DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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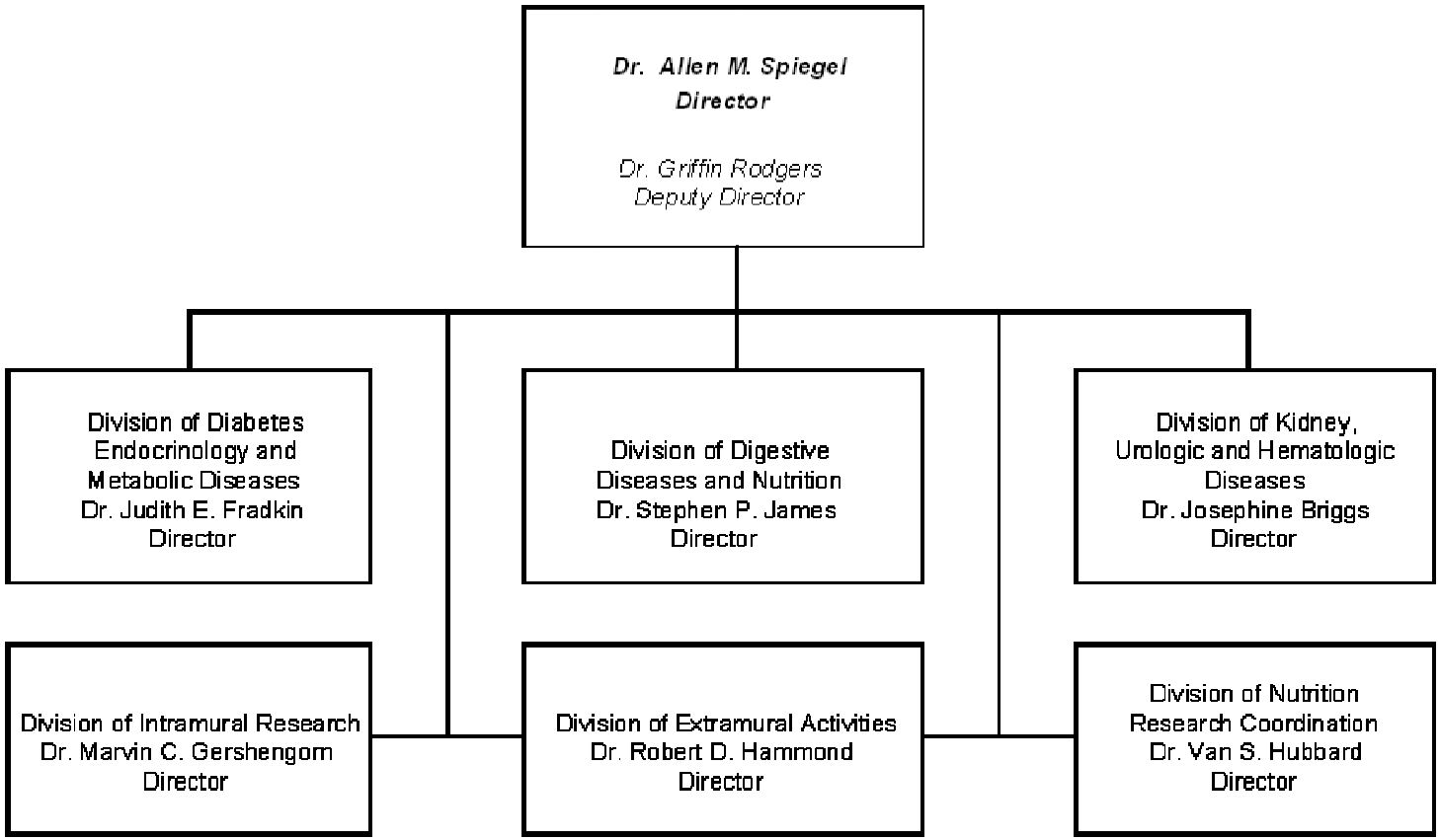
Organization Structure



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, [$1,727,696,000] *$1,722,146,000*.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act, 2005.]

National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$1,682,457,000	$1,727,696,000	$1,722,146,000
Type 1 Diabetes 2/	$150,000,000	$150,000,000	$150,000,000
Enacted Rescissions	(10,654,000)	(14,112,000)	0
Subtotal, Adjusted Appropriation	1,821,803,000	1,863,584,000	1,872,146,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	8,297,000	0	0
Comparative transfer to NIBIB for Radiology Program	(106,000)	0	0
Comparative transfer to Buildings and Facilities	(457,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	(8,297,000)	0	0
Subtotal, adjusted budget authority	1,821,240,000	1,863,584,000	1,872,146,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,821,240,000	1,863,584,000	1,872,146,000
Unobligated balance lapsing	(627,000)	0	0
Total obligations	1,820,613,000	1,863,584,000	1,872,146,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $10,221,000 FY 2005 - $12,610,000 FY 2006 - $12,862,000
Excludes $4,000,000 in FY 2005 and $4,500,000 in FY 2006 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 and title IV of the Public Health Service Act, as amended.

Budget Authority:

FY 2004 Actual		FY 2005 Final Conference		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
580		624		624		0	
Program Total	$1,821,240,000		$1,863,584,000		$1,872,146,000		$8,562,000
Type 1 Diabetes	-150,000,000		-150,000,000		-150,000,000		
Labor / HHS	1,671,240,000		1,713,584,000		1,722,146,000		$8,562,000

This document provides justification for the Fiscal Year 2006 activities of the National Institute of Diabetes and Digestive and Kidney Diseases, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 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 transferring new knowledge of biologic processes into appropriate clinical studies, and ultimately, to efforts to translate knowledge and medical discoveries into improved health care, with special emphasis on populations disproportionately affected by diseases within 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

Developmental Biology

Environmental Control of Blood Cell Differentiation: Stem cells, by definition, have the potential to differentiate into more than one cell type. The signals that influence a stem cell to divide or to follow any particular developmental path come from its environment in the body, typically from neighboring cells. Cells of the blood are continually replenished by hematopoietic (meaning blood-forming) stem cells, or HSCs. Although it has long been known that HSCs reside mostly or entirely in bone marrow, the mechanisms by which the bone environment controls their fates have been poorly understood. Researchers have shed light on the subject by using genetically engineered mice that have higher than normal levels of bone-forming cells called osteoblasts. They observed that these mice also have increased numbers of HSCs, suggesting that osteoblasts play a role in stem cell regulation. In particular, they found that it is the osteoblasts lining the inner surface of bone, where bone interfaces with marrow, that are associated with the stem cells. Finally, the researchers demonstrated that treatment with parathyroid hormone (PTH)—which is known to activate osteoblasts—caused the number of HSCs to increase in mice and dramatically improved the survival of mice that received a bone marrow transplant. Thus, PTH, which is currently used to treat osteoporosis, may have other potential clinical benefits. These results are important because understanding the molecular determinants of stem cell fate is key to realizing the potential of stem cell-based therapies.

Harnessing Technology

New Imaging Technology To Monitor Type 1 Diabetes Disease Progression: Type 1 diabetes is usually diagnosed very late in disease progression, when most of the beta cells of the pancreas (which produce insulin) have already been destroyed by an autoimmune attack. Currently, there is no way to detect the first signs of beta cell destruction to monitor disease progression. In

research toward overcoming this major research and clinical barrier, scientists discovered a new, non-invasive imaging technology that enabled them to monitor disease progression in a mouse model. The technology uses a vascular probe, containing magnetic nanoparticles that can be detected by magnetic resonance imaging (MRI). If type 1 diabetes has already begun to develop, the probe leaks out of the blood vessels of the pancreas and can be visualized by MRI. Vascular probes have already been successfully used in humans to detect prostate cancer metastases; therefore, this technology has high potential of being translated to the clinic for type 1 diabetes. Importantly, this technology can facilitate studies of the molecular underpinnings of disease onset and progression, which can lead to novel prevention and treatment strategies.

Minority Health Disparities

Patient Literacy Affects Success of Diabetes Disease Management: Patients with diabetes can minimize complications by reducing the level of sugar in their blood. While many diabetes disease management programs have helped patients reduce their blood sugar levels by using a combination of education, medication, diet and exercise regimens, and glucose monitoring, their use in socially disadvantaged populations has been less successful. Low literacy is common among patients and is associated with poor knowledge about diabetes. A recent study examined the role of literacy on the effectiveness of a comprehensive disease management program for patients with type 2 diabetes. In the study, half of the 217 patients received usual care from their primary care clinician, while the rest received usual care plus supplemental intensive diabetes management that included one-on-one counseling and medication management. The individualized care included tools to enhance comprehension such as simplified verbal explanations, picture-based materials and "teach-back" patient comprehension assessments. The supplemental intervention significantly improved the blood sugar control in patients with low literacy (below sixth-grade level). Patients with higher literacy showed improvement from the usual care regardless of whether or not they also received the individualized care. These results suggest that providing individualized care can improve the success of diabetes management, and that patients with low literacy stand to benefit the most from such care.

Diabetes, Endocrine and Metabolic Diseases

Insights into a Possible Cause of Type 2 Diabetes: To improve medical strategies for the prevention of diabetes, it is important to know the precise mechanisms underlying disease development. While obesity is a serious risk factor for type 2 diabetes, it does not fully explain the disease, because many obese people are not diabetic, and some people of normal weight develop diabetes. Identification of the biologic basis for diabetes susceptibility is key to development of new therapies. Several recent lines of evidence suggest that people with type 2 diabetes may have defects in the functioning of mitochondria, the structures in cells responsible for converting fat into useful energy. A new study reports that these defects precede the development of the disease: people at risk for type 2 diabetes accumulate fats in muscle cells, and this accumulation correlates with mitochondrial problems. Because the presence of such fats has been shown in experimental models to decrease the ability of cells to function properly in response to insulin, deficits in mitochondrial function could potentially contribute to the insulin-

resistance that can lead to type 2 diabetes. These insights may help pave the way to the development of therapies aimed at correcting mitochondrial function as a possible means of preventing or delaying onset of the disease.

Thyroid Hormone Requirements During Pregnancy: Thyroid hormone (TH) plays an important role in promoting normal fetal development during pregnancy. When maternal TH levels are too low (hypothyroidism) or too high (hyperthyroidism), the result could be increased fetal mortality or other fetal developmental problems. Hypothyroidism is treated with a synthetic form of TH, called levothyroxine. Pregnancy increases the requirement for TH, so the dose of levothyroxine in women with hypothyroidism is increased during pregnancy, usually after the first prenatal doctor's visit at approximately 10 weeks of gestation. However, it is unclear if this timing is sufficient to protect the fetus from harmful effects of low TH levels. To learn the timing pattern of TH requirement during pregnancy, researchers studied 19 women who had hypothyroidism and desired pregnancy. They determined that the requirement for increased levothyroxine occurs very early in pregnancy—as early as the fifth week of gestation. Based on these novel observations, the researchers recommend that women with hypothyroidism be counseled before pregnancy to increase their levothyroxine dose immediately upon confirming pregnancy, even before their first prenatal doctor's visit. Another study investigated the opposite situation—the effects of high TH levels on the developing fetus. Researchers studied individuals who have "resistance" to thyroid hormone (RTH), and whose thyroid produces very high levels of TH in compensation. Because mothers with RTH make high levels of TH during pregnancy, the researchers could investigate the effects of high TH levels on the fetus. The researchers observed a 3- to 4- fold increase in the rate of miscarriage in the women with RTH. In addition, they observed differences in birth weights of the babies born to women with RTH. When the newborn also had RTH, the birth weight was normal; however, if the newborn did not have RTH, the birth weight was low. These results suggest that high levels of TH could be damaging to the fetus and result in increased rates of miscarriage and low birth weights. Thyroid disorders are prevalent in women and TH is one of the most commonly prescribed medications. Taken together, these studies emphasize the importance of maintaining normal TH levels during pregnancy and suggest adjustment of TH medicines earlier in pregnancy than is the current practice.

Curcumin as a Potential Treatment for Cystic Fibrosis: Cystic fibrosis (CF) is a genetic disorder that results in the accumulation of thick, sticky mucus in the lungs, causing damage and facilitating infections. CF is caused by mutations in the gene encoding the CFTR protein, which resides in the outer surface of cells lining such tissues as the lung and intestine, where it regulates the movement of chloride. The most common mutation of the gene, ΔF508, yields a protein that would be functional, but which is degraded before it reaches the cell surface. Researchers have recently tested the effect of a compound called curcumin, purified from the spice turmeric, in a mouse model of CF. When given to mice that are genetically engineered to have the ΔF508 mutation, curcumin treatment enabled the mutant form of the CFTR protein to function effectively, presumably by allowing it to reach its normal cellular destination. Indeed, when cells cultured from animals with the ΔF508 mutation were treated with curcumin, the protein was properly routed to the cell surface. Importantly, the amount of curcumin that achieved these

promising results in mice is equivalent to a dose that has been well-tolerated by humans in previous studies. Therefore, curcumin, which is already known to be safe in people, has the potential to be of value for patients with this devastating illness.

Story of Discovery: Enzyme Replacement Therapy for Lysosomal Storage Disorders

The body's cells recycle many of the substances they no longer need by digesting them with enzymes inside cellular compartments called lysosomes. If these enzymes are missing or defective due to genetic mutations, toxic waste products are not properly degraded. Instead, they build up in the lysosomes and lead to severe organ damage. Diseases caused by these enzyme deficiencies, referred to as lysosomal storage disorders, are individually rare, but collectively affect about 1 in 7,700 infants born in the United States[1]. Symptoms vary, and are often not apparent at birth; however, as the undigested materials accumulate, they can cause serious problems such as weakness, severe pain, brittle bones, mental retardation, corneal clouding, organ failure and death.

Lysosomal storage disorder research, built on substantial NIH investments followed by recent commercial product development, is a classic story of translating remarkable findings from basic research into Food and Drug Administration-approved treatments for three of these serious disorders: mucopolysaccharidosis I (MPS I), Gaucher disease and Fabry disease. The critical discovery dates to work in the late 1960s, when NIDDK intramural researchers found that growth medium taken from a culture of normal cells relieved the lysosomal storage defect of cells cultured from a patient with MPS I. In essence, this meant that normal cells secrete the enzyme missing in MPS I patients; and more importantly, the MPS I cells can internalize that enzyme from the medium, and somehow send it to the lysosome, right where it needs to go. It was later discovered that this secretion and re-uptake process is a pathway common to many of the enzymes absent in these disorders. Thus, in theory, patients with such a disease might be treatable by administering purified forms of the enzymes they need—an approach referred to as enzyme replacement therapy.

Indeed, experiments in the 1970s suggested that an enzyme-replacement approach could be beneficial. For example, in separate but related work, NIH intramural scientists and NIDDK grantees treated Gaucher and Fabry patients with the enzymes they lacked, which the researchers had purified from human tissue. These studies were of short duration, and the long-term health effects could not be determined. However, the accumulation of undigested lysosomal materials was significantly reduced for a period of time after treatment, at least in some parts of the body. Therefore, researchers theorized that, if adequate supplies of the enzymes could be produced, there was reasonable hope that they might be effective therapeutically.

Tremendous advances in gene manipulation technology in the 1980s made it possible to isolate the normal versions of genes mutated in patients with lysosomal storage disorders. Researchers showed that active, properly modified, human lysosomal enzymes could be produced in cultured mammalian cells. With this technology, comparatively large amounts of the enzymes could be produced and purified—far more inexpensively and easily than was previously possible.

However, there was a pressing need for an animal model of a lysosomal storage disorder to facilitate studies of the long-term safety and efficacy of such treatments. Therefore, another key finding was that a natural mutation occurring in some breeds of dogs eliminates the same enzyme that is missing in MPS I patients. Because these dogs have symptoms quite similar to those of humans with the disease, they are a useful animal model that enabled pilot-tests of therapeutic strategies.

The combination of an improved enzyme supply and an animal model permitted testing of intravenous enzyme replacement therapy in MPS I dogs over a three month period. Some dogs developed immune reactions against the enzyme, but the problem could be managed through pre-medication with antihistamines and slower administration of the enzyme. More importantly, although lysosomal function remained unimproved in some parts of the body,

[1] Meikle PJ, Hopwood JJ, Clague AE and Carey WF, Prevalence of lysosomal storage disorders. JAMA 281:249-254, 1999.

including the brain, it was normalized in certain organs and greatly improved in others. With further work, methods were developed that avoided immune reactions from the animals, and enabled long-term treatment studies, as a prelude to clinical trials.

These ground-breaking basic and pre-clinical research advances were ultimately translated into valuable therapeutics by drug companies. Largely as a result of this translational research, the Food and Drug Administration granted approval for treatment of Gaucher, Fabry and MPS I patients with genetically engineered forms of their respective missing enzymes. The National Organization for Rare Diseases recognized this achievement by presenting its 2004 Corporate Awards to two of the companies which brought these products to market by building upon the earlier NIH-funded discoveries. Treatments for several more lysosomal storage disorders are currently in phase III clinical trials, and are likely to come to market soon.

As remarkable as these advances are, and although the improvements in quality of life for lysosomal storage disorder patients are potentially very significant, these treatments are not cures. Patients may have to see their physicians weekly to receive lengthy infusions of the enzymes. Moreover, some disease manifestations are unlikely to be alleviated, such as the corneal clouding, bone disease and mental retardation that often occur in MPS I patients. Therefore, the NIDDK continues to encourage research on lysosomal storage disorders.

One promising area for developing treatments that might avoid some of these limitations is the discovery of small molecules that can stabilize defective enzymes in patients in whom they are not entirely absent. To explore opportunities in this field, the NIDDK sponsored a workshop on "Protein Misfolding and Misprocessing in Disease." As part of its Roadmap Initiative, the NIH is establishing small molecule screening facilities, which could speed up the process of identifying new therapeutics for lysosomal storage disorders.

Obesity and Nutrition

Appetite-Suppressing Hormone Rewires Brain Circuitry: The hormone leptin suppresses food intake and helps regulate body weight by communicating signals from fat cells to a part of the brain known as the arcuate nucleus of the hypothalamus (ARH). Recent studies have now shown that leptin is also fundamentally involved in developing the neural circuits in the brain that control feeding. The studies compared normal mice with mutants that are obese because they cannot produce leptin. Distant brain cells communicate with each other by relaying electrical messages via long, wire-like connections called axons. In leptin-deficient mutant mice, the density of axons growing from the ARH was low, suggesting that one of the roles for leptin in normal mice is to promote axon outgrowth. In support of this, treating juvenile mutant mice with leptin during a critical window of time in their development restored normal patterns of brain growth. In another study, researchers found a method of distinguishing between the brain cells that control hunger and those that control satiety in a way that would permit assessment of leptin's effects on axons reaching these cells from elsewhere in the brain. Leptin-deficient mice exhibited an imbalance in physical and electrical input connections of these populations of leptin-sensitive cells. However, after just six hours of leptin treatment, the brains in the mutant mice were able to rewire and form new connections; these changes in the brain preceded observed changes in feeding behavior. Taken together, these studies mark the beginning of new and exciting advances that merge obesity research with neurobiology to demonstrate a new role for leptin in controlling the body's energy balance by regulating both long-term connections and dynamic changes in the brain.

Liposuction Does Not Improve Risk Factors for Diabetes and Coronary Heart Disease: Liposuction is a common surgical procedure that removes substantial amounts of fat from specific areas of the body including the abdomen, hips, and thighs. Researchers have now demonstrated that liposuction to decrease fat mass in obese individuals is not an effective approach to reduce risk factors for developing serious diseases associated with obesity such as type 2 diabetes and coronary heart disease. In a study of 15 obese women, seven of whom had type 2 diabetes, researchers evaluated key obesity-associated risk factors for heart disease and diabetes prior to and 10-12 weeks following abdominal liposuction. The risk factors included insulin action in fat, muscle, and liver tissues, levels of certain circulating blood inflammatory proteins, cholesterol levels, blood pressure, measures of different types of body fat, and other factors. Based on these risk factors, liposuction did not provide any health benefit to either group, even though it decreased the volume of fat beneath the skin of the abdomen by 44 percent in those without diabetes and 28 percent in those with diabetes. In comparing liposuction with other weight-loss treatments which do improve metabolic risk factors associated with heart disease and diabetes—the investigators noted that liposuction removes subcutaneous fat but does not affect energy balance, that is, the balance between calories eaten and calories the body burns. By contrast, conventional diet and exercise decrease fat mass in different locations, including the fat that surrounds body organs, and creates a "negative" energy balance, which results in weight loss. The research indicates that, although liposuction removes substantial amounts of fat from beneath the skin, it alone is not sufficient to protect against obesity-associated diseases. Thus, conventional weight-loss regimens, such as diet and exercise, should be employed for effective improvement of the status of diabetes and coronary heart disease risk factors.

Cells of the Immune System Accumulate in the Fat of People Who Are Overweight: More than 65 percent of U.S. adults are overweight or obese, with nearly 31 percent of adults—over 61 million people—meeting criteria for obesity [2],[3]. Some studies have found that obese and overweight individuals have elevated levels of certain compounds in the blood that are typically observed in cases of chronic, low-grade inflammation. However it has been unclear whether these compounds result from inflammation of a single discrete part of the body, or whether they are system-wide in origin. In any case, a better understanding of obesity-related inflammation may be valuable for improving treatment for overweight patients. Using DNA microarray technology that allowed them to probe a vast array of genomic elements, researchers recently identified genes that are turned on at higher levels in fat tissue of obese mice, as compared to lean mice. Many of these genes turned out to be those that are turned on in macrophages, which are cells that contribute to the immune response, in part by inducing inflammation. Indeed, they next observed that the number of macrophages in fat tissue increased in proportion to the weight of the mouse. When they examined cells from samples of fat tissue in humans, they found a similar correlation: about 10 percent of the cells in fat samples from lean people were identified as macrophages, whereas 40 percent of the cells were macrophages in fat samples obtained from

[2] Statistics related to overweight and obesity. NIH Publication No. 03-4158, 2003. (http://win.niddk.nih.gov/statistics/index.htm)

[3] Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, et al., Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 291:2847-2850, 2004.

severely obese subjects. These results suggest that the cellular functions of macrophages in fat tissue may play a role in obesity and its associated disorders, and may be important therapeutic targets as well.

Intervention Prevents Excessive Weight Gain During Pregnancy in Low Income Women: Excessive gestational weight gain can have deleterious effects on both mother and child, such as complications during pregnancy, increased risk of cesarean delivery, and high infant birth weight. Researchers have tested a two-part intervention for its effect on preventing excessive gestational weight gain. The first part consisted of a clinical component, in which the women's health care providers used new tools (such as a gestational weight gain grid) to provide guidance about monitoring weight gain. In the second part, the women received patient education materials by mail. The researchers tested the intervention on women who were either overweight or normal weight at early pregnancy, and followed them until one-year postpartum. Overall, the intervention did not have any effect on preventing excessive gestational weight gain or preventing weight retention at one-year postpartum. However, when the researchers analyzed a low-income subgroup of women, they observed that the intervention effectively prevented excessive weight gain in both the overweight and normal weight low-income women; it also effectively prevented one-year postpartum weight retention in overweight, low-income women. Previous studies have shown that low-income women are at increased risk for excessive gestational weight gain. Therefore, the researchers have identified a successful intervention for this high-risk group of women.

Digestive Diseases

A Gene Expressed in Paneth Cells May Contribute to Crohn's Disease(CD): CD is a chronic, currently incurable digestive disease, most commonly affecting either the colon or the portion of the small intestine nearest to it, the ileum. Symptoms frequently include abdominal pain, nausea, vomiting, weight loss, and diarrhea, which is occasionally bloody. The precise causes of CD are unknown, but bacteria in the gut are thought to contribute. There may also be a genetic component: the disease not only runs in families, but Americans and Europeans with the disease also frequently have particular variants of a gene called card15 which is expressed in immune cells, and believed to have a role in innate immunity to bacteria. In a new study, researchers found that the card15 gene is expressed at high levels in so-called Paneth cells, which lie at the base of invaginations in the small intestine. The Paneth cells secrete anti-microbial compounds, probably playing an important role in controlling gut bacteria. Thus, card15 and Paneth cells represent an apparent link between the genetic and bacterial risk factors for the illness, and are a promising target for development of therapeutics.

Children at Risk for Celiac Disease May Have Subclinical Symptoms: People with celiac disease develop severe digestive problems when they eat gluten, a major protein component of grains such as wheat, rye and barley. A small amount of any of these foods is all that is required to damage the intestines of susceptible individuals, limiting the absorption of vital nutrients. Malabsorption slows physical development in children, and can cause a host of other symptoms. Definitive testing for celiac disease requires an intestinal biopsy, and the disease often goes undiagnosed. However, a blood test can identify at-risk individuals. Thorough screening of

children born in Denver, Colorado, between 1993 and 1999 has shown that about 0.9 percent of children develop the disease by age five. A new study compares 18 children found to be at-risk but who had not developed overt celiac disease to 100 age- and gender-matched controls. The at-risk children had higher rates of some celiac disease symptoms, including irritability/lethargy and abdominal distension/gas, and were found to grow more slowly than their peers. These differences were small but statistically significant.

Combination Drug Therapy Effective for Hepatitis C: Currently, the best treatment for hepatitis C virus (HCV) infection appears to be a 24- or 48-week course of a combination drug therapy. The first component of this therapy is a form of the naturally-occurring interferon protein that has been chemically modified to protect it against breakdown through a process called pegylation. The second component is ribavirin, an anti-viral drug. Researchers have recently investigated whether patients with HCV who had previously been treated with—and not responded to—unmodified interferon alone would respond favorably to the combination. Over 600 patients who were nonresponders to previous interferon therapy, with or without ribavirin, were treated with pegylated interferon plus ribavirin. After 20 weeks, 35 percent of the patients had no detectable evidence of HCV infection in their blood. These patients continued on therapy for a total of 48 weeks. Following discontinuation of therapy, 18 percent of the initial number of patients achieved a sustained virologic response, which means that the virus remained undetectable in their blood. This study suggests that some patients who did not respond to initial therapy with interferon may benefit from re-treatment with pegylated interferon and ribavirin. This is an important finding because HCV is a leading cause of chronic liver disease in the U.S. It accounts for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer[4].

Symbiotic Bacteria May Promote Intestinal Health: The remarkably complex microenvironment of the intestine contains an abundance of microorganisms that provide health benefits to the host by inducing tolerance to substances in the environment or food that trigger an immune response. Although the gut is the site of rapid turnover of cells and propulsion of food and water, some microbes are able to latch-on to and colonize the intestine. Scientists continue to search for factors that differentiate microbial "residents" (those that successfully colonize) versus "tourists" (those that merely pass through the digestive system). The factors of interest are those that can promote initial gut attachment and resistance to the wash-out of beneficial bacteria, as well as factors that inhibit colonization of harmful ones. Recent studies suggest that the polysaccharide-rich mucus gel layer of the human intestinal wall provides a matrix capable of supporting a thin layer of helpful bacteria that functions to aid digestion of intestinal contents and augment host defenses against disease causing organisms. Events leading to the interruption of this symbiotic relationship may promote an immune response to specific microbes. Emerging data indicates that *B. thetaiotaomicron*, a predominant member of the intestinal bacteria, induces intestinal Paneth cells to secrete a protein called angiogenin-4. Angiogenin-4 kills certain types of bacteria and may function to prevent microorganisms from invading the intestinal lining. Hence, specific

[4] Chronic Hepatitis C: Current Disease Management. NIH Publication No. 03-4230, 2003. (http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/)

bacteria of the gut may regulate expression of natural antibiotics and regulate the microbial ecology of the intestine. These findings may lead to the development of therapeutic and preventative strategies to support beneficial bacteria or impede the effects of those that cause disease.

Immune Cell Transplantation for Liver Disease of Hereditary Tyrosinemia Type I:
New approaches for treating liver disease are emerging from laboratory studies of hereditary tyrosinemia type I—an inherited metabolic disorder associated with severe liver disease in infants and children. It is caused by a deficiency in an enzyme that breaks down the amino acid tyrosine, resulting in elevated tyrosine levels in the blood (tyrosinemia) and tissue damage. A drug for treating this disease was approved in 2002 that provides a means of long-term control of tyrosinemia. In cases of advanced disease, however, liver transplantation is the only effective current therapy. One way to correct the underlying defect in genetic diseases such as hereditary tyrosinemia would be through transplantation of cells with a functioning copy of the gene for the missing enzyme. In recent years, researchers have explored this possibility in mice that are deficient in the same enzyme that causes hereditary tyrosinemia type I in humans. They found that transplantation of stem cells derived from the bone marrow of healthy adult donor mice into the mice with tyrosinemia resulted in fusion between the healthy and diseased cells in the liver, correction of the genetic defect, and repair of the liver. However, the question remained of whether stem cells, with their ability to turn into a variety of cell types, were required, or if more mature cells—already committed to forming a particular cell type—could also work to correct the defect. Researchers addressed this by conducting a series of transplantation experiments using several different types of donor mice that were genetically engineered to produce only certain types of cells that originate in the bone marrow. They found that it was possible to correct the defect in mice with tyrosinemia by using macrophages—a kind of immune cell that develops from cells that form in the bone marrow. These results support the theory that donor stem cells used in prior experiments probably differentiated into macrophages prior to fusing with the recipient's liver cells. Importantly for potential clinical applications, this study also suggests that, in contrast to bone marrow transplantation, treatment with macrophages could be a less invasive, more efficient type of cell transplantation procedure for genetic liver diseases, such as hereditary tyrosinemia. A key benefit of macrophages or their immediate precursor cells is that they could be administered directly into the liver or bloodstream.

Flaws in Protein Processing: Insights from Alpha-1 Antitrypsin Deficiency

Inherited deficiencies in just a single protein can be devastating to the liver and the lungs. This protein is alpha-1 antitrypsin, or AAT. Secreted into the bloodstream primarily by the liver, this protein helps the body by inhibiting the activity of a group of enzymes, which have the power to destroy tissues.

In the genetic disease known as alpha-1 antitrypsin deficiency, this very important protein is impeded from doing its job. In severe cases, the AAT protein does not complete its journey from the interior to the exterior of the liver cell for secretion into the bloodstream. Rather, it forms polymers—orderly chains of AAT units—which aggregate in a place within liver cells that acts as a check-point to ensure the quality-control of proteins. The retention of polymerized AAT within the cells can then wreak damage on the liver. On the other hand, if inadequate levels of AAT reach the bloodstream, the protein cannot perform its important protective role of keeping a critical enzyme in check. If uncontrolled, that enzyme can cause lung tissue destruction that often progresses to emphysema. Thus, damage can come from either too much or too little AAT activity in key tissues.

NIH-funded research has helped to decipher the clinical manifestations and genetic underpinnings of AAT deficiency. Although the disease is caused by a single abnormal gene, its manifestations vary greatly depending upon whether a person inherits copies of the abnormal gene from one or both parents, and also on unknown genetic modifiers that affect gene expression. About 100,000 Americans have the severe form of AAT deficiency[5], which is the most common genetic cause of liver disease in children, and also predisposes adults to chronic liver disease and liver cancer[6]. Over 100 variants of the *AAT* gene have been discovered and grouped into three categories based on the level of AAT in the bloodstream—normal, deficient, or virtually undetectable.

With knowledge gained from research has come an expanded understanding of AAT deficiency disease, the differences among its various forms, and development of therapeutics based on this scientific foundation. The importance of AAT was originally recognized in studies of blood proteins when, in 1963, scientists found that the blood of emphysema patients lacked sufficient amounts of AAT. In 1966, other researchers observed that patients with a particular variant of the *AAT* gene have a high frequency of liver disease, including neonatal jaundice and cirrhosis. In addition, the patients had high concentrations of AAT in their liver cells. These and other observations about the disease enabled fundamental research to begin uncovering underlying mechanisms—a prelude to therapeutic development.

For example, in the 1980s, an important step forward in combating AAT lung disease was the demonstration that augmenting a patient's natural levels of AAT with externally administered protein was feasible and beneficial. AAT-deficient patients achieved an increase in their blood levels of the protein following the intravenous transfusion of purified AAT from the blood of healthy individuals. This finding led to FDA approval of the augmentation drug, Prolastin, which has become the most widely used treatment for AAT lung disease. Other related therapies on the horizon are intravenous augmentation products, inhalation delivery systems, and synthetic augmentation therapies.

Scientists supported by the NIH have focused intense research on liver damage arising from AAT deficiency disease. Researchers have searched for factors that might predispose patients to be susceptible to or protected from this liver damage. To this end, in 1994, researchers grew skin cells from AAT-deficient individuals who had never suffered from liver disease and who therefore might be "protected." Similar cultures were made with cells from AAT-deficient individuals who had severe liver disease and were therefore considered "susceptible." While cells from both cultures accumulated the AAT protein, only the "susceptible" cells exhibited a delay in degrading AAT, suggesting that some AAT-deficient patients have alterations in the degradation pathway for the protein in their liver cells—alterations that may predispose them to developing liver disease.

Additional research supported by the NIH substantiated, in 1989, that the aggregation of AAT protein within liver cells causes liver disease. The foundation for this discovery was a study of genetically engineered mice that produced sufficient AAT to protect them from lung disease, yet the mice still suffered from a build up of AAT in their liver cells. This finding led to research aimed at improving secretion of AAT, and pointed to discrete steps in protein processing that might be used as therapeutic targets. Researchers hope to build on previous NIH supported studies in which compounds known as "chemical chaperones" have been shown to be capable inducing AAT secretion into the bloodstream. In related research, studies have shown that patients with AAT deficiency sustain liver damage due to inflammatory immunological responses to the aggregated protein. The immunosuppressive drug cyclosporin A was shown to prevent AAT liver damage—a proof-of-principle for mechanism-based therapeutic approaches to AAT deficiency. These types of studies may lead to the testing of various drug combinations to arrest or mitigate one or more of the sequential steps in the cascade of events that culminates in liver cell injury.

[5] Sandhaus RA, alpha1-Antitrypsin deficiency . 6: new and emerging treatments for alpha1-antitrypsin deficiency. Thorax 59:904-909, 2004.

[6] Perlmutter DH, Liver injury in alpha1-antitrypsin deficiency: an aggregated protein induces mitochondrial injury. J Clin Invest 110:1579-1583, 2002.

A new research impetus comes from the study of small molecules that can be used therapeutically to ameliorate protein processing defects, such as those seen in AAT deficiency disease. It is expected that diseases involving abnormalities in protein processing—including AAT, cystic fibrosis, and others within the NIDDK mission—will benefit from the NIH Roadmap Initiative to develop libraries of small molecules with therapeutic potential. Knowledge about AAT deficiency and similar diseases is also being advanced by more general research conducted during the 1970s and 1980s on protein degradation. Protein processing and the degradation of old and malformed proteins are now acknowledged as essential in maintaining healthy cells. The Nobel Prize in Chemistry was awarded in 2004 in recognition of these discoveries. The NIH is proud that its sustained support of this research led to the prize-winning findings. Because AAT deficiency is an inherited disease, researchers also continue to pursue potential therapeutic approaches that could correct the genetic abnormality responsible for deficiencies in the protein. These approaches include laboratory studies of gene therapy and gene repair, as well as stem-cell approaches. The inclusion of AAT deficiency in the recently funded Cholestatic Liver Disease Consortium, jointly funded by the NIDDK and the Office of Rare Diseases, provides an opportunity to gather clinical and biochemical data and an adequate number of biosamples in a prospective manner to stimulate research on the pathogenesis and optimal diagnosis, as well as, chemoprevention and treatment of this disease. The rich variety of therapeutic approaches to AAT deficiency reflects both the complexity of the disease and the expanding possibilities for multiple types of interventions to arrest or ameliorate its underlying processes.

Kidney, Urologic, and Hematologic Diseases

Combined Drug Therapy for Benign Prostatic Hyperplasia: Benign prostatic hyperplasia, or BPH, is a condition that affects an estimated nine percent of men 30 years of age and older. Prevalence increases significantly in middle age, with the majority of cases reported in men age 55 and older. BPH can result in frequent urination, inability to urinate, and urinary tract infections. For many years, surgery was the only viable treatment option, although new drug therapies have recently emerged from research studies. The NIH launched the *Medical Therapy of Prostatic Symptoms (MTOPS)* clinical trial to assess the safety and efficacy of different interventions on BPH symptoms and progression. Study participants were divided into four groups, and received either placebo (sugar pill), one of two Food and Drug Administration-approved medications for BPH with different mechanisms of action, or the two drugs in combination. The study followed participants for an average of five years and the results were striking. Although each drug was effective when used alone (the risk of BPH progression was reduced by 39 percent with one and by 34 percent with the other), the combination drug therapy reduced the risk of BPH progression by 67 percent compared to placebo. The MTOPS trial conclusively demonstrated that combination therapy is safe, and is the most effective treatment for men with symptomatic BPH.

A Potential New Therapy for Polycystic Kidney Disease (PKD): PKD and other inherited cystic kidney diseases frequently cause kidney failure and death, often in children. There are no effective treatments. One characteristic common to several of these disorders is an elevated level of cyclic adenosine monophosphate (cAMP) in the kidneys. Within cells, cAMP transmits messages that affect their growth and function; abnormally high levels of cAMP in certain kidney cells are thought to contribute to cyst formation. Researchers treated animal models of the two predominant forms of human PKD and another cystic kidney disease using a chemical, OPC31260, which lowers cAMP production in the kidneys. The treatment halted disease progression, and in some cases resulted in improvement. OPC31260 and similar compounds are

currently undergoing testing in human clinical trials for treatment of other diseases and so far appear to be safe. Thus, drugs of this class are promising candidates for phase I clinical trials to treat patients with PKD.

Pinpointing the Location of Adult Kidney Stem Cells: The cells of a healthy adult kidney rarely divide to make new copies of themselves. However, kidneys retain a limited capacity for self-repair in case of injury. That repair requires replacing damaged cells of multiple types. This is the kind of task the body relegates to stem cells, which by definition can divide and differentiate into multiple cell types. Recent research using rodents has determined that stem cells capable of forming new kidney cell types are largely or entirely confined to a small portion of the kidney called the "renal papilla." Further research can now proceed to determine whether these cells can form any kidney cell type, or just a subset of them. Even more importantly, researchers will be seeking the specific signals that trigger kidney stem cells to form each cell type. With this knowledge, it may one day be possible to stimulate patients' innate ability to heal their kidneys, thereby reducing the need for dialysis and kidney transplantation.

Impact of Chronic Kidney Disease on Cardiovascular Health: Of the estimated eight million Americans with chronic kidney disease[7], more than 400,000 have end-stage renal disease, or ESRD, with over 300,000 requiring dialysis to live[8]. ESRD patients are known to have very high rates of cardiovascular disease (CVD), which kills about half of them. However, until recently, it was unknown to what degree less serious chronic kidney disease predisposes patients to develop CVD. The Modification of Diet in Renal Disease clinical trial provided strong evidence that kidney function can be reliably estimated by measuring the amount of a compound called creatinine in a patient's blood, and performing a calculation that also includes variables such as the person's size and sex. Now, researchers have built upon that finding by examining the results of creatinine tests from more than one million patients to assess kidney health and look for correlations with cardiovascular outcomes such as heart attacks. The researchers found a very clear pattern: the poorer a patient's kidney function, the more likely he or she was to develop CVD. Armed with the knowledge that kidney health is a predictor of CVD, health care providers can now determine that some of their patients are at risk, and may be more likely to benefit from earlier, more aggressive cardiovascular treatment than might otherwise have been prescribed.

Story of Discovery—Sensing Calcium, Treating Disease

New treatments are emerging to correct abnormal calcium levels, which are common in the majority of patients who suffer life-threatening kidney disease and in people with certain rare diseases of the parathyroid glands, including parathyroid cancer. These treatments build upon substantial NIH investments in research that elucidated the role of the parathyroid glands in regulation of calcium levels. A new treatment strategy derives from the identification of the body's master regulator of blood calcium levels: the calcium-sensing receptor protein.

[7] Coresh J, Astor BC, Greene T, Eknoyan G and Levey AS, Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 41:1-12, 2003.

[8] 2004 USRDS Annual Data Report Atlas. United States Renal Data System, 2004. (http://www.usrds.org/atlas.htm)

Because calcium is critical not only for bone formation but also for a myriad of other body functions, its levels are normally kept tightly controlled. In the 1960s and earlier, decades before the nature of the calcium-sensing receptor protein was defined, scientists studying large animal models found that low blood calcium levels cause the secretion of parathyroid hormone from parathyroid glands, while high blood calcium levels inhibit its release. Around 1960, NIDDK-supported scientists pioneered a method for preparing this hormone in a pure and stable form. They also developed what was then a new measuring technique, radioimmunoassay, to assay the very small quantities present in the human body. In the 1970s, these scientists devised a way to isolate cells from bovine parathyroid glands and grow them in the laboratory for study. These advances supplied the necessary tools for far more detailed experimentation.

From research supported by the NIDDK and others, scientists gained important insights into the regulation by calcium of parathyroid hormone secretion, the reciprocal influence of parathyroid hormone on calcium levels, and what happens when these processes go awry. Based on numerous studies over many years, scientists theorized that there is a calcium sensing mechanism on the surface of parathyroid cells that maintains constant surveillance of blood calcium levels. When calcium levels fall, this "calcium-sensing receptor" permits the secretion of parathyroid hormone, which then orchestrates a complex set of activities to help restore normal levels. These activities include the absorption of calcium from food in the intestines, its release from bones, and its reabsorption by the kidneys. When blood calcium levels become too high, the calcium-sensing receptor reins in parathyroid hormone. In diseases termed "hyperparathyroidism," this regulation is destroyed. Excess parathyroid hormone plunders the skeleton for its calcium, leaving bones more vulnerable to fracture and dumping potentially toxic amounts of calcium into the bloodstream. Patients may also experience fatigue, kidney stones, and impaired thinking.

In 1993, a group of scientists, funded in part by the NIDDK, identified the gene for the calcium-sensing receptor. Surprisingly, analysis of this gene revealed that the receptor is not, as previously thought, a channel through which calcium streams into cells. Rather, it is a novel member of a large family of proteins termed G protein-coupled cell-surface receptors. Because these proteins are prime drug targets for a number of health conditions, scientists had previously thought that the calcium-sensing receptor might be a good drug target for diseases marked by excess parathyroid hormone. Its landmark identification as a G protein-coupled receptor helped stimulate further research in this area.

With the gene for the calcium-sensing receptor in hand, scientists supported in part by the NIDDK discovered the underlying causes of some rare forms of "primary" hyperparathyroidism. People have two copies of the calcium-sensing receptor gene. A mutation that reduces function of one copy causes reduced sensitivity to calcium in the parathyroids and kidney resulting in a mild, generally asymptomatic disorder termed familial hypocalciuric hypercalcemia (FHH). When mutations impair both gene copies, parathyroid cells are essentially totally unable to "sense" calcium, leading to a severe increase in secretion of parathyroid hormone. The resulting neonatal disease is severe, and removal of the parathyroids is required for babies to survive. This past year, researchers found that another form of hyperparathyroidism is an autoimmune disease: the body mistakenly produces antibodies that interfere with the calcium-sensing receptor's functioning. Other forms of primary hyperparathyroidism have been shown to result from excess—and sometimes cancerous—growth of parathyroid tissue.

Researchers have also, over many years, gained an understanding of "secondary" hyperparathyroidism, which is associated with kidney disease. When the kidneys fail, blood phosphate levels increase and calcium levels drop, as a result of loss of certain kidney functions important in calcium regulation, such as production of the active form of vitamin D, calcitriol. The body—in a doomed attempt to normalize calcium levels without healthy kidneys—then increases parathyroid hormone secretion. One result of secondary hyperparathyroidism is weakened bones, termed renal osteodystrophy in this context. Patients may also suffer from cardiovascular disease, likely related to disturbances in blood calcium and phosphate.

Treatments for hyperparathyroidism have not been ideal. Surgery to remove excess or abnormal parathyroid tissue has been, to date, the only effective way to treat primary hyperparathyroidism. Hyperparathyroidism related to kidney disease has been treated with phosphate binders, with calcium supplementation to increase its levels and thus suppress parathyroid hormone release, and by administering calcitriol, which also reduces the amount of parathyroid hormone. However, these therapies can result in high blood calcium levels and other problems. Surgery may then be necessary.

Research on the calcium-sensing receptor has now led to the development of a new drug by scientists at a biotechnology company. In 2004, investigators reported the results of an industry-sponsored clinical trial demonstrating the effectiveness of this oral drug in kidney disease patients on dialysis. It has been approved by the Food and Drug Administration for treating hyperparathyroidism associated with kidney disease. The drug is one of a novel class of compounds that interact with the calcium-sensing receptor in a way that "mimics" calcium. Called calcimimetics, they cause the receptor to perceive calcium levels in the blood as higher than they really are and thus reduce parathyroid hormone secretion. Calcimimetics, whose characterization was supported in part by the NIDDK, are also being explored for treating other forms of hyperparathyroidism, including high calcium levels resulting from parathyroid cancer.

Scientists are also currently investigating "calcilytics," compounds that have the opposite effect on the calcium-sensing receptor by leading to increased parathyroid hormone secretion. Paradoxically, parathyroid hormone can either weaken or help build bones—depending on the timing and extent of its secretion from the parathyroids. An orally-administered calcilytic may thus help treat osteoporosis by stimulating endogenous secretion of parathyroid hormone, obviating the need for injections of synthetic parathyroid hormone, recently approved by the FDA as a treatment to build bone.

NIH funding has contributed to a mosaic of vital advances, progressing from early basic research on parathyroid hormone and calcium regulation to the recent development of a new drug. Collectively, these discoveries represent a striking example of "translational" research, in which both NIH- and industry-supported investigators have benefited patients by propelling science from the bench to the bedside.

AIDS

Hormonal Treatment for HIV-Infected Men with Lipodystrophy: Highly active anti-retroviral therapy and HIV infection are associated with a variety of metabolic complications, collectively termed "lipodystrophy syndrome." This syndrome may include abnormal distribution of body fat, dyslipidemia (elevated levels of unhealthy fats in the blood*)* and insulin resistance. These metabolic abnormalities are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. Some men with HIV lipodystrophy and excess visceral fat (the fat that surrounds and cushions certain organs) have reduced levels of growth hormone (GH). Restoring GH to normal levels is a potentially attractive approach to treating these individuals, as GH has been shown to reduce visceral fat in GH-deficient patients. However, excessive GH therapy can result in insulin resistance and other complications. An alternative strategy to normalize GH levels is to provide growth hormone-releasing hormone (GHRH), an agent that promotes increased secretion of GH by the pituitary gland. Because the body makes other hormones that suppress GH production if levels rise too high, GH might not reach harmful levels during treatment with GHRH. Researchers recently compared GHRH therapy with placebo (sugar pill) in 31 HIV positive men with lipodystrophy over 12 weeks. The effectiveness of the treatment was determined by measuring levels of IGF-1, a protein secreted in response to GH stimulation that mediates many of its actions. GHRH therapy significantly increased levels of IGF-1 in treated individuals, and was associated with significant improvements in a number of body mass parameters, including increased lean body mass, decreased trunk fat, and reduced abdominal visceral fat. Levels of blood glucose, insulin, and lipids did not change significantly. GHRH therapy, which is aimed at returning GH to a more normal range, may be beneficial in HIV positive individuals with diminished levels of the hormone.

Highlights of Ongoing and Planned Activities

Initiatives: In FY 2006, the NIDDK will pursue multiple and diverse avenues of fundamental and clinical research relevant to the diseases and health issues within its mission. To maximize the return on investments in basic research, the NIDDK has placed major emphasis for FY 2006 on its initiatives seeking to translate advances in basic research to significant improvements in the prevention and treatment of the multiple serious diseases within its research mission. The initiatives that follow are trans-NIDDK in nature, and are expected to improve outcomes for one or more of the diseases within each of NIDDK's three programmatic divisions.

The Institute will fund research into new "biomarkers" for diseases in the NIDDK mission for which there are few or none, and into new imaging methods for the solid abdominal organs and urinary tract. Another new initiative is designed to help identify new animal models for NIDDK-relevant diseases that are more predictive for testing therapeutic interventions. The NIDDK will seek to partner with industry in an initiative aimed at finding new drugs to treat polycystic kidney disease. To improve outcomes by enabling earlier diagnosis, the Institute is furthering statistical analyses for current and future data to determine the best markers that identify individuals at risk for kidney failure. The NIDDK will foster research to identify definitive diagnostic tests for interstitial cystitis. Another initiative is seeking to translate recent advances in the prevention and treatment of type 1 or type 2 diabetes into clinical practice for individuals and communities at risk. Recent data suggest that so-called "reactive oxygen species" (ROS) created in the cells of patients with high blood sugar are responsible for many diabetes complications, so another new initiative is designed to build on that knowledge by exploring treatment through inhibition of ROS production.

Several efforts are advancing understanding of the biological underpinnings of obesity. For example, one effort is planned to encourage mechanistic studies of the impact of the intrauterine and neonatal environment on the development of brain and other pathways involved in food intake and metabolism. Another initiative will help build understanding of the neurobiological basis of obesity. The Institute is also planning a new effort that would capitalize on existing resources from ongoing and completed longitudinal studies to help discover genetic influences on obesity. Ongoing initiatives aimed at exploring strategies to prevent and treat pediatric obesity will be complemented through a new effort, under development, targeted at identification of modifiable determinants of obesity in children. Also, to further understanding of obesity, support will continue for an initiative to investigate the basis for the differences between the body's fat stores, and their comparative impacts on morbidity.

Many current and planned initiatives focus on multiple diseases under the NIDDK aegis. For example, one initiative seeks to speed development of assays for high-throughput screening of candidate drugs. Many of the diseases within NIDDK's scope of study have disproportionate impacts on America's demographic groups. In particular, minority populations are disproportionately afflicted by high rates of diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder disease, ulcer-causing *Helicobacter pylori* infection, sickle cell disease, kidney diseases, and metabolic, gastrointestinal, hepatic, and renal complications from infection with HIV. Therefore, the Institute is continuing to promote work to understand and mitigate such health disparities.

A new initiative will fund a multi-center cohort study of gastroparesis, a condition characterized by delayed gastric emptying that often afflicts patients with diabetes. It will provide the infrastructure necessary to accelerate progress in diagnosis and management of this poorly understood and poorly treated disease. The Institute will continue to encourage rigorous testing of recently developed methods for diagnosis and treatment of pancreatic and biliary diseases, which are responsible for considerable morbidity, mortality and health care costs.

NIH Roadmap: The NIDDK has a leadership role for an NIH Roadmap initiative on "Metabolomics Technology Development." The "metabolome" is the complete set of small molecules in the body which function as nutrients, chemical signals and building blocks such as amino acids, peptides, and lipids. "Metabolomics" is the study of these small molecules. The purpose of this initiative is to promote the development of highly innovative and sensitive tools for studying metabolomics. The development of such novel technologies can directly benefit the study of diseases within the NIDDK mission. For example, metabolomics could lead to the identification and validation of surrogate markers that correlate with stage or rate of progression of diabetes and its complications. Furthermore, metabolomics technologies could be applied to the development of novel, less-burdensome diagnostic tests for pre-diabetes and type 2 diabetes.

Another Roadmap initiative on "Interdisciplinary Research" aims to overcome the current barriers that prevent experts from different fields from working together to advance medical research. Obesity—which is a serious risk factor for type 2 diabetes—is a key example of a disease that could benefit from increased partnerships among different communities. The increase in obesity has been fueled by a complex interplay of environmental, social, economic, and behavioral factors, acting on a background of genetic susceptibility. Therefore, researchers with expertise in numerous disciplines—such as genetics, behavioral science, and biochemistry—can offer important contributions to obesity research. Another example of an initiative that will benefit NIDDK programs is the establishment of "translational research core services" to promote translation of novel therapeutics from the bench-to-the-bedside by providing access to sophisticated manufacturing capacity and expert advice to ensure that drug-development regulations are observed.

AIDS: Research supported by the NIDDK has made important contributions to the current understanding of many of the metabolic complications associated with HIV infection and highly active anti-retroviral therapy (HAART). These complications include AIDS wasting syndrome and HIV- and HAART-related dyslipidemia, insulin resistance, and abnormal body fat distribution. Serious metabolic abnormalities may develop from these risk factors, such as diabetes and cardiovascular disease. The NIDDK also supports research to define the causes of liver disease associated with HIV, including pathogenic interactions between HIV and hepatitis viruses, and to develop means to prevent and treat liver disease in HIV-infected persons. 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 intramural program on structural biology which seeks to determine the structures of biologically significant proteins relative to HIV infection, replication, and integration.

Strategic Planning: Among the approaches the NIDDK is taking to maximize the public health benefit achieved with its resources is the development of scientific plans to focus research on areas of key importance to solving major health problems. Among these are:

Strategic Plan for NIH Obesity Research: This plan is the product of collaboration among many NIH Institutes and Centers, with critical and extensive input from the external scientific and lay communities. The *Strategic Plan for NIH Obesity Research* is a guide for coordinating obesity research activities across the NIH and for enhancing the development of new research efforts based on identification of areas of greatest scientific opportunity and challenge. The Strategic Plan represents a cohesive, multi-dimensional research agenda for addressing the problem of obesity. It includes short-, intermediate-, and long-term goals for basic, clinical, and population-based obesity research, along with strategies for achieving those goals that likewise range in timeframe. Building on scientific advances from previous NIH-supported efforts, the Strategic Plan seeks to maximize collaboration among the NIH Institutes, Centers, and Offices (ICs) and to capitalize on their expertise and interest in developing obesity research initiatives.

Action Plan for Liver Disease Research: To address the burden of liver diseases in the United States, the National Institutes of Health has developed an *Action Plan for Liver Disease Research* under the auspices of the Digestive Diseases Interagency Coordinating Committee. The Action Plan integrates guidance and input from a wide range of external scientific experts and patient advocates.

Action Plan for NIH Digestive Diseases and Nutrition Research: Still in development, this planning effort will be formulated in close consultation with the scientific community and the public.

Educational Programs: The NIDDK will continue to work toward improving the way diabetes is treated by communicating with health practitioners and the public through its educational programs. 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" campaign translates the positive results of the *Diabetes Prevention Program Clinical Trial (DPP)*, which showed that modest lifestyle changes dramatically prevented or delayed onset of type 2 diabetes in high-risk adults. The NDEP has launched the first national multicultural diabetes prevention campaign to reach high-risk groups, by empowering individuals to make modest lifestyle changes and lose a small amount of weight. The NDEP is partnering with the American Diabetes Association for the health awareness campaign, "Be Smart About Your Heart: Control the ABCs of Diabetes," which aims to help people with diabetes better understand the need to control all aspects of the disease to help prevent heart attacks or strokes. The NDEP also plans to develop educational materials to help women with gestational diabetes prevent the development of type 2 diabetes. The NDEP is also collaborating with the CDC to determine the economic impetus for diabetes prevention and control.

The NIDDK has launched the National Kidney Disease Education Program (NKDEP), an initiative designed to reduce the morbidity and mortality caused by kidney disease and its complications. The NKDEP aims to raise awareness of the seriousness of kidney disease, the

importance of testing those at high risk, and the availability of treatment to prevent or slow kidney failure. The program has initially focused on those at highest risk, particularly African Americans with diabetes, high blood pressure, or a family history of kidney failure, in a pilot program launched in four cities. The program also targets health care providers, who are reminded of the importance of testing kidney function in at-risk individuals. The program will widen its target audience to include other racial and ethnic groups.

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. This international network of clinical trial centers supports the development and implementation of clinical trials of agents to prevent or slow the progression of type 1 diabetes. Currently, several studies are enrolling patients. A clinical trial of mycophenolate mofetil (MMF) and daclizumab (DZB) is under way in individuals with new-onset type 1 diabetes. *The Natural History Study* is examining events leading to type 1 diabetes onset and will facilitate enrollment of eligible individuals into planned studies of interventions to arrest the disease process. Another study is comparing methods of assessing beta cell function in new onset type 1 diabetes to aid in measuring trial outcomes. A trial to determine if nutritional supplements with an omega 3 fatty acid for infants who are at high risk for type 1 diabetes will prevent the development of islet autoimmunty began in January 2005. Several other protocols are under development. Another study currently recruiting patients is *The Environmental Determinants of Diabetes in the Young (TEDDY)*. This study will analyze the infectious agents, dietary factors, and other environmental conditions that trigger type 1 diabetes in genetically susceptible newborns.

The NIDDK is pursuing follow-up studies of patients who participated in the *Diabetes Prevention Program (DPP)* clinical trial. This landmark 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 now determining 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 has launched *Studies To Prevent or Treat Pediatric Type 2 Diabetes* (*STOPP-T2D*), a clinical trial network. The group is conducting the 12-site *TODAY* (*Treatment Options for Type 2 Diabetes in Adolescents and Youth*) trial to seek the best treatment strategies. *STOPP-T2D* is also conducting pilot studies to assess the feasibility of a planned prevention trial designed to target food service and physical education changes in schools and to promote healthy habits.

The NIDDK continues to support significant clinical research on digestive diseases. In the area of obesity research, the *Look AHEAD (Action for Health in Diabetes)* clinical trial is examining the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term on cardiovascular disease outcomes in obese adults with type 2 diabetes. The *Longitudinal Assessment of Bariatric Surgery (LABS)* clinical research consortium will be accelerating research relevant to bariatric surgical procedures, which are being increasingly performed to treat

severe obesity. Several vigorous clinical research efforts are under way on liver disease. For example, the *Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL)* seeks to identify factors that influence outcomes for both donors and recipients; the *Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C)* study examines whether long-term treatment with peginterferon alpha in previous non-responders with liver disease can prevent liver disease progression; the *Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C)* is testing whether patients who are unresponsive to short-term therapy with peginterferon might benefit from long-term peginterferon and ribavirin therapy; the *Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C (Peds-C)* study is examining the benefit of peginterferon therapy with or without ribavirin in children with chronic hepatitis C; and the *High-dose Ursodiol Therapy of Primary Sclerosing Cholangitis (HUSC)* study is evaluating ursodiol therapy in patients with primary sclerosing cholangitis (PSC). 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. Additional networks include the *Drug-induced Liver Injury Network*, which is generating a database containing cases of drug-induced liver disease; and the *Nonalcoholic Steatohepatitis Clinical Research Network*, which seeks to define the etiology, complications and therapy of nonalcoholic fatty liver disease.

Important clinical trials are also under way or planned to combat kidney, urologic, and hematologic diseases. New trials of therapies to alleviate symptoms of chronic pelvic pain syndromes—interstitial cystitis and chronic prostatitis—are being designed in two multi-center clinical research networks that share a data coordinating center. With increased Institute support, the *Urinary Incontinence Treatment Network* has recently added a second clinical trial for incontinence interventions, the *Behavior Enhances Drug Reduction of Incontinence (BE-DRI)* trial; this trial is currently enrolling patients. Patient enrollment has begun in a trial led by the *Minimally Invasive Surgical Therapies (MIST) Consortium for Benign Prostatic Hyperplasia (BPH)*; the trial will compare the long-term benefits of minimally invasive surgeries *versus* medical therapy for BPH. Protocol planning is under way for a *Prospective Study of Chronic Kidney Disease in Children*, established in collaboration with the NINDS and the NICHD. Maintenance of vascular access is one of the major challenges in the care of dialysis patients, and two phase III clinical trials are recruiting patients to study the effects of anti-clotting agents in improving outcomes. Children and young adults are now being recruited for a trial to reduce proteinuria in focal segmental glomerulosclerosis (FSGS). Patients are being enrolled in two clinical studies that will address the feasibility and potential benefits of conducting large-scale randomized trials of frequent dialysis for end-stage renal disease. The *HALT-PKD* clinical trial will soon begin recruiting patients for a randomized, controlled study of interventions to slow the progression of polycystic kidney disease and its complications. Future plans include establishing a clinical trial for treatment of vesicocureteral reflux in children.

Many clinical trials should benefit from a new trans-NIDDK initiative inviting investigator-initiated research project applications for ancillary studies to ongoing large-scale clinical trials, epidemiological studies and disease databases supported by the Institute.

Innovations in Management and Administration

Action Plan for Liver Disease Research: This year the NIDDK's Division of Digestive Diseases and Nutrition, Liver Disease Research Branch, led the formulation of a trans-NIH "Action Plan for Liver Disease Research," (http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm) developed under the oversight of the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee (DDICC). The purpose of this Action Plan is to help advance research on liver and biliary disease with the aim of decreasing the burden of liver disease in the United States. This comprehensive Action Plan describes ongoing research efforts, as well as research goals for the future. In preparing the Action Plan, the NIDDK integrated guidance and input from external scientific experts and patient advocacy groups, and from the public via the Internet.

Translation Research Working Group: The NIDDK Translation Working Group was established in December 2003 to catalyze the effort to translate findings from basic biology into useful clinical innovations. In consultation with the Institute's National Advisory Council, the Working Group identified roadblocks to the translation process, and has developed research solicitations designed to help overcome them.

Leadership of the NIH Obesity Research Task Force: The Task Force, co-chaired by the Director of NIDDK and the Acting Director of NHLBI, developed the *Strategic Plan for NIH Obesity Research* with broad stakeholder input (http://www.obesityresearch.nih.gov/About/strategic-plan.htm). Published in August 2004, this plan is helping to synergize and guide the development of major obesity research initiatives across the NIH.

Report of Islet Transplantation Registry: The Collaborative Islet Transplantation Registry (CITR) released its first annual report this year to disseminate the knowledge gleaned from 86 transplantations of islet cells, the body's sole producers of insulin. The procedures have been performed as experimental treatments for type 1 diabetes in 12 U.S. medical centers. The report (www.citregistry.org) analyzes many factors that can affect the outcome of this experimental procedure for people with severe or complicated type 1 diabetes.

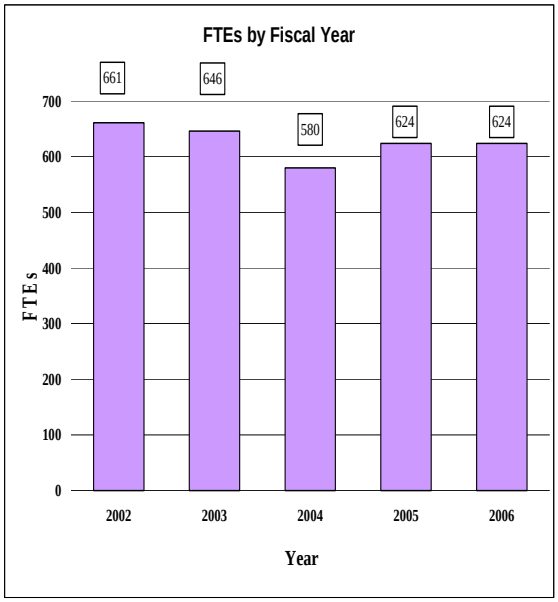
Electronic Government: The NIH Obesity Research Task Force launched a new website to help inform investigators about NIH funding opportunities for obesity research (http://obesityresearch.nih.gov). It also provides information on NIH-sponsored scientific meetings and other information relevant to NIH obesity research. Additionally, the website provided the venue for inviting public comments on the *Strategic Plan for NIH Obesity Research*, which was posted on the website in draft form prior to publication. The website also includes links to other NIH websites that provide information to the public and healthcare professionals on topics relevant to obesity. Similarly, public comments on the *Action Plan for Liver Disease Research* were solicited via the http://www.niddk.nih.gov/fund/divisions/ddn/ldrb website. Also, a new addition to the website dedicated to the *Special Statutory Funding Program for Type 1 Diabetes Research* is a link to help patients find clinical studies in which to participate (http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D_CTCR/studies.asp). The

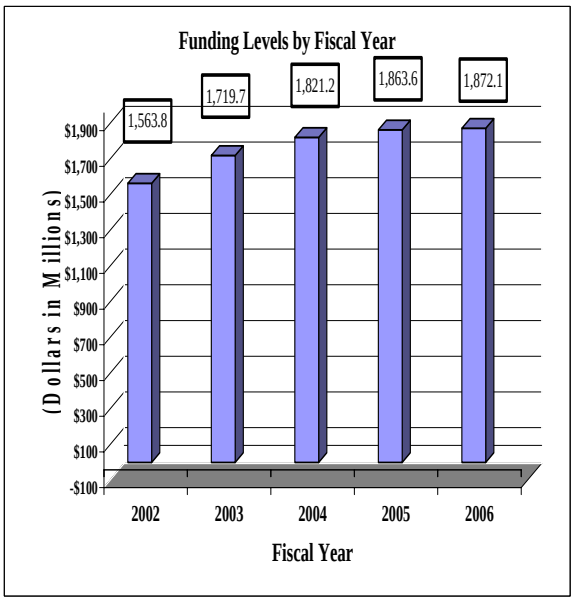
Institute continues to employ innovations in computer technology to increase the efficiency of its grants management and peer review activities, and has adopted a new computer coding and retrieval system to improve its ability to report on categorical areas within its broad research portfolio.

Budget Policy

The Fiscal Year 2006 budget request for the NIDDK is $1,872,146,000, an increase of $8,562,000 and 0.5 percent over the FY 2005 Final Conference Level. Also included in the FY 2006 request, is NIDDK's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 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.





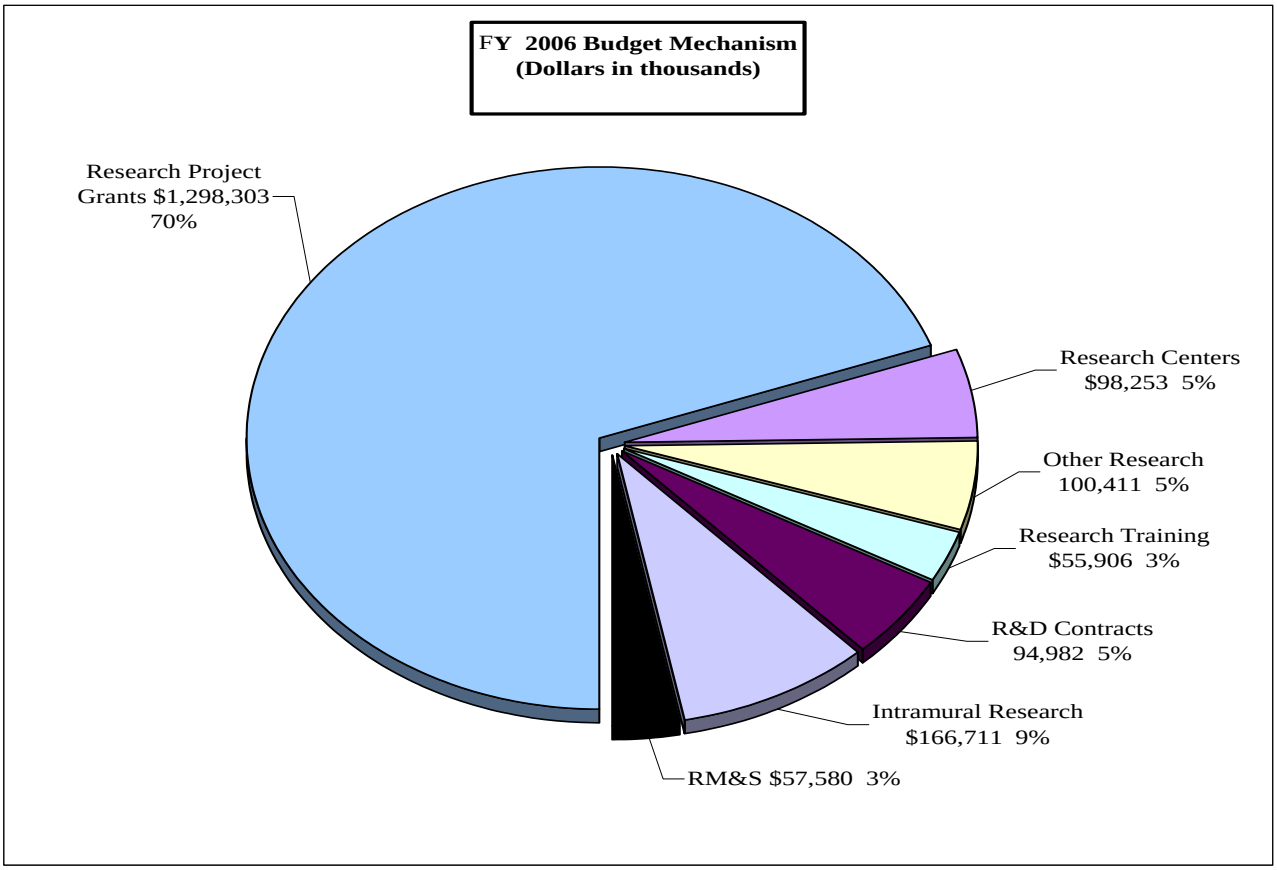
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $337,379 in FY2006. While no inflationary increases are provided for direct, recurring costs in non-competing RPG's, where the NIDDK has committed to a programmatic increase in an award, such increases will be provided.

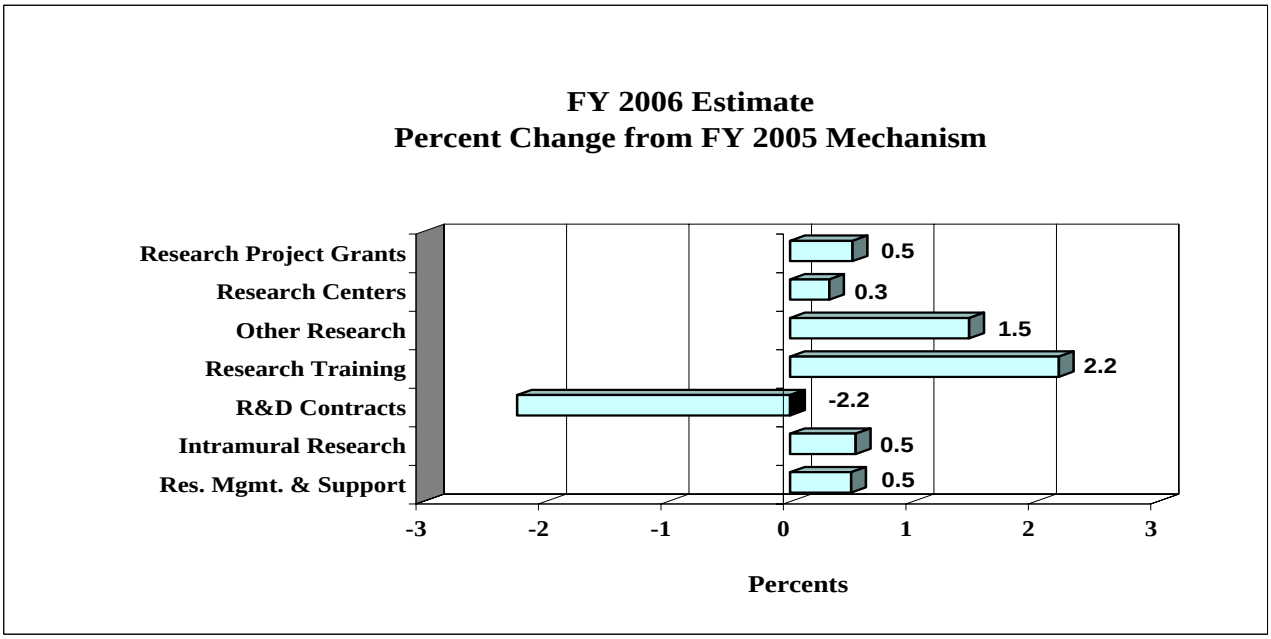
Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-

docs with 1-2 years of experience are increased by 4.0%. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY2006 request by reducing the number of Full-Time Training Positions, because NIH believes that it is important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The Fiscal Year 2006 request includes funding for 84 research centers, 607 other research grants, including 113 clinical career awards, and 409 R&D contracts. Intramural Research and Research Management and Support receive increases of 0.5 percent, the same as the NIH total increase.

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 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,449	$911,726,000	2,508	$956,879,000	2,422	$945,700,000
Administrative supplements	(349)	39,952,000	(211)	19,244,000	(211)	19,244,000
Competing:						
Renewal	253	99,613,000	228	91,864,000	243	97,953,000
New	631	193,316,000	570	178,510,000	608	190,143,000
Supplements	5	686,000	5	700,000	5	700,000
Subtotal, competing	889	293,615,000	803	271,074,000	856	288,796,000
Subtotal, RPGs	3,338	1,245,293,000	3,311	1,247,197,000	3,278	1,253,740,000
SBIR/STTR	130	42,796,000	140	44,515,000	142	44,563,000
Subtotal, RPGs	3,468	1,288,089,000	3,451	1,291,712,000	3,420	1,298,303,000
Research Centers:						
Specialized/comprehensive	76	82,923,000	78	93,130,000	80	95,025,000
Clinical research	0	0	0	0	0	0
Biotechnology	1	948,000	1	2,760,000	4	3,178,000
Comparative medicine	0	5,457,000	0	2,050,000	0	50,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	77	89,328,000	79	97,940,000	84	98,253,000
Other Research:						
Research careers	477	60,024,000	496	64,713,000	496	66,157,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	3,422,000	0	416,000	0	0
Biomedical research support	0	31,000	0	40,000	0	69,000
Minority biomedical research support	0	1,787,000	0	1,800,000	0	1,800,000
Other	98	25,373,000	111	31,995,000	111	32,385,000
Subtotal, Other Research	575	90,637,000	607	98,964,000	607	100,411,000
Total Research Grants	4,120	1,468,054,000	4,137	1,488,616,000	4,111	1,496,967,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	137	6,411,000	150	7,170,000	148	7,170,000
Institutional awards	1,017	46,602,000	1,022	47,535,000	1,012	48,736,000
Total, Training	1,154	53,013,000	1,172	54,705,000	1,160	55,906,000
Research & development contracts	422	87,387,000	409	97,148,000	409	94,982,000
(SBIR/STTR)	(5)	(1,251,000)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	417	158,287,000	449	165,821,000	449	166,711,000
Research management and support	163	54,499,000	175	57,294,000	175	57,580,000
Total, NIDDK	580	1,821,240,000	624	1,863,584,000	624	1,872,146,000
(RoadMap Support)		(5,742,000)		(10,833,000)		(15,400,000)
(Clinical Trials)		(177,000,000)		(181,000,000)		(181,000,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism - Type One Diabetes

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	61	$68,517,000	114	$81,464,000	110	$97,595,000
Administrative supplements	(11)	6,531,000	(0)	0	(0)	0
Competing:						
Renewal	0	0	0	0	0	0
New	74	45,800,000	74	47,281,000	38	24,015,000
Supplements	0	0	0	0	0	0
Subtotal, competing	74	45,800,000	74	47,281,000	38	24,015,000
Subtotal, RPGs	135	120,848,000	188	128,745,000	148	121,610,000
SBIR/STTR	7	4,203,000	6	3,980,000	7	4,167,000
Subtotal, RPGs	142	125,051,000	194	132,725,000	155	125,777,000
Research Centers:						
Specialized/comprehensive	0	308,000	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	0	2,000,000	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	0	5,308,000	0	2,000,000	0	0
Other Research:						
Research careers	7	2,371,000	7	2,385,000	7	2,398,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	3,422,000	0	416,000	0	0
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	5,793,000	7	2,801,000	7	2,398,000
Total Research Grants	149	136,152,000	201	137,526,000	162	128,175,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	0	0	0	0	0	0
Institutional awards	20	904,000	24	1,093,000	24	1,093,000
Total, Training	20	904,000	24	1,093,000	24	1,093,000
Research & development contracts	11	12,807,000	9	11,237,000	9	20,588,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	0	19,000	0	0	0	0
Research management and support	0	118,000	0	144,000	0	144,000
Total, NIDDK	0	150,000,000	0	150,000,000	0	150,000,000
(RoadMap Support)		(0)		(0)		(0)
(Clinical Trials)		(19,905,420)		(18,935,957)		(18,900,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity

(dollars in thousands)

ACTIVITY	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Endocrinology and Metabolic Diseases		797,860		815,440		819,111		3,671
Division of Digestive Diseases and Nutrition		404,664		411,870		413,724		1,854
Division of Kidney, Urologic and Hematologic Diseases		405,930		413,159		415,020		1,861
Subtotal, Extramural research		1,608,454		1,640,469		1,647,855		7,386
Intramural research	417	158,287	449	165,821	449	166,711	0	890
Research management & support	163	54,499	175	57,294	175	57,580	0	286
Total, NIDDK	580	1,821,240	624	1,863,584	624	1,872,146	0	8,562

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

Summary of Changes

FY 2005 Estimate				$1,863,584,000
FY 2006 Estimated Budget Authority				1,872,146,000
Net change				8,562,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$53,514,000		$745,000
b. Annualization of January 2005 pay increase		53,514,000		495,000
c. January 2006 pay increase		53,514,000		923,000
d. One less day of pay		53,514,000		(205,000)
e. Payment for centrally furnished services		29,487,000		147,000
f. Increased cost of laboratory supplies, materials, and other expenses		82,820,000		1,425,000
Subtotal				3,530,000
2. Research Management and Support:				
a. Within grade increase		22,935,000		319,000
b. Annualization of January 2005 pay increase		22,935,000		212,000
c. January 2006 pay increase		22,935,000		396,000
d. One less day of pay		22,935,000		(88,000)
e. Payment for centrally furnished services		8,793,000		44,000
f. Increased cost of laboratory supplies, materials, and other expenses		25,566,000		429,000
Subtotal				1,312,000
Subtotal, Built-in				4,842,000

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

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,508	$976,123,000	(86)	($11,179,000)
b. Competing	803	271,074,000	53	17,722,000
c. SBIR/STTR	140	44,515,000	2	48,000
Total	3,451	1,291,712,000	(31)	6,591,000
2. Research centers	79	97,940,000	5	313,000
3. Other research	607	98,964,000	0	1,447,000
4. Research training	1,172	54,705,000	(12)	1,201,000
5. Research and development contracts	409	97,148,000	409	(2,166,000)
Subtotal, extramural				7,386,000
	FTEs		FTEs	
6. Intramural research	449	165,821,000	0	(2,640,000)
7. Research management and support	175	57,294,000	0	(1,026,000)
Subtotal, program		1,863,584,000		3,720,000
Total changes	624		0	8,562,000

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

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	624	624	0
Full-time equivalent of overtime & holiday hours	2	2	0
Average ES salary	$0	$0	$0
Average GM/GS grade	11.4	11.4	0.0
Average GM/GS salary	$74,436	$76,409	$1,973
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$82,130	$84,019	$1,889
Average salary of ungraded positions	104,139	106,899	2,760

OBJECT CLASSES		FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$26,267,000	$26,871,000	$604,000
11.3	Other than Full-Time Permanent	23,073,000	23,603,000	530,000
11.5	Other Personnel Compensation	1,051,000	1,075,000	24,000
11.7	Military Personnel	1,290,000	1,335,000	45,000
11.8	Special Personnel Services Payments	10,467,000	10,676,000	209,000
	Total, Personnel Compensation	62,148,000	63,560,000	1,412,000
12.0	Personnel Benefits	13,016,000	13,315,000	299,000
12.1	Military Personnel Benefits	1,185,000	1,226,000	41,000
13.0	Benefits for Former Personnel	100,000	100,000	0
	Subtotal, Pay Costs	**76,449,000**	**78,201,000**	**1,752,000**
21.0	Travel & Transportation of Persons	2,814,000	2,802,000	(12,000)
22.0	Transportation of Things	297,000	294,000	(3,000)
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	1,000	1,000	0
23.3	Communications, Utilities & Miscellaneous Charges	1,092,000	1,085,000	(7,000)
24.0	Printing & Reproduction	868,000	859,000	(9,000)
25.1	Consulting Services	2,667,000	2,650,000	(17,000)
25.2	Other Services	11,082,000	11,080,000	(2,000)
25.3	Purchase of Goods & Services from Government Accounts	143,567,000	144,518,000	951,000
25.4	Operation & Maintenance of Facilities	1,942,000	1,932,000	(10,000)
25.5	Research & Development Contracts	55,020,000	53,793,000	(1,227,000)
25.6	Medical Care	1,935,000	1,920,000	(15,000)
25.7	Operation & Maintenance of Equipment	3,531,000	3,510,000	(21,000)
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**219,744,000**	**219,403,000**	**(341,000)**
26.0	Supplies & Materials	16,470,000	16,467,000	(3,000)
31.0	Equipment	17,603,000	17,550,000	(53,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,528,146,000	1,535,384,000	7,238,000
42.0	Insurance Claims & Indemnities	85,000	85,000	0
43.0	Interest & Dividends	15,000	15,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,787,135,000**	**1,793,945,000**	**6,810,000**
	Total Budget Authority by Object	**1,863,584,000**	**1,872,146,000**	**8,562,000**

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

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$26,267,000	$26,871,000	$604,000
Other Than Full-Time Permanent (11.3)	23,073,000	23,603,000	530,000
Other Personnel Compensation (11.5)	1,051,000	1,075,000	24,000
Military Personnel (11.7)	1,290,000	1,335,000	45,000
Special Personnel Services Payments (11.8)	10,467,000	10,676,000	209,000
Total Personnel Compensation (11.9)	**62,148,000**	**63,560,000**	**1,412,000**
Civilian Personnel Benefits (12.1)	13,016,000	13,315,000	299,000
Military Personnel Benefits (12.2)	1,185,000	1,226,000	
Benefits to Former Personnel (13.0)	100,000	100,000	0
Subtotal, Pay Costs	**76,449,000**	**78,201,000**	**1,752,000**
Travel (21.0)	2,814,000	2,802,000	(12,000)
Transportation of Things (22.0)	297,000	294,000	(3,000)
Rental Payments to Others (23.2)	1,000	1,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,092,000	1,085,000	(7,000)
Printing and Reproduction (24.0)	868,000	859,000	(9,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	2,667,000	2,650,000	(17,000)
Other Services (25.2)	11,082,000	11,080,000	(2,000)
Purchases from Govt. Accounts (25.3)	69,294,000	69,228,000	(66,000)
Operation & Maintenance of Facilities (25.4)	1,942,000	1,932,000	(10,000)
Operation & Maintenance of Equipment (25.7)	3,531,000	3,510,000	(21,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**88,516,000**	**88,400,000**	**(116,000)**
Supplies and Materials (26.0)	16,428,000	16,425,000	(3,000)
Subtotal, Non-Pay Costs	110,016,000	109,866,000	(150,000)
Total, Administrative Costs	**186,465,000**	**188,067,000**	**1,602,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE APPROPRIATIONS COMMITTEE REPORT

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Irritable bowel syndrome – The Committee remains concerned about the increasing frequency of irritable bowel syndrome (IBS), a chronic complex of disorders that malign the digestive system. This common disorder strikes people from all walks of life affecting between 25 and 45 million Americans and results in significant human suffering and disability. The Committee encourages NIDDK to support irritable bowel syndrome/functional bowel disorders research and to give priority consideration to funding grants that will continue to increase the IBS portfolio. The Committee requests that NIDDK actively pursue the development of a strategic plan for IBS research, and would like to receive a report on the progress made by NIDDK to develop this plan in next year's hearings. (p.73)

Action Taken or to be Taken

The NIDDK supports a broad-based research approach to IBS that includes fundamental research in gastrointestinal motility, immunology, cell biology, and clinical research in patients. This research is aimed at understanding the development of the pathways that control motility mechanisms in the gut; research on the integration of pain, motility, and behavioral neural circuits; the relationship of gut inflammation to these pathways; translational research aimed at moving discoveries in animal models into clinical studies in humans.

The NIDDK is in the process of formulating a broad Action Plan for NIH Digestive Diseases and Nutrition Research and IBS research will be an important component of this plan. The first step of planning is nearing completion for liver disease, under the auspices of the statutory Digestive Diseases Interagency Coordinating Committee, chaired by the NIDDK. The NIDDK intends to follow a similar planning process for the other portions of the Digestive Diseases Plan, in which IBS and related bowel disorders will be an area of focus. Working groups of expert research scientists will meet and prepare a document outlining the current status of knowledge and research, the major gap areas and challenges to further advances, compelling opportunities, and specific goals for future research. Scientific professionals and patient advocacy groups will be informed of this process and asked to provide input. As the document's chapters are completed, they will be posted on the NIDDK website (http://www.niddk.nih.gov) to solicit broad public input. NIDDK believes that this process will help to increase the attention of the digestive diseases research community on IBS and other functional bowel disorders, and will identify compelling research needs and opportunities to help guide NIH research efforts to combat these needs.

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. 73)

Action Taken or to be Taken

In building the digestive diseases research portfolio, the NIDDK seeks and appreciates the input from the scientific and lay community external to the NIH. Such stakeholder input has been valuable in propelling research on the two major forms of inflammatory bowel disease (IBD)—Crohn's disease and ulcerative colitis. The NIDDK works closely with the Crohn's and Colitis Foundation of America (CCFA), and has found these interactions to be very productive. Joint planning efforts with the CCFA and investigator groups, such as the American Gastroenterological Association, are an important dimension of the Institute's planning and program development process and were instrumental in the development of its long-range research plan to spur more development of more effective treatments and ultimately, the prevention of IBD.

The NIDDK is strongly committed to enhancing translational research in IBD. For example, NIDDK-funded investigators demonstrated that the diabetes drug rosiglitazone has anti-inflammatory effects in an animal model of IBD. Subsequently, an NIDDK-sponsored multi-center clinical trial of this drug for treatment of ulcerative colitis was initiated and is currently in progress. There are approximately ten new drugs under development for the treatment of IBD.

The NIDDK has established a new multi-center Genetics Consortium to speed the search for new IBD genes, including those that confer susceptibility to this disease. The pace of discovery in the genetics of IBD is accelerating, as evidenced by the publication in April 2004 of the identification of two new candidate genes involved in Crohn's disease.

An important step forward in treating Crohn's disease was approval of infliximab by the Food and Drug Administration. In 2004, the *New England Journal of Medicine* reported that infliximab is particularly effective in healing fistulas (invasive tracts), which are common complications of Crohn's disease.

Item

Interstitial cystitis – The Committee is pleased by the unprecedented scientific advances in the area of interstitial cystitis (IC) research, particularly in the area of urinary markers. The Committee understands that this progress is due in large part to investments in basic science research. Therefore, the Committee encourages NIDDK to continue to aggressively support IC-specific basic science initiatives, particularly through program announcements. The Committee also encourages NIDDK to work closely with the IC patient community on developing and funding an IC awareness campaign for both the public and professional community, as well as to host a consensus conference on the definition of IC. The absence of a uniform definition which accurately captures the condition and the affected population is negatively impacting patients in terms of diagnosis and treatment as well as researchers in terms of literature review and their research activities. The Committee was very encouraged by the progress reported at the 2003 NIDDK-sponsored scientific symposium on IC and encourages NIDDK to further this scientific momentum by hosting the next international symposium on IC in 2005. (p. 73)

Action Taken or to be Taken

The NIDDK has multi-pronged research efforts to combat IC, including its continuing support of basic science to increase understanding of the cause(s) of IC and its symptoms--knowledge that will enable development of better treatments and possibly a cure. On October 20-21, 2004, the Institute held a meeting of the over 20 grantees funded through an FY 2003 Request for Applications (RFA), "Basic Research in Interstitial Cystitis." In addition to discussion of ongoing work funded under the RFA, there was description of encouraging results and future plans for work on a promising biomarker for IC, antiproliferative factor (APF). The Institute is currently developing a translational research initiative that will accelerate efforts to validate APF's usefulness as a diagnostic tool for IC. To continue to foster basic research projects on IC and to capitalize on previous efforts, such as the exploratory research studies funded under the FY 2003 RFA, the NIDDK is planning to issue a Program Announcement in this area. The NIDDK also plans to support another meeting of the investigators funded under the FY 2003 RFA in 2005; this meeting will help continue the critically important cross-fertilization of ideas among researchers in the field, and will also help guide the Institute's decisions regarding support for larger meetings of IC investigators in the future.

In fall 2004, the NIDDK initiated its new Interstitial Cystitis Awareness Campaign that will reach out to three specific audiences: urologists, the public, and family care practitioners. Outreach materials for this campaign include information on therapeutic options for IC patients. The National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC) is the primary distribution channel for campaign materials. To ensure that the campaign is achieving its goals of increasing awareness about symptoms, diagnosis, research, and resources on IC among the target audiences, there will be a preliminary process evaluation of the program's activities at the end of its first year. In developing this important awareness campaign for patients and healthcare practitioners, the NIDDK received input from a patient-based advocacy group for IC through its participation in an *ad hoc* coordinating panel for the NKUDIC, and through discussions with the president and founder of this advocacy group, who recently served as a member of the NIDDK's National Advisory Council.

Efforts to inform physicians and the public about IC will be significantly enhanced when there is a consistent and clinically useful definition of IC. Although some progress has been made in identifying common clinical symptoms among some IC patients, the NIDDK shares the Committee's concern about the lack of a consensus definition for IC. The NIDDK anticipates that recent efforts to review the rapidly evolving science surrounding IC will lead to a better scientific basis with which to approach the development of a consensus definition for IC. Examples of these efforts include: the work of the IC Epidemiology Task Force convened by NIDDK in October 2003; the work of the NIDDK Subcommittee on the Diagnosis of Interstitial Cystitis and Painful Bladder Syndrome, which presented its recommendations at the 2003 IC research symposium co-sponsored by the Interstitial Cystitis Association and is currently preparing them for publication; and the planned initiative to validate APF as a diagnostic tool.

Item

Incontinence – Many otherwise healthy, active individuals suffer from incontinence. Fecal incontinence, also called bowel incontinence, affects people of all ages and is associated with a wide variety of causes. The Committee encourages NIDDK to develop a standardization of scales to measure incontinence severity and quality of life and to develop strategies for primary prevention of fecal incontinence associated with childbirth. (p. 74)

Action Taken or to be Taken

The NIDDK recognizes that incontinence is a serious problem for many individuals. The NIDDK is contributing new funding to the National Health and Nutrition Examination Survey to obtain epidemiological information on both fecal and urinary incontinence as a means of informing research studies. This effort will help to contribute to standardization of approaches to measure incontinence. With respect to fecal incontinence resulting from obstetrical injury related to childbirth, this is one of the most common causes of incontinence and it falls within the mission of NICHD. The NICHD is taking several actions to help address prevention and improve treatments for fecal incontinence. First, the issue is being addressed in the Institute's Pelvic Floor Disorders Network. One Network study is identifying risk factors for pelvic floor disorders, including fecal incontinence, with the goal of obtaining the data needed to design a trial of pelvic muscle physiotherapy. Another study is designed to give clinicians the information that they need to better evaluate and manage women after anal sphincter disruption and repair at delivery, a serious complication that occurs in up to 20 percent of women delivering their first baby. However, the potential to prevent such adverse outcomes along with the flexibility gained for the medical community has helped to popularize elective cesarean sections. The NICHD is concerned that elective cesarean sections are being widely adopted without evaluating the evidence – especially the need to weigh the potential urogynecologic benefits against the risks to both the mother and fetus. To address this serious lack of systematic review, the NICHD is planning a state-of-the-science conference to rigorously evaluate the data, to raise the public health awareness of the findings, to identify research goals, and to guide practitioners in discussing the options and assessing risks and benefits of elective cesarean section, including for fecal incontinence.

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 ninety percent of patients with systemic sclerosis have gastrointestinal (GI) involvement and that of that number fifty percent have clinically significant manifestations. GI involvement can manifest as gastroesophageal reflux disease, dysphagia, Barrett's esophagus, gastroparesis, "watermelon stomach," malabsorption, and fibrosis of the small and large intestines. Renal crisis affects twenty percent of those with systemic sclerosis often within the first five years after diagnosis. More research is needed in order to develop safe and effective treatments and to identify the cause or causes of the complications of scleroderma. (p. 74)

Action Taken or to be Taken

Scleroderma is a rare but devastating autoimmune disease that causes thickening of tissue and thereby alters the function of many organs of the body. With respect to the digestive system, the NIDDK has strong research programs on complications that can be caused by scleroderma--gastroesophageal reflux disease (GERD), Barrett's esophagus, gastroparesis, motility disorders, abnormalities of digestion, and fibrosis of the gut in inflammatory diseases. In each of these areas, the NIDDK is supporting research to address fundamental scientific aspects of the cells, organs, and systems that comprise the digestive system, as well as translation of basic research findings to clinically relevant treatment and prevention strategies. These areas of research may provide important insights that will lead to better treatments for the secondary complications of scleroderma. For example, research aimed at common motility disorders such as gastroparesis or constipation predominant in irritable bowel syndrome may lead to better treatments that will also benefit patients with scleroderma. The Institute supports significant translational research on GERD, one of the most common gastrointestinal manifestations of scleroderma.

With regard to kidney disease, many patients who develop renal crisis as a result of scleroderma have elevated levels of renin in their blood. Renin may cause renal crisis, and the NIDDK supports research examining the regulation of renin synthesis and secretion. For example, the NIDDK is supporting research at Weill Medical College of Cornell University, New York, to study the mechanisms that direct appropriate cell-specific expression of the renin gene, as well as research at the University of Utah to elucidate the molecular pathways that determine renin secretion.

The NIDDK participates in NIH-wide efforts to assist the scientific community in promoting research on scleroderma. These efforts include active participation in the NIH Autoimmune Disease Coordinating Committee, which is led by the NIAID. In addition, the NIDDK coordinates research efforts with NIAMS, which is the lead NIH institute for scleroderma research, including the support of two Specialized Centers of Research in Scleroderma. The NIDDK will continue to facilitate investigator-initiated research project applications that focus on specific target organs within the Institute's mission that can be affected by scleroderma.

Item

Acute liver failure – The Committee is pleased that NIDDK has funded an Acute Liver Failure Study Group (ALFSG) that will improve medical knowledge necessary to prevent and treat acute liver failure. The Committee is pleased with the progress of the ALFSG, and encourages increased attention to pediatric issues. (p. 74)

Action Taken or to be Taken

The NIDDK continues to support the Acute Liver Failure Study Group (ALFSG) in their efforts to conduct both basic and clinical research to enhance medical knowledge of the treatment of acute liver failure. Although initially focused on adults, with the support of the NIDDK, the group now includes studies of children. The NIDDK has encouraged the pediatric investigators to form their own pediatric group within the existing ALFSG focused exclusively on children and will give priority to funding new meritorious proposals in pediatric acute liver failure.

Item

Auto-immune liver diseases – These diseases are the primary indication for liver transplantation in adolescents. The Committee encourages targeted research to improve the prevention and treatment of auto-immune liver diseases in children. (p. 74)

Action Taken or to be Taken

A major area of research on autoimmune liver disease is autoimmune hepatitis (AIH). This is an uncommon but severe disease of the liver that primarily affects women during adolescence, but can occur in men as well and at any age and among any race or ethnicity. It can also arise in children, in whom it often runs a severe and progressive course. The cause of the disease is unknown, but it is believed to be due to an abnormal immune response that is directed at normal liver cells and leads to injury, inflammation, cell death, scarring, and, ultimately, cirrhosis of the liver. If the abnormal immune response is not controlled, patients can suffer severe liver damage and cirrhosis, which necessitates liver transplantation. In children, the disease is especially devastating as it is one of the top five causes for liver transplantation in this patient population.

Appropriate treatment is dependent upon early diagnosis of AIH, which is difficult. A wide range of symptoms and abnormal test results is seen with this condition, and no specific tests are available for reliable diagnosis. Treatment consists of medications that suppress the immune system, usually corticosteroids and azathioprine. However, long-term use of corticosteroids poses many deleterious side effects and is not effective in all patients. In some cases, the disease progresses despite therapy and eventually requires liver transplantation.

Pediatric autoimmune hepatitis is a special focus of NIDDK research efforts and is currently being addressed in part by the recently funded “Studies in Pediatric Liver Transplantation” (SPLIT) Consortium. Additionally, a current Program Announcement for innovative clinical research projects specifically requests grant applications to study the pathogenesis of auto-immune liver diseases such as autoimmune hepatitis. Finally, NIDDK staff, in collaboration

with the American Association for the Study of Liver Diseases (AASLD), has organized a Focused Topic meeting on clinical challenges and future research in autoimmune hepatitis to be held at the annual AASLD Meeting in Boston on November 1, 2005.

Item

Alpha-1 antitrypsin deficiency – The Committee is aware that alpha-1 antitrypsin deficiency liver disease is a leading cause of pediatric transplantation and can manifest at any age. The Committee is encouraged that NIDDK has invested in research on this devastating disorder. The Committee encourages NIDDK to maintain its research funding and encourages NIDDK to collaborate with NHLBI and other institutes to enhance its research portfolio, encourage screening and detection, raise public awareness about alpha-1 and provide appropriate information to health professionals. (p. 74)

Action Taken or to be Taken

Alpha-1 antitrypsin (AAT) deficiency is an inherited disease caused by a mutation in the *AAT* gene. Proteins coded from this gene form polymers that aggregate and cannot be secreted into the blood stream. Instead, the polymers build up causing damage to the liver cells. Mechanisms involved in this process have been elucidated and point to discrete steps in protein processing that can be used as therapeutic targets. These new targets, along with the potential of promising NIDDK new drugs, provide proof-of-principle for mechanism-based therapeutic approaches to AAT deficiency disease. Previous studies show that certain molecules mediate a partial but significant increase in the secretion of the polymerized AAT proteins. It is now possible to consider therapeutic strategies using drug combinations that affect sequential steps in liver cell injury.

In May 4-5, 2004, the NIDDK co-sponsored a meeting, "Protein Misfolding and Misprocessing in Disease," with the Office of Rare Diseases and the Oxalosis & Hyperoxaluria Foundation. The meeting focused on the extensive new research in developing treatments for protein misfolding and misprocessing and the mechanisms responsible for cell injury, including polymerization of AAT that leads to AAT deficiency. The NIDDK has an initiative to encourage research to develop high throughput screening assays for molecules that enhance correct folding and processing of mutant proteins. The NIDDK also supported the Alpha-1 Foundation in sponsoring a meeting on, "Alpha-1: The Challenge of a Genetic Condition," in June 2001.

The NIDDK supports basic research aimed at understanding the mechanisms of liver injury and translational efforts to develop treatment options for liver disease. The inclusion of AAT deficiency in the recently funded Cholestatic Liver Disease Consortium (CLIC) provides an opportunity to gather clinical and biochemical data and an adequate number of biosamples in a prospective manner to stimulate research on the pathogenesis and optimal diagnosis of this disease, as well as its prevention and treatment.

The NIDDK supports a toxicology study of an adeno-associated virus/AAT vector in the liver of hepatitis C-infected chimpanzees through the National Gene Vector Laboratories, a resource supported by 10 Institutes including NIDDK and National Heart, Lung, and Blood Institute

(NHLBI), and led by the National Center for Research Resources. In addition, the NIDDK and the NHLBI staffs consult regularly on the application of gene therapy to AAT deficiency diseases. The two Institutes support initiatives jointly and independently to encourage research in response to emerging scientific opportunities.

Studies of AAT deficiency are included in the recently-released trans-NIH "Action Plan for Liver Disease Research," spearheaded by the NIDDK Liver Disease Branch and the Liver Disease Subcommittee of the congressionally-authorized Digestive Diseases Interagency Coordinating Committee (http://liverplan.niddk.nih.gov). The NHLBI and other NIH Institutes and Centers are active members of the Subcommittee and contributors to the development of this plan for future research in liver disease.

Finally, the NIDDK is making efforts to raise awareness about AAT deficiency. For example, a "story of discovery" featuring historical and recent achievements in AAT basic and clinical research is included in the NIDDK narrative that accompanies the President's FY 2006 Budget Request. In addition, the story of discovery and a "patient profile" of an individual with AAT deficiency will be featured in the upcoming annual NIDDK compendium, "Recent Advances and Emerging Opportunities." Also, the NIDDK-supported Digestive Disease Clearinghouse website has a link to the Alpha One Foundation website, http://digestive.niddk.nih.gov/resources/professional.htm, so that patients, scientists, and clinicians may be directed to the helpful materials provided by this organization.

Item

Fatty liver disease – The Committee notes that there is an emerging obesity-related chronic liver disease--nonalcoholic fatty liver disease, which may affect as many as one in every four adults over the age of eighteen. This diagnosis encompasses a spectrum of severity, with many cases evolving into non-alcoholic steatohepatitis (NASH) and, ultimately, cirrhosis. NASH-related liver disease has already become an important indicator for liver transplantation, and, in the absence of better treatments, the need for NASH-related liver transplantation will increase significantly over time. The Committee appreciates NIDDK's existing programs in this area but encourages additional basic and clinical research focused both on interventions needed to prevent the onset of NASH and improved protocols for treatment of established cases. The Committee also suggests that the Institute review opportunities to expand current clinical programs, where appropriate, to permit the enrollment and follow up of larger numbers of patients. Finally, the Committee suggests a public awareness campaign with a voluntary health agency to address this growing and preventable public health problem. (p. 74)

Action Taken or to be Taken

In an effort to expand knowledge of the natural history of fatty liver disease and prevention and treatment options for nonalcoholic steatohepatitis (NASH), the NIDDK has initiated the NASH Clinical Research Network (NASH CRN). This multi-center collaborative effort of researchers is funded largely by the NIDDK, with cofunding from the NICHD and industry sponsors. The Network will support research on a large cohort of both adults and children with the disease. Its goal is to study natural history, pathogenesis, and therapy. Two intervention trials in patients, one in adults and one in children, are currently under way. In addition, studies of basic science

that encourage a multi-disciplinary approach are also being supported by NIDDK, both within the Network, as well as through investigator initiated research projects. The NIDDK continues to encourage outstanding new research in both basic and clinical research areas aimed at combating this important pubic health problem.

Presently, the known major risk factors for NASH—obesity and diabetes—are the subject of a number of programs across NIH to increase awareness of the adverse medical consequences of these conditions. The Network has a public website, which includes educational material and links to other sites that provide helpful information relating to fatty liver disease. In addition, the NIDDK has produced and distributes a fact sheet on NASH that soon will be available in a Spanish version. This link can be accessed at the following URL: http://digestive.niddk.nih.gov/ddiseases/pubs/nash/index.htm.
Information for the general public on the disease and its prevention is also included in a publication by the NIDDK on the health risks of being overweight.

Item

Hepatitis C in children – The Committee is pleased that NIDDK has launched a pediatric hepatitis C trial that will permit long term follow up of children enrolled in treatment protocols, particularly as these treatment regimens impact the growth and development of the children. The Committee looks forward to being informed about the progress of this trial at upcoming appropriations hearings. (p. 75)

Action Taken or to be Taken

The NIDDK is pleased to support an important trial of treatment for hepatitis C in children. This trial is called the Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C trial (Peds-C). This multi-center, clinical trial is studying antiviral therapy of hepatitis C in children—specifically peginterferon and ribavirin. This trial 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. Careful analysis will be performed of both short- and long-term benefits and risks of peginterferon therapy for hepatitis C in children. Support for the trial is also being provided by the Office of Orphan Products Development of the Food and Drug Administration and industry. Industrial support includes medications and funding for virological testing and a data coordinating center. Enrollment in this study began in January 2005, and, as this clinical trial moves forward, the NIDDK will provide updates on its progress.

Item

Hepatitis B conference – Hepatitis B remains a common cause of acute hepatitis affecting 1,250,000 Americans. Among the Asian and Pacific Island populations the rate of infection rate is even higher, affecting up to 15 percent of individuals. In order to address this health issue, the Committee encourages NIDDK to convene an expert panel in FY 2005 to reach consensus on the best treatment protocols. (p. 75)

Action Taken or to be Taken

Although a safe and effective hepatitis B vaccine has existed for more than twenty years, cases of acute hepatitis B still appear due to new infections among unvaccinated persons in this country, as well as emigrations of persons from areas of the world where hepatitis B virus is endemic. The NIDDK continues to pursue research efforts to develop more effective hepatitis B treatment strategies. Several new drugs targeting hepatitis B have recently been licensed and are currently under investigation in clinical studies that are expected to continue into early 2006. The NIDDK has formed an organizing committee which will provide the groundwork for a conference to evaluate the effectiveness of these drugs in treating hepatitis B-infected individuals. The conference is being planned for late 2005 or early 2006.

Item

Kidney disease clinical research – The Committee previously noted the problem in conducting kidney disease research due to lack of a permanent infrastructure, such as a Clinical Trials Cooperative Group. The Committee wishes to command NIDDK for its leadership in moving forward in this area, by holding an initial workshop and developing strategies that will strengthen kidney research. The Committee encourages NIDDK to work with the renal community to continue these efforts in important research areas such as hypertension, uremic toxicity, diabetic nephropathy and transplant immunology. (p. 75)

Action taken or to be taken

The NIDDK recognizes and appreciates the vital role played by the renal research community in complementing the Institute's research efforts. As one example of the valuable contributions made by this community, during the past year, the American Society of Nephrology has hosted a series of strategic planning meetings from which important information about renal research opportunities has emerged. These meetings, which have focused on transplantation, uremic toxins, diabetic nephropathy, and hypertension, have featured presentations by many of the leaders in the renal research community. The NIDDK intends to use the recommendations from these meetings as part of a review of its renal research portfolio, and will seek to identify areas of investigation for enhancement.

In addition to these meetings, the NIDDK has for the past two years sponsored a pilot program aimed at providing supplements to investigators to encourage the development of novel ideas for clinical interventions related to kidney disease. The "Kidney Disease Clinical Studies Initiative" (KDCSI) is an outgrowth of a task force meeting convened in March 2002 by the NIDDK and the Council of American Kidney Societies (CAKS). The first meeting of the KDCSI was held in February 2003. The NIDDK is now seeing greater demand from the research community for this funding, and has developed new funding mechanisms for concept development and ancillary studies. The NIDDK anticipates holding a follow-up meeting in fiscal year 2005 or 2006 with the renal research community to discuss ways of strengthening this program. Also, plans for a program of small planning grants for clinical studies have grown out of the experience with supplemental awards. This planning grant program is expected to be launched in 2005 or 2006.

Item

Pediatric kidney disease – Chronic kidney disease is the ninth leading cause of death and one of the costliest illnesses in the U.S. Although significant strides have been made in understanding kidney disease in adults, much less is known about its manifestations in children. This breach has taken on greater significance in recent years as the number of children who are overweight and obese has skyrocketed, giving rise to an increased incidence of type 2 diabetes, hypertension and chronic kidney disease in this population. Given the long-term implications of diabetes-related kidney problems initiating in childhood, NIDDK is encouraged to undertake longitudinal studies of the natural history, prevention and treatment of kidney disease in type 2 diabetes and its antecedents in children and adolescents. The Committee is pleased that NIDDK has assigned priority to clinical studies related to the treatment of focal segmental glomerulosclerosis, the most common acquired cause of kidney disease in children, and to longitudinal epidemiological studies of children. In both instances, NIDDK is encouraged to support ancillary studies aimed at discovering new prevention and treatment strategies for children. (p. 75)

Action Taken or to be Taken

The NIDDK is committed to research that will develop new knowledge and effective prevention and treatment strategies for combating kidney disease in children, including kidney disease associated with type 2 diabetes and focal segmental glomerulosclerosis (FSGS). For example, the NIDDK-sponsored TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study is the first clinical study to look at the effects of intensive lifestyle change aimed at lowering weight by cutting calories and increasing physical activity in youths with type 2 diabetes. The TODAY study's main goal is to determine how well and for how long each of three different treatments controls blood glucose levels: (1) metformin alone, (2) metformin and rosaglitazone in combination, (3) and metformin plus intensive lifestyle change aimed at losing weight and increasing physical activity. The study will also evaluate a wide range of other outcomes in participants, including the effect of treatment with respect to risk factors for kidney disease in participants, as well as risk factors for eye, nerve, and heart disease.

The NIDDK also encourages research on kidney diseases in children as part of its efforts to spur ancillary studies to ongoing clinical trials in patients with diseases within the scope of the Institute's research mission. Each of these studies represents a substantial financial commitment from the NIDDK to establish an infrastructure for patient recruitment and follow-up. To fully exploit the research potential of each of these established cohorts, the NIDDK has released a Special Emphasis Program Announcement to support projects designed to provide additional information concerning the primary and secondary objectives of the parent study. These ancillary studies must be integrated with and complementary to the studies carried out in the parent study, and there must be close collaboration between ancillary study and parent study investigators. Studies of kidney disease eligible for support under this Program Announcement include the Pediatric Chronic Renal Insufficiency Cohort Study, the Focal Segmental Glomerular Sclerosis (FSGS) Trial in Young Adults and Children, the Consortium for Radiologic Imaging of Polycystic Kidney Disease (CRISP), and the HALT-PKD trial.

Item

Polycystic kidney disease – The Committee is pleased that a series of synergistic events in PKD research has culminated in the development of therapies to potentially halt disease progression for the 600,000 Americans who suffer from PKD. Key to such therapies is the discovery that an existing drug controlling other abnormal fluid-retention diseases in humans also retards the production of cysts and disease progression in all forms of PKD in the laboratory. Also, the NIDDK funded CRISP study for PKD proves the value of innovative imaging methods to measure disease progression, thus reducing by forty-fold the number of patients needed to adequately assess clinical research outcomes. Moreover, the possibility that future PKD clinical trials can be conducted simultaneously with other research protocols under the NIDDK funded Halt-PKD Interventional Trials infrastructure, is also encouraging. The Committee has encouraged public-private research partnerships, thus in this instance the collaborative efforts by the NIDDK, patient advocacy and industry organizations, are positive examples of how new strategies to energize clinical research enterprises has the potential to benefit PKD sufferers, save billions of Federal dollars otherwise paid by Medicare and Medicaid for renal replacement therapy and free-up several thousand spots on the kidney transplant waiting list. Given these exciting scientific developments, the Committee encourages NIDDK to aggressively pursue clinical trials regarding these recent breakthroughs and to expand its infrastructure for PKD clinical research, while expeditiously implementing the new PKD Strategic Plan it recently developed. (p. 76)

Action Taken or to be Taken

The NIDDK will build upon two ongoing major investments in clinical research on PKD: the CRISP cohort study and the HALT-PKD trial network.

CRISP was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for autosomal-dominant polycystic kidney disease (PKD). This trial, currently in its final year, has followed 240 patients with annual glomerular filtration rate evaluation and magnetic resonance imaging to assess changes in renal volume over time. The Institute has proposed an initiative to expand the CRISP infrastructure to permit long-term longitudinal follow-up of the cohort and to provide infrastructure support for collaboration between the CRISP investigators and industry in early clinical studies with new and promising investigational drugs for the treatment of PKD in this well-characterized cohort of patients.

The second major ongoing trial, the “Polycystic Kidney Disease Clinical Trials Network,” co-funded by the PKD Foundation, is conducting two phase III-type studies in the HALT-PKD trial—one in patients with early kidney disease and another in patients with more advanced disease. HALT-PKD is testing whether optimum blood pressure management—and either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers—will slow progression of PKD. A potential partnership with industry to provide drugs for these studies is currently being negotiated.

These studies are expected to yield insights that will provide a foundation for future clinical research and progress in combating PKD.

The NIDDK is also supporting additional studies into the causes and treatments of PKD. Most PKD patients have a mutation in one of two genes, *PKD1* or *PKD2*, which code for the proteins polycystin-1 and 2, respectively. Scientists are now conducting research to figure out how disruptions in PKD-related genes derail normal kidney tissue development to cause cyst formation and progressive kidney disease. Scientists at "Interdisciplinary Centers for Polycystic Kidney Disease Research" are studying genetic mechanisms, the biology of polycystin function, physiology, pathogenesis, and progression of PKD. An initiative on "Ancillary Studies of Kidney Disease" encourages researchers to use current clinical trials such as CRISP and HALT-PKD, as well as already- completed studies, as resources for new research, including translational studies. Additionally, an initiative on "Research Grants for Clinical Studies of Kidney Diseases," announced in February 2004, encourages new and innovative pilot and feasibility studies, clinical trials, and epidemiological studies on kidney disease.

Item

Tuberous sclerosis complex – Tuberous sclerosis complex (TSC) is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body including the kidneys, where patients are at risk for polycystic kidney disease, cancer or, most commonly, benign growths known as angiomyolipoma that can result in kidney failure. The Committee encourages NIDDK to support studies examining the molecular and cellular basis of these manifestations of TSC as well as pre-clinical and clinical studies. (p. 76)

Action Taken or to be Taken

Tuberous sclerosis complex is a rare, multi-system genetic disease that causes benign tumors to grow in vital organs, including not only the kidneys, but also the heart, eyes, lungs, skin, or brain. A small number of individuals with TSC develop large, numerous kidney cysts similar to those seen in polycystic kidney disease (PKD). In these cases, kidney function is compromised and kidney failure occurs. There is evidence suggestive of a functional interaction between the genes responsible for TSC and a genetic form of PKD, as there are some patients in whom genes for both diseases are disrupted. These patients develop cystic kidneys and renal failure as young children, while symptoms typically appear in adulthood for either single disease. To address the molecular and cellular mechanisms underlying TSC and its renal complications, the NIDDK supports a number of research projects. These efforts include investigator-initiated basic science studies designed to elucidate the genetic factors that lead to TSC, as well as preclinical studies in mouse models that are testing a key immune system regulator known as interferon gamma as a prevention or treatment agent. In addition, the NIDDK participates in the inter-Institute TSC Research Coordination Committee that is working toward implementation of the NIH Tuberous Sclerosis Research Agenda.

Item

Celiac disease – The Committee commends NIDDK for recognizing the lack of understanding, and under-diagnosis of the genetic, autoimmune disorder, Celiac disease (CD), and for including CD in the NIH Consensus Development Program for 2004. Although readily diagnosed in European countries, it takes on average eleven years for Americans to be properly diagnosed.

Delays in diagnosis place individuals at risk for osteoporosis, anemia, miscarriages, and small bowel cancer. Current evidence demonstrates that CD is the most common genetic disorder in the world, with a treatment--strict, gluten-free diet--that can be managed almost exclusively by the individual, or family. Education about CD is needed for health care professionals and patients. The Committee encourages NIDDK to coordinate informational and educational programs directed at health professionals, patients and the public to raise awareness and understanding about CD, and the need for early diagnosis. (p. 77)

Action Taken or to be Taken

In June 2004, a Consensus Development Conference on Celiac Disease was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Medical Applications of Research (OMAR) to explore and assess current scientific knowledge regarding celiac disease. The consensus statement of this expert panel contained several recommendations including the following:

> "Celiac disease is an immune-mediated intestinal disorder with protean manifestations. Celiac disease is common, affecting 0.5 to 1.0 percent of the general population of the United States, but is greatly underdiagnosed. There are new specific and sensitive serologic tests available to aid in diagnosis that needs to be more widely applied. The treatment of celiac disease remains a lifelong gluten-free diet, which results in remission for most individuals. The classic presentation of diarrhea and malabsorption is less common and atypical and silent presentations are increasing. Most individuals are being seen by primary care providers and a broad range of specialists. Therefore, heightened awareness of this disease is imperative. Education of physicians, registered dietitians, and other health providers is needed."

In response to the recommendations of a June 2004 Consensus Development Conference on Celiac Disease, the NIDDK is currently formulating a celiac disease awareness campaign.

Item

Digestive diseases – Diseases of the digestive system continue to affect more than one-half of all Americans at some time in their lives. Serious disorders such as colorectal cancer, inflammatory bowel disease, irritable bowel syndrome, hemochromatosis, celiac disease, and hepatitis take a tremendous toll in terms of human suffering, mortality, and economic burden. The Committee commends NIDDK on the success of its Digestive Disease Centers program in addressing a wide range of disorders. The Committee continues to encourage NIDDK to expand this important program, with an increased emphasis on irritable bowel syndrome. (p. 77)

Action Taken or to be Taken

The NIDDK is grateful for continuing support for the Silvio O. Conte Digestive Diseases Research Core Centers program. The NIDDK supports a broad-based investigator-initiated approach using multiple grant mechanisms to study irritable bowel syndrome (IBS). This effort

includes fundamental research in gastrointestinal motility, immunology, and cell biology, as well as clinical research in patients with IBS. This research is aimed at understanding the development of the pathways that control motility mechanisms in the gut; research on the integration of pain, motility behavioral-neural-circuits, and the relationships of gut inflammation to these pathways; translational research aimed at moving discoveries in animal models into studies in humans; and clinical studies. In 2003, in cooperation with NIH Office of Research on Women's Health, the NIDDK funded a Specialized Center of Research at the University of California, Los Angeles that has an emphasis on IBS. In 2004, in cooperation with the NIH Office of Behavioral and Social Sciences Research through the Mind-Body Initiative, the NIDDK funded a Gastrointestinal Biopsychosocial Research Center grant at the University of North Carolina, Chapel Hill, for behavioral research on IBS. The NIDDK will continue to use all available funding mechanisms to encourage outstanding new research projects to develop new knowledge about and to combat this important health problem.

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 encourages NIDDK to continue its support for CF researchers engaged in basic and clinical CF research. (p. 77)

Action Taken or to be Taken

The NIDDK will continue to fund both basic and clinical research on CF, maintaining a large portfolio of grants to study and improve treatment of the disease. In these research efforts, the NIDDK seeks to harness new technology, such as proteomics techniques, and also to translate laboratory discoveries into clinical research that can directly benefit patients. For example, NIDDK-funded researchers have recently demonstrated that a compound purified from the spice turmeric corrects cystic fibrosis defects in animal models of the disease. New research will build on these insights to determine their significance and potential clinical application. Key to the NIDDK's cystic fibrosis research efforts are its Molecular Therapy Core Centers, which support important research on CF and other genetic diseases that result in metabolic abnormalities. Formerly focused on gene therapy research, these centers are now bringing an expanded array of molecular approaches based on new technologies to bear on treatment-oriented studies.

This year, the NIDDK has sought to expand CF research by issuing a Request for Applications for a CF Research and Translation Core Center, to support both basic and clinical work. Core Centers provide shared vital resources to spur researchers in developing and testing new therapies for CF, and they foster collaborations among institutions with a strong existing research base in CF. The Center will also support pilot and feasibility studies to develop and test new approaches to therapy.

The NIDDK recognizes the great potential for proteomics in finding new treatments for inborn metabolic diseases such as CF. This burgeoning field focuses on studies of the structure, function and expression of proteins, whose work in the body is directed by each person's genes.

Scientists can now use proteomic technologies to determine which proteins are involved in a specific disease, how these proteins function in cells and how they interact with each other to cause disease. Once it is known how disease occurs on a molecular level, proteomic technology can then be used to develop innovative therapeutic strategies such as small molecules that will block harmful protein interactions and prevent disease. To capitalize on recent proteomics advances, the NIDDK has also released a Program Announcement on Proteomics in Diabetes and Other Endocrine and Metabolic Diseases. This initiative is part of a larger NIDDK and NCI initiative to promote the use of proteomic technologies to gain new knowledge in the fight against disease. The development and improvement of these innovative research techniques are being encouraged through application to relevant biological questions related to diabetes, endocrinology and metabolic diseases. Furthermore, as part of the NIH Roadmap Initiative, the NIH is convening workshops to establish quality and data standards in proteomics, and to identify critical reagents to promote the emerging field. These initiatives have great potential to propel research on CF and a wide range of other diseases.

Item

Mucopolysaccharidosis (MPS) – The Committee recognizes the efforts of NIDDK to enhance research efforts to achieve a greater understanding of and pursue development of effective therapies for MPS disorders. In addition to the general overall support of broad-based MPS research, the Committee supports studying bone and joint disease in MPS disorders. Research into the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored and potential therapeutic approaches should also be studied. The Committee encourages NIDDK's continued efforts to collaborate with NIAMS on bone and joint research in lysosomal storage disorders. (p. 77)

Action Taken or to be Taken

The NIDDK is strongly committed to research designed to generate new knowledge about MPS and other lysosomal storage disorders and to translate those insights into effective therapies. With respect to the Committee's specific interest in bone research, the NIDDK supports a vigorous program of research on bone growth and metabolism, which has the potential to impact MPS research both directly and indirectly. The Institute works closely with NIAMS and other NIH components which also have research activity on or related to bone diseases.

On a broader research level, last year, the long-term commitment of the NIDDK to MPS-related research achieved fruition when the Food and Drug Administration approved enzyme replacement therapies for patients with MPS I and for patients with Fabry disease. Similar therapeutics for other forms of MPS and other lysosomal storage disorders are in development, and are likely to be approved soon for the benefit of patients and their families.

Although these new therapies represent major improvements in health care for patients with lysosomal storage disorders, they are most effective in organs that are well-perfused by the circulatory system. Different approaches will have to be taken to achieve similar success in other parts of the body, such as bone, the cornea and brain. Therefore, the NIDDK is now concentrating its efforts on methods, such as gene therapy and the use of small molecule

chaperones, which may be able to treat organs refractory to enzyme replacement therapy. Indeed, gene therapy has already been shown to be effective in preventing heart, eye, bone and joint abnormalities, as well as other symptoms of the disease in dogs with the canine form of MPS VII. NIDDK-funded work is under way to extend the approach to the more common form of MPS—MPS I.

NIDDK's Molecular Therapy Core Centers support research on gene and other molecular therapy research for a variety of genetic diseases. Two of the four Centers study MPS. Their basic objective is 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 will continue to work with investigators to encourage bone disease research, and work with NINDS and NICHD to support studies of therapeutic approaches for MPS disorders with an ultimate goal of finding more effective therapies for human patients.

Item

Gastroesophogeal reflux disease (GERD) -- The Committee is aware of new research which indicates a controlled carbohydrate diet may dramatically reduce the incidence of gastroesophogeal reflux (heartburn). The Committee encourages NIDDK to support research into the effectiveness of this approach in treating GERD. (p. 78)

Action Taken or to be Taken

The NIDDK has a very active research portfolio in basic and clinical research related to GERD. Because obesity is a risk factor for GERD and several other diseases within the NIDDK and NIH mission—as well as a health problem in its own right—NIDDK has numerous initiatives to address the obesity epidemic. A variety of dietary factors have been implicated as contributing to GERD, although there is not yet strong evidence that any specific diet is a contributing factor. The NIDDK will continue to support outstanding research proposals that address the multiple dimensions of GERD.

Item

Adhesion related disorder – This little known condition commonly leads to abnormal attachments between the organs inside the abdomen. The adhesions generally are composed of scar tissue resulting from previous operations. Very little is known about why adhesions form more aggressively in some people. Diagnosis of the disease is typically difficult, and surgical correction is often unsuccessful. The Committee encourages NIDDK to investigate this disease, supporting research to find treatments and understand causation and to communicate these findings to broaden knowledge of the disease in the medical community. (p. 78)

Action Taken or to be Taken

Adhesion related disorder is not a single disease, but rather describes a type of scarring, particularly in the abdominal cavity. Scars form as a necessary part of the wound healing process following any type of injury or surgery. Scar tissue may form beyond the surgical wound itself and in some cases interfere with normal health.

Apart from surgery, there are many diseases that can precipitate adhesion formation in the abdomen. Important examples are the inflammatory bowel diseases known as Crohn's disease and ulcerative colitis, in which inflammation can cause scar formation and complications requiring multiple abdominal operations. The NIDDK is committed to expanding the knowledge base of these diseases as a foundation for developing treatment and prevention approaches to preclude complications and the need for surgery. For example, the NIDDK supports a broad-based research approach to study IBD using multiple grant mechanisms. The IBD Genetics Consortium is taking full advantage of the first gene identified that increases susceptibility to Crohn's disease, and also is enhancing the search for other contributing genes in this complex disease. The Silvio O. Conte Digestive Diseases Research Core Centers provide a mechanism for funding shared resources that serve to integrate, coordinate, and foster interdisciplinary cooperation between groups of established investigators who conduct digestive disease research. The work of five of these centers specifically focuses on IBD. The Institute also funds a number of exploratory/developmental grants (R21s) to foster the development of high-risk pilot and feasibility research by established or newly independent investigators to develop new ideas sufficiently to allow for submission of a full regular research grant (R01) application. Examples of NIDDK-funded research programs through the exploratory grant mechanism include investigation into a new subclass of regulatory T cells that may suppress inflammation and disease progression, and further studies of the protective action of certain intestinal proteins. The Institute also supports four program project grants investigating IBD, including projects to study

the genetic mechanisms predisposing to IBD in mouse models. This research may speed identification of homologous human genes and potential pathways for therapeutic intervention, and help to pinpoint genetic factors and immunological processes controlling human intestinal inflammation.

The development of the drug infliximab, the first treatment specifically approved by the FDA for Crohn's disease, was based on a foundation of NIDDK-supported basic research. Future plans for NIDDK research on IBD and other adhesion-related disorders will include the continued pursuit of new drug therapies, the development of surrogate markers of disease, the maximization of research investment in animal models of disease, and the establishment of a repository that will collect and make available to investigators various types of human samples including blood, biopsied tissue, genetic material, and datasets.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORT

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Acute Liver Failure – The Committee is pleased that the NIDDK has funded an Acute Liver Failure Study Group [ALFSG] that will improve medical knowledge necessary to prevent and treat acute liver failure. The Committee is pleased with the progress of the ALFSG, but notes that funding for the pediatric component of this initiative is limited. The Committee therefore urges increased funding for the ALFSG, particularly to permit a focus on pediatric issues. (p. 110)

Action Taken or to be Taken

Please refer to page 41 of this document for the NIDDK's response to this significant item regarding acute liver failure.

Item

Auto-Immune Liver Diseases – These diseases are the primary indication for liver transplantation in adolescents. The Committee urges additional research to improve the prevention and treatment of auto-immune liver diseases in children. (p. 110)

Action Taken or to be Taken

Please refer to pages 41-42 of this document for the NIDDK's response to this significant item regarding auto-immune liver diseases.

Item

Behavioral Research – The Committee encourages NIDDK's initiative to expand research on childhood obesity, particularly behavioral research on physical activity in children in various site-specific settings (schools, after-school care, or other community venues). The goal of such research would be to explore methods in pediatric populations for the prevention of inappropriate weight gain among those not overweight; to prevent further weight gain among those already overweight or obese; or treatment of overweight or obesity to prevent the complications of associated co-morbidities. The Committee applauds NIDDK's proposed long-term effort to address the relative contributions of the environmental and behavioral factors that lead to excessive weight gain and obesity among children. (p. 110)

Action Taken or to be Taken

The NIDDK is bolstering research towards preventing and treating childhood obesity, a serious and urgent health problem. The new research efforts are also consistent with recommendations in the recently-released Strategic Plan for NIH Obesity Research. As one of many efforts in this area, the NIDDK, in collaboration with other NIH components, launched an initiative to encourage new research to develop and test intervention approaches to prevent or manage overweight in children and adolescents. Sites for which meritorious research proposals would be supported include the family/home, day-care or preschool, school, or other appropriate community venues. Additionally encouraged are integrated cross-site studies that would provide synergy and reinforcement for prevention and management of overweight. This initiative would thus capitalize on the strengths of various sites where children and adolescents spend the majority of their time and where obesity prevention or treatment interventions could be delivered. Targeted interventions would focus on behavioral or environmental modifications, either individually or in combination, and could address physical activity and/or diet. The goal is to test strategies to foster energy balance to prevent inappropriate weight gain in children who are not overweight, to achieve age-appropriate body weight in those at risk of becoming overweight, or to reduce degree of overweight in those who are already overweight. These strategies would ultimately help prevent or reduce complications of obesity-associated co-morbidities. To help inform the development of this initiative, the NIDDK convened a workshop in the summer 2004 to solicit advice from experts external to the NIH. This initiative also complements another new effort, in which the NIDDK is collaborating with other NIH components to foster new research on prevention and treatment of childhood obesity in primary care settings.

Item

Cooley's Anemia – The Committee continues to support the high quality research being conducted by the NIDDK on such issues as iron chelation, non-invasive iron measurement, fetal hemoglobin, and other topics critical to improving the lives of Cooley's anemia patients. The development of a less burdensome means of iron chelation is urgently needed. In addition, the Committee encourages NIDDK to continue to work closely with NIBIB to develop and perfect non-invasive means of iron measurement. (p. 110)

Action Taken or to be Taken

The NIDDK recognizes the need for the development of less burdensome therapies for removing toxic excess iron levels from patients with thalassemia (Cooley's anemia), sickle cell disease, and other disorders involving blood transfusion. Researchers are specifically seeking more effective and more easily administered alternatives to the injected iron chelating drug, desferrioxamine. One drug that is moving into clinical trials (HBED), appears to be a more effective chelator, and thus, may need to be used less frequently and for shorter periods of time. Such improvements would be of great benefit to patients. However, the drug still must be injected, so the NIDDK continues to search for better iron chelating drugs. Already, these NIDDK-supported studies have resulted in successful preclinical evaluation of a re-engineered version of the oral chelator, desferrithiocin, and this new compound is currently being tested in

an industry-supported clinical study. The NIDDK plans additional studies on related chelators that may prove even more effective. Two new chelators have entered the NIDDK toxicology contract program for preclinical toxicity testing. Finally, studies supported by NIDDK have led to a better understanding of how the different iron chelating drugs remove iron from body tissues. This, in turn, has led NIDDK-supported investigators to start testing whether "smart" combinations of chelators may both maximize iron removal and enable use of lower doses of the drugs; early results are encouraging.

In related research, the NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) continue to collaborate in support of projects that may improve the utility of magnetic resonance imaging (MRI) as a non-invasive 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 October 2004, the NIDDK and the NIBIB hosted a meeting for investigators funded under an FY 2003 Request for Applications (RFA) to improve the utility of MRI as a method for quantitative determinations of tissue iron, especially in the liver, heart, and brain. This meeting gave grantees the opportunity to describe the background, goals, and future development of these projects, which are still in their initial stages, but already have shown impressive potential to provide information useful to clinicians and patients about their iron stores. Non-invasive imaging approaches to measure iron stores can contribute greatly to the effective clinical management of patients with diseases of iron overload.

Item

Cystic Fibrosis – Over the last three decades, advances in the treatment of cystic fibrosis have resulted in improvements in the life expectancy of individuals with CF. However, much more remains to be done to find new treatments for CF. One promising area of research is proteomics, which is focused on the CF Transmembrane Conductance Regulator and its abnormalities, the many proteins that interact with CFTR, and the identification of novel targets for new CF drugs. The Committee encourages NIDDK to expand its support for basic and clinical CF research and to place a special emphasis on proteomics in CF. (p. 110)

Action Taken or to be Taken

Please refer to pages 50-51 of this document for the NIDDK's response to this significant item regarding cystic fibrosis.

Item

Diabetes in Native Hawaiians – The Committee recommends investigating the incidence of diabetes 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. 111)

Action Taken or to be Taken

The NIDDK continues to pursue research efforts with respect to diabetes in Native Americans and other native populations of the U.S. The Diabetes Prevention Program (DPP) multi-site clinical trial demonstrated that type 2 diabetes could be prevented or delayed in people at high-risk for the disease. The study compared: (1) intensive lifestyle changes consisting of diet and exercise; (2) treatment with the diabetes drug metformin; and (3) standard information on diet and exercise. The 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; metformin decreased the risk by 31 percent. One of the centers at which the DPP was conducted was in Hawaii, and the study also included sites focused on American Indians. The NIDDK is now conducting a follow-up study of the DPP participants, the DPP Outcomes Study (DPPOS). The DPPOS will investigate the incidence of new-onset type 2 diabetes in these high-risk participants over time in order to assess the long-term effect of the original DPP interventions.

To bring to high-risk communities the important prevention message of the DPP clinical trial--that modest lifestyle changes can dramatically reduce the risk of type 2 diabetes in high-risk groups--the National Diabetes Education Program (NDEP) has launched the first national multicultural diabetes prevention campaign, "Small Steps. Big Rewards. Prevent Type 2 Diabetes." Components of this campaign include, "We Have the Power to Prevent Diabetes," which is tailored for American Indians and Alaska Natives, and "Two Reasons to Prevent Diabetes…My Future and Theirs," tailored for Asian Americans and Pacific Islanders. The NDEP is jointly-sponsored by the NIDDK and the Centers for Disease Control and Prevention (CDC) and includes participation of numerous partner organizations.

In co-sponsoring 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 focuses on establishing the prevalence of diabetes cases in children. The NIDDK and CDC have expanded support for the study to assess, prospectively, the incidence (new cases) of diabetes in these six regions.

An initiative, co-sponsored by the NIDDK and the Indian Health Service (IHS), to enhance a diabetes-focus on science education in Tribal Schools has 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. In addition, the NIDDK and IHS plan to sponsor a conference on the prevention of cardiovascular disease and type 2 diabetes in American Indians and Alaska Natives in 2005. The conference will convene health care providers, community health professionals, and Tribal leaders, and will include discussion of how to integrate prevention and treatment strategies into American Indian and Alaska Native communities.

Item

Digestive Diseases – The Committee commends NIDDK on the success of its Digestive Disease Centers program in addressing a wide range of disorders that result in tremendous human suffering and economic cost. The Committee continues to encourage NIDDK to expand this important program with an increased emphasis on irritable bowel syndrome. (p. 111)

Action Taken or to be Taken

Please refer to pages 49-50 of this document for the NIDDK's response to this significant item regarding digestive diseases.

Item

Fatty Liver Disease – The Committee notes that there is an emerging obesity-related chronic liver disease, nonalcoholic fatty liver disease, which may affect as many as 1 in every 4 adults over the age of 18. This diagnosis encompasses a spectrum of severity with many cases evolving into non-alcoholic steatohepatitis [NASH] and, ultimately, cirrhosis. NASH-related liver disease has already become an important indicator for liver transplantation, and, in the absence of better treatments, the need for NASH-related liver transplantation will increase significantly over time. The Committee appreciates NIDDK's existing programs in this area but urges expanded basic and clinical research focused both on interventions needed to prevent the onset of NASH and improved protocols for treatment of established cases. The Committee also urges the Institute to review opportunities to expand current clinical programs, where appropriate, to permit the enrollment and follow up of larger numbers of patients. Finally, the Committee urges a public awareness campaign with a national voluntary health agency with State and local affiliates to reverse this growing and preventable public health epidemic linked to the broader issue of obesity. (p. 111)

Action Taken or to be Taken

Please refer to pages 43-44 of this document for the NIDDK's response to this significant item regarding fatty liver disease.

Item

Fragile X – Fragile X mental retardation is one of the most common single gene disorders, and yet there exists almost no research on its effects outside the central nervous system. Fragile X causes a broad range of symptoms including premature ovarian failure, macroorchidism (large testicles), and malformations in the urogenital track, digestive problems including excessive vomiting and increased motility. The fact that these diverse symptoms arise from one gene mutation offers an invaluable opportunity to understand and develop treatments for these disorders. The Committee urges NIDDK to expand its research activities on Fragile X and to coordinate these efforts with other Institutes working on related activities, including NIMH and NICHD. (p. 111)

Action Taken or to be Taken

Because Fragile X is a genetic, developmental disorder that most dramatically affects the central nervous system, other components of the NIH (in particular NICHD, NIMH and NINDS) have primary responsibility for research on this disease. The NIDDK contributes its expertise in digestive diseases and urology to those NIH institutes in order to promote understanding of and treatments for Fragile X, which, as the Committee notes, can include among its symptoms such digestive problems as vomiting. In addition, among the research areas being pursued by the intramural scientists in NIDDK's Laboratory of Cellular and Molecular Biology is the etiology of Fragile X through analysis of the gene that is mutated in this disorder. More generally, the Institute supports four Molecular Therapy Core Centers which pursue the goal of gene therapy, which would be of potential benefit to patients with Fragile X, as well as those with other genetic diseases. While the NIDDK does not currently fund work specific to digestive complications of Fragile X, the NIDDK pursues research on the development of and disorders relating to the digestive system, including motility problems. Such work could also benefit Fragile X patients with these conditions.

Item

Hepatitis B Conference – Hepatitis B remains a common cause of acute hepatitis affecting 1,250,000 Americans. Among the Asian and Pacific Island populations the rate of infection rate is even higher, affecting up to 15 percent of individuals. In order to address this health issue, the Committee urges NIDDK to convene an Expert Conference in fiscal year 2005 to reach consensus on the best treatment protocols. (p. 112)

Action Taken or to be Taken

Please refer to pages 44-45 of this document for the NIDDK's response to this significant item regarding hepatitis B conference.

Item

Hepatitis C in Children – The Committee is pleased that the NIDDK has launched a pediatric hepatitis C trial that will permit long-term follow up of children enrolled in treatment protocols, particularly as these treatment regimens impact the growth and development of the children. The Committee looks forward to being informed on the progress of this trial during the fiscal year 2006 appropriations hearings. (p. 112)

Action Taken or to be Taken

Please refer to page 44 of this document for the NIDDK's response to this significant item regarding hepatitis C in children.

Item

Incontinence – Fecal incontinence, also called bowel incontinence, affects people of all ages and is associated with a wide variety of causes. The Committee encourages NIDDK to develop a standardization of scales to measure incontinence severity and quality of life, and to develop strategies for primary prevention of fecal incontinence associated with childbirth. (p. 112)

Action Taken or to be Taken

Please refer to page 39 of this document for the NIDDK's response to this significant item regarding incontinence.

Item

Interstitial Cystitis – The Committee is pleased by recent advances in the area of interstitial cystitis research, particularly in the area of urinary markers. The Committee urges the NIDDK to continue to aggressively support IC-specific basic science initiatives, particularly through program announcements. The Committee also encourages the NIDDK to work closely with the IC patient community on developing and funding an IC awareness campaign for both the public and professional communities, and to host a consensus conference on the definition of IC. The absence of a uniform definition that accurately captures the condition and the affected population is negatively impacting patients in terms of diagnosis and treatment as well as researchers in terms of literature review and their research activities. The Committee was very encouraged by the progress reported at the 2003 NIDDK-sponsored scientific symposium on IC, and it urges the NIDDK to further this scientific momentum by hosting the next international symposium on IC in 2005. (p. 112)

Action Taken or to be Taken

Please refer to pages 38-39 of this document for the NIDDK's response to this significant item regarding interstitial cystitis.

Item

Irritable Bowel Syndrome – The Committee encourages NIDDK to provide adequate funding for irritable bowel syndrome/functional bowel disorders research and to give priority consideration to funding grants that will continue to increase the IBS portfolio. The Committee requests that NIDDK actively pursue the development of a strategic plan for IBS research. (p. 113)

Action Taken or to be Taken

Please refer to page 36 of this document for the NIDDK's response to this significant item regarding irritable bowel syndrome.

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. In addition to the general overall support of broad based MPS research, the Committee supports studying bone and joint disease in MPS disorders. Research into the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored and potential therapeutic approaches are of interest to the Committee. The Committee encourages NIDDK's continued efforts to collaborate with NIAMS on bone and joint research in Lysosomal Storage Disorders and commends the NIDDK on its performance in collaborating with NINDS, NICHD, NCRR, and ORD in advancing MPS-related research. (p. 113)

Action Taken or to be Taken

Please refer to pages 51-52 of this document for the NIDDK's response to this significant item regarding muccopolysaccharidosis.

Item

Osteoporosis – The Committee encourages NIDDK, in concert with other NIH institutes, to increase research into disease-related osteoporosis and/or bone disorders. This research should include studies of the role of genetics, the effects of these diseases on bone turnover and altered bone metabolism, the impact of environmental and lifestyle factors, their effects on bone quality and fracture incidence, the role of bone marrow changes, the use of agents to increase bone mass, and the therapeutic use of new technologies to combat osteoporosis. (p. 113)

Action Taken or to be Taken

The NIDDK funds important research on the factors affecting bone health—with emphasis on the effects of hormones and metabolic processes on bone formation and integrity. For example, the NIDDK funds extensive research on anabolic (growth-promoting) factors in bone, including parathyroid hormone (PTH), PTH-related protein, the Wnt family of nuclear receptors and other bone-specific anabolic factors, such as the bone morphogenetic proteins. NIDDK-supported research on PTH has led to the development of this hormone as a newly approved therapeutic agent for osteoporosis. Studies of nuclear receptors may be particularly helpful in understanding glucocorticoid-induced osteoporosis and the bone loss that results from excess thyroid hormone.

The NIDDK continues to work in concert with NIAMS, the institute with the primary role in supporting work on the genetics and cell biology of bone cell function, as well as with NIA, which plays a key role in research on age-related changes in bone health. In keeping with its emphasis on the role of hormones in bone health, the NIDDK is currently funding several small-scale trials of anabolic agents in bone, including one on PTH-related protein; studies that attempt to stem glucocorticoid-induced osteoporosis; and studies to address metastases in bone that result from prostate cancer. The Institute also supports research on the basic biology of the skeletal system, including a project that looks at the factors responsible for proper development of joints

in the mouse—with a view toward translating these insights into studies of human bone disease. The knowledge gained may be useful in determining what goes wrong in some of the joint diseases that afflict many Americans.

Item

Pediatric Urology – The Committee remains concerned with the lack of research dedicated to pediatric urologic conditions. According to the NIDDK Bladder Research Review Group document "Overcoming Bladder Disorders: A Strategic Plan for Research," the gaps and requirements for pediatric disease research remain substantial, particularly for conditions such as vesicoureteral reflux and bladder dysfunction. The Committee urges NIDDK to commit the necessary resources to expand research on pediatric urologic conditions, which may in turn provide additional insight into adult urologic problems. (p. 114)

Action Taken or to be Taken

The NIDDK has begun a strategic planning effort for pediatric urology research. Two preliminary meetings of a Task Force to develop an NIDDK Pediatric Urology Strategic Plan occurred in April and July 2004, and a final meeting is planned for February 2-4, 2005. Recommendations ensuing from this effort will help guide the Institute in its commitment of resources and targeting of activities in pediatric urologic diseases to ensure that the most compelling and promising research opportunities are pursued. The NIDDK is currently acting on recommendations from the May 18, 2003, meeting of the Vesicoureteral Reflux (VUR) Task Force, which focused on the potential for conducting a randomized, controlled clinical trial in children diagnosed with VUR. The group identified several aspects of disease progression and treatment that are poorly understood and about which a clinical trial could provide important insights. In July 2004, the NIDDK issued a Request for Applications (RFA) inviting cooperative agreement applications for pediatric nephrology/urology clinical treatment centers and a data coordinating center for the design and conduct of treatment trials and studies in children with VUR. The primary goals for this program are to study disease progression in a cohort of 600 children with mild to moderate VUR and to determine which interventions are most beneficial. Contingent upon the receipt of scientifically meritorious applications, the NIDDK anticipates that planning for a clinical trial for VUR will begin in late 2005.

Item

Polycystic Kidney Disease [PKD] – Recent breakthroughs in PKD research have culminated in the development of therapies to potentially halt disease progression for the 600,000 Americans who suffer from PKD. Key to such therapies is the discovery that an existing drug controlling other abnormal fluid-retention diseases in humans also retards the production of cysts and disease progression in all forms of PKD in the laboratory. Also, the NIDDK-funded CRISP study for PKD proves the value of innovative imaging methods to measure disease progression, thus reducing by forty-fold the number of patients needed to adequately assess clinical research outcomes. Moreover, the possibility that future PKD clinical trials can be conducted simultaneously with other research protocols under the NIDDK-funded Halt-PKD Interventional Trials infrastructure is also encouraging. The Committee urges the NIDDK to pursue clinical

trials regarding these recent breakthroughs and to expand its infrastructure for PKD clinical research, while expeditiously implementing the new PKD Strategic Plan it recently developed. (p. 114)

Action Taken or to be Taken

Please refer to pages 47-48 of this document for the NIDDK's response to this significant item regarding polycystic kidney disease

Item

Prostate Diseases – Prostate diseases are highly prevalent and poorly understood. 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. In particular, the current efforts to develop biomarkers for benign prostate diseases should be expanded. (p. 114)

Action Taken or to be Taken

Through the use of biomarkers and other tools, the NIDDK is continuing to enhance efforts to understand more fully the fundamental biology of the prostate--knowledge that can be a platform for research on improved therapeutic approaches for diseases of the prostate. In FY 2002, the Institute, in collaboration with the National Cancer Institute and the National Institute of Child Health and Human Development, issued a Program Announcement (PA) to encourage research projects that would develop cell-selective tools to study the prostate and other organs of the lower urinary tract. This PA is one of a subset of active program announcements (PAs) that are of sufficiently high priority to warrant NIDDK "Special Emphasis" funding. Several projects funded through this PA are focused on developing tools that could enable researchers to better understand cellular and molecular changes in the prostate that occur in or contribute to prostate diseases. The Institute will also encourage submission of biomarker studies for benign prostate diseases under an initiative currently planned for release in FY 2005 and funding in FY 2006 to foster efforts to identify and validate needed biomarkers for well-defined human diseases within the NIDDK mission. Moreover, the NIDDK is already capitalizing on an opportunity to identify biomarkers for prostate disease that arose from the clinical trial on "Medical Therapy of Prostate Symptoms (MTOPS)." The MTOPS trial, which was completed in 2002, compared the efficacy of two drugs, alone or in combination, in reducing progression of benign prostatic hyperplasia in over 3,000 men with symptomatic disease, including men clinically defined as being at high risk for progression. Serum and prostate tissue samples collected during the trial from the well-characterized participants are now being used for study by the MTOPS Prostate Samples Analysis consortium. This multi-center consortium, co-funded by the National Institute on Aging, is using the samples to identify genes and proteins that can be used in the diagnosis, prognosis, and/or treatment of BPH. Already, the consortium has uncovered promising candidate biomarkers associated with BPH symptoms and with prostate tissue growth. Progress by the consortium and future efforts in this area were discussed at the August 5, 2004 meeting of

the Urology Interagency Coordinating Committee led by the NIDDK, and also at the September 2004 meeting of the Division of Kidney, Urologic, and Hematologic Diseases' subcouncil of the NIDDK's National Advisory Council.

Item

Prostatitis – The Committee encourages the Institute to provide more diverse medical specialties to supplement and build upon the insufficient treatment options and the background of basic information now available. The genetic and molecular epidemiology, the management of pelvic pain, the infectious origins and the symptoms of prostatitis that are identical to symptoms of prostate cancer need special attention. (p. 114)

Action Taken or to be Taken

The NIDDK is taking a number of approaches to support studies that could enhance the understanding, management, and treatment of chronic prostatitis, including approaches that encourage the application of diverse medical specialties to such studies. The Chronic Prostatitis Collaborative Research Network (CPCRN) was established in 1997 as part of an effort to standardize and evaluate various methods of diagnosing and treating chronic prostatitis, with the long-term goal of preventing and effectively treating this condition. In spring 2003, the CPCRN completed a randomized, placebo-controlled clinical trial comparing the efficacy of two drug treatments (the alpha-blocker, tamsulosin hydrochloride and the antibiotic, ciprofloxacin), singly or in combination, in improving symptoms and quality-of-life for men with chronic prostatitis. Patients enrolled in the trial had long-standing chronic prostatitis/chronic pelvic pain syndrome and had not responded to previous treatments. Although the trial results show that none of the treatments substantively improved symptoms or quality-of-life for these patients, researchers can now assess whether longer courses of treatment or earlier interventions may be of benefit for men with chronic prostatitis. Through successful recompetition in FY 2003, a new, expanded CPCRN has been organized that will conduct additional clinical trials of promising therapeutic interventions over a second five-year period. To fully capitalize on this resource, the NIDDK has required the network to develop and conduct ancillary studies in conjunction with the clinical trials. The new CPCRN is currently in the process of developing a set of clinical trials that will focus on the potential benefit of earlier treatment for chronic prostatitis; based upon recent research, investigators are optimistic that this approach will have a positive impact on outcomes for men affected by this condition. CPCRN investigators are also able to draw upon other urological chronic pelvic pain syndrome experts by their participation in the NIDDK-established Urological Pelvic Pain Collaborative Research Network. Also benefiting research on chronic prostatitis, the Institute, in collaboration with the National Cancer Institute and the National Institute of Child Health and Human Development, issued a Program Announcement in FY 2002 to encourage research projects that would develop cell-selective tools to study the prostate and other organs of the lower urinary tract. This program announcement is one of a subset of active program announcements that are of sufficiently high priority to warrant a set-aside of NIDDK "Special Emphasis" funds. Several projects funded through this program announcement are focused on developing tools that could enable researchers to better understand cellular and molecular changes in the prostate that may contribute to onset and/or progression of chronic prostatitis. Finally, a new initiative is being developed by the NIDDK that will encourage the

development and implementation of new imaging methods for the solid abdominal organs and the urinary tract. Tools or techniques developed through this translational research initiative, which is currently planned for funding in FY 2006, may help researchers better assess the burden of inflammatory cells in the prostates of men with chronic prostatitis, and to tease out the role of inflammation in different sub-populations of men with this condition. All of these efforts complement the Institute's ongoing support for investigator-initiated basic research projects in prostate biology and prostatitis.

Item

Scleroderma – The Committee encourages the 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, Barrett'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 5 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. 114)

Action Taken or to be Taken

Please refer to page 40 of this document for the NIDDK's response to this significant item regarding scleroderma.

Item

Tuberous Sclerosis Complex – Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body including the kidneys, where patients are at risk for polycystic kidney disease, cancer or, most commonly, benign growths known as angiomyolipoma that can result in kidney failure. The Committee strongly urges NIDDK to support studies examining the molecular and cellular basis of these manifestations of TSC as well as pre-clinical and clinical studies. (p. 115)

Action taken or to be taken

Please refer to page 48 of this document for the NIDDK's response to this significant item regarding tuberous sclerosis complex.

Item

Urogynecology Program − The Committee is pleased that the NIDDK has supported the Urinary Incontinence Treatment Network and urges increased funding and expansion for this important and productive clinical network. While recent studies have yielded gains in understanding these conditions, 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 supports the NIDDK in the creation of a team focused on urogynecology and encourages a dedicated study section in this area. (p. 115)

Action Taken or to be Taken

The NIDDK appreciates the Committee's positive comments on the Urinary Incontinence Treatment Network (UITN). The NIDDK is strengthening this effort by providing additional funds to support the study of behavioral interventions to treat urinary incontinence. Currently, the NIDDK, with co-sponsorship from the National Institute of Child Health and Human Development, supports nine clinical Continence Treatment Centers and a data coordinating center in the Network. The NIH Office of Research on Women's Health (ORWH) has also provided support for the establishment of the Network's clinical centers. The UITN has already begun a randomized, controlled clinical trial comparing two surgical treatments for stress and mixed incontinence--the "Stress Incontinence Surgical Treatment Efficacy Results (SISTER)" trial. A second clinical trial planned by the UITN is focused on treating women with pure or predominantly urge incontinence. This trial, the "Behavior Enhances Drug Reduction of Incontinence (BE-DRI)" trial, will compare effects of two interventions, drug therapy alone and combination drug therapy and behavioral treatment, on the frequency of urinary incontinence and success in withdrawing patients from drug therapy. This trial is currently enrolling patients, with anticipated complete enrollment in mid-2005. The NIDDK has also partnered with the NIH ORWH to support an interdisciplinary Specialized Center of Research on Sex and Gender Factors Affecting Women's Health that is conducting basic and clinical studies on urinary incontinence. Recognizing that urinary incontinence and other urologic health problems that affect primarily women constitute an enormous public health burden, the Institute continues to strengthen its basic and clinical research portfolios in these areas, including through its current national search to recruit an individual with appropriate expertise to foster scientific and science-based education programs in these areas, either a urologist or urogynecologist. Regarding the establishment of a dedicated study section for urogynecology, decisions regarding study section formation are the responsibility of the NIH Center for Scientific Review.

Item

Urology Research – The Committee commends NIDDK's release of the first report on the burden of urologic disease through its "Urologic Diseases in America" project, with a final compendium due out in 2006. The Committee urges NIDDK to allocate resources to ensure that updated reports are sustained in the future and to provide a report on the plan for this activity. The Committee is pleased that NIDDK has recognized the interconnection between obesity and diabetes and urologic disorders as shown by the December 2003 NIDDK meeting "Urologic Complications of Diabetes" and the NIDDK Bladder Research Review Group document "Overcoming Bladder Disorders: A Strategic Plan for Research" that dedicated an entire section to the urologic problems associated with diabetes and obesity. The Review Group specifically addressed research goals including programs to assess the effect of obesity on genitourinary tract function and to clarify the biologic mechanisms for bladder and urethral dysfunction in diabetes. The Committee encourages NIDDK to ensure that the NIH Obesity Research Task Force includes adequate resources for research addressing often-overlooked urologic problems

associated with diabetes and obesity. In particular, the Committee recommends that the Urinary Incontinence Treatment Network continue observational and interventional trials in the area of incontinence associated with obesity and diabetes. (p. 115)

Action Taken or to be Taken

The NIDDK appreciates the Committee's continued interest in issues surrounding urology research and the impact of urological disorders on all Americans. The NIDDK supports a broad spectrum of research efforts in urology, from basic research to clinical trials. Planning efforts are under way for research initiatives in FY 2005 and beyond. 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.

The NIDDK appreciates the Committee's commendation regarding the UDA interim compendium. This important project is closing many of the former gaps in knowledge about the prevalence, incidence, treatment, and economic impact of urologic disease in the U.S. The interim presentation covers urolithiasis, benign prostatic hyperplasia, urinary incontinence, urinary tract infection, and sexually transmitted diseases. The full report will include pre-natal hydronephrosis, male reproductive health, urethral diseases, interstitial cystitis, chronic prostatitis, and cancers of the prostate, bladder, kidney, and testis. The UDA project has an External Consulting and Advisory Committee (ECAC). NIDDK plans to solicit advice from the ECAC as well as other representatives from the urological community concerning plans for follow-up activities after the completion of the UDA.

Regarding urologic health and obesity, the NIDDK and the NIH Obesity Research Task Force recognize the importance of obesity and/or diabetes in contributing to urologic problems, including urinary incontinence. Several research efforts are addressing these health problems. For example, the newly-funded Program to Reduce Incontinence by Diet and Exercise (PRIDE) will evaluate the impact of weight loss, resulting from a behavioral program, on urinary incontinence in overweight and obese women. Assessment of urinary incontinence is part of the NIDDK-sponsored Look AHEAD multi-center clinical trial; Look AHEAD is evaluating the long-term health effects of weight loss from physical activity and reduced caloric intake in obese adults with type 2 diabetes. New results from the Diabetes Prevention Program (DPP) multi-center clinical trial also address urinary incontinence. The DPP had demonstrated dramatically reduced risk of type 2 diabetes as a result of a lifestyle intervention of modest weight loss and exercise; the drug metformin also reduced risk. Further analysis has now shown that prevalence of stress urinary incontinence was substantially reduced among women with impaired glucose tolerance (blood glucose levels that are high but not yet diabetic) who were assigned to the DPP's lifestyle intervention. Urinary incontinence is also a component of the follow-on Diabetes Prevention Program Outcomes Study. In another effort, the Urinary Incontinence Treatment Network is collecting data on body weight and diabetes, and this information could thus serve as a resource for ancillary studies related to obesity and diabetes. Urologic complications may also be associated with type 1 diabetes, and research in this area is a component of the NIDDK-supported Epidemiology of Diabetes Interventions and Complications study (EDIC).

Item

Urology Research – The Committee urges the NIDDK to provide to the Committee the reports for the urology Interagency Coordinating Committee meetings for the past 5 years and the collaborative initiatives that have resulted from these meetings, and to provide the plan for the next year on collaborative Interagency and Interinstitute urology research. In particular, treatment for prostate cancer is associated with significant incidence of urinary incontinence and erectile dysfunction that severely affect quality of life. NIDDK is urged to cooperate with the National Cancer Institute on studies of the cause, prevention, and treatment of urinary incontinence and erectile dysfunction after treatment for prostate cancers. Incidence of urologic disorders increases with aging; for example, urinary incontinence is one of the leading causes of admission to nursing homes. NIDDK is urged to work with the National Institute on Aging to develop a comprehensive cooperative program to address these costly and pervasive urology health issues related to aging. In this regard, the Committee is pleased to learn that NIDDK leadership has taken steps to enhance integration of urologic diseases in initiatives within NIDDK and between and across the NIH, and urges continuation of these activities. A recently-appointed NIDDK Senior Advisor for Urology is working to coordinate urology research activities across the NIH. (p. 115)

Action Taken or to be Taken

The NIDDK has developed many fruitful collaborations with other NIH Institutes that have urologic diseases within their purview, including the National Cancer Institute (NCI) and the National Institute on Aging (NIA). Collaborations also extend beyond the NIH through interactions developed through the NIDDK's leadership of the Urology Interagency Coordinating Committee (UICC), which is a subcommittee of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee (KUHICC). Due to their length, the requested reports for the UICC meetings for the past 5 years, which describe these interactions and the collaborative initiatives that have grown out of them, will be provided to the Committee under separate cover, accompanied by a transmittal letter that will also outline collaborative plans for the future. Examples of important activities that have been fostered by the UICC include the work of the Bladder Research Progress Review Group, which was a collaborative effort that grew out of discussions by the UICC. Similar discussions have also led to several NIDDK initiatives, such as the NIDDK's development and adoption of modified review criteria for career development awards (K08 and K23 awards) for urologic surgeons who pursue basic and patient-oriented research. These criteria are meant to address the difficulties faced by these investigators in balancing required time commitments for research and for surgical training, and to thereby enhance their competitiveness for the "K" awards. (A Notice to this effect was published in April 2003 and is available on the internet at http://grants.nih.gov/grants/guide/notice-files/NOT-DK-03-004.html.) The NIDDK is now working with the NCI to expand this "K" program for urologic surgeons to include urologic cancer researchers. The UICC has also fostered progress in pediatric urology by complementing the work of the Vesicoureteral Reflux (VUR) Task Force to assess opportunities for clinical trials for treating this disease--now being addressed by NIDDK in a clinical trial initiative. Finally, the UICC has also conferred over advances and opportunities in regenerative medicine for urologic diseases. The committee members have reviewed and discussed up-to-date experimental

findings in the application of adult stem and progenitor cells and tissue engineering to bladder regeneration and replacement--areas of scientific opportunity for which the NIDDK is providing increased support.

Regarding studies of the cause, prevention, and treatment of urinary incontinence and erectile dysfunction after treatment for prostate cancers, the NIDDK maintains a strong basic and clinical research portfolio devoted to understanding the development, function, and innervation of the bladder, prostate, and other tissues and organs of the genitourinary tract. The fundamental understanding of these tissues and their reaction to or recovery from trauma such as that suffered in surgical treatments for prostate disease, including prostate cancer, is key to advancing the ability to prevent or treat such potential complications as urinary incontinence and erectile dysfunction. The NIDDK maintains strong collaborations with NCI in this area. The NCI, along with the National Institute of Child Health and Human Development, is co-sponsoring an NIDDK Program Announcement (PA) to encourage research projects that would develop cell-selective tools to study the prostate and other organs of the lower urinary tract. Moreover, through its continued co-sponsorship with the NIDDK of the George M. O'Brien Urology Research Centers program, the NCI has provided collaborative support for multidisciplinary research and exploratory studies relevant to prostate biology and prostate cancer. This program was competitively renewed in FY 2003, and the NCI is providing support for two of the five funded Centers.

The NIDDK also continues to collaborate with NIA for work on urologic health issues associated with aging in both men and women. For example, 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 PA is inviting research applications to address biologic mechanisms related to aging processes that underlie the initiation and progression of prostate growth processes in middle-age, and the pathophysiologic connections of those growth processes with the prostate diseases prevalent in older men--BPH and prostate cancer.

Item

Urology Research – The Committee is impressed with the results produced by the George M. O'Brien urology research centers that bring together a critical mass of scientists who focus on urologic disease. The Committee recommends that NIDDK ensure adequate support to enhance the successes and to provide for collaboration among these centers. (p. 115)

Action Taken or to be Taken

Please refer to page 68 of this document for the NIDDK's response to this significant item regarding the George M. O'Brien Centers ("Urology Research-- The Committee urges the NIDDK to provide to the Committee…")

Item

Urology Research – Prostate diseases are highly prevalent and poorly understood. 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. In particular, the current efforts to develop biomarkers for benign prostate diseases should be expanded. (p. 116)

Action Taken or to be Taken

Please refer to pages 63-64 of this document for NIDDK's response to this significant item regarding prostate diseases, including prostatitis and benign prostatic hyperplasia, and biomarker development.

Item

Urology Research – The Committee is concerned about the continuing world-wide HIV epidemic. HIV is readily transmitted through sexual contact, yet little work is being done to examine the specific role of semen in this transmission. The Committee believes that a better understanding of these fundamental issues will contribute significantly to research for a vaccine and more effective treatments, and is pleased with the NIDDK's recent initiative to encourage basic and clinical research studies that will elucidate the factors that determine HIV release in the male genital tract. The Committee urges the Institute to continue enhancing its grant portfolio on the role of semen in HIV transmission. (p. 116)

Action Taken or to be Taken

The transmission of the human immunodeficiency virus (HIV) in semen is one the major factors in the progression of the AIDS epidemic. However, several aspects of the biology of HIV in semen are still unclear--including the relationship between systemic host factors, the immunology of the male urogenital tract, and levels of potentially infectious HIV in the semen. The anatomical origins and sources of HIV in the male genital tract have not been positively identified; neither have the effects of therapeutic interventions, specifically antiviral therapies, on HIV infectivity and transmission in semen. To address these knowledge gaps, the NIDDK, in collaboration with NICHD, issued a Program Announcement (PA), "Transmission of Human Immunodeficiency Virus (HIV) in Semen." This PA encourages basic and clinical research studies that will elucidate the factors that determine HIV shedding (release) in the male genital tract. Active until June 2006, this PA is intended to attract new investigators with diverse expertise into the field, thereby increasing opportunities for interdisciplinary research and enhancing the scope and effectiveness of research in this area.

Item

Urology Research – The Committee remains concerned with the lack of research dedicated to pediatric urologic conditions. According to the NIDDK Bladder Research Review Group

document “Overcoming Bladder Disorders: A Strategic Plan for Research,” the gaps and requirements for pediatric disease research remain substantial, particularly for conditions such as vesicoureteral reflux and bladder dysfunction. The Committee urges NIDDK to commit the necessary resources to expand research on pediatric urologic conditions, which may in turn provide additional insight into adult urologic problems. (p. 116)

Action Taken or to be Taken

Please refer to page 62 of this document for NIDDK’s response to this significant item regarding pediatric urologic conditions, including vesicoureteral reflux.

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

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,808,879,000	Indefinite	$1,816,240,000
Digestive and Kidney Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	54,705,000		55,906,000
Total, Budget Authority				1,863,584,000		1,872,146,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

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/
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/, 3/	951,203,000	994,218,000	1,021,218,000 4/
Rescission	0	0	0	(659,000)
2000	1,002,747,000 2/	1,087,455,000	1,130,056,000	1,174,588,000 5/
Rescission				(6,112,000)
2001	1,186,266,000 2/	1,315,530,000	1,318,106,000	1,470,385,000 6/
Rescission				(429,000)
2002	1,457,915,000 2/	1,446,705,000	1,501,476,000	1,563,833,000 7/
Rescission				(453,000)
2003	1,706,292,000 2/	1,731,754,000	1,731,754,000	1,733,347,000 8/, 11/
Rescission				(10,617,000)
2004	1,820,000,000	1,820,007,000	1,833,007,000	1,821,240,000 9/, 11/
Rescission				(10,654,000)
2005	1,877,696,000	1,876,196,000	1,889,100,000	1,863,584,000 10/, 11/
Rescission				(14,112,000)
2006	1,872,146,000 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/ Reflects a decrease of $2,790,000 for the budget amendment for bioterrorism.
4/ Excludes enacted administrative reductions of $659,000.
5/ Excludes enacted administrative reductions of $6,112,000.
6/ Excludes enacted administrative reductions of $429,000.
7/ Excludes enacted administrative reductions of $453,000.
8/ Excludes enacted administrative reductions of $10,617,000.
9/ Excludes enacted administrative reductions of $10,654,000.
10/ Excludes enacted administrative reductions of $14,112,000.
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 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	60	61	56
Division of Diabetes, Endocrinology and Metabolic Diseases	21	28	29
Division of Digestive Diseases and Nutrition	15	18	23
Division of Kidney, Urologic and Hematologic Diseases	15	20	24
Division of Nutrition Research Coordination	8	8	8
Division of Extramural Activities	44	40	35
Division of Intramural Research	417	449	449
Total	580	624	624
FTEs supported by funds from Cooperative Research and Development Agreements	(4)	(4)	(4)

FISCAL YEAR	Average GM/GS Grade
2002	12.8
2003	11.0
2004	11.3
2005	11.4
2006	11.4

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

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	0	0	0
Total - ES Salary	$0	$0	$0
GM/GS-15	40	39	39
GM/GS-14	52	52	52
GM/GS-13	59	60	60
GS-12	52	55	55
GS-11	47	49	49
GS-10	2	2	2
GS-9	22	36	36
GS-8	27	29	29
GS-7	11	29	29
GS-6	3	5	5
GS-5	8	10	10
GS-4	1	1	1
GS-3	2	3	3
GS-2	0	0	0
GS-1	3	3	3
Subtotal	329	373	373
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	9	9	9
Director Grade	6	6	6
Senior Grade	2	2	2
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	17	17	17
Ungraded	240	278	278
Total permanent positions	363	373	373
Total positions, end of year	624	624	624
Total full-time equivalent (FTE) employment,end of year	580	624	624
Average ES salary	$0	$0	$0
Average GM/GS grade	11.3	11.4	11.4
Average GM/GS salary	$72,870	$74,837	$76,858