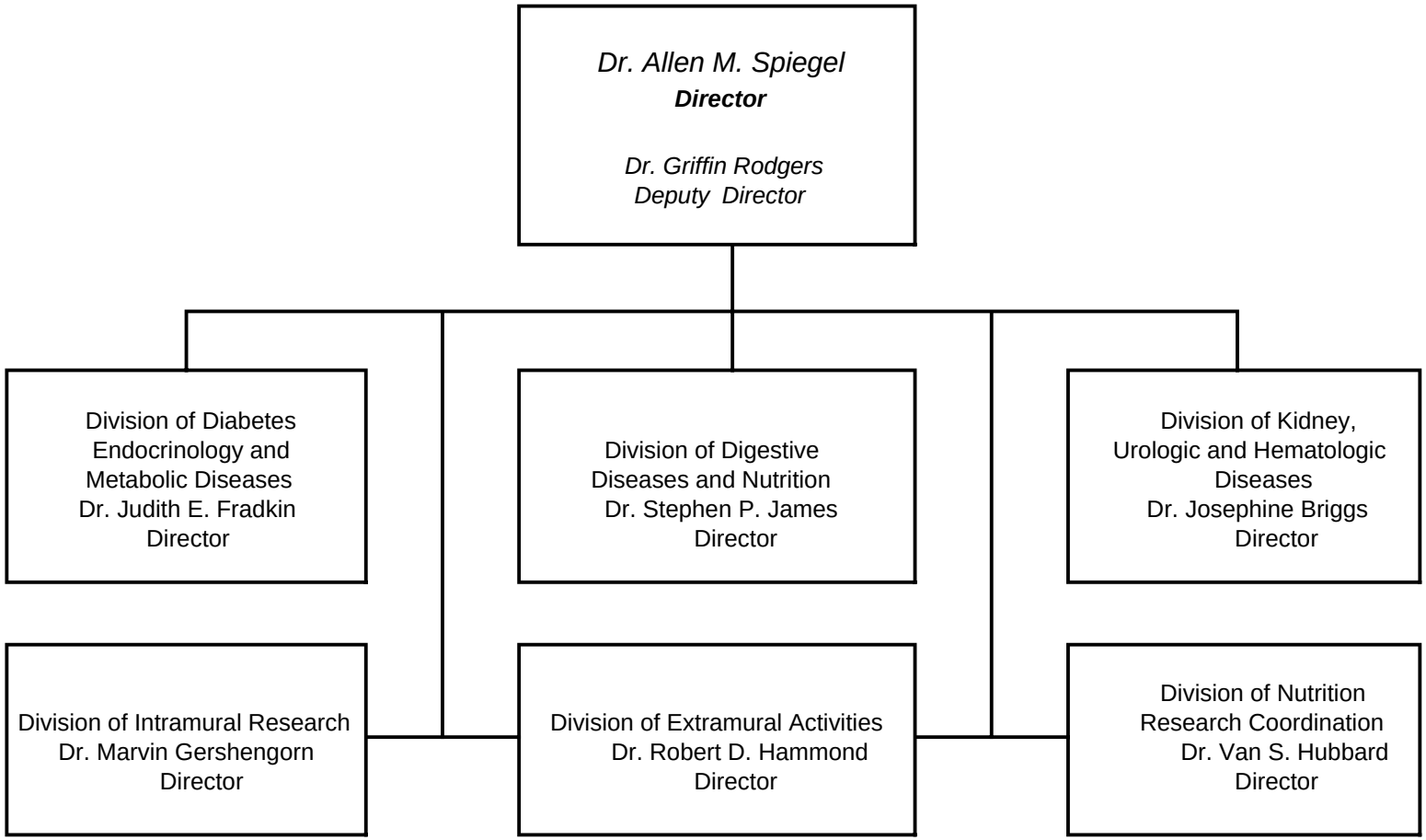
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [$1,682,457,000] *$1,726,196,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004.]

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Appropriation	$1,633,347,000	$1,682,457,000	$1,726,196,000
Type 1 Diabetes 2/	$70,000,000	$150,000,000	$150,000,000
Enacted Rescissions	(10,617,000)	(10,654,000)	---
Subtotal, Adjusted Appropriation	1,692,730,000	1,821,803,000	1,876,196,000
Real transfer from:			
State Children's Health Insurance Program in the Health Care Financing Administration for Type 1 Diabetes Research	30,000,000	0	0
Comparative transfer from:			
Fogarty International Center for International Services Branch	120,000	0	0
Comparative transfer to NIBIB for Radiology Program	(107,000)	(106,000)	(0)
Comparative transfer to Buildings and Facilities	(475,000)	(457,000)	(0)
Comparative transfer to Office of the Director for program changes	(1,185,000)	(0)	(0)
Subtotal, adjusted budget authority	1,721,083,000	1,821,240,000	1,876,196,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,721,083,000	1,821,240,000	1,876,196,000
Unobligated balance lapsing	(6,772,000)	---	---
Total obligations	1,714,311,000	1,821,240,000	1,876,196,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2003 - $12,015,000; FY 2004 - $12,475,000 ; FY 2005 - $12,610,000
Excludes $3,406,000 in FY 2003 and $4,000,000 in FY 2004 for royalties.

2/ Includes Type 1 Diabetes Funds in Accordance with P.L. 106-554 and P.L. 107-360.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
646		657		658		1	
Program Total	$1,721,083,000		$1,821,240,000		$1,876,196,000		$54,956,000
Type 1 Diabetes	-100,000,000		-150,000,000		-150,000,000		
Labor / HHS	1,621,083,000		1,671,240,000		1,726,196,000		$54,956,000

This document provides justification for the Fiscal Year 2005 research activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The NIDDK conducts and supports research on many serious and costly chronic diseases affecting the 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. The economic burden of these diseases represents a major proportion of U.S. health care expenditures. A focus on basic research has traditionally guided the Institute's programs. A fundamental understanding of biologic systems will ultimately explain the abnormalities underlying disease and thus is imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, the Institute has a strong commitment to transfer new knowledge of biologic processes into appropriate clinical studies, and ultimately, into efforts to translate knowledge and medical discoveries into improved

health care, with special emphasis on populations disproportionately affected by diseases in the mission of the NIDDK.

The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases is responsible for extramural research and research training related to diabetes mellitus; endocrinology, including osteoporosis; and metabolic diseases, including cystic fibrosis; this Division also supports research on obesity, a major risk factor for type 2 diabetes. The Division of Digestive Diseases and Nutrition has responsibility for managing research programs related to liver and biliary diseases; gastrointestinal diseases, including motility, immunology, and digestive disorders; pancreatic diseases; nutrient metabolism; and obesity, eating disorders, and energy regulation. The Division of Kidney, Urologic, and Hematologic Diseases supports research on the normal and disease processes of the kidney, genitourinary tract, and the blood-forming organs to improve or develop preventive, diagnostic, and treatment methods. The Division of Intramural Research conducts research and research training within the Institute's laboratories and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Shared interests in the biochemical and genetic processes underlying disease link the programs and divisions of the Institute, while close communication between the NIDDK and other NIH programs also fosters a confluence of fundamental knowledge in these vital areas of investigation.

Science Advances

Genetics and Genomics

Novel Technology Approach for Identifying Genes Involved in Type 2 Diabetes: To understand the underlying genetics of human disease, scientists have used a powerful research tool, called a "microarray," which is a means for rapidly analyzing thousands of genes. Microarray technology allows researchers to compare differences in gene expression in healthy and diseased tissues and cells, with the goal of identifying genes that may contribute to disease development. In order to identify genes that may contribute to type 2 diabetes development, researchers studied the expression of the genes in skeletal muscle biopsies from diabetic and non-diabetic individuals--both with and without a family history of diabetes. The scientists used a novel microarray technology approach where they looked at the expression of multiple genes. The expression of many genes was altered in diabetic patients and in those with a family history of diabetes. Strikingly, when the scientists studied the genes whose expression was decreased in diabetes, they found that many of them were part of a single biological pathway. The expression of this group of genes is regulated by a single master gene, PGC-1, suggesting that PGC-1, as well as the genes it regulates, may be therapeutic targets for type 2 diabetes. The knowledge gained from these studies can be used to understand the underlying physiological defects in diabetes as a basis for determining additional therapeutic targets for prevention or treatment.

Developmental Biology

Protein To Reduce Autoimmunity: Autoimmune diseases occur when a person's own immune system mistakenly attacks and destroys its own cells. Therefore, it is very important that the immune system distinguishes between "self," or one's own cells, and "non-self," or foreign substances, to prevent autoimmunity. The body has a way to ensure this happens, which involves destroying any immune cells that will react with "self" cells. A recent study showed that a protein, called AIRE, plays a role in this process. Researchers genetically engineered mice to lack AIRE, and found that those mice developed autoimmune disease. Furthermore, they found that AIRE turned on genes that had a role in the process of destroying immune cells that will react with "self" cells. Researchers can use these results as a basis to elucidate the processes that are important in development of human autoimmune disease.

Harnessing Technology

Molecular Library Approach Identifies Small Molecule Targeting Key Protein: "Small molecules" have proved to be important tools to manipulate biological processes, many times leading toward therapeutic advances to overcome disease. In order to find an appropriate molecule to interact with a protein of interest, scientists may screen a large number of small molecules from a "molecular library" of thousands of molecules. This approach was used to identify small molecules to interact with FXR, a key protein involved in bile acid and cholesterol metabolism. Researchers used a molecular library of over 10,000 small molecules in a high throughput screening assay to identify any that would activate FXR. The result was identification of small molecules that had specific effects on FXR. This allowed for more refined screening to finally arrive at a class of small molecules with better effects on FXR than natural compounds. Since disorders of bile and cholesterol metabolism are often interconnected, these findings now open the door for future research to develop additional small molecules that can have a bearing on diseases that these processes may regulate. This type of molecular library approach can also be used for a wide range of other proteins to gain insights into important biological and disease-related processes, and serve as the basis for the generation of new drugs.

Minority Health Disparities

Diabetes, obesity, hepatitis C, end-stage renal disease, benign prostate disease, and several other diseases within the NIDDK research mission place a disproportionately heavy burden on racial and ethnic minority groups.

Nurse-Directed Diabetes Care Is Beneficial to Minority Diabetes Patients: Most diabetes patients do not achieve the recommended strict control of their disease that decreases their risk for developing disease complications. This is a serious problem in minority populations, who are already at disproportionately increased risk for developing complications. A recent study determined that type 2 diabetes care directed by specially-trained nurses, who are under the

direction of a physician, improved disease management in minority patients, compared to standard physician-only directed care. Nurse-directed care was already known to improve diabetes management in middle-class populations, and this study confirms the same benefits in a minority population of Hispanic and African American patients. Researchers studied several parameters of diabetes management, such as the number of times patients visited the clinic for routine diabetes monitoring. In nearly every parameter, patients under the care of a nurse had better management than patients under standard physician-directed care. Thus, nurse-directed care can improve disease management, which may have a dramatic effect in reducing morbidity and mortality in this high-risk population.

Type 2 Diabetes Prevention Strategy in High-Risk Population: Gestational diabetes is a form of diabetes that sometimes develops in women during pregnancy. Women who suffer from gestational diabetes are at increased risk of delivering a child with abnormalities and are also at increased risk of subsequently developing type 2 diabetes themselves. Researchers recently examined the ability of an insulin-sensitizing drug to prevent the development of full-blown type 2 diabetes in Hispanic women who previously had gestational diabetes. These drugs act by increasing the sensitivity of target tissues to insulin, and simultaneously lowering blood sugar levels and relieving stress on pancreatic beta cells to produce more insulin. Researchers found that the insulin-sensitizing drug could delay or prevent type 2 diabetes in this high-risk population. Furthermore, the benefits of drug therapy persist for at least eight months after the medication is stopped. Therefore, a proactive approach of drug treatment can reduce the risk of developing the disease. Further research is needed to determine the longer term risks and benefits of therapy and define the optimal use of drugs in this class for prevention of type 2 diabetes in women with gestational diabetes.

Testing the Effects of Lowered Blood Pressure on Kidney Disease in African Americans: High blood pressure (hypertension) is a leading cause of end-stage renal disease (ESRD). African Americans have a disproportionately high risk for developing ESRD as a result of hypertension. The African American Study of Kidney Disease and Hypertension was a clinical trial of over 1,000 African Americans with signs of hypertensive kidney disease. Participants received one of three medications--a beta-blocker, a calcium channel blocker, or an ACE inhibitor--and were treated with the goal of lowering blood pressure to either normal levels or lower-than-normal levels. During the trial, treatment with the calcium channel blocker was discontinued because it was less effective than either of the other two drugs at slowing the progression of kidney disease. Recent analysis of the data reveals that there was no difference in rates of kidney disease progression between the “normal” and “low” blood pressure groups. However, kidney function in patients taking the ACE inhibitor was better than in those taking the other drugs. This study has important implications for the medical management of hypertensive kidney disease.

Drug To Prevent Diabetic Eye Disease in Animal Model: Both type 1 and type 2 diabetes patients have an increased risk for developing serious vascular complications, such as blindness. Researchers have shown that sustained high blood glucose (sugar) levels are a major factor in promoting development of diabetic complications. Researchers tested the ability of a vitamin-B related molecule, called "benfotiamine," to stop the adverse effects of high blood sugar levels. Specifically, they determined that benfotiamine can stop the development of retinopathy, a form of eye disease, in diabetic rats. In contrast, untreated diabetic rats developed the disease. If benfotiamine has the same effect in humans, it would be a promising therapeutic agent for diabetes patients that may prevent development of diabetic retinopathy, and possibly other vascular complications.

Sustained Benefits of Intensive Blood Glucose Control: The landmark Diabetes Control and Complications Trial (DCCT) previously showed that intensive control of blood glucose levels reduced the risk of developing damage to small blood vessels and nerves in type 1 diabetes patients. The follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), continues to demonstrate long-term benefits of intensive therapy in these patients. While the DCCT proved that glucose control could prevent small vessel damage, controversy remained about the effect of high glucose on the large vessels damaged in cardiovascular disease. Recent results have shown that patients who received intensive therapy had less thickening of the wall of the carotid artery over time, a measurement of atherosclerosis, than patients on standard therapy. These significant results demonstrate the importance of strict blood glucose control on preventing damage to large blood vessels, as well as small vessels.

Dual Mechanism of Action of Type 2 Diabetes Drug Candidate: Type 2 diabetes patients are impaired both in their ability to produce and respond to insulin. Previous research by NIH-supported scientists has shown that mutations that impair the function of an enzyme, called "glucokinase" (GK), causes a rare form of type 2 diabetes, called "Maturity-Onset Diabetes of the Young"; GK regulates the sensitivity of insulin secreting beta cells to glucose and regulates liver release of glucose. Based on this research, scientists hypothesized that a drug that would activate GK would help to restore normal glucose levels in type 2 diabetes. Working toward this goal, they screened 120,000 drugs and identified a single one that activated GK. The drug dramatically and effectively restored normal glucose levels in diabetic mice. Importantly, the drug achieved this by a dual mechanism: it stimulated insulin production by pancreatic beta cells and inhibited glucose production by the liver. This is the first identified drug to have an effect on both insulin production and insulin action--two processes that are impaired in type 2 diabetes. This study is a key example of how the NIH investment in basic research enabled researchers to identify a potential therapeutic agent for type 2 diabetes.

Story of Discovery: Preventing or Delaying Complications of Diabetes:
20 Years of Study by the DCCT/EDIC Research Group

In type 1 diabetes, the patient's own immune system mistakenly attacks and destroys the beta cells of the pancreatic islets, the sole producers of insulin. Without insulin, the tissues of the body cannot absorb or use glucose (sugar), the major cellular fuel. Type 1 diabetes patients require insulin administration for survival. Insulin, however, is a treatment for the disease and not a cure. Diabetes slowly damages major organs in the body, such as the eyes, kidneys, and cardiovascular system. Thus, it is imperative to better understand and intervene in the development of diabetes complications to improve longevity and quality-of-life of type 1 diabetes patients.

Impressive research progress toward combating diabetes complications was achieved through a large clinical trial which the NIDDK launched in 1983. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial of over 1,400 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive *versus* conventional treatment of blood glucose levels and the development of disease. Patients on intensive treatment kept their blood glucose levels and hemoglobin A1c (HbA1c) levels (which reflect average blood glucose levels over a 2- to 3-month period) as close to normal as safely possible with frequent monitoring of blood glucose, and at least three insulin injections a day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections a day, with once-a-day urine or blood glucose testing. The result was a large difference in the mean HbA1c levels in the two groups and a striking difference in their development of microvascular complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease, by 35 to 76 percent compared with conventional treatment. This dramatic, positive result has had a profound impact on clinical practice for the management of type 1 diabetes: it led to the development of clinical guidelines by the American Diabetes Association and other groups; it spurred the creation of the National Diabetes Education Program to disseminate the findings to the public; and it stimulated multifaceted research efforts to develop tools and therapies that enable patients to achieve tight control of blood glucose levels.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all patients were encouraged to use intensive treatment. Nearly all patients who participated in the DCCT volunteered for the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to determine the long-term outcome of reducing exposure of the body's tissues and organs to high blood glucose levels.

Now, 10 years after the end of the DCCT, further seminal insights are emerging regarding long-term benefits of intensive blood glucose control. In May 2002, EDIC investigators reported that the 6.5 year period of intensive treatment during the DCCT continued to reduce the risk of eye disease as long as seven years after the study ended. Building on this exciting finding, a study in October 2003, showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group eight years after the end of the DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the patients after completion of the DCCT. Analysis shows these long lasting differences in development of complications can be explained by the difference in control of glucose levels between the two treatment groups during the DCCT.

While DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye and nerve problems, controversy remained about the effect of glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlated with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven. In June 2003, the DCCT/EDIC research group showed that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared to the patients in the former conventional therapy group. This was demonstrated using both ultrasound to measure thickening of the wall of the carotid artery and also electron beam computed tomography (EBCT) to measure coronary calcification.

Twenty years after the beginning of the DCCT, there is now evidence that intensive glucose control prevents damage to large blood vessels. This is a significant finding because CVD causes death in two-thirds of patients with diabetes.[1]

These findings of the DCCT/EDIC research team raise interesting questions about the "metabolic memory" that enables the beneficial effect of intensified blood glucose control to persist long after the period of intensive therapy has ended. The biologic basis of metabolic memory–how a difference in glucose control for a finite period can have striking effects long after the conclusion of the study–has been explored in a symposium that marked the 20th anniversary of the initiation of the DCCT. Held at the NIH in April 2003, the symposium, "Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back," included an overview of the DCCT/EDIC trials as well as presentations from leading investigators studying diabetic complications. These investigators are vigorously pursuing possible explanations for the enduring effects of intensive therapy, that outlast the period of improved glucose control. One possibility is suggested by the demonstration of long standing tissue changes associated with high blood sugar, particularly the attachment of end products of sugar metabolism to collagen, a component of the matrix that surrounds most cells. Continued efforts by scientists will unravel the underlying molecular mechanisms by which elevated glucose levels damage small and large blood vessels, and the tissues and organs that are affected. The symposium underscored that, even though the results of the DCCT/EDIC studies show that intensive therapy is beneficial for long-term prevention of complications, a severe limitation to the practice of intensive therapy is the potential for acute episodes of hypoglycemia, or low blood sugar. Thus, it is imperative that researchers seek new methods to improve blood glucose monitoring and insulin delivery, or develop new beta cell replacement therapy to cure type 1 diabetes.

The DCCT and the EDIC studies have directly and positively affected the manner in which patients and physicians manage diabetes. They have provided conclusive evidence that patients should begin intensive therapy as early as safely possible. By maintaining intensive therapy, patients have significantly reduced development of diabetic complications, which directly translates into an improved quality-of-life. Researchers will continue to investigate mechanisms by which glucose exerts its devastating effects, in the development of complications, with a goal of discovering therapeutic targets to treat or prevent complications.

Endocrine and Metabolic Diseases

Small Molecules To Correct Impairment in Cystic Fibrosis: Cystic fibrosis (CF) is caused by mutations in the gene encoding the CFTR protein. The most common mutation, ΔF508, causes a misfolded protein that is unable to move to its proper location at the cell membrane or function properly as a chloride ion channel. The gene is widely expressed, including in lung, the gastrointestinal tract, and the kidney, yet patients with mutant CFTR have impaired lung function as well as digestive problems, but no overt kidney disfunction. To help understand this paradox, researchers studied mouse kidney cells expressing the mutant CFTR grown under hyperosmolar conditions, by increasing the concentration of small molecules and ions in the growth medium of the cells. This environment mimics the normal extracellular conditions surrounding kidney cells. The hyperosmolar conditions had the effect of correcting the CFTR protein defect. These results may explain why CF patients do not have impaired kidney function, and demonstrate the

[1]National Institute of Diabetes and Digestive and Kidney Diseases, Diabetes in America, 2nd Ed., 1995. NIH Publication No. 95-1468.

feasibility of using a small molecule approach to promote proper folding and cellular trafficking of mutant CF protein as a therapeutic treatment. Another research group screened 100,000 small molecules and identified six classes that were able to restore the ion channel function in ΔF508, using a cell culture model system. Both of these studies successfully showed that small molecules can correct defects in the ΔF508 mutant protein, which suggests that small molecule intervention may be a useful approach for treating CF.

Obesity and Nutrition

Animal Model To Study the Metabolic Syndrome: Animal models of specific diseases or syndromes are critical tools to advance research. The metabolic syndrome is a cluster of medical problems, including obesity, insulin resistance, high blood pressure, and hyperlipidemia, that appear in varying combinations and that put people at increased risk for cardiovascular disease and for type 2 diabetes and its complications. Researchers have recently generated a mouse model that mimics the human metabolic syndrome. These mice were genetically-engineered to have fat cells containing extra amounts of a cortisol-producing enzyme. The researchers had previously shown that the mice developed abdominal obesity and insulin resistance. They have now determined that the mice also have high blood pressure. This mouse model will be a useful tool to understand biological processes that are important in metabolic syndrome. In addition, the cortisol-producing enzyme appears to be important in regulating many aspects of the metabolic syndrome, including high blood pressure. Identification of agents that target this enzyme may be a useful approach for treating the metabolic syndrome.

Effect of Diet Macronutrient Content on Weight Loss in Obese Adolescents: Previously known as adult-onset diabetes, type 2 diabetes is increasingly being diagnosed in young people. Most youth with this form of diabetes are obese, and it is therefore imperative to design interventions to prevent obesity, or to promote weight loss in adolescents who are already obese. In order to understand the role of diet macronutrient content in weight loss in obese adolescents, researchers have compared a conventional, low-fat diet with an experimental diet that has a reduced glycemic-load (GL). GL is based on another parameter, called the "glycemic index," which is a measurement of how a food changes blood glucose levels in a short period of time. The researchers found that obese adolescents who ate a low-GL diet lost more weight compared to those on a conventional diet. This was an especially interesting result, because the adolescents on the low-GL diet were allowed to eat until they reached satiety, but the low-fat diet group were only permitted to eat a certain number of calories. Another benefit from the low-GL diet was that it reduced the progressive rise in insulin resistance seen during the study more than the low-fat diet. Because this was a small study of 14 adolescents, further studies will have to be performed to determine if a low-GL diet has the same benefit in a larger group. If so, this may be a potential intervention strategy to promote weight loss and improve insulin sensitivity in obese adolescents.

New Insights into Adult Liver Transplantation from Living Donors: The practice of using an adult living donor for liver transplantation in children began over a decade ago in response to a lack of cadaveric liver donors. The smaller size liver required for transplants in children made removal of part of the liver from an adult living donor feasible. Recently, due to a severe shortage of cadaveric organs available for transplantation, living donors are increasingly volunteering to enable liver transplantation in adults, but the procedure, requiring the resection of a larger portion of the donor's liver, poses a much greater risk. In order to understand this increasing trend and the complications that can result from this procedure, researchers surveyed all liver-transplantation programs in the U.S. and received data from 69 percent of the programs. They found that the number of liver transplantations from living donors greatly increased: from one transplant in 1997, when this procedure began, to 266 transplants in 2000. In addition, they found that overall mortality among donors is low, approximately 0.2 percent. A larger percentage of donors develop complications; serious complications occur in approximately 14 percent of donors. The researchers conclude that it is critical to continue to study the effects of the procedure on both the donors and recipients in order to improve strategies to combat adverse effects.

First Study of Incidence of Celiac Disease: Celiac disease is an autoimmune, gastrointestinal disorder characterized by intolerance to dietary gluten. Children with the disease have symptoms that can include chronic diarrhea, bloating, anemia, and failure to grow at a normal rate. There is a genetic predisposition to developing celiac disease, and a large majority of patients have at least one copy of a gene, called HLA-DR3. In order to estimate incidence of the disease in the general population, researchers conducted a large, genetic screen of over 22,000 newborns in Denver, Colorado. A subset of the infants were followed for five years to compare disease development in those having zero, one, or two copies of the susceptibility gene. Overall, roughly one percent of all children at age 5 were estimated to have the disease. The children who had either one or two copies of the susceptibility gene were at an increased risk compared to children without the gene. In addition, the researchers found that females had a higher risk for disease development than males. These results show that celiac disease is common in a population representative of the general population, and new screening strategies based on the study may help identify children at increased risk.

"Good" Bacteria--How Do They Help?: Many strains of bacteria cause illness--they are unwanted invaders that the immune system must eliminate. However, not all bacteria are unwanted; "good" bacteria live throughout the body with benefit to both host and microbe. Recent studies have shed light on how "good" bacteria found in the gut are beneficial to the host. A type of cell found in the gut, the "Paneth" cell, appears to have a significant role in fighting disease. Researchers showed that the Paneth cells in mice produced a molecule, called Ang4, which is important in preferentially attacking harmful, invading microbes. Interestingly, the

resident “good” bacteria in the gut were responsible for directing the Paneth cells to make Ang4. Another research team showed that the “good” bacteria, again working through Paneth cells, had an important role in developing the capillary networks found in the small intestine. In the absence of bacteria, the networks, which are important for absorption of nutrients, do not form properly. These studies showed how the “good” bacteria, through interactions with the host’s intestinal cells, are important factors in fighting off harmful infection and in promoting normal development of the small intestine.

The IBD5 Gene Confers Susceptibility to Inflammatory Bowel Disease: Inflammatory bowel disease (IBD) is a debilitating inflammatory disease of the lower intestine and colon. Crohn's disease (CD) and ulcerative colitis (UC) are the two primary forms of IBD. In 2001, a landmark achievement occurred when scientists demonstrated that the *NOD2* gene (also called *CARD15*) confers susceptibility to CD. In a recent NIH-supported controlled study of Canadian CD patients, scientists subsequently identified *IBD5*, located on the chromosomal region 5q31, as a CD susceptibility region that contains a number of potential candidate susceptibility genes. Now, these scientists have replicated the findings of that study with a second study in a German population of CD patients. In addition, the same susceptibility region on chromosome 5q31 was found to contain one or more likely susceptibility genes for UC. Further analysis revealed that *IBD5* and *CARD15* act independently to confer either risk (*IBD5*) or clinical manifestations (*CARD15*) of CD. The data also suggest that *IBD5* and *CARD15* may act synergistically to promote the development of UC. Molecular classification of patients with IBD, combined with clinical data, may lead to the identification of patient subgroups and to greater precision in tailoring treatments for IBD patients.

Comparing Psychological Treatment Strategies for Women with Bowel Disorders: Patients with functional bowel disorders (FBD) have symptoms, such as abdominal pain and altered bowel habits, that can vary from person to person. Patients with moderate to severe symptoms often suffer from greater depression and psychological distress than those with less severe symptoms. A randomized, multicenter clinical trial of 431 women compared the value and utility of different approaches for treating psychological disabilities associated with FBD. In one comparative study, researchers compared two different types of sessions with trained psychologists. One group of women received educational training on their disorder, while the other group underwent cognitive-behavioral therapy (CBT), a type of therapy that emphasizes the role of using conscious thoughts to develop more effective coping strategies. In a second comparative study, separate groups of patients were treated with either an antidepressant or a placebo. Researchers found that CBT was far more beneficial than education therapy. Antidepressant therapy was equally effective as CBT, but the drug had side effects that prevented some patients from staying on the medication. The researchers compared subpopulations of patients, such as those with differing severity of illness or depression. Subgroup analysis demonstrated that both treatments were more effective in patients with moderate symptoms than in those with severe symptoms. However, FBD symptoms of patients

who also had depression were not improved with CBT or antidepressant therapy. This study suggests that patients with FBD can benefit from these types of treatment strategies which can, in turn, improve their quality-of-life.

Story of Discovery: The Art of Liver Transplantation

It was the 2002 Winter Olympic Games at Park City, Utah and the world looked on in awe as 29-year-old American snow boarder Chris Klug competed in the giant slalom race wearing a broken boot held together with duct tape. The crowd cheered as he crossed the finish line. Chris had won the bronze medal with tape securing his boot, but even more amazing, 18 months earlier he had undergone a liver transplant. Chris had spent years training for this event, encountering hurdles, large and small, and now he had medaled. Chris continues in his pursuit for excellence and in the 2006 Winter Olympic Games, he will be aiming for the gold.

Success in clinical research is similar to striving for the gold. It does not come with one major victory, but instead it requires persistent small but steady progress, punctuated with major achievements along the way. One scientist has shown the courage and commitment to perfect liver transplantation therapy in just this manner. Dr. Thomas Starzl, with continued NIDDK support, performed the first human liver transplant in 1963 and has spent the last 40 years perfecting this procedure. The achievements of Dr. Starzl and many other dedicated scientists save the lives of thousands of patients annually who have end-stage liver disease (ESLD).

Liver transplantation in humans was preceded by careful animal studies that enabled researchers to develop and test surgical procedures, and the result is that the procedure is safer and more successful. For example, NIDDK investigators developed a venous-venous bypass technique that reduces excessive blood loss and renal failure that sometimes seriously compromised the health of previous liver transplant recipients.

Preserving donor organs to be used as transplants was another research hurdle. In 1984, an NIDDK grantee developed a preservation solution-called the "UW solution" -- that effectively doubled the time a donor liver remains usable, to an average of 12 hours. Donor livers could then be procured from much greater distances and still arrive in a viable state for transplant.

In the late 1950s, animal research provided the foundation for determining that the drug combination of azathioprine and prednisone was the most effective immunosuppressive therapy at that time. Immunosuppressive therapy was greatly enhanced in the early 1980s with the introduction of cyclosporine, first as a single agent and then in combination with steroids. Largely as a result of cyclosporine's arrival, the frequency and success of liver transplant therapy began to grow. Indeed, a 1983 National Institutes of Health Consensus Development Conference concluded that liver transplantation was a therapeutic modality for ESLD.

Now, tacrolimus is the drug of choice. Discovered in 1984, it is effective and has fewer side effects than cyclosporine. Drugs like tacrolimus prevent graft rejection by inhibiting the immune system, but this does not come without a price. An inhibited immune system leaves the body susceptible to opportunistic infections and puts patients at higher risk for cancer. Thus, the drugs that prevent graft rejection can cause serious illnesses themselves.

Dr. Starzl and his colleagues are now taking a new approach to the concept of graft rejection. Rather than striving to suppress the immune response that threatens graft survival, they are seeking to minimize the patient's dependence on anti-rejection drugs following transplant surgery. Patients are pretreated with a broadly reacting drug before their transplants, and then are treated by tacrolimus monotherapy beginning the day after transplantation. This regimen

diminishes, but does not destroy, the immune system's ability to attack the new organ. It also enables the immune cells from the host and the "passenger" immune cells that are transplanted with the donor organ to interact with each other. Eventually, a type of peaceful co-existence develops, imparting a degree of host tolerance to the engrafted organ. At that point, medication is gradually reduced. Weaning from tacrolimus is continued until the patient is receiving a very low dose. Mild graft rejection is allowed; however, if serious symptoms begin to develop, the patient's medication is increased to a higher dose until he or she is ready to begin the weaning process again. This new regimen has been highly successful for patients who have received the treatment. Most are able to reduce their medication, and some take as little as one dose of tacrolimus a week. The timing and dosage of this regimen is based on principles of organ engraftment and acquired tolerance and, therefore, is effective for the transplantation of other organs, as well as the liver.

Although great strides have been made in facilitating liver transplantation, a chronic problem remains. There are far fewer livers available than are needed, and many lives are being lost because of the lack of available donor livers. Therefore, novel approaches to transplantation are being developed to fill this void. In December 2000, the NIDDK held a workshop on Living Donor Liver Transplantion. With this protocol, a donor gives part of his or her liver to an individual with ESLD. Ideally, the partial livers regenerate quickly into complete livers. However, this protocol presents a serious potential risk to the donor. The NIDDK is supporting research to improve the safety and outcomes of living donor transplantation therapy.

Another therapeutic approach is the transplantation of liver cells (hepatocytes). This avenue of treatment is particularly suitable for patients with metabolic disorders. With this regimen, liver cells from a donor are infused into to the portal vein of a recipient, take up residence in the patient's liver, and become fully functional. In 1998, a child with Crigler-Najjar syndrome, which causes a build up of serum bilirubin levels, received a hepatocyte transplant. The engraftment improved her condition and lasted 11 months until she was able to receive a liver transplant. Recently, an infant received a hepatocyte transplant for a urea cycle disorder, a condition that results from a missing enzyme normally produced by liver cells. Her condition was also improved temporarily as a result of the transplanted cells.

Dr. Starzl and his colleagues are also exploring genetically-altered pigs as potential organ donors. Pigs normally express the antigen 1,3- galactose (1,3-Gal) on their cells surface. Because this protein is not synthesized in humans, it is the major cause for rejection of pig-to-human liver grafts. Starzl's group developed genetically engineered pigs that no longer make the 1,3-Gal protein by "knocking out" both copies of the pig's 1,3-Gal gene. Without this antigen on their cells surface, the pig organs are much safer to use as donors for human transplants.

Improved surgical procedures, preservation solutions, immunosuppressive drugs, and protocols designed to use the body's natural mechanisms for tolerance are major successes that were achieved because of smaller research accomplishments along the way. These advances, as well as the novel approaches to liver transplantation that are in various stages of development today, are being pursued by dedicated scientists "aiming for the gold," a cure for liver disease.

Kidney, Urologic, and Hematologic Diseases

Bacterial Biofilm-like Pods in Acute Urinary Tract Infections: Urinary tract infections (UTIs) and their recurrence are extremely common in women. Most infections are caused by the common *Escherichia coli* (*E. coli*) bacterium. Some strains of bacteria are able to persist in the

bladder despite a vigorous host-immune response coupled with antibiotic treatment. To find out how bacteria are able to survive, researchers used microscopy to examine the bladders of mice inoculated with *E. coli*. While the inner surface of uninfected bladders was smooth, the surface of infected bladders was covered with pod-like protrusions filled with bacteria. The pod's contents resembled a "biofilm," a complex microbial community consisting of bacterial cells suspended in a matrix. Biofilms have previously been shown to protect bacteria from immune defenses and antibiotics. These structures may represent a mechanism through which the bacteria avoid being eliminated by host responses, and thus survive to repeatedly reinfect bladder cells. In addition, biofilm-like structures might prove to be important in many kinds of bacterial infections in humans, such as those in pneumonia and cystic fibrosis, that are either caused by bacterial infections or in which bacterial infections are frequent complications.

Recommended Dialysis Dose for Patients with Kidney Failure: People with irreversible kidney failure, also known as end-stage renal disease (ESRD), require dialysis to survive. Although current standards for hemodialysis treatment are effective, some physicians believed that an increased dialysis dose or the removal of larger waste particles, using a high-flux dialysis filter, would improve survival. The Hemodialysis (HEMO) Study Group directly tested this hypothesis in a large-scale, randomized clinical trial. Over 1,800 patients received either standard or high-dose hemodialysis, through either a low- or high-flux dialyzer, thrice weekly. Patients were followed for an average of over three years. Researchers found that, overall, patients on the high-dose therapy or using a high-flux dialyzer did not experience any additional benefit over patients treated with standard therapy or a low-flux filter. These results suggest that physicians should continue to administer hemodialysis to their patients using current clinical practice guidelines.

Underlying Mechanisms of Polycystic Kidney Disease: Polycystic kidney disease (PKD) is characterized by a massive enlargement of the kidneys due to the presence of fluid-filled cysts. The cysts are lined with kidney epithelial cells, which normally have a specialized hair-like structure on the cell surface, called a cilium. Recent studies in model organisms have suggested that mutations in PKD-related genes cause structural or functional defects in cilia. PC1 and PC2 are proteins encoded by mouse versions of the human PKD disease genes *PKD1* and *PKD2*, respectively. PC1 and PC2 have been observed in the cilium of mouse kidney epithelial cells grown *in vitro*. Researchers recently studied the effects of blocking the activation of PC1 or PC2 on cultured mouse kidney epithelial cells and then using fluid flow to bend the cells' cilia. Under these conditions, the cells no longer engaged in normal calcium-ion-mediated signaling pathways in response to mechanical stress. This suggests that the presence of PC1 or PC2 in the cilium is necessary for fluid-flow sensation, which may, in turn, help regulate tissue growth and change in the kidney. This study underscores the importance of normal functioning of the cilium, and also suggests mechanisms by which defects in these structures may lead to disease development.

Regression to Normal Kidney Function Is Common in Type 1 Diabetes Patients: Type 1 diabetes patients are at increased risk for developing complications, such as kidney disease. Previous research suggested that patients who secreted very slightly elevated levels of the protein albumin in their urine (microalbuminuria) had a very high risk of developing kidney damage. Researchers conducted a six-year study of nearly 400 type 1 diabetes patients, all of whom had microalbuminuria. Strikingly, they found that only 19 percent of these patients developed kidney disease, while approximately 60 percent underwent a regression to normal levels of urinary albumin. They found the regression to be dependent on factors such as age, cholesterol or triglyceride levels, blood pressure, and hemoglobin-A1c levels (a measure of long-term blood glucose control). Therefore, microalbuminuria in patients with type 1 diabetes does not always lead to diabetic kidney disease. The study also suggests therapeutic avenues--such as control of blood pressure, lipids, and HbA1c levels--that may promote this beneficial regression.

Story of Discovery: Evolving Therapies for Benign Prostatic Hyperplasia

If you are a man, chances are that someday you will have an enlarged prostate. Benign prostatic hyperplasia, or BPH, is a condition that affects more than half of all men in their sixties and as many as 90 percent over the age of 70,[2] even if they are unaware of it. Not everyone with BPH will develop symptoms, but--for those who do--until recently, surgery provided the only relief. Now, new medical approaches to the treatment of BPH, built on basic research stretching back over 50 years, offer an effective, non-surgical option. For men who still require surgery, less invasive techniques may provide effective, less traumatic alternatives.

The walnut-sized prostate gland is located below the bladder and surrounds the urethra as it leaves the bladder. The urethra and the fluids it transports pass through the prostate. One important function of the prostate gland is to release seminal fluid into the urethra at sexual climax to provide a vehicle for sperm.

The prostate gland undergoes two phases of growth. The first, during puberty, results in a relatively rapid doubling in size of the gland. The second, slower phase begins at around age 25 and continues throughout a man's life. As the region of the prostate immediately surrounding the urethra grows, it can, in some men, compress the urethra and inhibit the flow of urine. As a result, the bladder does not empty completely during urination. The narrowing of the urethra and partial emptying of the bladder are the cause of the complaints most commonly associated with BPH, such as frequent urination, inability to urinate, and urinary tract infections. Thus, while prostatic hyperplasia is "benign" in the sense that it is not cancerous, it can nevertheless cause serious health problems.

The male sex hormone testosterone plays an important role in a wide range of biological and physiological processes, ranging from development of the male urogenital tract during embryogenesis to the emergence of secondary sexual characteristics, such as facial and body hair, in the post-pubescent adult. In the late 1950s, researchers working with rats knew that experimental administration of testosterone resulted in an accumulation of protein in the male urogenital tract. By the mid-1960s, scientists could purify the hormone from these cells, but found--to their great surprise--not testosterone, which had been given to the animals, but a closely-related derivative: dihydrotestosterone, also known as DHT. Previously, it had been widely thought that DHT was a relatively unimportant breakdown product of testosterone. However, the finding of DHT in testosterone's target cells caused researchers to take a second look at this molecule.

[2]National Institute of Diabetes and Digestive and Kidney Diseases. Prostate Enlargement: Benign Prostatic Hyperplasia, September, 1998. NIH Publication No. 98-3012.

An important role for DHT in male urogenital development was postulated in the mid-1970s from studies of a rare inherited form of hermaphroditism. Individuals with this condition are genetically male but appear female at birth, insofar as they lack external male genitalia and a prostate gland. Oddly, blood tests of these individuals found normal circulating levels of testosterone. However, closer analysis revealed markedly reduced levels of DHT. This finding suggested that the genitalia and prostate require DHT to develop, because these features were absent in affected individuals, while other components of the male urogenital tract, which were present, do not. Years later, in the 1990s, sophisticated molecular analysis would reveal that the cause of this condition is a mutation in one of the proteins that converts testosterone to DHT, an enzyme known as 5-alpha reductase.

In the late 1970s, scientists had developed a model system in which they could induce prostatic hyperplasia in dogs by administering male sex hormones. Furthermore, they could block or reverse it by administering agents that inhibited 5-alpha reductase. This observation suggested that it was DHT that was responsible for the continued growth in the prostate in the adult, and stimulated pharmaceutical firms to pursue drugs that target the 5-alpha reductase enzyme as possible therapies for BPH. In 1992, the Food and Drug Administration approved for use in humans the drug finasteride–the first drug to block the conversion of testosterone to DHT by inhibiting 5-alpha reductase.

In the early 1990s, treatment of BPH generally involved a surgical procedure called Transurethral Resection of the Prostate, or TURP. As its name implies, TURP involves inserting a small scope up the urethra to the prostate and cutting away the obstructing tissue, thereby restoring normal urine flow. While TURP is an excellent treatment for BPH, it is expensive, requires several weeks of convalescence during recovery, and carries risks inherent in any surgical procedure. Because of these drawbacks, as an alternative to surgery some physicians began using finasteride to inhibit DHT production and thereby shrink the size of the prostate. Others used alpha blockers, a class of drugs that relax the smooth muscle in the prostate and bladder neck, and thus allow urine to flow more easily. However, urologists were not sure whether medical therapy was truly treating the BPH or was only relieving the symptoms while the underlying disease silently progressed.

To help answer this question, the NIH launched the Medical Therapy of Prostatic Symptoms (MTOPS) trial in 1994. A large, randomized clinical trial to assess the overall effectiveness of medical therapy on BPH symptoms and progression, the MTOPS trial would ultimately enroll over 3,000 men with BPH. Participants received one of four interventions: placebo (sugar pill), the 5-alpha reductase inhibitor finasteride, the alpha blocker doxazosin, or finasteride and doxazosin together. The study followed participants for an average of five years and monitored them for signs of BPH progression such as an inability to urinate, incontinence, or recurrent urinary tract infections. The results of the MTOPS trial were announced in 2002 and were unequivocal: combination therapy, consisting of finasteride and doxazosin together, reduced the risk of BPH progression by 67 percent compared to placebo. Each drug was also effective when used alone: the risk of progression was reduced by 39 percent with doxazosin and by 34 percent with finasteride. However, the results with combination therapy surprised all involved and will likely lead to important changes in the way BPH is treated.

Even with improvements in drug therapy, a fraction of men will ultimately require a surgical procedure to alleviate symptoms of BPH. While TURP remains the “gold standard,” a number of new surgical treatments for BPH have been developed over the past decade. These procedures aim to achieve the same long-term outcomes of TURP, but to do so with lower costs, more rapid recovery, and less risk. However, the relative effectiveness and long-term safety of these new surgical approaches is unknown. To bridge this gap in knowledge, the newly-launched Minimally Invasive Surgical Therapies (MIST) clinical trial will compare two new, less invasive surgical approaches, Transurethral Needle Ablation (TUNA) and Transurethral Microwave Therapy (TUMT), with combination medical therapy in men with BPH. The results of this trial are expected to further expand treatment options for men with BPH, to provide both physicians and patients with valuable information, and to give all involved the knowledge needed to make the most appropriate choices for long-term management of BPH.

Sustained Benefits of Insulin-sensitizing Drug Therapy in HIV-positive Individuals: The widespread adoption of highly active anti-retroviral therapy (HAART) has markedly improved survival in patients infected with HIV. Unfortunately, in many cases, HAART is associated with a variety of metabolic complications, including elevated blood lipid (fat) and cholesterol levels, insulin resistance, and abnormal distribution of body fat (lipodystrophy). These metabolic abnormalities are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. Researchers have previously demonstrated that short-term (three month) treatment of HIV-infected individuals with metformin, a drug used to improve glucose metabolism and insulin sensitivity, decreases insulin resistance and improves several cardiovascular risk factors. These investigators have now evaluated the metabolic and cardiovascular benefits of continued metformin therapy for HIV-infected patients with lipodystrophy. Continued treatment with metformin for an additional six months resulted in further significant reductions in tissue plasminogen activator antigen levels, a marker for cardiovascular disease, and body mass index. Reductions in insulin levels and waist circumference were also observed during the treatment extension. Lipid levels were not affected. These data demonstrate a sustained benefit of metformin treatment to reduce insulin levels and certain risk factors of cardiovascular disease in patients with HIV infection and lipodystrophy.

Highlights of Ongoing and Planned Activities

Initiatives: In FY 2005, the NIDDK will pursue multiple and diverse avenues of fundamental and clinical research relevant to the diseases and health issues within its mission. Because many people with type 2 diabetes are undiagnosed, a new effort will seek to find approaches to accurately and effectively diagnose type 2 diabetes. A new initiative is planned to study the process of angiogenesis--the formation of new blood vessels--as it relates to complications in type 1 diabetes. In addition, a network is planned to study human islet transplantation in adult type 1 diabetes patients. The NIDDK will enhance efforts in a long-term study of liver transplantation from one living adult to another. The study will identify factors that influence outcomes for both donors and recipients. Research will continue in hepatitis C virology, natural history, pathogenesis, therapy, and prevention. A new effort will apply a powerful technology to study proteins in order to gain insights into digestive diseases, and other diseases within the NIDDK-mission. The NIDDK will propel research on the genetics and heritability of calcium oxalate stone diseases, and the development of new treatments for the disorder. To extend the understanding of the risk factors for developing kidney disease and associated co-morbid illnesses, the NIDDK is supporting ancillary studies to ongoing or completed clinical trials and

epidemiological studies of kidney disease. Support will also continue for the development of new research tools and innovative methods to study the cells of the bladder, prostate, and other organs of the genitourinary tract. A new NIDDK initiative is planned to study vesicoureteral reflux in children, in order to frame management strategies and improve treatment approaches. The Institute will enhance efforts of a trans-NIDDK initiative to investigate variation in genetic background of individuals that may affect the prevalence, severity, or clinical symptoms of genetically-inherited disorders within the NIDDK mission.

The NIDDK will intensify its efforts to combat obesity as a serious health problem in its own right, and as a risk factor for type 2 diabetes. Basic, clinical, and behavioral studies will be aimed at understanding the important processes that may lead to obesity, in order to design effective intervention and prevention strategies. A new long-term effort is planned to address the relative contributions of the environmental and behavioral factors that lead to excessive weight gain and obesity among children. The NIDDK will also begin studies to prevent or treat pediatric obesity in various site-specific settings, such as the home, day-care or pre-school, school, or other appropriate community venue. A new NIDDK initiative will support collaborative programs in obesity focusing on behavior/cognition, nutrition, animal studies, functional imaging, body composition, or other fields of relevance to obesity; the goal of this initiative is to bridge the gap between understanding at the molecular and genetic level of neural pathways involved in food intake, and the understanding of behavioral influences on human obesity. Support will continue for a basic research initiative to study the genetics influencing obesity-related traits in model organisms, which can be used to help identify analogous genes in humans. Another study is using proteomics technology to understand biological processes in obesity and its co-morbidities. A NIIDK initiative on understanding the life cycle of the adult fat cell, as well as understanding characteristics of visceral fat that may be associated with morbidity, may help identify markers of obesity-associated disease risk. Basic and clinical studies are investigating the underlying mechanisms of long-term weight maintenance and what processes may contribute to weight regain after weight loss. Studies in humans and animals are determining the impact of diet on weight loss, energy expenditure, body composition, and obesity-related risk factors. Studies will also continue on energy balance. One effort is encouraging research in animals to help clarify the influences on overweight and obesity of environmental factors present during development; this research may lead to the design of new strategies to improve the health of mothers and their offspring. Another NIDDK initiative on energy balance is seeking ways to enhance understanding of how many different biological processes affect one another so as to assemble an integrated picture of their interrelated effects on obesity and health. The NIDDK will enhance efforts on an obesity initiative promoting partnerships among basic and clinical researchers to ensure that observations from the laboratory are quickly translated into a clinical setting.

NIH Roadmap: The NIDDK will be implementing an NIH Roadmap initiative on "Metabolomics Technology Development." The "metabolome" is the complete set of

metabolites in an organism; examples of metabolites include amino acids, peptides, and lipids. "Metabolomics" is the study of these low-molecular weight molecules. The purpose of this initiative is to promote the development of highly innovative and sensitive tools for studying metabolomics. The development of novel technologies can directly benefit the study of diseases within the NIDDK mission. For example, this technology can be used to develop surrogate markers to predict risk, aid in diagnosis, and assess progression of the complications of diabetes. Metabolomics technology can also be applied to advance understanding of the metabolic changes that occur with obesity and its co-morbidities. The ability to study metabolites at the single cell level would also aid in characterizing tissues and organs containing a variety of specialized cell types, such as the kidney. The "Molecular Libraries" Roadmap initiative will also accelerate research on diseases within the NIDDK mission. Studies using a molecular library approach, in which scientists screen a large number of small molecules to find one that interacts with a protein of interest, have already been performed by NIDDK-supported researchers to study diabetes, bile acid and cholesterol metabolism, and cystic fibrosis. This initiative will help researchers use this approach to study a wide range of diseases within the NIDDK mission. In addition, a new NIDDK initiative to develop assays for small molecule screening for potential therapeutics for diseases within the NIDDK mission will enhance application of the NIH Roadmap effort to NIDDK diseases.

AIDS: Research supported by the NIDDK has contributed to current understanding of the AIDS wasting syndrome. The widespread adoption of highly active anti-retroviral therapy (HAART) has markedly improved survival and decreased the incidence of this condition, but has led to metabolic changes related to the treatment. The NIDDK supports research efforts into the causes of and treatment for these HAART-associated changes in metabolism. In addition, the NIDDK supports studies of the neurological, gastrointestinal, endocrine, renal, liver, and hematologic manifestations and complications of HIV infection. The NIDDK maintains a highly productive structural biology intramural program that seeks to determine the structures of biologically significant proteins relative to HIV infection, replication, and integration.

Strategic Planning: In framing new and expanded Institute initiatives, the NIDDK continues to be guided by several strategic planning efforts. A recent report on the Special Type 1 Diabetes Research program describes the unique, innovative, and collaborative research groups, clinical trial networks, and consortia involved in the program. It also highlights future research opportunities, which will serve as a framework for future planning efforts. The new Liver Disease Research Branch, in the NIDDK Division of Digestive Diseases and Nutrition, is developing a Research Action Plan that will provide an overview of current research in liver disease and identify areas of future opportunities. The NIH Obesity Research Task Force will also develop a strategic plan for NIH obesity research, with external scientific and public input, in order to address areas of scientific promise that can benefit from collaborative efforts.

Educational Programs: Through a variety of educational programs, the NIDDK will continue to provide important health information to health practitioners and the public. The National Diabetes Education Program (NDEP) is a partnership among the NIDDK, the CDC, and over 200 public and private organizations. The NDEP's "Small Steps, Big Rewards, Prevent Type 2 Diabetes" is a campaign to translate the positive results of the Diabetes Prevention Program (DPP), which showed that modest lifestyle changes dramatically prevented or delayed onset of type 2 diabetes in high-risk adults. The educational material contains a "Game Plan" that provides patients with information about implementing a program to prevent or delay disease onset. The NDEP's health awareness campaign, "Be Smart About Your Heart: Know the ABCs of Diabetes," is aimed at helping people with diabetes to better understand the need to control all aspects of their diabetes to help prevent heart attacks or strokes. The NDEP also has valuable resources for children with diabetes and their caregivers. "Helping the Student with Diabetes Succeed, A Guide for School Personnel" is a comprehensive guide designed to empower school personnel, parents, and students to ensure a safe learning environment and promote a team approach to carry out a student's diabetes care plan. The NIDDK plans to distribute this important Guide to all schools in the country.

The Weight-control Information Network (WIN) develops and distributes materials on obesity, weight control, physical activity, and nutrition. A new brochure series, "Across the Lifespan," offers brochures in English and Spanish for older adults, parents, pregnant women, and young and middle aged adults that explain healthy choices. WIN recently released three new publications relevant to healthy eating and weight management: "Just Enough for You: About Food Portions," "Medical Care for Obese Patients," and "Weight and Waist Measurement: Tools for Adults." Based on the latest research findings on weight control, WIN is updating several of its fact sheets and brochures, including "Choosing a Safe and Successful Weight Loss Program," "Helping your Overweight Child," "Physical Activity and Weight Control," and "Very Low Calorie Diets." The NIDDK's National Kidney Disease Education Program (NKDEP) is a pilot program that aims to prevent kidney disease by raising awareness about the seriousness of the problem and the importance of early diagnosis and appropriate treatment. The NKDEP is designed to close the gap between evidence and practice by educating people at risk and physicians, with the goal of identifying kidney disease in its early, treatable stages. The NKDEP pilot phase will initially target primary care providers and people at highest risk for kidney disease--particularly African Americans with diabetes, high blood pressure or a family history of kidney disease--in four cities: Baltimore; Cleveland; Jackson, Mississippi; and Atlanta. The NIDDK also plans to undertake a Women's Urologic Health Outreach Initiative in partnership with the American Urological Association and the Interstitial Cystitis Association. The program will be a campaign to increase awareness and knowledge among primary care physicians about current health care recommendations for women's urological problems, including interstitial cystitis, urinary incontinence, and urinary tract infections.

Other Areas of Interest

The NIDDK will also continue vigorous support of its clinical trials programs. In the area of type 1 diabetes, support will continue for TrialNet--a nationwide network of clinical trial centers that supports the development and implementation of clinical trials of agents to prevent or slow the progression of type 1 diabetes. Another study, The Environmental Determinants of Diabetes in the Young (TEDDY), will analyze the infectious agents, dietary factors, and other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. The NIDDK is also creating a major new islet transplantation network to design and implement human islet transplantation studies in adult type 1 diabetes patients that may eventually result in improved treatment of the disease.

In the area of type 2 diabetes, the Diabetes Prevention Program (DPP) clinical trial demonstrated that type 2 diabetes could be delayed or prevented by lifestyle intervention or drug treatment in high-risk adults, including minorities who suffer disproportionately from the disease. The NIDDK is continuing follow-up studies of the DPP participants to determine the durability of the DPP interventions in preventing or delaying type 2 diabetes, as well as studying the long-term effect of the interventions on the development of complications. The NIDDK also supports a multicenter trial, TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth), that will seek to identify the best treatment of type 2 diabetes in children and teens.

NIDDK continues to support significant clinical research on digestive diseases. In the area of obesity research, the Look AHEAD (Action for Health in Diabetes) trial, set to complete enrollment soon, will examine the health effects of interventions designed to produce voluntary, long-term weight loss in 5,000 obese people with type 2 diabetes. The NIH has now established a Bariatric Surgery Clinical Research Consortium (BSCRC) to facilitate research that would enhance patient evaluation and selection, and may also lead to improved understanding of factors underlying the development of obesity, with implications for new strategies for prevention and treatment. Several robust clinical research efforts on liver disease include evaluating adult-to-adult living donor liver transplantations through the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL), now gathering data on application, risks, and outcomes for donors and recipients. Two clinical trials of hepatitis C currently enrolling patients are the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, to study patients who are unresponsive to short-term therapy with peginterferon alfa and test whether long-term treatment might prevent their liver disease progression, and the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C), to examine resistance to antiviral therapy, particularly as it affects African American patients. The Biliary Atresia Research Consortium (BARC) is collecting data on children with this liver disease to facilitate meaningful clinical trials on etiology, diagnosis and treatments, including a recent trial of treatments to improve bile flow after surgery. Two other networks recently established to support clinical research on liver disease are the Nonalcoholic Steatohepatitis Clinical Research Network and the Hepatotoxicity

Clinical Research Network. Additional clinical research efforts include studies of pancreatic disease and biliary disease, intestinal failure and short bowel syndrome, and Barrett's esophagus.

In the areas of kidney, urologic, and hematologic diseases, the Institute will continue its strong support of clinical trials. Trials of therapies to alleviate symptoms of chronic pelvic pain syndromes will continue through the recent expansion of two clinical trial networks--the Interstitial Cystitis Clinical Research Network (ICCRN), which will build upon the work of the Interstitial Cystitis Clinical Trials Group (ICCTG) to develop and conduct future clinical trials of novel therapies for IC (a chronic and painful bladder disease), and the Chronic Prostatitis Clinical Research Network (CPCRN). Both networks will conduct ancillary studies in conjunction with clinical trials. The interstitial cystitis and prostatitis investigators will also work together in a new umbrella network on shared needs and goals in clinical trial development. Two trials of treatments for benign prostatic hyperplasia (BPH) are moving forward, one evaluating minimally invasive surgical treatments, the other testing phytotherapies. Progress will continue toward identifying factors that drive the progression of kidney disease and its complications: the new Prospective Study of Chronic Kidney Disease in Children, established in collaboration with the NINDS and the NICHD, aims to characterize determinants of disease progression, developmental deficits, and long-term health risks in children with impaired kidney function. Patient enrollment has begun in a second large-scale study that will evaluate prospectively the factors influencing rapid loss of kidney function and the link between kidney disease and heart disease in adults. Another study is examining the genetics of diabetic kidney disease. Patients are also being recruited for trials addressing how to improve cardiovascular outcomes in kidney transplant recipients, and how to reduce proteinuria in focal segmental glomerulosclerosis (FSGS). Newly launched clinical studies will address the feasibility and potential benefits of conducting large-scale randomized trials of frequent dialysis for end-stage renal disease. Plans are under way for a trial of an intervention to halt progression of polycystic kidney disease and its complications. Current and future kidney disease clinical trials should benefit from the NIDDK Kidney Disease Clinical Studies Initiative (KDSCI), which aims to encourage the full and effective use of resources from completed clinical trials and epidemiological studies, and to increase the number of new investigator-initiated clinical studies through innovative funding mechanisms--thereby maximizing the outcomes of kidney disease clinical research.

Innovations in Management and Administration

Liver Disease Research Branch: In June 2003, the NIDDK Director created the Liver Disease Research Branch within the Division of Digestive Diseases and Nutrition (DDN). The Branch

will focus and accelerate research on liver disease in the NIDDK and help to coordinate and stimulate liver-related research across the NIH.

Office of Obesity Research: In late 2002, the NIDDK created the Office of Obesity Research to encourage multidisciplinary approaches to obesity and to coordinate all obesity-related research within the Institute. The new office will coordinate the work of more than 11 programs with major obesity-related components--ranging from basic research to large clinical trials.

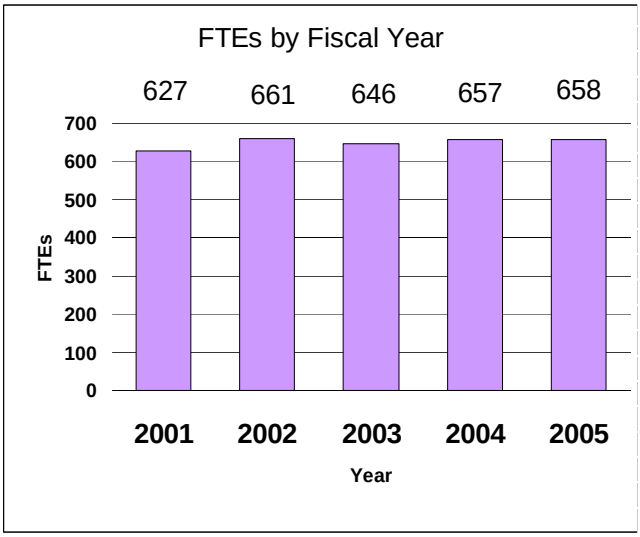
NIDDK Participation in the NIH Obesity Research Task Force: The Director of the NIDDK and the Acting Director of the National Heart, Lung, and Blood Institute serve as co-chairs of the NIH Obesity Research Task Force, which was established by the NIH Director to coordinate and accelerate obesity research efforts across the NIH. The Task Force membership also includes NIDDK senior scientific staff.

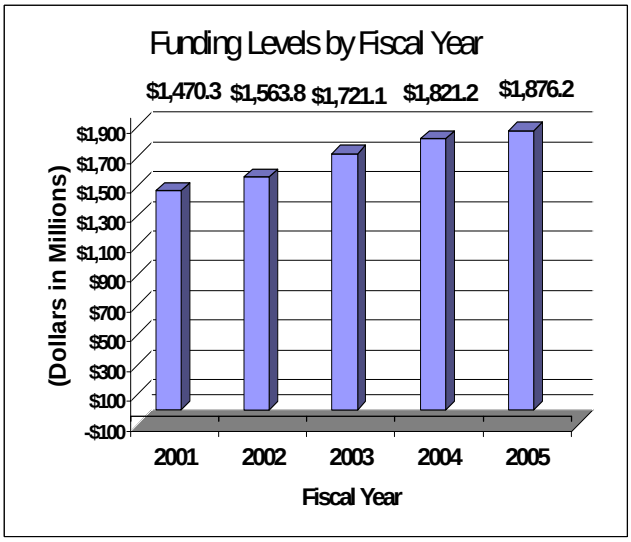
Electronic Government: The NIDDK has begun to use an NIH Electronic Council Book (ECB) in order to increase efficiency of National Advisory Council meetings. The ECB, which is continually updated, allows Advisory Council members to read relevant information before each Council round. The NIDDK has also expanded its website to facilitate information dissemination to investigators and the public. This includes a recently launched website dedicated to the Special Statutory Funding Program for Type 1 Diabetes Research. The website, http://www.niddk.nih.gov/fund/diabetesspecialfunds/, is a resource for type 1 diabetes investigators in that it highlights current research funding opportunities. The websites of the National Diabetes Education Program (http://www.ndep.nih.gov/) and the National Kidney Disease Education Program (http://www.nkdep.nih.gov/) contain valuable information for patients. Patients can also directly order educational material from the National Diabetes Information Clearinghouse, the National Digestive Diseases Information Clearinghouse, and the National Kidney and Urologic Diseases Information Clearinghouse at http://catalog.niddk.nih.gov/cgi-bin/cp/cp-app.cgi . As co-lead Institute of the NIH Obesity Research Task Force, the NIDDK is involved in developing a new website on NIH obesity research.

Budget Policy

The Fiscal Year 2005 budget request for the NIDDK is $1,726,196,000, an increase of $54,956,000 and 3.3 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NIDDK's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIDDK are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.





NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NIDDK is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NIDDK will support 1,155 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 91 research centers, 604 other research grants, including 117 clinical career awards, and 436 R&D contracts. Intramural Research and Research Management and Support receive increases to support increased pay and estimated inflationary increases in FY 2005.

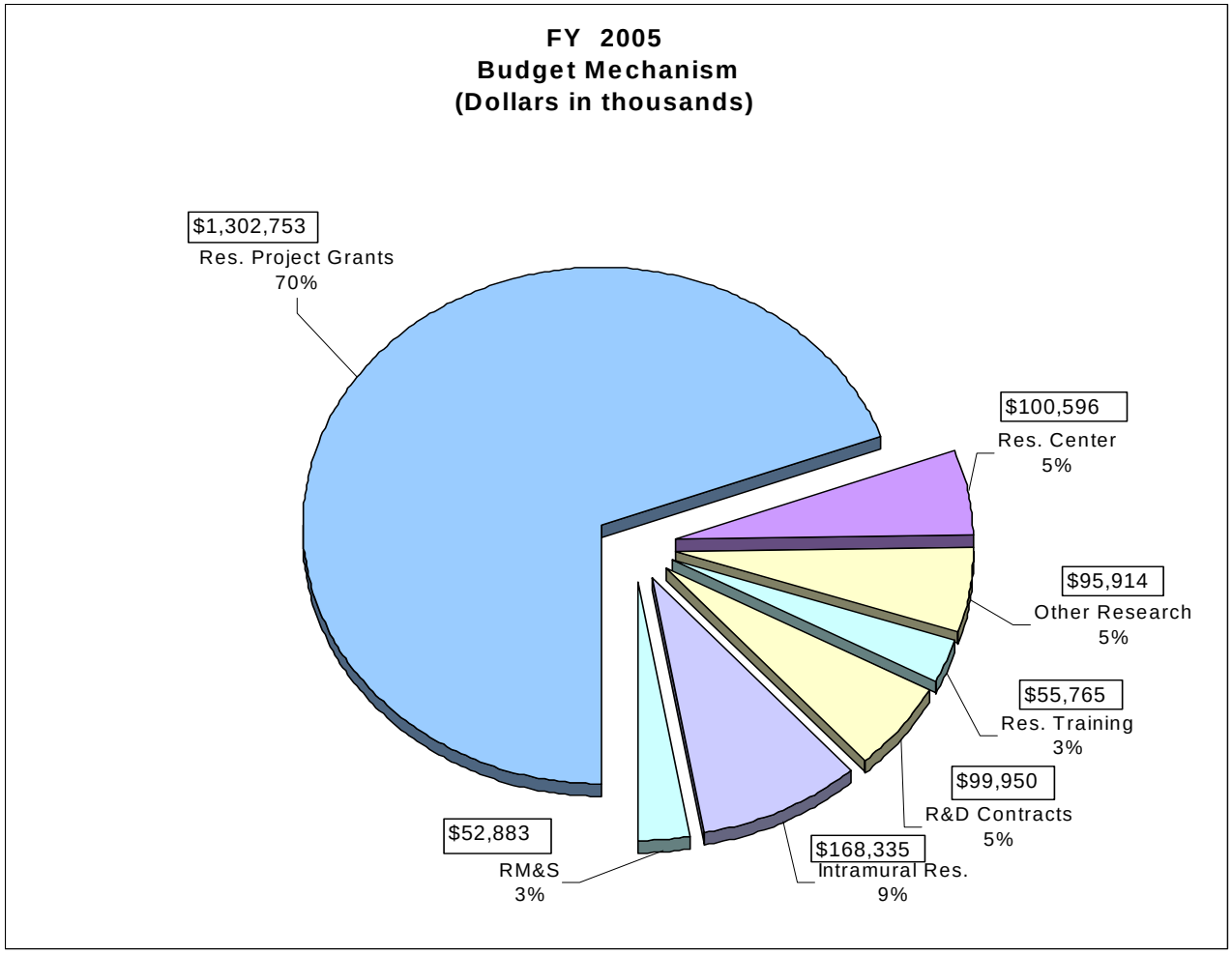
In the fiscal year 2005 budget request additional funding in the amount of $5,652,000 will be allocated to greatly enhance NIDDK research in obesity. This funding is planned to help support several of the NIDDK's many planned obesity research efforts. A new NIDDK initiative aims to develop effective, primary care office-based programs to prevent and/or treat childhood obesity.

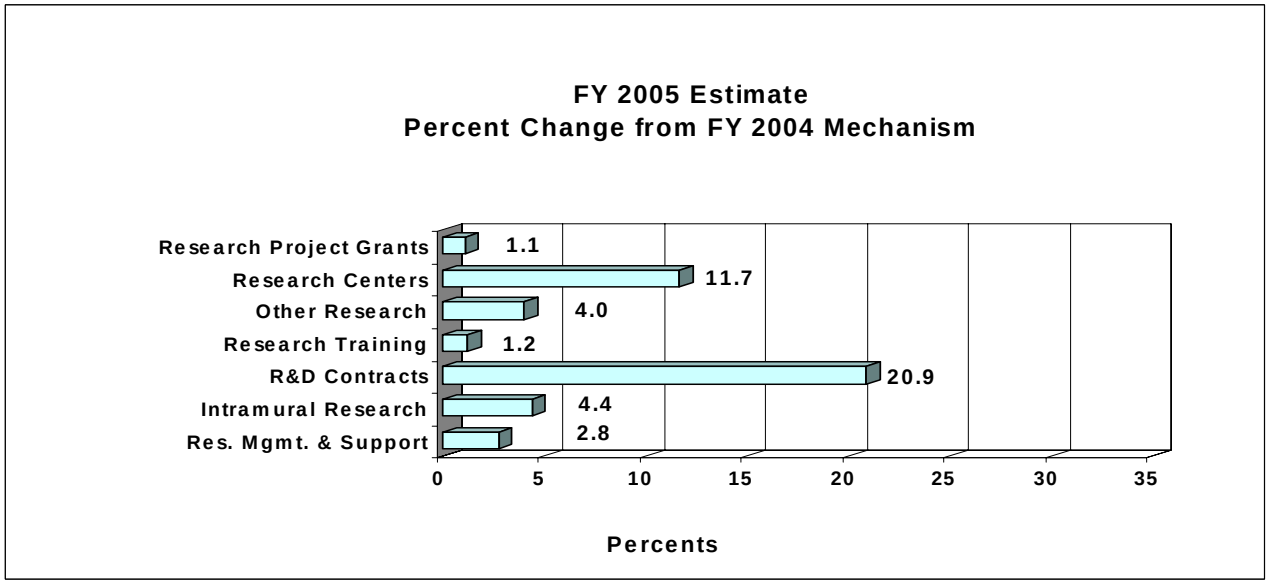
This initiative will lead to the development and testing of such programs for efficacy in accomplishing weight loss in overweight children and in preventing excessive weight gain in children at risk for overweight. The NIDDK will also foster new research on the prevention or treatment of pediatric obesity in various other site-specific settings, such as the home, day-care or pre-school, school, or other appropriate community venue. The goal would be to explore methods in pediatric populations for the primary prevention of inappropriate weight gain among those not overweight; secondary prevention to prevent further weight gain among those already overweight or obese; or tertiary prevention, i.e., treatment of overweight or obesity to prevent the complications of associated co-morbidities. A new long-term effort is planned to address the relative contributions of the environmental and behavioral factors that lead to excessive weight gain and obesity among children. Knowledge of important factors will help craft the most rational and effective interventions directed at diet and physical activity. The targeted amount for these activities is $2,500,000.

In the area of neurobiologic research, a new NIDDK initiative will support collaborative programs in obesity focusing on behavior/cognition, nutrition, animal studies, functional imaging, body composition, or other fields of relevance to obesity; the goal of this initiative is to bridge the gap between understanding at the molecular and genetic level of neural pathways involved in food intake, and the understanding of behavioral influences on human obesity. The targeted amount for this activity is $1,000,000.

Additionally, the supplemental funding will also help the NIDDK support an "Obesity Clinical Research Center" in the NIH Intramural Research Program to generate new knowledge regarding the prevention, treatment, and underlying molecular mechanisms of obesity and its associated diseases. The Center will include a "magnet" approach, in which expertise and resources from across a wide-spectrum of the Intramural Research Program are focused on state-of-the-art clinical investigative strategies, laboratory support, and imaging capabilities to pursue obesity research in a synergistic manner. The targeted amount for these activities is $2,152,000.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,252	$830,779,000	2,519	$916,444,000	2,465	$924,049,000
Administrative supplements	(340)	29,939,000	(210)	19,009,000	(211)	19,244,000
Full funded	6	906,000	19	3,909,000	19	3,948,000
Single year	885	289,981,000	955	306,279,000	965	311,490,000
Renewal	314	121,767,000	337	128,210,000	337	129,135,000
New	568	167,714,000	615	177,543,000	625	181,825,000
Supplements	3	500,000	3	526,000	3	530,000
Subtotal, competing	891	290,887,000	974	310,188,000	984	315,438,000
Subtotal, RPGs	3,143	1,151,605,000	3,493	1,245,641,000	3,449	1,258,731,000
SBIR/STTR	132	37,615,000	144	42,810,000	148	44,022,000
Subtotal, RPGs	3,275	1,189,220,000	3,637	1,288,451,000	3,597	1,302,753,000
Research Centers:						
Specialized/comprehensive	78	82,311,000	78	84,361,000	79	93,502,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	250,000	1	717,000	1	1,094,000
Comparative medicine	0	5,300,000	10	5,000,000	11	6,000,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	78	87,861,000	89	90,078,000	91	100,596,000
Other Research:						
Research careers	457	57,607,000	485	60,995,000	504	63,041,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	3,604,000	5	2,424,000	4	3,772,000
Biomedical research support	0	0	0	32,000	0	40,000
Minority biomedical research support	0	1,690,000	0	1,440,000	0	1,440,000
Other	44	26,433,000	94	27,320,000	96	27,621,000
Subtotal, Other Research	501	89,334,000	584	92,211,000	604	95,914,000
Total Research Grants	3,854	1,366,415,000	4,310	1,470,740,000	4,292	1,499,263,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	150	6,871,000	150	7,320,000	150	7,320,000
Institutional awards	994	45,767,000	992	47,776,000	1,005	48,445,000
Total, Training	1,144	52,638,000	1,142	55,096,000	1,155	55,765,000
Research & development contracts	392	95,600,000	415	82,678,000	436	99,950,000
(SBIR/STTR)	(4)	(1,513,000)	(2)	(750,000)	(2)	(750,000)
	FTEs		FTEs		FTEs	
Intramural research	438	155,918,000	438	161,268,000	438	168,335,000
Research management and support	208	50,512,000	219	51,458,000	220	52,883,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIDDK	646	1,721,083,000	657	1,821,240,000	658	1,876,196,000
(RoadMap Support)		(0)		(5,740,000)		(10,867,000)
(Clinical Trials)		(172,842,000)		(177,000,000)		(181,000,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases Type One Diabetes Only

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	110	$63,502,000	148	$46,727,000	197	$106,190,000
Administrative supplements	(6)	1,597,000	(0)	0	(0)	0
Full funded	0	0	0	0	0	0
Single year	16	9,680,000	280	80,079,000	26	7,800,000
Renewal	0	230,000	0	0	0	0
New	16	9,450,000	280	80,079,000	26	7,800,000
Supplements	0	0	0	0	0	0
Subtotal, competing	16	9,680,000	280	80,079,000	26	7,800,000
Subtotal, RPGs	126	74,779,000	428	126,806,000	223	113,990,000
SBIR/STTR	0	0	14	4,165,000	14	4,165,000
Subtotal, RPGs	126	74,779,000	442	130,971,000	237	118,155,000
Research Centers:						
Specialized/comprehensive	0	0	0	0	0	0
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	5,000,000	10	5,000,000	11	6,000,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	0	5,000,000	10	5,000,000	11	6,000,000
Other Research:						
Research careers	7	2,371,000	7	2,369,000	7	2,383,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	3,604,000	5	2,424,000	4	3,772,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	0	0	0	0	0
Other	0	0	0	0	0	0
Subtotal, Other Research	7	5,975,000	12	4,793,000	11	6,155,000
Total Research Grants	133	85,754,000	464	140,764,000	259	130,310,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	0	0	0	0	0	0
Institutional awards	19	1,102,000	7	1,086,000	7	1,090,000
Total, Training	19	1,102,000	7	1,086,000	7	1,090,000
Research & development contracts	0	12,987,000	9	8,000,000	10	18,450,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	0	0	0	0	0	0
Research management and support	0	157,000	0	150,000	0	150,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIDDK T1D	0	100,000,000	0	150,000,000	0	150,000,000
(RoadMap Support)		(0)		(0)		(0)
(Clinical Trials)		(18,827,000)		(43,500,000)		(43,500,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Division of Diabetes, Endocrinology and Metabolic Diseases		$712,555		$777,865		$798,852		$20,987
Division of Digestive Diseases and Nutrition		411,334		426,400		439,000		12,600
Division of Kidney, Urologic and Hematologic Diseases		390,764		404,249		417,126		12,877
Subtotal, Extramural research		1,514,653		1,608,514		1,654,978		46,464
Intramural research	438	155,918	438	161,268	438	168,335	0	7,067
Res. management & support	208	50,512	219	51,458	220	52,883	1	1,425
Type One Diabetes		(100,000)		(150,000)		(150,000)		
Total	646	1,721,083	657	1,821,240	658	1,876,196	1	54,956

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

FY 2004 Final Conference				$1,821,240,000
FY 2005 Estimated Budget Authority				1,876,196,000
Net change				54,956,000
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$55,656,000		$780,000
b. Annualization of January 2004 pay increase		55,656,000		570,000
c. January 2005 pay increase		55,656,000		626,000
d. One less day of pay		55,656,000		(213,000)
e. Payment for centrally furnished services		25,870,000		776,000
f. Increased cost of laboratory supplies, materials, and other expenses		79,742,000		1,395,000
Subtotal				3,934,000
2. Research Management and Support:				
a. Within grade increase		22,844,000		320,000
b. Annualization of January 2004 pay increase		22,844,000		234,000
c. January 2005 pay increase		22,844,000		257,000
d. One less day of pay		22,844,000		(88,000)
e. Payment for centrally furnished services		7,050,000		193,000
f. Increased cost of laboratory supplies, materials, and other expenses		21,564,000		312,000
Subtotal				1,228,000
Subtotal, Built-in				5,162,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,519	$935,453,000	(54)	$7,840,000
b. Competing	974	310,188,000	10	5,250,000
c. SBIR/STTR	144	42,810,000	4	1,212,000
Total	3,637	1,288,451,000	(40)	14,302,000
2. Research centers	89	90,078,000	2	10,518,000
3. Other research	584	92,211,000	20	3,703,000
4. Research training	1,142	55,096,000	13	669,000
5. Research and development contracts	415	82,678,000	21	17,272,000
Subtotal, extramural				46,464,000
	FTEs		FTEs	
6. Intramural research	438	161,268,000	0	3,133,000
7. Research management and support	219	51,458,000	1	197,000
Subtotal, program		1,821,240,000		49,794,000
Total changes	657		1	54,956,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	657	658	1
Full-time equivalent of overtime & holiday hours	2	1	(1)
Average ES salary	$0	$0	$0
Average GM/GS grade	10.9	10.9	0.0
Average GM/GS salary	$69,794	$71,190	$1,396
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$78,740	$80,315	$1,575
Average salary of ungraded positions	103,661	105,734	2,073

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$28,000,000	$29,000,000	$1,000,000
11.3 Other than Full-Time Permanent	23,000,000	23,835,000	835,000
11.5 Other Personnel Compensation	1,100,000	1,140,000	40,000
11.7 Military Personnel	1,200,000	1,243,000	43,000
11.8 Special Personnel Services Payments	9,950,000	10,310,000	360,000
Total, Personnel Compensation	63,250,000	65,528,000	2,278,000
12.1 Civilian Personnel Benefits	13,500,000	13,980,000	480,000
12.2 Military Personnel Benefits	1,750,000	1,813,000	63,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**78,500,000**	**81,321,000**	**2,821,000**
21.0 Travel & Transportation of Persons	2,635,000	2,700,000	65,000
22.0 Transportation of Things	413,000	423,000	10,000
23.1 Rental Payments to GSA	1,000	1,000	0
23.2 Rental Payments to Others	57,000	59,000	2,000
23.3 Communications, Utilities & Miscellaneous Charges	1,203,000	1,233,000	30,000
24.0 Printing & Reproduction	930,000	953,000	23,000
25.1 Consulting Services	1,551,000	1,590,000	39,000
25.2 Other Services	8,180,000	8,380,000	200,000
25.3 Purchase of Goods & Services from Government Accounts	130,060,000	138,104,000	8,044,000
25.4 Operation & Maintenance of Facilities	4,424,000	4,585,000	161,000
25.5 Research & Development Contracts	61,700,000	73,006,000	11,306,000
25.6 Medical Care	667,000	694,000	27,000
25.7 Operation & Maintenance of Equipment	2,193,000	2,277,000	84,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**208,775,000**	**228,636,000**	**19,861,000**
26.0 Supplies & Materials	14,455,000	14,930,000	475,000
31.0 Equipment	11,825,000	12,225,000	400,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,502,439,000	1,533,708,000	31,269,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	7,000	7,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,742,740,000**	**1,794,875,000**	**52,135,000**
Total Budget Authority by Object	**1,821,240,000**	**1,876,196,000**	**54,956,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$28,000,000	$29,000,000	$1,000,000
Other Than Full-Time Permanent (11.3)	23,000,000	23,835,000	835,000
Other Personnel Compensation (11.5)	1,100,000	1,140,000	40,000
Military Personnel (11.7)	1,200,000	1,243,000	43,000
Special Personnel Services Payments (11.8)	9,950,000	10,310,000	360,000
Total Personnel Compensation (11.9)	**63,250,000**	**65,528,000**	**2,278,000**
Civilian Personnel Benefits (12.1)	13,500,000	13,980,000	480,000
Military Personnel Benefits (12.2)	1,750,000	1,813,000	63,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**78,500,000**	**81,321,000**	**2,821,000**
Travel (21.0)	2,635,000	2,700,000	65,000
Transportation of Things (22.0)	413,000	423,000	10,000
Rental Payments to Others (23.2)	57,000	59,000	2,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,203,000	1,233,000	30,000
Printing and Reproduction (24.0)	930,000	953,000	23,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,392,000	1,426,000	34,000
Other Services (25.2)	8,180,000	8,380,000	200,000
Purchases from Govt. Accounts (25.3)	35,267,000	36,371,000	1,104,000
Operation & Maintenance of Facilities (25.4)	4,424,000	4,585,000	161,000
Operation & Maintenance of Equipment (25.7)	2,193,000	2,277,000	84,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**51,456,000**	**53,039,000**	**1,583,000**
Supplies and Materials (26.0)	14,390,000	14,864,000	474,000
Subtotal, Non-Pay Costs	71,084,000	73,271,000	2,187,000
Total, Administrative Costs	**149,584,000**	**154,592,000**	**5,008,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-188)

Item

Translational research – The Committee commends NIDDK for its development of the platform technologies of genomics and proteomics to expand clinical research capability. The Committee urges NIDDK to continue the effort to remove the most common barriers between laboratory discoveries and clinical trials, including by making available on a competitive basis the resources for pre-clinical development of drugs and therapies. (p. 63)

Action taken or to be taken

The NIDDK has recently begun a collaboration with the National Cancer Institute's Rapid Access to Intervention Development (RAID) program in order to foster development of new therapeutics for type 1 diabetes (T1D). The new T1D-RAID program is a special mechanism to make available to academic investigators the necessary resources to move novel molecules and concepts from the bench to the bedside more rapidly and effectively. T1D-RAID will assist investigators by providing the preclinical development steps that may be obstacles to using their therapeutics in a clinical setting. The goal of T1D-RAID is to support the preclinical work needed for the clinical "proof-of-principle," which is the study that will determine if a new molecule or novel approach is a viable candidate for expanded clinical evaluation. Therapeutics, such as small molecules or biologics for the treatment or prevention of type 1 diabetes and its complications, would be candidates for development through this program. T1D-RAID is designed to accomplish the tasks that are rate-limiting in bringing discoveries from the laboratory to the clinic.

The NIDDK sponsors other initiatives that promote the movement of therapeutics from the laboratory to clinical trials. For example, the NIDDK has sponsored a Request for Applications (RFA) on "Bench-to-Bedside Research on Type 1 Diabetes and Its Complications." This is a collaborative effort with the National Institute of Allergy and Infectious Diseases (NIAID), the National Eye Institute (NEI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke, and the Office of Dietary Supplements. This RFA promotes collaborations between clinical and basic biomedical researchers in order to translate promising advances in the laboratory into new therapies for the prevention, treatment,

and cure of type 1 diabetes. The goal is for these promising therapies to be tested in patients or in preclinical studies in animal models. The NIDDK is also sponsoring an RFA on type 1 diabetes and its complications through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (SBTT) program. This research solicitation is a collaboration with the NIAID, NEI, NHLBI, the National Institute of Nursing Research, and the National Institute of Child Health and Human Development. It encourages the small business community to participate in the research and development of commercial products, such as therapeutics, in the area of type 1 diabetes and its complications.

Item

Irritable bowel syndrome (IBS) – The Committee is pleased that NIDDK is considering the development of a strategic plan for IBS research. The Committee, however, remains concerned about the increasing frequency of IBS, a chronic complex of disorders that affect the digestive system. These common dysfunctions strike approximately sixty million Americans annually and result in significant human suffering and disability. The Committee encourages NIDDK to give priority consideration to funding grants that will increase the IBS portfolio. (p. 64)

Action taken or to be taken

Irritable bowel syndrome and related functional GI disorders, including esophageal reflux, non-ulcer dyspepsia, and fecal incontinence affect a large proportion of the U.S. population and account for considerable health care costs. While progress in diseases such as esophageal reflux (GERD) have led to the widespread availability of highly effective drug therapies, progress in the other conditions has occurred more slowly, probably related to the great variability and complexity of these conditions. Because of our limited understanding of these conditions at present, NIDDK has supported a broad-based research approach which includes fundamental research aimed at understanding the development of the pathways that control gut motility; the integration of pain, motility and behavioral neural circuits; the relationship of gut inflammation to these pathways; as well as translational research in animal models and clinical trials. Recent fundamental research has already led to novel insights into less common but severe functional GI disorders, such as Hirschsprung's disease, and it is anticipated that a continued investment in basic research in research areas related to functional GI disorders will ultimately lead to novel insights into the more common, but complex functional disorders. NIDDK is pleased to have supported the most rigorous randomized controlled treatment trial of IBS that has yet been conducted, a randomized controlled trial which compared treatment with desipramine to cognitive behavioral therapy. In FY03, NIDDK sponsored a meeting of the Digestive Diseases Interagency Coordinating Committee on Functional GI Disorders. Scientific leaders in the community participated and provided guidance for the development of future initiatives in this area.

Item

Inflammatory bowel disease – The Committee has been encouraged in recent years by discoveries related to Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD). These extremely complex disorders represent the major cause of morbidity and mortality from intestinal illness. The Committee commends NIDDK for its strong leadership in this area and encourages the Institute to continue to give priority consideration to the following areas of IBD research: (1) investigation into the cellular, molecular and genetic structure of IBD, (2) identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and (3) translation of basic research findings into patient clinical trials as outlined in the research agenda developed by the scientific community entitled, "Challenges in Inflammatory Bowel Disease." Finally, the Committee also encourages NIDDK to continue to strengthen its partnership with the IBD community on innovative research projects. (p. 64)

Action taken or to be taken

The inflammatory bowel diseases (IBD) – Crohn's disease and ulcerative colitis – are important conditions which provide numerous research challenges and opportunities, and the NIDDK continues to support IBD related research as a high priority area. With the completion of the first draft of the human genome and the discovery of *nod2/card15* mutations in patients with Crohn's disease, interest in genetic research in IBD has accelerated. Beginning in FY 2003, the Institute funded a new initiative, the IBD Genetics Research Consortium, comprised of leading IBD genetics investigators in the U.S. and Canada. With active leadership from the NIDDK, this consortium will pool resources from multiple institutions to tackle the difficult problem of identifying additional genes that contribute to the development of these diseases. An expansion of the funding for this initiative will begin in FY 2004.

In addition, the NIDDK continues to fund meritorious investigator-initiated projects aimed at the discovery of the complete genetic basis of IBD. Discovery of the genes alone is not sufficient to provide progress in fully understanding IBD. The NIDDK will continue to provide support for projects that aim to discover the function of genes such as *nod2/card15* that are abnormal in IBD. With NIDDK support, investigators recently have identified a specialized cell in the intestine, the Paneth cell, which expresses the *nod2/card15* gene. This specialized cell has been shown to act as a sensor for bacterial products in the gut, and in response produces molecules that defend the host against bacterial invasion. This research is closely related to other NIDDK-supported research projects, conducted in NIDDK-supported IBD Centers, that are unraveling the fundamental biology of the epithelial cells lining the gastrointestinal tract, including how they respond to bacterial invasion and inflammation, and then repair the intestine following injury, as well as the immunology of the gastrointestinal tract.

The NIDDK is currently supporting the development of large scale research resources, so-called genome anatomy projects, which will provide investigators with specialized molecular tools to understand the adult tissue-specific stem cells in the intestine that are the origin of Paneth cells and other cells of the gut. The Institute actively supports research projects aimed at understanding how the microbial flora exacerbate or ameliorate inflammation in the gut. This line of research may yield insights as to whether probiotic approaches may provide novel therapies. Based on many fundamental discoveries in recent years, funded in part by NIH, the pharmaceutical industry world-wide has maintained a strong interest in developing new biological treatments for IBD.

To promote this area of development, the NIDDK, in partnership with the Food and Drug Administration and the Crohn's and Colitis Foundation of America (CCFA), sponsored a major meeting in FY 2003 at the NIH, with the goal of improving the design of clinical trials in IBD. The NIDDK also supports clinical trials in IBD that are not likely to be conducted by the pharmaceutical industry. For example, in FY 2003, the Institute funded a multicenter, controlled clinical trial to determine whether use of the generic drug 6-mercaptopurine (or azathioprine) in IBD can be improved by adjustment of doses of the drug using newly developed laboratory tests. The NIDDK maintains a close partnership with the IBD research community. In FY 2003, the NIDDK sponsored a meeting of the statutory Digestive Diseases Interagency Coordinating Committee that highlighted new research opportunities in IBD, including those outlined in the CCFA's document, "Challenges in Inflammatory Bowel Disease," which will be used by Institute staff to help guide new initiatives in IBD.

Item

Urologic disorders – Bladder diseases, such as interstitial cystitis, urinary tract infections and urinary incontinence, disproportionately affect women, and the Committee urges NIDDK to develop a comprehensive program to address these and other urological needs of women. The report of the Bladder Research Progress Review Group outlines a strategic plan for research in this area. The Committee encourages NIDDK to pursue promising leads on bladder epithelium, bladder afferent nerve cells, and urinary markers of IC patients. This report also identifies the considerable urologic complications of diabetes, which continue to worsen. Related to this problem is the issue of obesity and incontinence, which particularly affects minority women and should be given priority in the Institute's plans for the coming fiscal year. (p.64)

Action taken or to be taken

The Institute committed significant resources in FY 2003 to support both new initiatives and expansions or recompetitions of ongoing initiatives to enhance research on interstitial cystitis, urinary incontinence, and urinary tract infections. These are extensively described in response to the items, "Bladder Disease" (pp. 18-19), "Interstitial Cystitis" (pp. 17-18), and "Urinary

Incontinence" (pp. 26-27). In addition to basic and clinical research efforts in these important areas, the Institute is working to ensure that advances in clinical knowledge are translated into better health care for patients. In response to recommendations of both the American Urological Association and the Interstitial Cystitis Association, the NIDDK plans to launch a Women's Urologic Health Outreach Initiative in partnership with these two groups. The program will undertake a campaign to increase primary care physician awareness of and knowledge about the current health care recommendations for women's urological problems, including IC, urinary incontinence and urinary tract infections. Planning for this new program will begin in FY 2004.

Please see Senate Significant Item, "Urology Research" and subsequent items (pp 27-32), for extensive information about the NIDDK's efforts regarding the urologic complications of diabetes and the interrelationship of obesity and incontinence.

Item

Glomerular injury research – The Committee is pleased with NIDDK's glomerular injury research initiatives, including a clinical trial for patients with focal segmental glomerulosclerosis. The Committee understands that in addition to the clinical trial, NIDDK is collaborating on a joint research program with a voluntary association to include basic and genetic studies. Further, the Committee continues to encourage NIDDK to consider initiating a scientific conference on glomerular injury research, and to explore support for gathering prevalence data on glomerular injury. (p. 65)

Action taken or to be taken

Many children and young adults with nephrotic syndrome caused by focal segmental glomerulosclerosis (FSGS) are at high risk for kidney failure because they are resistant to standard therapy with prednisone, a form of cortisone. The NIDDK has formed a collaborative network of research centers that will test the effects of cyclosporin or other immune system modulation agents on reduction of protein in the urine (proteinuria) in these patients. Approximately 400 children and young adults will be enrolled in the five-year study. The NephCure Foundation will fund ancillary studies to examine molecular processes that may cause the breakdown and scarring of the kidney filter seen in patients with FSGS.

In addition to the efforts detailed above, the NIDDK supports a broad base of investigator-initiated projects that are relevant to glomerular injury. This aspect of the Institute's research program has grown substantially recently as a result of a number of scientific breakthroughs that have greatly enhanced our knowledge about filtration in the kidney.

The NIDDK is planning to convene a Workshop on Glomerular Diseases in Bethesda, Maryland next winter. This meeting will be co-sponsored with the NephCure Foundation, which

represents patients with glomerular disease. The meeting, consistent with our interest in emphasizing translational medicine, will focus on potential clinical applications of new insights into the biology of the glomerulus. The Institute anticipates a two-day meeting, bringing together basic scientists and experts in clinical disorders including primary glomerulonephritis, focal sclerosis, and lupus nephritis. Although the primary focus of this meeting will be the identification of improved strategies for treatment, the NIDDK we will ask a panel of nephrologists and epidemiologists to evaluate the feasibility of improving estimates of disease prevalence. Better epidemiologic data is urgently needed; however, this is a difficult problem to solve, because current diagnostic methods are dependent upon renal biopsy, limiting applicability to national studies.

Item

Scleroderma – The Committee encourages NIDDK to support scleroderma relevant research. Scleroderma is a chronic and progressive disease that predominantly strikes women. It is estimated that 90 percent of patients with systemic sclerosis have gastrointestinal (GI) involvement and of that number 50 percent have clinically significant manifestations. GI involvement can manifest as gastroesophageal reflux disease, dysphagia, Barrette's esophagus, gastroparesis, "watermelon stomach", malabsorption, and fibrosis of the small and large intestines. Renal crisis affects 20 percent of those with systemic sclerosis often within the first five years after diagnosis. More research is urgently needed in order to develop safe and effective treatments and to identify the cause or causes of the complications of scleroderma. (p. 65)

Action taken or to be taken

Scleroderma is a rare but devastating disease that affects many organs of the body, including those within the NIDDK research mission – the digestive system and the kidneys. The NIDDK is aware of this very serious condition and has participated in NIH-wide efforts to assist the scientific community in research efforts on this disease. These efforts include active participation in the Autoimmune Disease Coordinating Committee (led by NIAID), coordination of research efforts in autoimmunity with the staff of NIAMS, and a meeting in FY 2003 with leaders of the scleroderma research community. The NIDDK participates in the effort to enhance progress in scleroderma by conducting a wide range of research on the fundamental biology of the gastrointestinal tract, such as motility research, that may provide the knowledge base necessary for further understanding of scleroderma. The Institute also supports a significant translational research effort in gastroesophageal reflux disease (GERD), one of the most common gastrointestinal manifestations of scleroderma. Similar NIDDK-supported fundamental and clinical research on renal disease may provide the foundation for developing better treatments for kidney involvement in scleroderma. The NIDDK will continue to facilitate

investigator-initiated research project applications that focus on specific target organs within the NIDDK research mission that are involved in this important disease.

Item

Cooley's anemia – The Committee continues to support the outstanding work being done at NIDDK on such issues as iron chelation, non-invasive iron measurement, fetal hemoglobin and other topics that are critical to the health and well-being of Cooley's anemia patients. The development of a less burdensome method of iron chelation, which currently involves a daily infusion of up to twelve hours, is urgently needed. In addition, NIDDK is urged to continue its collaboration with the National Institute of Biomedical Imaging and Bioengineering on imaging issues related to iron measurement. (p. 65-66)

Action taken or to be taken

In response to recommendations developed at an April 2001 workshop, the NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) have been collaborating to solicit new research grants for projects that may improve the utility of magnetic resonance imaging (MRI) as a method for quantitative determinations of body iron. MRI potentially provides a useful and widely available technique for monitoring excess iron in the body in conditions of iron overload, such as found in thalassemia (Cooley's anemia) and sickle cell disease patients. In early FY 2003, the NIDDK and the NIBIB issued a Request for Applications (RFA) inviting research grant applications (R01 or R21) for projects that have the potential to improve the utility of MRI as a method for quantitative determinations of tissue iron, especially in the liver, heart, and brain. As a result of the RFA, a total of four grants were awarded by the two Institutes. The NIH continues to have a keen interest in stimulating this type of research, and the unfunded applicants have been encouraged to revise their applications and reapply through the regular grant application process.

The Institute also continues its support for research to find effective and less burdensome alternatives to the injected iron chelating drug, desferrioxamine. One drug that is moving into clinical trials, appears to be a more effective chelator, and thus, may need to be used less frequently and for shorter periods of time. However, it still must be injected, so the NIDDK continues to search for better iron chelating drugs. Already, these studies have resulted in successful preclinical evaluation of a re-engineered version of the oral chelator desferrithiocin, and this new compound has recently been approved by the FDA for use in clinical studies. The NIDDK plans additional studies on related chelators that may be even more effective.

Item

Living donor liver transplants – . . . The Committee encourages additional research that would facilitate the success of living donor liver transplants and the number of livers available for transplantation. (p. 66)

Action taken or to be taken

The NIDDK began funding a large, multicenter prospective and retrospective cohort study of adult-to-adult living donor liver transplantation (A2ALL) in 2002. The protocol for this study is now in its final phases of completion. This cohort study will compare the course and outcome of liver transplantation using living versus cadaveric donors. The ultimate aim of this study is to optimize the safety and efficacy of using living donors in liver transplantation. Areas of focus will be donor safety, informed consent, and quality-of-life of donors during long-term follow up, i.e., comparing people who donated to those who offered to donate but were found ineligible or were not needed. Long-term follow-up is planned on both recipients and donors. Research areas of special interest in A2ALL include hepatitis C and liver cancer, which are currently the two major reasons for liver transplantation in the U.S. The NIDDK is now developing a mechanism with which to fund addition ancillary studies on hepatitis C and liver cancer as a part of the A2ALL cohort study.

Item

Pediatric liver disease database – The Committee encourages NIDDK to consider supporting a pediatric liver disease national database and registry. Such a registry would permit hypothesis testing and outcomes research to determine the health and financial impact of liver transplants on a child and the child's family. (p. 66)

Action taken or to be taken

Liver transplantation for children remains the major means of management for end-stage liver disease, and is a life saving and life-sustaining procedure. Approximately 600 transplants are done yearly in children with liver disease; five and ten-year patient survival is excellent. During the past seven years, the pediatric liver transplant community has created a interactive database on children undergoing liver transplantation known as SPLIT. This database has been supported by industry-sponsored grants and academic societies. Over the last two years, NIDDK staff have met with the SPLIT investigators in an attempt to develop a means of continuing this database with NIH support. Accordingly, the SPLIT investigators have recently submitted a large research project grant application to NIDDK for long-term support. This application will be given high priority for funding consideration and support will be shared by other NIH institutes.

Item

Hepatitis C in children – The Committee is aware that recent studies have indicated that one in every 200 children over the age of twelve is infected with the hepatitis C virus. The Committee urges NIDDK, with appropriate support from the National Institute of Child Health and Human Development (NICHD), to study the natural history of hepatitis C in infected children to help determine the optimal timing and medical regimen for treatment. (p. 66)

Action taken or to be taken

A multicenter clinical trial of therapy of hepatitis C using peginterferon and ribavirin in children has recently been reviewed and approved for funding by the NIDDK with support from the Orphan Drugs Division of the Food and Drug Administration. Working with the investigators, NIDDK has arranged for major support from Roche Laboratories to provide the medications and funding for virological testing and a central data coordinating center. This study will document the response rate to peginterferon with and without ribavirin in children, and will also provide information on growth and development during therapy as well as during long-term follow-up in all cases. This study will permit careful analysis of both the short- and long-term benefits and risks of peginterferon therapy in children.

Item

Lupus – Because more than one-third of lupus patients have some form of kidney disease, a leading cause of death among the 1.5 million Americans afflicted with lupus, the Committee encourages NIDDK to increase support for studies that will lead to better understanding of this dangerous manifestation of lupus. (p. 66)

Action taken or to be taken

The NIDDK recognizes that kidney disease is a leading cause of death among lupus patients and is supporting ongoing research to address this issue. In FY 2002, the NIDDK awarded 13 grants to 12 different investigators whose research addresses issues directly related to kidney disease associated with lupus. Among these, a Program Project is receiving support to investigate risk factors for renal involvement in human systemic lupus. Also, four "Manpower Awards," which are Research Career Development Awards, focus on research addressing lupus nephritis.

In September 2003, the NIDDK co-sponsored a conference that highlighted key research accomplishments and what impact they may have on the future management of lupus. This meeting, entitled "Lupus Today: Research into Action," included discussions about the impact of lupus on the kidneys. The NIDDK has co-sponsored similar meetings in the past. In January, 2002, the NIDDK co-sponsored a scientific conference entitled "Systemic Lupus Erythematosus (SLE): Targets for New Therapeutics."

The NIDDK also conducts research into kidney disease and lupus as part of its intramural research program. These efforts include research into possible therapies for immunologically-mediated glomerular diseases, particularly lupus nephritis, and multi-pronged approaches to study the development of and treatments for focal segmental glomerular sclerosis (FSGS).

In addition to these ongoing efforts, research to achieve a better understanding of the mechanisms of glomerular injury should yield insights into ways to prevent and treat kidney disease in all people. Thus, the Institute's efforts to assess different therapies for FSGS and the workshop on glomerular diseases (pp. 5-6) are relevant to those who have lupus.

Item

Cystic fibrosis – Advances have been achieved in the treatment of cystic fibrosis (CF), resulting in significant improvements in life expectancy for individuals with CF. This progress can be attributed to strong public and private sector investment in CF research, including clinical trials evaluating a wide range of possible new treatments. The Committee urges NIDDK to continue its support for CF researchers engaged in basic and clinical CF research. (p. 67)

Action taken or to be taken

The NIDDK supports both basic and clinical research in cystic fibrosis. The NIDDK has recompeted its Molecular Therapy Core Centers, which support research on cystic fibrosis and other genetic metabolic diseases. Formerly focused on gene therapy research, the types of studies supported within these centers now include an expanded array of molecular approaches to developing therapies for cystic fibrosis based on new technologies.

The NIDDK Advisory Council has undertaken a review of the Institute's Centers Programs, including Specialized Centers for Research on CF. The Council has recommended restructuring of these Centers to enhance the support of basic and clinical research to develop therapies for CF. Based on these recommendations, the NIDDK will be issuing an RFA for CF Core Centers in 2004.

The NIDDK also supports clinical trials in CF. In one example, NIDDK-supported scientists recently reported encouraging results from a multi-center trial to test the effects of a specific treatment for lung infection with *Pseudomonas aeruginosa* bacteria in very young children with CF. Chronic lung infection with these bacteria is a major cause of illness and death in patients. The treatment used in the trial, administration of the inhaled antibiotic tobramycin, had previously been tested in older individuals. Because the recent trial showed that this therapy significantly reduced lung bacteria in young children, a follow-up study is now under way to optimize this treatment and to assess how long the effects will last.

The NIDDK developed a new initiative to enhance basic genetic research on CF and other diseases in which a single gene plays the predominant role in disease development--but in which other genes, termed "modifier genes," likely contribute to the variability in symptoms and severity seen among patients. Through this new effort, the NIDDK will foster research to identify these modifier genes, as such knowledge would have implications for predicting disease severity and symptoms in a particular individual and for designing improved therapies that may be tailored to specific patients or subsets of patients. One of the projects the NIDDK plans to fund as part of this effort studies the role of modifier genes in cystic fibrosis-associated liver disease.

Item

Mucopolysaccharidosis (MPS) – The Committee recognizes the efforts of the NIDDK to enhance research efforts to achieve a greater understanding and pursue development of effective therapies for MPS disorders. The Committee encourages continued investment in MPS-related research and enhanced collaborative efforts with the NINDS, NICHD, and appropriate institutes and centers involved in this crucial research, including bone and joint involvement in MPS disorders and pathophysiology of brain damage as they relate to MPS disorders. (p. 67)

Action taken or to be taken

This year the research supported by NIDDK to develop enzyme replacement therapy for MSP I has lead to development of the first drug to be tested in MPS I patients. This drug, aldurazyme, is being tested by Genzyme with evaluation of its effects on multiple organs affected by the disorder. Although its effects on the neuronal symptoms have not yet been studied, it is likely that this drug will not improve these symptoms since it does not cross the blood brain barrier. Therefore, the NIDDK is concentrating its efforts on methods, such as gene therapy, which may be able to treat the brain. The NINDS recently issued a program announcement to encourage studies focused on understanding the blood-brain barrier and enhancing the effectiveness of drug and gene delivery strategies for the treatment of neurological diseases, including lysosomal storage disorders like MPS.

NIDDK's "Molecular Therapy Core Centers" support gene and other molecular therapy research on CF and other genetic diseases. These centers were recently recompeted, and two of the four successful Centers study MPS . The objectives of the Molecular Therapy Core Centers are to bring together investigators from relevant disciplines in a manner which will enhance and extend the effectiveness of their research. In addition to collaborations between scientists within an institution, core centers can foster interaction and collaborations between investigators at multiple institutions to promote a multifaceted approach to a common goal. The Centers include

new technologies, such as homologous recombination and RNA-interference, in addition to gene therapy.

The NIDDK, NINDS, and NICHD support research to test therapeutic interventions in a variety of animal models of MPS. Last year, NIDDK supported researchers used a gene therapy approach to treat dogs with MPS VII. The researchers found that the gene therapy treatment prevented heart, eye, bone, and joint abnormalities, and other symptoms of the disease. The NIDDK has funded a new grant to expand these very promising results to study MPS I--the most common form of MPS. The NIDDK, NINDS, and NICHD will continue to support studies of therapeutic approaches for MPS disorders with an ultimate goal of finding effective therapies for human patients.

FY 2004 Senate Appropriations Committee Report Language (S. Rpt. 108-10)

Item

Behavioral Research – Diabetics who have co-occurring depressive symptoms have less success managing their illnesses. The Committee also notes that NIDDK's recent clinical trial, the Diabetes Prevention Program, demonstrated that diet and exercise could be more successful than medication alone in preventing the development of diabetes in groups who faced a high risk of diabetes. The NIDDK is strongly encouraged to build upon its investment in behavioral research, particularly in areas that would add to the science base on the maintenance of positive behavior change. (p. 115)

Action taken or to be taken

The NIDDK has developed a vigorous ongoing research base in behavioral research stemming from the outcomes of several clinical trials. These behavioral studies address aspects of intensified diabetes management, which has been demonstrated to reduce the risk for diabetes-related complications, and interventions that can delay or prevent the onset of type 2 diabetes, as shown by the Diabetes Prevention Program (DPP). To further research in implementing the treatment and lifestyle changes required to prevent diabetes in high-risk groups or to improve outcomes in individuals with diabetes, two Program Announcements (PAs) have recently been released. These are titled: "Translational Research for the Prevention and Control of Diabetes," and "Planning Grants for Translational Research for the Prevention and Control of Diabetes." The purpose of these PAs is to foster the development of innovative clinical and behavioral programs to translate recent advances in diabetes research into practice for individuals and communities. The latter is to enable new investigators to obtain pilot and feasibility data leading to larger scale studies. In addition, the DPP study group has been awarded, through a competitive grant application process, continued funding to support the DPP Outcomes Study (DPPOS). The DPPOS will follow the DPP cohort through continued lifestyle and drug intervention and study behavioral approaches for long-term implementation.

The NIDDK is also supporting research to study the interactive nature of diabetes and co-occurring depression. The NIDDK collaborated with the National Institute of Mental Health (NIMH) and the NIH Office of Behavioral and Social Sciences Research (OBSSR) in holding a major conference titled: "Depression and Mental Disorders in Patients with Diabetes, Kidney Disease, and Obesity and Eating Disorders." This successful conference, held in January 2001, was designed to assess the state of knowledge with regard to the co-morbid condition of depression and to propose a research agenda for the future. Based on recommendations from this conference a Request for Applications (RFA) was released. The purpose of the RFA was to increase research activity in the field of depression in relationship to diabetes, chronic renal disease and obesity and eating disorders. As a result, research efforts and interest in this field

have expanded significantly. Additional NIDDK-supported research in this area includes, for example, a recent study demonstrating that major depression is an independent risk factor for the development of coronary heart disease in women with diabetes.

In a further step to enhance research on positive behavior change, the NIDDK co-sponsored an OBSSR-led RFA on "Maintenance of Long-term Behavioral Change." Through this RFA, the NIDDK solicited new research on approaches to maintenance of physical activity behaviors and on factors associated with long-term weight loss in formerly overweight or obese individuals. Projects from the solicitation that NIDDK is funding focus on strategies for weight loss maintenance in primary care and long term exercise maintenance *via* Internet support.

Item

Cooley's anemia – The Committee continues to support the outstanding research being supported by NIDDK on such issues as iron chelation, non-invasive iron measurement, fetal hemoglobin, and other topics of importance to Cooley's anemia patients. The development of a less burdensome method of iron chelation, which currently involves a daily infusion of up to 12 hours, is desperately needed. In addition, NIDDK is urged to continue its collaboration with NIBIB on imaging issues related to iron measurement. (p.115)

Action taken or to be taken

Please refer to page 43 of this document for the NIDDK response regarding Cooley's anemia.

Item

Diabetes in Native Hawaiians – As the NIDDK develops expanded plans for diabetes research, the Committee recommends investigating the incidence in Native American, Hawaiian, and Alaskan populations, as well as the Mississippi Band of the Choctaw Indians and the Eastern Band of the Cherokee Indians. (p. 115)

Action taken or to be taken

The NIDDK continues to pursue research efforts with respect to diabetes in Native Hawaiians and other native populations of the U.S. In cosponsoring the CDC-led "SEARCH" epidemiological study, the NIDDK seeks to determine the prevalence and incidence of both type 1 and type 2 diabetes in children, with centers located in six geographic regions around the nation, including Hawaii. The first part of the SEARCH study was to establish the prevalence of diabetes cases in children. Now, the NIDDK and CDC have expanded support for the study to assess, prospectively, the incidence (new cases) of diabetes in these six regions.

The Diabetes Prevention Program (DPP) multi-site clinical trial demonstrated that a lifestyle intervention, which included modest weight loss and physical activity, reduced the risk of developing type 2 diabetes by 58 percent in people at high risk for the disease, and the DPP also demonstrated that the drug metformin reduced the risk by 31 percent. One of the centers at which the DPP was conducted was in Hawaii, and the participants of the DPP additionally included members of American Indian and other minority groups disproportionately affected by type 2 diabetes. The NIDDK has now begun a follow-up study of the DPP participants, the DPP Outcomes Study (DPPOS), to examine the durability of the interventions in preventing or delaying the onset of type 2 diabetes and its cardiovascular complications.

To bring to communities the important prevention message of the DPP clinical trial – that modest lifestyle changes can dramatically reduce the risk of type 2 diabetes in those at risk – the National Diabetes Education Program (NDEP) has launched an educational campaign: "Small Steps. Big Rewards. Prevent Type 2 Diabetes." Among the audiences that this campaign seeks to reach are Americans at risk for type 2 diabetes. The campaign includes a Native American component with a specific focus on communicating the message of the DPP to this population. The NDEP is jointly-sponsored by the NIDDK and CDC and includes participation of numerous partner organizations.

The NIDDK's initiative to enhance a diabetes-focus on science education in Tribal Schools has now progressed from the planning phase to full studies. This effort is designed to develop a curriculum useful for teaching Native American middle and high school students about biology in the context of diabetes. The curriculum is intended both to inform the students about lifestyle changes that can dramatically reduce the risk of diabetes--and thus potentially impact the health of their families--and also to encourage them to prepare for biomedical careers.

Item

End-stage renal disease – Diabetes is the leading cause of kidney failure and end-stage renal disease. The Committee urges the NIDDK to expand research into early prevention and therapeutic intervention of kidney disease to prevent end-stage renal failure. It has been brought to the Committee's attention that rural Native Hawaiians with end stage renal disease have a particularly high rate of repeated infections. The Committee strongly urges the NIDDK to increase research targeted to end stage renal disease in the rural Native Hawaiian population. (p. 116)

Action taken or to be taken

The NIDDK shares the Committee's interest in expanding efforts regarding early prevention and therapeutic intervention of kidney disease to prevent end-stage renal disease (ESRD). As the Committee may be aware, despite evidence that kidney failure may be prevented or slowed

through blood glucose and blood pressure control and the use of drugs called angiotensin converting enzyme inhibitors, only a fraction of people who are at high risk for kidney disease or who are in early stages of the disease are being screened or managed appropriately. It is critical for both patients and their primary care physicians to know the risk factors for kidney disease and its warning signs.

To help raise awareness of this critical health care issue among patients and health care providers, the NIDDK has launched a National Kidney Disease Education Program (NKDEP) to help to close the gap between evidence and practice. This program, currently in its pilot phase, is targeting primary health care providers and people at highest risk for kidney disease – particularly African Americans with diabetes, hypertension and/or a family history of kidney failure – in four pilot cities: Baltimore, Maryland; Atlanta, Georgia; Jackson, Mississippi; and Cleveland, Ohio. Patients are urged to be aware of any risk factors for kidney disease, such as hypertension, diabetes, and family history, and to talk to their physicians about being tested for kidney function. Health professionals are reminded of the importance of testing kidney function in at-risk individuals. The pilot phase of this program is being evaluated, and it is anticipated that a wider effort, targeting a broader range of individuals, will be launched based on the results of the pilot phase.

As the Committee notes, diabetes is the leading cause of kidney disease in Native Hawaiians. The NIDDK supports numerous efforts to prevent diabetes and its complications, and these programs feature messages tailored to high-risk populations, including racial and ethnic minorities such as Native Hawaiians. The National Diabetes Education Program (NDEP) produces and disseminates information to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and to prevent the onset of diabetes. Also, under the direction of the NIDDK, the National Kidney and Urologic Diseases Information Clearinghouse produces and disseminates materials on kidney diseases and on treatments for ESRD. In addition, the NIDDK and National Center on Minority Health and Health Disparities (NCMHD) fund the National Minority Organ and Tissue Transplant Education Program, which supports grassroots efforts to encourage minorities to donate organs and to prevent the need for transplantation by increasing awareness about causes of ESRD. The NCMHD also supports a Project EXPORT Center of Excellence at the University of Hawaii at Manoa, which is examining the prevalence, incidence and underlying clinical causes for ESRD in Asian Americans and Pacific Peoples living in Hawaii.

Item

Glomerular Injury Research – The Committee is pleased with NIDDK's glomerular injury research initiatives, including a clinical trial for patients with focal segmental glomerulosclerosis. The Committee understands that in addition to the clinical trial, NIDDK is collaborating on a joint research program with the NephCure Foundation to include basic and genetic studies.

Further, the Committee continues to encourage NIDDK to consider initiating a scientific conference on glomerular injury research, and to explore support for gathering prevalence data on glomerular injury. (p. 116)

Action taken or to be taken

Please refer to pages 41-42 of this document for the NIDDK response regarding glomerular injury research.

Item

Hepatitis C in children – Recent studies indicate that 1 in every 200 children over the age of 12 is infected with the hepatitis C virus. The Committee urges the NIDDK, with appropriate support from the NICHD, to study the natural history of hepatitis C in infected children to help determine the optimal timing and medical regimen for treatment. (p. 116)

Action taken or to be taken

Please refer to page 45 of this document for the NIDDK response regarding hepatitis C in children.

Item

Hematology – The Committee encourages NIDDK to sponsor a conference of experts to develop a blueprint for further study into the microvascular and thrombotic complications of metabolic disease, such as limb ischemia, vision loss, and renal failure. (p. 116)

Action taken or to be taken

Patients with type 1 or type 2 diabetes are at high risk for developing serious complications, such as blindness, kidney failure, chronic wounds and skin ulcers, nerve pain and other neurological problems, limb amputation, heart disease and heart attacks, stroke, high blood pressure, and gum disease. Because these complications affect a wide range of organ systems, it will take a collaborative effort of researchers in diverse fields to fully understand development of complications. To enhance this coordination, the NIDDK has recently formed a Diabetes Complications Working Group. This Group will integrate all NIDDK activities relevant to diabetes complications, including workshops, initiative planning, and oversight of existing projects and trials. The Group will also include representatives from other NIH Institutes and Centers, such as the National Eye Institute (NEI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Dental and Craniofacial Research (NIDCR), which have research efforts that are relevant to the complications of diabetes.

Because collaboration in the field of diabetes complications is essential to progress research, the NIDDK has sponsored several meetings of scientific experts in this area. In April 2003, the NIDDK sponsored a 20th Anniversary Symposium of the Diabetes Complications and Control Trial (DCCT). This symposium, "Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back," focused on the underlying mechanisms leading to the development of diabetes complications. Immediately following this meeting, the Diabetes Mellitus Interagency Coordinating Committee (DMICC), composed of representatives from multiple components of the Department of Health and Human Services, met to discuss future opportunities in the field of diabetes complications. The NIDDK, in collaboration with NEI, NHLBI, the National Institute of Neurological Disorders and Stroke, and the Juvenile Diabetes Research Foundation (JDRF), sponsored a meeting in October, 2003, on Diabetic Complications in Animal Models. This meeting convened an international group of basic and clinical researchers to discuss diabetic complications. The emphasis was on the use of animal models in discovery and translational research. The NIDDK has also participated in a meeting on wound healing that was held in September, 2003, co-sponsored by the JDRF and the Defense Advanced Research Projects Agency (DARPA). An examination of current therapies for wound healing and how research findings these might best be incorporated into clinical practice were also the subject of a DMICC meeting in November, 2003. All of these meetings serve to identify research opportunities, propel progress toward development of new therapeutic approaches, and foster a coordinated approach to research and research translation.

The microvascular complications of metabolic diseases reflect loss of small blood vessels in some cases (e.g., foot ulceration), and improper proliferation of blood vessels in others (e.g., diabetic eye disease). Understanding and characterizing the molecular factors and mechanisms that inhibit or promote blood vessel development – angiogenesis – is also a crucial area of investigation in cancer biology. Because angiogenesis research has important implications both for diabetes complications and cancer therapy, the NIDDK, in collaboration with the National Cancer Institute and the JDRF, is planning a scientific workshop that will focus on angiogenesis – including angiogenesis in microvascular complications. This meeting is slated for Spring 2004, and will assist both Institutes in identifying scientific opportunities to pursue in this area.

Item

Interstitial Cystitis (IC) – The Committee commends the NIDDK for its recent investment in IC-specific basic science research and continuation of the IC Clinical Trials Group. However, the Committee is concerned about the current direction of the epidemiology studies on pelvic pain of bladder origin and IC currently being funded by the NIDDK. In fiscal year 2000, the Committee urged the NIDDK to undertake a comprehensive epidemiology study of IC that would include scientifically valid statistics of the incidence of the disease, the demographics, occurrence in minority populations, and the health care costs. The Committee is concerned that the current studies will not adequately address these goals. Therefore, the Committee urges the

NIDDK to rectify any shortcomings in the epidemiology effort, including funding additional studies if necessary. (p. 117)

Action taken or to be taken

To address scientific issues regarding the epidemiology of IC, the Institute has established an Interstitial Cystitis Epidemiology Task Force. The Task Force is co-chaired by a leading urologist and a leading epidemiologist and consists of approximately 30 experts in IC and the epidemiology of urologic disorders. The panel was convened with the advice of the health advocacy community and includes experts recommended by the Interstitial Cystitis Association. The Institute will be asking advice of this panel for new studies, and plans to implement their recommendations, including establishing new studies if appropriate. The NIDDK is also aware of concerns of the health advocacy community about ongoing studies of the epidemiology of interstitial cystitis and pelvic pain of bladder origin. Under the direction of the Review Branch in the NIDDK Division of Extramural Activities, the Institute convened an independent panel to provide a mid-course review of those projects. The findings of this panel will be shared with the Scientific Advisory Committee for that study. This advice will allow us to identify any appropriate change in direction the Institute should take regarding these studies.

Item

[Bladder diseases] – The Committee urges the NIDDK to pursue additional studies on bladder epithelium, bladder afferent nerve cells, and urinary markers of IC patients. In addition, the Committee urges the NIDDK to work with the Interstitial Cystitis Association to undertake a national IC awareness campaign aimed at reducing the delay in diagnosing IC, which currently takes an average of 5 to 7 years. (p. 117)

Action taken or to be taken

The NIDDK will continue to promote research on the basic science of the bladder and IC in FY 2004 through recent and ongoing grant initiatives and meetings. For example, the Institute recently funded new grants received in response to the Request for Applications (RFA), "Basic Research Studies Related to IC." These studies will employ a variety of research approaches to improve our understanding of the IC bladder and the molecular mechanisms underlying the cause(s) and symptoms of IC. The competitive renewal and expansion of the former IC Clinical Trials Group, now known as the IC Clinical Research Network, will additionally provide new opportunities and funding to conduct ancillary studies in conjunction with IC clinical trials. Past ancillary studies conducted under the Trials Group include studies of candidate biomarkers of IC, such as anti-proliferative factor. To help accelerate the pace of IC research, the NIDDK and the Interstitial Cystitis Association recently co-sponsored a major scientific workshop on IC, "Research Insights into Interstitial Cystitis." The workshop addressed both new insights into the

basic science of the bladder and new clinical approaches to IC, and provided investigators with an opportunity to exchange ideas and establish new collaborative research efforts in IC.

The Institute is also engaged in efforts relevant to increasing IC awareness among physicians. In response to recommendations of both the American Urological Association and the Interstitial Cystitis Association, the NIDDK plans to undertake a Women's Urologic Health Outreach Initiative in partnership with these advocacy groups and other interested non-profit groups. The program will launch a campaign to increase primary care physician awareness of and knowledge about the current health care recommendations for women's urological problems, including IC and painful bladder syndrome, urinary incontinence and urinary tract infections. The NIDDK is recruiting a qualified individual to lead this program and anticipate planning will begin in FY 2004.

Item

Juvenile Diabetes – The Committee commends the NIDDK for its development of the platform technologies of genomics and proteomics to expand clinical research capability. The Committee urges the Institute to continue the effort to remove the most common barriers between laboratory discoveries and clinical trials; this effort should include making available on a competitive basis the resources for pre-clinical development of drugs and therapies. The Committee applauds the NIDDK for the launch of TrialNet, which establishes an infrastructure to coordinate and support clinical trials dealing with the preservation of pancreatic beta cell function to prevent juvenile diabetes in high-risk individuals. (p. 117)

Action taken or to be taken

In order to foster development of new therapeutics for type 1 diabetes (T1D), the NIDDK has begun a collaboration with the National Cancer Institute's Rapid Access to Intervention Development (RAID) program. The new T1D-RAID program is a special mechanism to make available to academic investigators the necessary resources to move novel molecules and concepts from the bench to the bedside more rapidly and effectively. T1D-RAID will assist investigators by providing the preclinical development steps that may be obstacles to using their therapeutics in a clinical setting. Therapeutics, such as small molecules or biologics for the treatment or prevention of type 1 diabetes and its complications, would be candidates for development through this program.

The NIDDK sponsors other initiatives that promote the movement of therapeutics from the laboratory to clinical trials. For example, the NIDDK, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the National Eye Institute (NEI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke, and the Office of Dietary Supplements, is sponsoring a Request for Applications (RFA) on "Bench-to-Bedside Research on Type 1 Diabetes and Its Complications."

This RFA promotes partnerships between clinical and basic biomedical researchers with the goal of translating advances in the underlying mechanisms of type 1 diabetes and its complications into new therapies for the prevention, treatment, and cure of this disease. In these partnerships, a team of clinical and basic scientists will conduct collaborative research that will bring basic research advances from the laboratory to a point where a potential new therapy can be tested in patients or in preclinical studies in animal models. The NIDDK, in collaboration with NIAID, NEI, NHLBI, the National Institute of Nursing Research, and the National Institute of Child Health and Human Development, has just issued an RFA on type 1 diabetes and its complications through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (SBTT) program. The purpose of this RFA is to encourage the small business community to participate in the research and development of commercial products, such as therapeutics, in the area of type 1 diabetes and its complications.

Item

Metabolic Bone Disease – The Committee urges NIDDK to expand genetic research focusing on bone mass and functional genomics to further disease prevention and treatment of metabolic bone diseases. The Committee encourages NIDDK to support further research into drugs and mechanisms that can build better bone and comparison drug trials to determine best treatments. (p. 118)

Action taken or to be taken

Metabolic bone diseases, such as osteoporosis and hereditary vitamin D-dependent rickets, weaken bone and increase a patient's risk for bone fracture and breakage. Bone is a living tissue, which is continually being broken down and reformed. In is important to understand how this natural process works in order to identify therapeutic targets to prevent metabolic bone disease.

The NIDDK has sponsored Genome Anatomy Projects (GAPs) in order to accelerate research that applies the recent data that has emerged from the Human Genome Project. These projects strive for insights into developmental programs and disease progression that may eventually be useful in diagnosis and treatment of disease. Specifically, the NIDDK issued a Request for Applications (RFA) for Progenitor Cell GAPs. Through this RFA, the NIDDK funded a project that focuses on osteoblasts, or bone forming cells. This study will provide information on the mechanisms of bone development, which may help researchers comprehend the problems that occur in metabolic bone disease and thus design effective therapy. In addition, in collaboration with the National Cancer Institute, the NIDDK co-sponsored an RFA to investigate bone metastases in cancer, which contribute heavily to cancer morbidity and mortality. The investigators who were recently funded by this RFA will contribute to the understanding of the molecular underpinnings of the development of bone metastases.

The NIDDK has also made significant contributions in the development of a recently approved therapeutic agent for the treatment of osteoporosis. This agent is a synthetic form of parathyroid hormone (PTH). Over the last 20 years, NIDDK intramural and extramural scientists have contributed to understanding how this hormone works and discovered that intermittent exposure to PTH can increase bone formation – the basis for using this hormone in treatment for osteoporosis. The hormone was approved for clinical use by the Food and Drug Administration in December 2002. In a recent clinical study of 16 post-menopausal women with osteoporosis, NIDDK supported researchers found that a related hormone, parathyroid hormone-related protein (PTHrP), significantly increased bone formation over a 3-month period.

NIDDK-supported researchers have recently identified other promising therapeutic approaches for metabolic bone disease. For example, researchers have found that treatment with a "beta-blocker" can increase bone formation in a mouse model. Beta-blockers are currently used as a treatment for high blood pressure in humans. In another study, researchers found that a slightly altered version of vitamin D can prevent osteoporosis in a mouse model of the disease. Finally, researchers have promising preliminary data on a chemically-altered version of vitamin D as a therapeutic agent for hereditary vitamin D-resistant rickets. Thus, all of these agents show therapeutic promise for metabolic bone diseases.

Item

Mucopolysaccharidosis (MPS) – The Committee recognizes the efforts made by the NIDDK to achieve a greater understanding and pursue development of effective therapies for MPS disorders. The Committee encourages continued investment in MPS related research and is further encouraged to enhance collaborative efforts with the NINDS, NICHD, and appropriate institutes and centers involved in this crucial research, including bone and joint involvement in MPS disorders and pathophysiology of brain damage as they related to MPS disorders. (p.118)

Action taken or to be taken

Please refer to pages 47-48 of this document for the NIDDK response regarding MPS.

Item

Pediatric kidney disease – . . . the Committee continues to urge the NIDDK to undertake research into the history and treatment of cardiovascular problems in children suffering from chronic kidney disease, giving careful consideration to (1) the role of hypertension, lipid abnormalities, obesity, cardiovascular calcification and cardiac arrhythmia; and (2) neurocognitive and developmental deficits including learning disabilities, with related issues of chronic neurological, intellectual and emotional impairment; poor linear growth; and abnormal bone formation. Funding for ancillary studies to determine the pathophysiology of these

problems in children, including the ongoing clinical trial for focal segmental glomerulosclerosis, should be supported in order to develop new approaches to their treatment and prevention. (p. 118)

Action taken or to be taken

The NIDDK is committed to understanding kidney disease and its complications in children. To stimulate research in this important area, in November 2002, the NIDDK – in collaboration with the National Institute of Neurological Disorders and Stroke and the National Institute of Child Health and Human Development – invited cooperative agreement applications for two clinical coordinating centers and a data coordinating center to conduct a prospective epidemiological study of children with chronic kidney disease. The primary goals of this study are to determine the risk factors for the decline in kidney function; the incidence of, and risk factors for, impaired neurocognitive development and function in these children; prevalence of risk factors for cardiovascular disease; and long-term effects of growth failure and its treatment in these children. The information obtained from this prospective cohort study of chronic kidney disease will establish natural history and outcome measures for future intervention or prevention trials.

The NIDDK shares the Committee's view that ancillary studies also represent a valuable means to maximize ongoing clinical efforts in pediatric kidney disease research. Thus, the NIDDK is hoping to build upon insights generated by the study of children with chronic kidney disease through a Program Announcement issued in March 2003, that invited investigator-initiated research applications for ancillary studies to ongoing or completed clinical trials and epidemiological studies of kidney disease, as well as clinical trials and epidemiological studies for other diseases or populations that lend themselves to the study of kidney disease. It is expected that such studies will complement the results of the clinical trials. In addition, the NIDDK is funding a study of focal segmental glomerular sclerosis (FSGS) in children and young adults that may yield further insights into the problem of kidney disease in young people.

Item

Pediatric Liver Disease – The Committee is pleased that the NIDDK has taken steps to increase research on biliary atresia, the most common cause of liver transplantation in children. The Committee notes that metabolic causes of liver disease and non-alcoholic steatohepatitis [NASH] are also significant causes of liver disease in children. Therefore, it urges additional research focused on these diseases and other forms of pediatric liver disease. (p. 118)
Action taken or to be taken

In 2002, the NIDDK created the Biliary Atresia Research Consortium (BARC) that has developed clinical protocols and ancillary studies to help define the cause and means of treatment and prevention of biliary atresia, the major cause of end-stage liver disease in

childhood. This consortium has developed a clinical trial meant to optimize the success of the Kasai procedure, surgery which, if successful, can reverse the effects of this disease on the liver and obviate the need for liver transplantation. The consortium also has developed ancillary studies directed at defining the cause of biliary atresia through basic research studies on samples and tissues accrued by the Consortium. The consortium is funded by NIDDK, with support from the Office of Rare Diseases.

In addition, the NIDDK is funding a clinical research network on nonalcoholic steatohepatitis (NASH). The NASH network of investigators includes eight clinical centers, each of which has a pediatric liver disease component. In the next year, the NASH network expects to initiate two prospective clinical trials of antioxidants and insulin-sensitizing agents for patients with NASH – one study in adults and a parallel study in children. The NASH clinical research network is funded by NIDDK, with support from Office of Rare Diseases and NICHD and newly-initiated Cooperative Research and Development Agreements.

Item

Pediatric Liver Disease – National Database and Registry – The Committee is aware of a privately funded initiative which that follows the natural history of infants and children who receive liver transplants until they are 18 years of age. With increased financial support, this national database and registry could permit more adequate hypothesis testing and outcomes research to determine both the health and financial impact of liver transplants on the child and the child's family. The Committee encourages NIDDK to favorably consider a pediatric liver disease national database and registry. (p. 118)

Action taken or to be taken

Please refer to page 44 of this document for the NIDDK response regarding the pediatric liver disease national database and registry.

Item

PKD (Polycystic Kidney Disease) – The Committee anticipates important scientific advances in this exciting field of research resulting from the NIDDK sponsored International PKD Strategic Planning Meeting in late fiscal year 2002. Furthermore, the Committee is pleased the "Halt PKD Interventional Trials Network" is beginning and will identify therapeutic strategies to retard the progression of PKD, the result of which will forestall kidney failure for PKD patients, free up more than 3,000 spots on the kidney transplant waiting list, save $2,000,000,000 annually in PKD-caused Medicare costs for End-Stage Renal Disease, and alleviate pain, suffering, and premature death for 600,000 American PKD patients. Likewise, the Committee is gratified such novel discoveries as the recent "abnormal fluid-flow sensation" phenomenon, involving cilia

located PKD proteins, bodes well for developing drug therapies to decrease abnormal cell growth in the PKD disease process. Therefore, because of such extraordinary scientific momentum, the Committee urges NIDDK to expeditiously implement the new PKD Strategic Plan and thus intensify its efforts to find a treatment and cure for PKD by establishing two additional PKD Centers and by issuing RFA's to develop Surrogate Markers of Disease Progression and for Testing Innovative Treatment Strategies using knowledge based studies of pathophysiology and cellular pathobiology. (p. 119)

Action taken or to be taken

The NIDDK is undertaking a series of efforts in response to the recommendations of the PKD strategic planning group, which the Institute convened in June 2002. The Institute has already made substantial progress toward three of the four ten-year goals developed by that advisory group. The first goal was to define the functions of molecules that cause PKD. The Institute's robust portfolio of investigator-initiated research includes a number of grantees who are making excellent progress in delineating the function of the proteins altered in PKD, and it appears likely that this goal will be met. The second goal was to outline future directions for genetic research in PKD. The NIDDK has recently funded two new genetic studies that are designed to assess genetic modifiers of PKD, an explicit aim of this part of the strategic plan.

The third goal is to develop treatments that improve the quality of life and longevity of patients with PKD. The Institute is funding two major clinical consortia for PKD research, in response to this third objectives of the strategic plan. The CRISP consortium is a study group funded by NIDDK in May 1999 to determine the value of imaging methods for study of the natural history of this disease. This group has established the value of MRI methods for measuring kidney size to test new therapies. These measurements appear likely to very dramatically improve the ability to assess progression of disease, a critical step in assessing whether or not drug therapy improves outcomes. The recently-funded Polycystic Kidney Disease Treatment Network has established two clinical trials to test interventions that may be effective in slowing kidney growth in patients suffering from polycystic kidney disease. The HALT PKD trial has recently been expanded, with one study focusing on early PKD and another on later forms of PKD. The fourth goal of the strategic plan was to ascertain the potential value and feasibility of registries of PKD patients. The Institute convened a working group to advise on this topic in the summer of 2002. This panel advised the Institute that a registry of recessive PKD patients would be of value. Currently, two independent organizations maintain patient registries, and the NIDDK is assessing the feasibility of working together with these organizations for a national registry.

Item

Prostatitis – The Committee recognizes the efforts of the CPCRN (Chronic Prostatitis Collaborative Research Network) funded by the NIDDK. The Committee encourages inclusion of more diverse medical specialties to supplement and build upon the background of basic

information developed. The genetic and molecular epidemiology, the management of pelvic pain, the infectious origins and the symptoms identical to prostate cancer need intense scrutiny.

Action taken or to be taken

Chronic prostatitis is a disabling condition affecting an untold number of men of all ages and ethnic origins. The most common – but least well understood – form of the disease is known as chronic prostatitis/chronic pelvic pain syndrome, a disorder in which patients experience chronic pelvic pain but doctors are unable to detect infectious bacteria using conventional techniques. As the Committee notes, the Chronic Prostatitis Collaborative Research Network – established by the NIDDK in 1997 – conducts epidemiological studies and clinical trials in men with chronic prostatitis in order to better define the characteristics of individuals with this condition as well as to test possible therapies. Funding for the CPCRN has recently been renewed for an additional five years. Additional funding for ancillary studies about possible infectious origins and studies of the genetic and molecular epidemiology of the disease should provide further insights into the origins and possible therapies for this common, largely mysterious condition. The CPCRN has recently completed a clinical trial comparing an alpha blocker (Flomax) and an antibiotic (Cipro). This trial was completed in the Spring of 2003 and the data are currently being analyzed. CPCRN researchers also developed a Chronic Prostatitis Symptoms Index (CPSI), a questionnaire-style form that attempts to quantify the extent to which chronic prostatitis.

Furthermore, because there are similar approaches to conducting clinical trials for chronic prostatitis, chronic pelvic pain syndrome, and interstitial cystitis, the new CPCRN will collaborate with the newly-established Interstitial Cystitis Collaborative Research Network in a overarching organization that will be called the Urological Pelvic Pain Collaborative Research Network. This Network will help develop research protocols, including the establishment of disease and enrollment criteria, outcome measures, and therapies to be evaluated; develop common definitions and criteria; and facilitate common data collection to permit comparisons between clinical trials.

Additional insights into related aspects of prostate biology and disease that may be relevant to prostatitis may come from ancillary studies to the recently-completed Medical Therapy of Prostatic Symptoms (MTOPS) trial. As part of the trial, serum and prostate biopsy samples were stored for later analysis. The MTOPS Prostate Samples Analysis Consortium (MPSA) will use archived specimens from the MTOPS trial to evaluate genetic, immunologic, or biochemical biomarkers relevant to the progression prostate disease, response-to-therapy, and the development of prostate cancer. The consortium will generate and validate biomarkers that will later be made available to research community for use in a variety of investigations and will also produce research tools such as serum protein arrays, layered expression arrays, or tissue arrays. The MTOPS found that combination therapy of finasteride (an inhibitor of the 5-alpha reductase

enzyme) and doxazosin (an alpha blocker) together could significantly reduce the risk of progression in men with benign prostatic hyperplasia compared to either drug alone or placebo.

Item

[Prostatitis] – The Committee encourages additional funding for educational efforts aimed at reaching primary care physicians, the patients and general public in an effort to prevent all prostatitis from becoming chronic and removing the stigma many patients feel after being diagnosed with a disease of unknown origin. (p.119)

Action taken or to be taken

The NIDDK disseminates information and educational materials regarding prostatitis and other urologic health issues through its National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). The NKUDIC was established in 1987 to increase knowledge and understanding about diseases of the kidneys and urologic system among people with these conditions and their families, health care professionals, and the general public. To carry out this mission, the NKUDIC works closely with a coordinating panel of representatives from Federal agencies; voluntary organizations on the national level; professional groups; and State health departments to identify and respond to informational needs about kidney and urologic diseases. The NKUDIC publishes information about specific kidney and urologic diseases; these items are available online or as free booklets and brochures, and include information on prostatitis (online at http://kidney.niddk.nih.gov/kudiseases/pubs/prostatitis/index.htm). Additionally, the NKUDIC exhibits materials at professional meetings specific to kidney and urologic diseases, as well as cross-cutting professional meetings, including the annual meetings of the Society of Urologic Nurses and Associates, American Urologic Association, American Society of Nephrology, National Kidney Foundation, Polycystic Kidney Disease Research Foundation, American Academy of Family Physicians, American Academy of Physician Assistants, American Nurses Association, and the National Conference for Nurse Practitioners.

Item

Scleroderma – The Committee encourages the NIDDK to support scleroderma relevant research. Scleroderma is a chronic and progressive disease that predominantly strikes women. Many patients have Gastrointestinal involvement include gastroesophageal reflux disease, dysphagia, Barrette's esophagus, gastroparesis, malabsorption, and fibrosis of the small and large intestines. (p. 119)

Action taken or to be taken

Please refer to pages 42-43 of this document for the NIDDK response regarding scleroderma.

Item

Urinary Incontinence – The Committee is pleased that the NIDDK has developed the Urinary Incontinence Treatment Network and urges increased funding for this important clinical network. Recent studies have yielded gains in understanding these conditions but the Committee is equally concerned that more needs to be done with basic and translational research in order to create better foundations for clinical care. The Committee encourages the Institute to provide more resources to investigator-initiated applications to ensure a self-sustaining core of ongoing research and encourages a dedicated study section in this area. (p. 119)

Action taken or to be taken

In FY 2000, NIDDK, in collaboration with the National Institute of Child Health and Human Development (NICHD), established the Urinary Incontinence Treatment Network. The purpose of the Network is to establish a group of collaborating investigators who will conduct long-term studies, including clinical trials, of the most commonly used surgical, pharmacological, and behavioral approaches to the management of urinary incontinence in women diagnosed with stress and mixed incontinence. In FY 2001, NIDDK increased the number of clinical centers in the Network to enhance the ethnic and racial diversity of trial participants. In FY 2003, the NIDDK provided additional funds to expand the scope of the Network. Currently, the NIDDK, with co-sponsorship from the NICHD, supports nine clinical Continence Treatment Centers and a data coordinating center. The NIH Office of Research on Women's Health has also provided support for the establishment of the Network's clinical centers. The Network is conducting a randomized, controlled clinical trial comparing two surgical treatments for stress and mixed incontinence, and is currently recruiting patients.

To further advance basic and clinical research in urinary incontinence and other disorders of the genitourinary tract, the NIDDK issued a Program Announcement (PA) in August 2002, "Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract." The first set of applications received in response to this research solicitation is currently undergoing scientific peer review. This initiative is co-sponsored by the National Cancer Institute (NCI) and the NICHD. The goal is to encourage the development of much-needed new research tools and methods applicable to studies of the individual cell types that make up the bladder and other organs of the genitourinary tract – thereby enhancing future opportunities for investigators to effectively study the function of these cells and the organs they comprise in both normal and disease states. For example, studies are encouraged on the identification or development of cell-selective gene expression, scientifically relevant mouse models, and cell-specific biomarkers.

In addition to these efforts, most investigator-initiated research grant applications for urologic research will now be reviewed by a newly formed Renal and Urological Sciences Integrated Review Group (IRG) in the Center for Scientific Review (CSR), which has three study sections, including a study section for Urologic and Kidney Development and Genitourinary Diseases (UKGD). This study section will be responsible for review of applications in several specified areas, including male and female incontinence and pelvic floor dysfunction.

Item

Urology Research –. . . The report of the Bladder Research Progress Review Group outlines a strategic plan for research in this neglected area. Bladder diseases, such at interstitial cystitis, urinary tract infections, and urinary incontinence, disproportionately affect women, and the Committee urges NIDDK to develop a comprehensive program to address these and other urological needs of women. (p. 119)

Action taken or to be taken

The NIDDK is committed to issues surrounding urology research and the impact of urological disorders, especially bladder disorders, on men, women, children, and minority groups. The NIDDK supports a broad spectrum of research efforts in urology, from basic research to clinical trials, and has recently launched a number of new initiatives. Planning efforts are under way for research initiatives in FY 2004 and beyond. Recommendations contained within the report from the Bladder Research Progress Review Group, "Overcoming Bladder Disease: A Strategic Plan for Research," have been pivotal in the Institute's recent strategic planning efforts in urology. The ultimate goals for these efforts are to increase basic knowledge about the bladder and other organs of the urinary tract and to decrease the burden of urological disease on the nation. Recent and current NIDDK efforts in urology in areas of particular concern to the committee are as follows:

The Institute committed significant resources in FY 2003 to support both new NIDDK initiatives and expansions or recompetitions of ongoing initiatives to enhance research on interstitial cystitis, urinary incontinence, and urinary tract infections. These are extensively described in response to the items, "Bladder Disease" (pp. 18-19), "Interstitial Cystitis" (pp. 17-18), and "Urinary Incontinence" (pp. 26-27). In addition to basic and clinical research efforts in these important areas, the Institute is working to ensure that advances in clinical knowledge are translated into the most effective health care for patients. In response to recommendations of both the American Urological Association and the Interstitial Cystitis Association, the NIDDK plans to undertake a Women's Urologic Health Outreach Initiative in partnership with these two groups. The program will initiate an awareness campaign to increase primary-care physician awareness of and knowledge about the current health care recommendations for women's

urological problems, including IC, urinary incontinence and urinary tract infections. The Institute intends to hire an additional urologist within its Division of Kidney, Urologic, and Hematologic Diseases, who will assist in the development of the program. Planning for this new program will begin in FY 2004, with anticipated full implementation in FY 2005.

Item

[Diabetes research] – This report identifies the considerable urologic complications of diabetes. Until the epidemic of diabetes is conquered, the incidence of these complications will only increase. Significant resources have been directed to diabetes research, but this area is underfunded. The Committee urges that a cooperative program of research be developed by the Division of Diabetes and the Urology program to address this unmet need. (p. 120)

Action taken or to be taken

The prevalence, severity, and specific risk factors for urologic complications in persons with diabetes are still incompletely characterized. In addition to funding individual investigator-initiated basic, clinical, and epidemiological studies to tackle these questions, the NIDDK Division of Kidney, Urologic, and Hematologic Diseases and the Division of Diabetes, Endocrinology, and Metabolic Diseases have worked closely in the review and coordination of ancillary studies to large-scale clinical trials which are investigating diabetes treatment and/or prevention strategies that should provide important insights into urologic complications of the disease. For example, the Epidemiology of Diabetes Interventions and Complications (EDIC) study offers a unique opportunity to study urologic complications of diabetes. The goal of the EDIC study is to determine the long-term outcome of intensive blood glucose control on micro- and macrovascular complications in participants of the landmark Diabetes Control and Complications Trial (DCCT). The DCCT had documented significant reductions in diabetic eye, kidney, and nerve disease in individuals with type 1 diabetes undergoing intensive versus conventional treatment of blood glucose levels. A urologic component is included in the EDIC study, and the wealth of data on the study's participants, including aspects of their treatment, will permit correlation of urologic outcomes with other factors.

Furthermore, a urologic component was included within the Diabetes Prevention Program clinical trial (DPP) and its follow-up outcomes study (DPPOS). The large, multi-site DPP trial demonstrated that a lifestyle intervention of moderate weight loss and physical activity dramatically reduced the risk for type 2 diabetes – by 58 percent – in individuals at high risk for this disease. In another treatment approach used in the DPP, the drug metformin reduced the risk for type 2 diabetes by 31 percent. The nature of the DPP trial, which enrolled participants who had pre-diabetes (blood glucose levels higher than normal but not yet diabetic) and who were overweight or obese, will contribute to the understanding of the early stages of diabetes and its complications. The goal of the ancillary study is to determine if pre-diabetes, like diabetes, is a

risk factor for urinary incontinence, and whether interventions that reduce the risk of developing diabetes also reduce the risk of developing incontinence.

To galvanize research in this area, the Institute recently sponsored a scientific meeting, "Urologic Complications of Diabetes." At this meeting, held in December 2003, an international group of clinical and basic researchers gathered to discuss urologic complications of diabetes, including bladder, sexual, and erectile dysfunction, as well as urinary tract infections. Meeting participants gave presentations on the current understanding of, knowledge gaps in, and future directions for research on urologic complications among men and women with diabetes. The NIDDK will encourage research in this area.

Finally, to provide seamless integration of NIDDK's planned and ongoing efforts related to complications of diabetes, including urologic complications, the Institute has established a new Diabetes Complications Working Group. This Working Group also plans to establish liaison with other NIH Institutes and to develop activities that will increase interest in diabetes complications in other scientific communities. The group will integrate its liaison efforts with the activities of the Diabetes Mellitus Interagency Coordinating Committee, which the NIDDK chairs. The Working Group will also lead future strategic planning activities on diabetes complications.

Item

[Prostate biology initiative] – . . . Benign diseases of the prostate affect men of all ages. While progress has been made, the Committee encourages the Institute to develop a comprehensive initiative on basic prostate biology that can lead to improved diagnosis and treatment of diseases such as prostatitis and BPH. (p. 120)

Action taken or to be taken

A better basic understanding of prostate biology is key to the rapid development of improved prevention and treatment measures for benign disorders of the prostate, which include benign prostatic hyperplasia (BPH) and prostatitis. To further advance research in benign prostate disease and other disorders of the genitourinary tract, the NIDDK issued a Program Announcement (PA) in August 2002, "Development of Cell-Selective Tools for Studies of the Bladder, Prostate, and Genitourinary Tract." The goal of this PA, which is co-sponsored by the National Cancer Institute (NCI) and the National Institute of Child Health and Human Development, is to encourage the development of much-needed new research tools and methods applicable to studies of the individual cell types that make up the prostate, bladder, and other organs of the genitourinary tract. Such tools would enhance future opportunities for investigators for effectively studying the function of these cells and the organs they comprise in

both normal and disease states. This may in turn aid in the development of therapeutics for a number of urologic diseases, including BPH and other benign prostate diseases.

Together with the NCI and the NIEHS, the Institute is also a co-sponsor on an NIA-led Program Announcement on the biology of the prostate. This solicitation is inviting research applications addressing biologic mechanisms related to aging processes that underlie the initiation and progression of prostate growth processes in middle-age, and the pathophysiologic connections of that growth process with the prostate diseases prevalent in older men, BPH and prostate cancer.

Complementing these efforts to increase basic knowledge of prostate biology are important new clinical initiatives evaluating treatment options for BPH. For example, men with symptoms of BPH are increasingly treating themselves with plant therapies (phytotherapies) that are sold over the counter, but rigorous clinical trials of the efficacy and long-term effects of these therapies have been lacking. In late FY 2002, the NIDDK, with the National Center for Complementary and Alternative Medicine (NCCAM) and the NIH Office of Dietary Supplements (ODS), launched CAMUS. CAMUS (Complementary and Alternative Medicine for Urological Symptoms) is a randomized, controlled clinical trial that is testing the ability of two commonly used phytotherapies for BPH, *Serenoa repens* (saw palmetto) and *Pygeum africanum*, to prevent clinical progression of BPH. Approximately 3,000 men will be enrolled in the trial and followed for 4 to 6 years. In the past year, the clinical protocol has been developed, and patient enrollment is about to begin. The NIDDK is also supporting clinical studies of new surgical treatments for BPH. The MIST (Minimally Invasive Surgical Therapies) Treatment Consortium for BPH was formed to develop and conduct randomized, controlled clinical trials that will give a clearer picture of the benefits and risks of these new methods. Currently, the consortium is evaluating the safety and effectiveness of transurethral needle ablation (TUNA), transurethral microwave therapy (TUMT) and a medical therapy regimen. The results of this first trial will provide both physicians and patients with the knowledge needed to make the most appropriate choices for long-term management of BPH.

Finally, the NIDDK is supporting a research consortium whose goal is to identify and validate biomarkers for the detection, risk assessment, and disease progression assessment of BPH. The MTOPS Prostate Samples Analysis Consortium (MPSA) was established in late 2002 to analyze serum and tissue samples collected in a large completed clinical trial called Medical Therapy of Prostatic Symptoms, or MTOPS. The MTOPS clinical trial investigated two drug treatments for BPH, finasteride and doxazosin. The serum and tissue samples collected from nearly 1,200 men during the trial are an invaluable resource for the ongoing biomarker studies and for future genetic and biomolecular studies of BPH. Through support for this initiative and its other ongoing basic and clinical research efforts, the Institute hopes to build a comprehensive knowledge base in prostate biology and pathology that will lead to improved therapies for benign prostate diseases.

Item

[Pediatric urology review group] – Urologic problems in children are often the result of congenital anomalies at birth. The Committee urges the Institute to organize a pediatric urology review group to identify the priority research needs in this area and to formulate a research plan that addresses them. (p. 120)

Action taken or to be taken

Genitourinary birth defects are the most common congenital abnormalities in newborns. Many congenital defects in the bladder and urinary tract can have both immediate life-threatening consequences to the newborn and long-term effects on proper bladder and kidney function. In FY 2002 and FY 2003, the NIDDK convened a number of Task Forces to review research needs and opportunities in pediatric urologic diseases, and to provide a foundation for new research initiatives that will address research gaps. The Institute recently issued a Program Announcement, "Basic And Clinical Studies of Congenital Urinary Tract Obstruction," which grew out of recommendations from a March 2002 strategic planning meeting on this pediatric urological disorder. Similarly, in response to recommendations emanating from the April 2002 meeting of its Task Force on Chronic Kidney Disease in Children, the NIDDK, the NICHD, and the NINDS issued an Request for Applications in FY 2003 to establish a long-term prospective cohort study of kidney disease in children ("Pediatric Chronic Renal Insufficiency Cohort (CRIC)"). Two clinical centers and a data coordinating center were recently funded. For FY 2004, the NIDDK is planning an initiative on vesicoureteral reflux (VUR), a urologic disease affecting primarily children that can lead to serious infection and kidney failure. The initiative is building upon recommendations of the NIDDK-sponsored Vesicoureteral Reflux (VUR) Task Force. The Task Force met in May 2003 to discuss the potential for conducting a randomized controlled clinical trial for children diagnosed with this disorder, and the questions that need to be addressed in such a trial. The meeting summary is available at the URL, http://www.niddk.nih.gov/fund/divisions/kuh/vur-task-force.pdf .

In the spring of FY 2004, at the recommendation of the Kidney, Urology and Hematology Interagency Coordinating Committee meeting, the NIDDK will be convening a panel to undertake a complete review of our pediatric urology programs and develop a strategic plan for the future. The Institute has identified two leading individuals to chair this group, and has asked then to develop a panel with the appropriate expertise. The NIDDK expects that this endeavor will be a cooperative process with the NICHD.

[Stone disease] – . . . Stone disease afflicts millions of Americans each year, particularly in certain regions of the country. While effective treatments are available, there is little understanding of ways to prevent the formation of kidney stones. The Committee urges NIDDK

to work with the scientific community to formulate a research plan to address prevention needs in this area. (p. 120)

Action taken or to be taken

Stone disease encompasses a number of disorders and conditions that lead to the formation of crystalline stones in the urinary tract, with subsequent pain, blockage, and other serious symptoms. Causes of stone disease include several inherited metabolic disorders, urinary tract blockages and infections, excess vitamin D consumption, and use of certain medications. However, many questions remain regarding the biologic and environmental factors influencing the initiation and development of stones, information which could provide key insights for stone prevention. Similarly to its recent efforts for bladder disease, the Institute intends to undertake a 2 year strategic planning effort for the development of a long-term strategic plan for stone disease research. This process will be initiated in Summer 2004; a group of external experts in stone disease will be convened at that time.

Item

Hepatitis C in children – The Committee is aware that recent studies have indicated that 1 in every 300-400 children over the age of 12 is infected with the hepatitis C virus. The Committee urges NIDDK, with appropriate support from NICHD, to study the natural history of hepatitis C in infected children to help determine the optimal timing and medical regimen for treatment. (P. 130-131)

[Assigned to NIDDK but located within NICHD language]
Action taken or to be taken

Please refer to page 45 of this document for the NIDDK response regarding hepatitis C in children.

Item

Living donor liver transplants – The Committee is aware that more than 1,774 people died over the past year waiting for a liver transplant due to a lack of a donor liver. As of March 6, 2003 there were almost 16,934 on the list waiting for a liver transplant. In view of the continuing shortage of livers available for transplantation, the Committee is pleased with the award in the past year of funding for a study of adult-to-adult living donor liver transplants which will compare outcomes of living donor transplants to cadaver transplants. The Committee urges additional research that would facilitate the success of a living donor liver transplant and the number of livers available for transplantation. (p. 131)

[Assigned to NIDDK but located within NICHD language]

Action taken or to be taken

Please refer to page 44 of this document for the NIDDK response regarding living donor liver transplants.

Item

Scleroderma – The Committee encourages the NIDDK to support scleroderma relevant research. . . . More research is critically needed in order to develop safe and effective treatments and to identify the cause or causes of the devastating complications of scleroderma. (P. 133)

[Assigned to NIDDK but located within NICHD language]

Action taken or to be taken

Please refer to pages 42-43 of this document for the NIDDK response regarding scleroderma.

FY 2004 Conference Committee Report Language (H. Rpt. 108-10)

Item

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
The conference agreement includes $1,633,347,000 for the National Institute of Diabetes and Digestive and Kidney Diseases instead of $1,637,347,000 as proposed by the Senate and $1,532,394,000 as proposed by H.R. 246. The conferees are concerned about the alarming growth in kidney disease and end stage renal disease and anticipated shortages of the professionals in nephrology that will be needed to handle these cases. NIDDK is encouraged to consider launching new training initiatives and workshops such as grant writing seminars to foster increased interest in this subspecialty.

Action taken or to be taken

Although the NIDDK supports vigorous research training and career development programs and participates in the NIH Loan Repayment Program (which seeks to recruit and retain highly qualified health professionals in clinical and pediatric research through educational loan repayment), the Institute recognizes that additional efforts are necessary to foster interest in nephrology. In Spring 2004, the NIDDK will sponsor its third workshop on "Preparing for a Career in Clinical Research in Nephrology." This workshop will provide the opportunity for researchers to learn the skills needed to have a successful clinical research career and to effectively compete for research funding. The training program will include lectures, mentored training sessions on clinical research and study design, manuscript and grant writing, and a mock study section. The Institute has also prepared informative displays for presentation at meetings of nephrologists, with the goal of educating young investigators about the grants process and important issues in grantsmanship.

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,766,144,000	Indefinite	$1,820,431,000
National Institute of Diabetes and Digestive and Kidney Diseases	Section 426	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	55,096,000	b/	55,765,000
Total, Budget Authority				1,821,240,000		1,876,196,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1996	748,798,000 2/	771,252,000	738,456,000 2/	771,252,000 3/
Rescission				(670,000)
1997	758,847,000 2/	806,542,000	787,473,000 2/	815,607,000
1998	821,164,000 2/	874,337,000	883,321,000	900,860,000
1999	924,702,000 2/,4/	951,203,000	994,218,000	1,021,218,000 5/
Rescission				(659,000)
2000	1,002,747,000 2/	1,087,455,000	1,130,056,000	1,174,588,000 6/
Rescission				(6,112,000)
2001	1,186,266,000 2/	1,315,530,000	1,318,106,000	1,470,385,000 7/
Rescission				(429,000)
2002	1,457,915,000 2/	1,446,705,000	1,501,476,000	1,563,833,000 8/
Rescission				(453,000)
2003	1,706,292,000	1,731,754,000	1,731,754,000	1,733,347,000 9/,11/
Rescission				(10,617,000)
2004	1,820,000,000	1,820,007,000	1,833,007,000	1,821,240,000 10/,11/
Rescission				(732,000)
2005	1,876,196,000 11/			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $670,000.
4/ Reflects a decrease of $2,790,000 for the budget amendment for bioterrorism.
5/ Excludes enacted administrative reductions of $659,000.
6/ Excludes enacted administrative reductions of $6,112,000.
7/ Excludes enacted administrative reductions of $429,000.
8/ Excludes enacted administrative reductions of $453,000.
9/ Excludes enacted administrative reductions of $10,617,000.
10/ Excludes enacted administrative reductions of $732,000.
11/ Includes Type One Diabetes funds.

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	68	74	67
Division of Diabetes, Endocrinology and Metabolic Diseases	25	29	33
Division of Digestive Diseases and Nutrition	21	22	25
Division of Kidney, Urologic and Hematologic Diseases	24	24	25
Division of Nutrition Research Coordination	8	8	8
Division of Extramural Activities	63	62	62
Division of Intramural Research	437	438	438
Total	646	657	658
FTEs supported by funds from Cooperative Research and Development Agreements	(4)	(4)	(4)

FISCAL YEAR	Average GM/GS Grade
2001	11.0
2002	12.8
2003	11.0
2004	10.9
2005	10.9

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	0	0	0
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	0	0	0
Total - ES Salary	$0	$0	$0
GM/GS-15	41	34	35
GM/GS-14	56	57	57
GM/GS-13	53	55	55
GS-12	52	54	54
GS-11	46	47	47
GS-10	3	4	5
GS-9	45	46	45
GS-8	34	37	37
GS-7	38	36	36
GS-6	6	7	7
GS-5	9	10	10
GS-4	5	4	4
GS-3	0	1	1
GS-2	2	1	1
GS-1	1	1	1
Subtotal	391	394	395
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	9	10	10
Senior Grade	6	5	5
Full Grade	0	1	1
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	15	16	16
Ungraded	223	225	227
Total permanent positions	380	392	393
Total positions, end of year	629	635	638
Total full-time equivalent (FTE) employment,end of year	646	657	658
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$0	$0	$0
Average GM/GS grade	11.0	10.9	10.9
Average GM/GS salary	$67,761	$69,794	$71,190

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases

New Positions Requested

	FY 2005		
	Grade	Number	Annual Salary
Health Scientist Administrator for NIDDK Obesity Initiative	15	1	$115,000
Total Requested		1	