DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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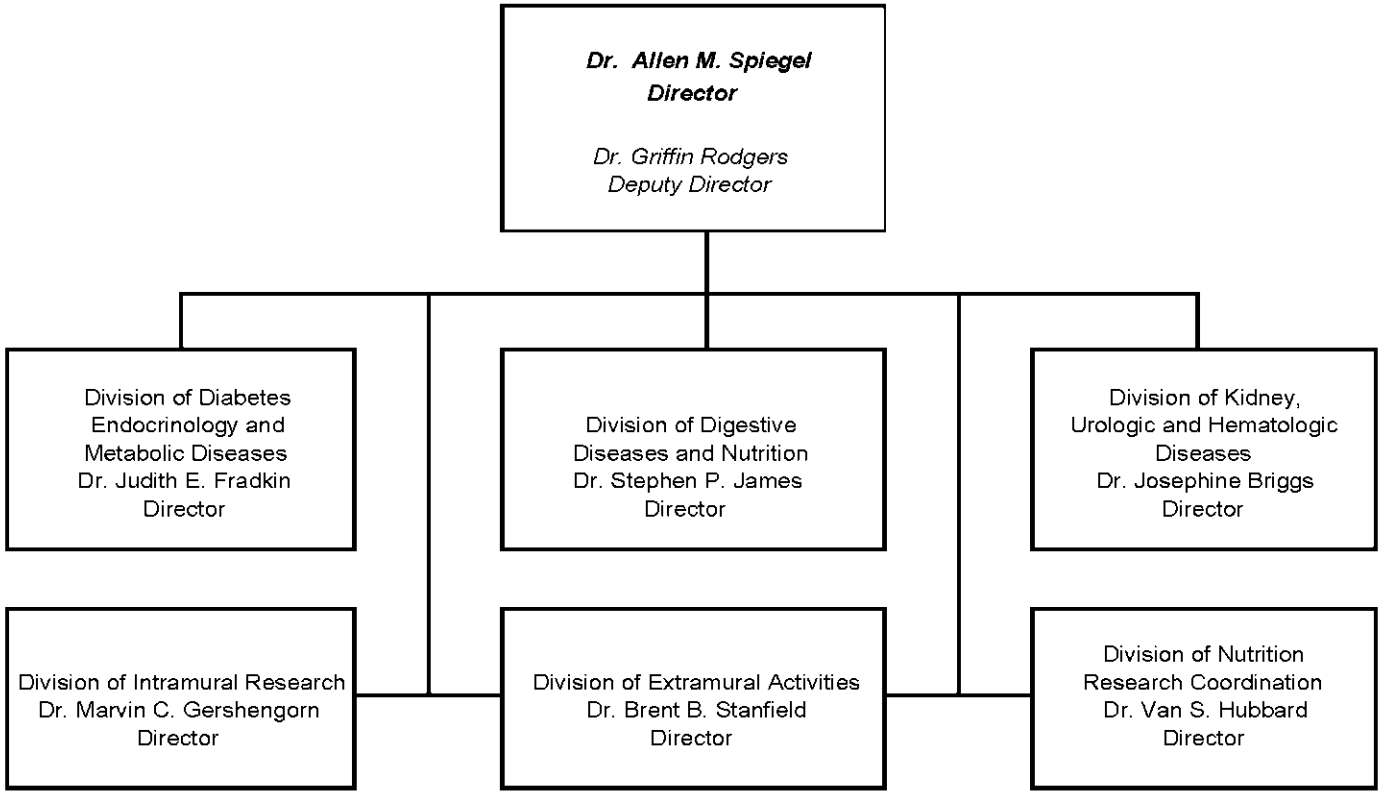
Organization Structure



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, [$1,722,146,000] *$1,694,298,000.*

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2006, as enacted by Public Law (109-149)]

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$1,727,696,000	$1,722,146,000	$1,694,298,000
Type 1 Diabetes 2/	$150,000,000	$150,000,000	$150,000,000
Enacted Rescissions	(14,112,000)	(17,221,000)	0
Subtotal, Adjusted Appropriation	1,863,584,000	1,854,925,000	1,844,298,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(10,833,000)	(15,236,000)	0
Comparative transfer from OD for NIH Roadmap	10,833,000	15,236,000	0
Subtotal, adjusted budget authority	1,863,584,000	1,854,925,000	1,844,298,000
Unobligated balance lapsing	(159,000)	0	0
Total obligations	1,863,425,000	1,854,925,000	1,844,298,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $10,494,000 FY 2006 - $12,750,000 FY 2007 - $12,950,000
Excludes $4,500,000 in FY 2006 and $5,000,000 in FY 2007 for royalties.

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

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
625	$1,863,584,000	640	$1,854,925,000	643	$1,844,298,000	3	(10,627,000)
Type 1 Diabetes:							
	-150,000,000		-150,000,000		-150,000,000		
Labor/HHS	1,713,584,000		1,704,925,000		1,694,298,000		

This document provides justification for the Fiscal Year 2007 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 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

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 translating new knowledge of biologic processes into appropriate clinical studies, and ultimately, to efforts to bring medical discoveries to bear on improved health care, with special emphasis on populations disproportionately affected by diseases within the NIDDK mission.

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

Diabetes, Endocrine and Metabolic Diseases

Insulin as an Autoantigen in Type 1 Diabetes—Recent exciting reports have suggested that the hormone insulin may be the critical initiator of the autoimmune destruction of insulin-producing pancreatic beta cells that leads to type 1 diabetes. Patients with the disease are known to have antibodies directed against insulin, and these antibodies are used to identify individuals at risk for the disease. However, it has been unclear whether insulin itself is the "key" autoantigen that triggers the autoimmune attack. Two new lines of evidence have now emerged—one in a genetically engineered mouse model of diabetes and the other using isolated T-cells (a type of cell in the immune system) from pancreatic lymph nodes of people with and without type 1 diabetes. A type 1 diabetes mouse model engineered to express an insulin molecule not recognized by the mouse's immune system did not develop diabetes. Moreover, T-cells from the lymph nodes of people with type 1 diabetes had large numbers of cells that recognized insulin, but those from non-diabetic persons did not. This research suggests that the immune systems of patients who are susceptible to developing type 1 diabetes do not respond appropriately to insulin—a generally beneficial hormone that all humans naturally produce. This derangement in recognizing insulin may provoke the immune system's misguided destruction of the body's own insulin-producing cells.

Gene Expression Changes Associated with Type 2 Diabetes—Although key aspects of the underlying disease process in type 2 diabetes are different from type 1 diabetes, both forms of the disease have in common a dysfunction of the insulin-producing beta cells of the pancreas. In advanced type 2 diabetes, it is not well understood how beta cells lose their ability to secrete insulin in response to high blood sugar (glucose) levels. To study the molecular mechanisms, scientists compared gene expression patterns in pancreatic islets—where beta cells reside—from people with type 2 diabetes and from those with normal blood glucose control. They observed a marked decrease in expression of a gene called ARNT (or HIF1β) in patients with type 2 diabetes. ARNT encodes a transcription factor, a protein that can regulate the expression of many other genes. In cultured islet cells and a mouse model, diminished expression of ARNT or its absence in pancreatic islets resulted in defects in glucose-dependent insulin release and changes in gene expression patterns similar to those seen in patients with type 2 diabetes. ARNT controls many genes involved in diabetes, and these observations suggest a key integrating role for ARNT/HIF1β in the beta cell dysfunction that is associated with human type 2 diabetes.

A Novel Genetic Link Between Cardiovascular Disease Risk Factors and the Cell's Energy-Generating Machinery—Many people have high blood pressure along with high cholesterol, but it hasn't been clear why there is often a combination in some individuals of these metabolic

defects, which are serious risk factors for cardiovascular disease. Scientists recently discovered a genetic cause for the clustering of these and other metabolic defects by studying a large family in which many members suffer from high blood pressure and high cholesterol, along with abnormal blood magnesium levels. The scientists traced these medical conditions to a DNA mutation in affected family members, but this mutation was in an unusual place: the cellular mitochondria. While most of a cell's DNA is in the cell nucleus, a small amount is harbored by the mitochondria, which are the cell's energy-generators, providing the necessary fuel for biological processes. The initial clue as to the nature of the mutation came from the fact that the family members seemed to inherit this trait only from their mothers. Because mitochondria are passed on from one generation to the next only by mothers, the researchers homed in on mitochondrial DNA, and subsequent analyses revealed the likely causative mutation. This finding builds upon earlier hints of a possible link between mitochondrial defects and high blood pressure, and adds a further dimension to previous research suggesting a role for mitochondrial defects in other serious metabolic conditions: insulin resistance and type 2 diabetes. This research has several implications for metabolic diseases. First, although the particular mutation in the family examined in this study is rare, the loss of mitochondrial function is known to occur with aging. Thus, either aging-related or other mitochondrial defects may contribute to the clustering of high blood pressure and high cholesterol seen in the general population. Further investigation would help address this possibility. Second, and importantly, this insight into a potential cause of common metabolic problems may spur new ideas for therapeutic approaches.

Story of Discovery: Glucagon-like Peptides

By deciphering how the body maintains normal blood sugar levels, researchers are finding clues to combat diabetes. In healthy individuals. the beta cells of the pancreas respond to elevated levels of sugar in the blood by releasing insulin. and the insulin, in turn, causes cells to absorb sugar. The pancreas reacts to low levels of blood sugar, on the other hand. by releasing glucagon from its alpha cells, triggering the liver to release part of its store of sugar into the blood. These are crucial steps in normal metabolism. In diabetes, this exquisite regulation is disturbed either by loss of cells that produce insulin (type 1 diabetes) or by inadequate amounts of insulin to compensate for diminished responsiveness of cells to the hormone—mostly in muscle and fat (type 2 diabetes).

This fairly simple paradigm is by no means the whole story. however. In the 1960s. researchers showed that sugar triggers more insulin to be released if the sugar is absorbed through the digestive system rather than injected directly into the blood. The underlying reasons were a mystery, but scientists speculated that the presence of sugar or other food in the gut might trigger the release of some hormone that increases the pancreatic insulin response. The putative insulin production-promoting hormone or hormones were called "incretins." A vital clue to the incretin mystery was uncovered in 1982 by Dr. Joel Habener and colleagues when they cloned the gene that encodes the glucagon protein. Inspection of the gene revealed that it also encodes two other proteins similar, but not identical. to glucagon. These were called "glucagon-like peptides," or GLPs. The NIDDK-supported researchers later demonstrated that a truncated form of one of these. GLP-1, was able to act as an incretin: pancreatic beta cells release more insulin in response to sugar in the presence of GLP-1 than in its absence. Thus "Glucagon-Like Peptide 1" actually has effects somewhat opposite to those of glucagon, in that it helps to lower blood sugar. As expected for an incretin, GLP-1 is produced by intestinal cells when stimulated by the presence of food. In addition to its effect on promoting the insulin response, GLP-1 also has the important effect of slowing stomach emptying, essentially helping a person "feel full." More recently, mounting evidence suggests that GLP-1 can stimulate the multiplication of insulin-producing beta cells, while simultaneously protecting them from so-called "programmed cell death."

Properties of GLP-1 suggested that it might be of potential therapeutic benefit for some people with type 2 diabetes. By boosting their natural insulin secretion in response to food, GLP-1 could reduce their need for injected insulin or other therapies. Unfortunately, scientists soon discovered a major potential barrier to this approach: GLP-1 lasts

only a very short time in the blood stream before it is digested by an enzyme called dipeptidyl peptidase IV (DPP IV). A solution to this problem was found in the unlikeliest of places: the venom of a lizard native to the Sonora desert. At about the same time that the glucagon-like peptides were being discovered by NIDDK grantees, NIDDK intramural scientists studying the so-called "Gila monster" discovered that proteins in the lizard's venom stimulate the release of digestive enzymes by cells of the pancreas. Because the reptile typically goes months between meals, these proteins may serve to "jump-start" its digestive system when it feeds. Among the proteins isolated from the venom was one, designated exendin-4, with considerable similarity to GLP-1. Scientists showed that exendin-4 and GLP-1 are both capable of stimulating gastric secretions in guinea pigs, though exendin-4 is the more potent of the two. Indeed, two labs have independently demonstrated that both proteins work by stimulating the same cellular receptor. Furthermore, exendin-4 is not digested by DPP IV, and therefore can last much longer in the blood than GLP-1.

The discovery and characterization of the GLPs and of exendin-4 are the fruits of basic research, much of which was funded by NIDDK. Based upon this critical foundation, pharmaceutical companies have developed an important new treatment for patients with type 2 diabetes. A synthetic version of exendin-4 (the manufactured form is referred to as "exenatide," but is chemically identical to exendin-4) was recently tested for therapeutic benefit in industry-supported randomized controlled clinical trials. . The studies enrolled patients with type 2 diabetes whose blood sugar was inadequately controlled. Patients then received either standard treatment or standard treatment plus a high or low dose of exenatide. At the conclusion of the studies, those patients who had received exenatide were found to have maintained significantly healthier levels of blood sugar. and those receiving the high dose of the new drug had done better than those with the low dose. Another exciting finding was that the patients who had received exenatide lost weight compared to the control group. A possible explanation for the latter finding is the effect that GLP-1/exendin-4/exenatide have on slowing stomach emptying and creating a sense of fullness. This result is particularly important because type 2 diabetes is associated with overweight and obesity. Again. those receiving the higher dose of exenatide achieved the better result, losing more weight. In April. 2005. the Food and Drug Administration approved exenatide as a supplementary treatment for type 2 diabetes in patients whose blood sugar is not otherwise well-controlled.

Scientists are eager to explore potential benefits of exenatide in treating or preventing type 1 diabetes. This disease results when a person's immune system attacks and destroys his or her own insulin-producing pancreatic beta cells. The landmark NIDDK-sponsored Diabetes Control and Complications Trial (DCCT) had demonstrated that a significant percentage of people with type 1 diabetes retain the capacity to produce a small amount of their own insulin. This finding suggests that, in some patients at least. the process of autoimmune beta cell destruction may be modestly offset by beta cell regeneration. NIDDK intramural researchers Drs. David Harlan and Kristina Rother are currently testing whether exenatide can help capitalize on the presumed natural regenerative capability in patients who, although they have had type 1 diabetes for several years. still produce some insulin. Study volunteers are receiving exenatide either alone or in combination with an immunosuppressive drug designed to blunt the continuing autoimmune attack on their beta cells. Researchers in the newly formed Clinical Islet Transplantation Consortium plan to test the value of exenatide in enhancing the viability of transplanted islets and the Type 1 Diabetes TrialNet is considering studies to assess the potential of exenatide to prevent or delay onset of type 1 diabetes in patients with autoimmunity directed at the beta cell, but who have not yet developed symptoms of the disease. These impressive research advances have rapidly taken a newly discovered protein from the laboratory to an approved drug. Further studies unfolding in this field may extend the clinical utility of this new class of therapeutics.

DPP Continues To Underscore the Benefits of Preventing Type 2 Diabetes—Additional analyses of data from a landmark clinical trial have revealed more detailed information about the impact of the interventions. Researchers are continuing to gain new insights from the Diabetes Prevention Program (DPP) clinical trial, which examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk for this disease. The DPP compared intensive lifestyle modification, treatment with the drug metformin, and standard medical advice. Published in 2002, the DPP results showed that participants who received the lifestyle intervention had a dramatically reduced risk—by 58 percent—of developing type 2 diabetes. Metformin reduced diabetes risk by 31 percent. New data analyses show that

hypertension, a classic risk factor for cardiovascular disease, was present in about 30 percent of all participants at the beginning of the study, and increased in the patients who received either placebo or metformin. However, hypertension significantly decreased in the lifestyle intervention group. Levels of recently-identified, non-traditional risk factors for cardiovascular disease—such as C-reactive protein and fibrinogen—were lower in the metformin and lifestyle groups, with a larger reduction seen in the lifestyle group. About half of all DPP participants had a condition known as the "metabolic syndrome," which is defined by the presence several conditions that increase risk for the development of type 2 diabetes and cardiovascular disease. Both lifestyle modification and metformin therapy reduced the development of the metabolic syndrome, with lifestyle modification more effective. Years later, the DPP continues to yield important insights into the prevention of type 2 diabetes in at-risk people.

Potential Source of Islet Cells for Future Cell Therapies—Studies by intramural scientists may discover ways to increase the supply of cells that could be transplanted into patients with type 1 diabetes to restore their insulin-producing capacity. The scientists have induced human insulin-producing beta cells, found in clusters called islets in the pancreas, to revert to islet precursor cells, proliferate, and then differentiate into islet-like cells again. The researchers first removed islets from human cadaver pancreata, and exposed them to a medium containing animal serum. Over time, cells migrated out until the original islets were depleted. These migrating islet cells, identified as insulin-expressing cells, then turned into more primitive precursor cells that do not produce insulin. The new cells, called human islet-derived precursor cells, reproduce easily to form many more cells. They also appear to naturally and efficiently differentiate into clusters of islet-like cells when subsequently exposed to a serum-free medium. The differentiated cells produce much less insulin than the original cells, but do show many of the characteristics of the original cells. While these cells appear to be different from stem cells, the scientists noted that their studies do not preclude the possibility that adult islet stem cells may exist. In the future, the researchers hope to define the optimal environmental conditions to grow precursor cells and to stimulate them to differentiate into hormone-producing cells. Their goal is to design a cellular environment as close as possible to the natural environment of a healthy human pancreas. Another challenge is to develop a culture medium that does not rely on animal serum, so cells grown in the laboratory could be transplanted back into people with a minimum risk of side effects. Because of the relatively small number of cadaveric donor pancreata available for obtaining insulin-producing cells for transplantation, it is critically important to develop new sources of islets for clinical research and for potential future use in medical practice.

Link Found between a Saturated Fat Diet and Unhealthy Blood Fat—Researchers are uncovering the metabolic pathways that link several health problems. For example, elevated levels of fat and cholesterol in the blood are significant known risk factors for cardiovascular disease (CVD). Similarly, diets high in saturated and *trans* fats are strongly associated with high levels of fats and LDL cholesterol ("bad" cholesterol) in the blood. In studying these types of associated health problems, scientists recently discovered a link between a diet high in saturated fat; changes in gene expression in the liver; and levels of fat and cholesterol in blood. In mice fed large amounts of saturated fat, they noted increased expression of a set of genes involved in fat synthesis in the liver, including one that augments the expression of many genes involved in fat metabolism, PGC-1β. The protein encoded by this gene works with members of a family of other genes (SREBP transcription factors) to help regulate fat synthesis in the liver. The PGC-1β gene also influences the activity of a nuclear hormone receptor in the liver (LXR), which is

involved in lipid and cholesterol metabolism. A treatment to boost the PGC-1β-regulated protein in the livers of rats was found to reduce fat levels in liver, but to raise them in the blood, thereby suggesting that the protein activates pathways leading to fat export. The PGC-1β gene therefore seems to lie at the nexus of two important pathways of fat metabolism in the liver: fat synthesis and export. These studies suggest that the PGC-1β gene may be a good target for novel therapies aimed at reducing elevated circulating fat levels that arise from diets high in saturated fats.

Newly-discovered Links between Inflammation and Mediators of Metabolism — In recent years, researchers have uncovered intriguing links between the molecular mediators of inflammation and a number of human diseases. The enzyme IKKβ is a central coordinator of inflammatory responses through its activation of the transcription factor NF-κB. Researchers studying severe muscle wasting that is often seen in AIDS, diabetes, and end-stage heart and kidney diseases engineered mice that had a constitutively active form of IKKβ in their skeletal muscle. These mice developed severe wasting, and inhibition of NF-κB activity could partially reverse this condition. Mice with the "always on" form of IKKβ in their livers developed symptoms similar to type 2 diabetes, with high blood sugar, severe insulin resistance in their livers, and moderate insulin resistance in muscle; drugs that block IKKβ and NF-κB activity were able to ameliorate these complications. In another study, mice were engineered to lack IKKβ in either their livers or in myeloid cells, a type of white blood cell. In response to a high fat diet or obesity, mice lacking IKKβ in their livers retained insulin sensitivity in this organ, but developed insulin resistance in muscle and fat. In contrast, mice lacking IKKβ in their myeloid cells retained global insulin sensitivity under the same conditions. These observations suggest that IKKβ acts locally in liver cells but systemically through myeloid cells to influence insulin sensitivity. Taken together, these results identify IKKβ as a key player in modulating metabolism and insulin sensitivity. These studies also provide evidence that IKKβ-mediated inflammation links obesity to insulin resistance. Drugs that target the inflammatory signaling pathway may be useful in treating both muscle wasting and insulin resistance.

Digestive Diseases

A New Model System To Study Hepatitis C—Hepatitis C virus (HCV) is a major cause of liver disease worldwide. Current therapies for HCV are not optimally effective and a vaccine is not yet available to prevent the disease. Clinical progress has been hampered because the virus grows poorly in culture and does not produce infectious viral particles. To solve this research problem, scientists recently designed a molecular HCV replication system that is capable of producing viral particles *in vitro*. HCV was detectable inside of the cells and mature viral particles in the culture medium. These particles were able to infect cultured cells and an animal model of HCV. With this advance, researchers will be better able to study the life cycle and biology of this virus, and to test antiviral compounds as potential therapies for the liver disease it causes.

Molecular Factors Underlying Liver Development—Understanding how a single fertilized egg develops into a complex, multicellular organism is one of the most fascinating questions in all biology. Scientists studying liver development have found that the *Foxa1* and *Foxa2* genes play an important role in the developing liver. It is thought that embryonic liver development proceeds in a two-stage process whereby factors first make the tissue "competent" to respond to

subsequent organ-specific signals that direct tissue differentiation into specific organs. To explore this area, investigators derived a strain of mice lacking the *Foxa1* gene entirely and lacking the *Foxa2* gene in endoderm—the embryonic tissue that gives rise to the liver. Embryos in which these genes were made non-functional (knocked out) were smaller than normal counterparts and failed to develop an embryonic liver. When normal mouse endoderm is grown in culture in the presence of certain growth factors, the tissue begins to express proteins characteristic of mature liver. In contrast, endoderm from *Foxa1/Foxa2* knockout embryos grown under these conditions did not express liver-specific proteins, suggesting that this tissue is not able to respond to the growth factors. This observation suggests that the proteins encoded by *Foxa1* and *Foxa2* genes act early in liver differentiation as competence factors that render the tissue able to respond to subsequent signals. This experimental system may be very useful in the study of organ development, because the endoderm gives rise to many tissues, including the gut, pancreas, thyroid, and lungs.

Story of Discovery: Combating Toxic Iron Overload

Most people know that iron is essential for good health. What people may be surprised to learn is that too much iron—a condition called iron overload—can actually threaten health by damaging tissues and organs. Iron overload occurs in diseases such as hemochromatosis and Cooley's anemia. Although these conditions have different causes, they both involve the accumulation of excess iron, which is stored in the heart and/or liver. This excess iron can damage these organs so that they no longer work properly. Unfortunately, the human body does not have a natural way to rid itself of excess iron. To address these problems, NIH-funded research is providing insights regarding the regulation of iron metabolism and methods for removing toxic excess iron.

In hemochromatosis, genetic mutations alter control mechanisms that would otherwise precisely regulate iron absorption. The standard therapy for treating this condition is blood-letting (phlebotomy), which is equivalent to blood donation and is a relatively simple means of restoring normal iron stores in the body. However, research into the genetic basis of the disease could provide a platform for developing more effective treatments and prevention strategies. For example, a genetic screen to identify those at risk for hemochromatosis could permit early intervention (by phlebotomy) to prevent progression to organ toxicity caused by iron overload.

A decade ago very little was known about the genes that harbor the disease-causing mutations in hemochromatosis and the proteins these genes encode. A major advance occurred when mutations in a gene called *"HFE"* were discovered to underlie the most common form of the disease in humans.

The discovery of variants of the *HFE* gene that lead to mutant proteins provided an opportunity for early and rapid genetic identification of individuals at risk for development of hereditary hemochromatosis. A majority of patients diagnosed with iron overload due to hereditary hemochromatosis have been found to have two copies of a mutant HFE gene referred to as "C282Y" (one mutant gene copy inherited from each parent); a second *HFE* mutation (H63D) has also been associated with hemochromatosis but only if it occurs in association with C282Y. To further explore the potential for population screening for common *HFE* mutations, NIDDK-supported researchers screened a large number of people for the presence of *HFE* mutations and associated symptoms of hemochromatosis. In the study, among the individuals found to have two copies of the C282Y mutation, many had elevated iron levels. Researchers also observed an increase in liver disorders seen in those with *HFE* mutations, but did not observe greater frequency of most other symptoms characteristically associated with hemochromatosis. In fact, most of the people with mutant *HFE* genes had not developed clinical symptoms and signs of organ toxicity, indicating that having the *HFE* mutations does not guarantee clinical symptoms. This study revealed that additional mutations or environmental factors contribute to hereditary hemochromatosis. In a more recent study of an even larger population, NIH-funded researchers found similar results. Their study also revealed that the C282Y mutation likely does not account for high iron levels seen in non-Caucasian populations; the C282Y mutation had previously been found to be more common in Caucasians than in other groups. These findings will likely spur new research to identify other genetic or environmental factors that influence the development of clinical symptoms of hemochromatosis.

Other insights into hemochromatosis emerged from studies showing the significance of hepcidin as a regulatory protein that controls iron balance in the body. These findings emerged from a series of seemingly unrelated studies in mice. One group of researchers found that mice fed a diet high in iron express in their livers high levels of *Hepc*, a gene encoding the antimicrobial peptide hepcidin. Other scientists made the fortuitous finding that iron overload develops in mice carrying a genetic mutation (in the *upstream stimulatory factor 2 gene, Usf2)*. Additional experiments indicated that these mutant mice have completely lost their ability to express the *Hepc* gene in the liver. A year later, this same group of scientists reported that forced overexpression of the *Hepc* gene in the liver of mice led to offspring with pale skin, anemia, and decreased body iron levels—with death frequently occurring within a few hours of birth. These mice thus displayed characteristics of an experimental form of iron deficiency. Collectively, these studies highlight the important role the liver plays in sensing excessive levels of iron.

But how does hepcidin—the protein product of the *Hepc* gene—regulate the level of iron that is transferred from the intestine into the circulation? NIH-supported scientists hypothesized and demonstrated that, by binding to and destroying an iron exporter (FPN1), hepcidin prevents the transfer of iron from the intestinal cell into the circulation. Hepcidin causes the iron to be retained in the intestine cell, and thus protects other tissues and organs from iron overload. In addition, it is now known that hemochromatosis patients carrying mutations in several different genes each have inappropriately low levels of hepcidin..

Another group of patients who face problems with iron overload are those affected with anemias, such as Cooley's anemia, which require lifelong blood transfusions as a treatment regimen. Transfusions provide anemia patients with desperately needed functional red blood cells that their bodies cannot make in sufficient quantity. However, there is a serious downside to this treatment. Because the transfusions provide iron-rich blood directly into the circulation, they by-pass the normal intestinal control of iron absorption. As a result, toxic levels of iron build up in blood and body tissues—producing symptoms similar to those of untreated hemochromatosis. To combat iron overload, the NIH has supported research to develop agents, known as iron chelators, to remove excess iron from the body. The standard chelator, deferoxamine, generally must be administered under the skin using a pump for 10 to 12 hours per day, 5 days per week. Although this intervention will extend life in chronic severe anemias, it is enormously time-consuming, inconvenient and painful for patients, especially young patients, who find compliance with this regimen extremely difficult and frustrating. A new oral chelator has recently come on the market, but it alone may not remove sufficient iron to prevent lifelong problems.

To improve treatment options for patients with chronic severe anemia, the NIH continues to seek new and better iron chelators. In animal tests, one new agent (HBED) has been shown to remove three times more iron than the standard chelator. Although this new chelator must be injected, researchers hope that treatment may be limited to one short injection two or three times a week, which would be less demanding on patients. Phase I clinical trials of this new chelator are under way, supported by the pharmaceutical industry. The NIH is also supporting the adaptation of magnetic resonance (MR) technology for the measurement of body iron. This noninvasive technique would be enormously helpful in monitoring the effectiveness of new iron chelating agents and in the possible refinement of therapeutic approaches aimed at achieving iron homeostasis in patients.

Multiple studies by many research teams have shed new light on the mechanisms by which iron is regulated with respect to absorption and movement throughout the body. These research findings are thus helping to lay the groundwork for more accurate means of screening for genetic hemochromatosis and better and safer treatment strategies for combating iron overload in patients with hemochromatosis or Cooley's anemia. The NIH will continue to propel the translation of these and other discoveries into improvements in patient care.

Insights into Crohn's Disease from Two New Mouse Models—Crohn's disease (CD) is a chronic inflammatory bowel disease thought to arise from a combination of genetic susceptibility and environmental factors. Previous studies have identified mutations in the *Nod2* gene as playing an important role in the development of CD in humans. To better clarify the role of *Nod2*, researchers have developed two new mouse models of the disease. One group of researchers generated mice lacking the *Nod2* gene entirely. The animals were resistant to infection from bacteria introduced intravenously, but were more susceptible than normal animals to infection resulting from orally-administered bacteria. This finding highlights the protective role *Nod2*

plays in fighting bacterial infection in the gut. Another group of researchers generated mice in which the normal *Nod2* gene was replaced with the most common mutant form seen in human CD. A chemical agent that damages the cells lining the intestine caused greater weight loss, increased mortality, and more severe colonic ulcerations in animals with the mutant *Nod2* gene than in normal animals. This ulceration could be minimized by the co-administration of antibiotics, suggesting that the increased damage resulted from interactions among the chemical, the bacteria present in the intestine, and the *Nod2* gene. Immune cells cultured from mice with the mutant *Nod2* gene showed increased production of a number of pro-inflammatory proteins including one of the interleukins (IL-1β). *Nod2* mutant mice treated concomitantly with an agent that blocks IL-1β activity and the chemical agent showed improvements with respect to weight maintenance and colonic ulcerations, compared to mutant animals not receiving the blocking agent. Together, these studies identify important new roles for *Nod2* in the development and progression of CD.

Important Insights into the Causes of Side Effects of Radiation Therapy—Scientists have recently shed new light on a very old treatment for cancer. Radiation therapy (sometimes called radiotherapy) was first used to treat cancer more than 100 years ago, and it remains a critical part of the treatment approach for almost half of cancer patients. Radiation kills living cells, but is particularly damaging to cells that divide frequently, such as cancer cells. However, the damage to other tissues caused by radiation therapy can limit the usefulness of the approach. Scientists have recently found evidence that the degree of radiation sensitivity in the intestine may be influenced in part by the trillions of bacteria that reside there. The researchers showed that mice raised in a germ-free environment are more resistant to the side effects of radiation than mice grown in the conventional way. Bacteria play a valuable role in the digestive process for all mammals, including people, but scientists are just beginning to appreciate the complex physiological interaction between animals and the bacteria that reside in their bodies. One effect the microbes have is that they decrease the expression level of a particular protein that may help protect against radiation. This finding raises the possibility that radiation therapy might be enhanced if physicians are able to either manipulate the microbial environment of the intestines or influence the expression level of this protein. Physicians may one day be able to reduce side-effects and improve survival in patients receiving radiation therapy.

Obesity and Nutrition

Possible Role for Non-Exercise Activity in Preventing Obesity—Scientists are gaining insights into factors that influence weight gain—a problem that is on the rise in America. Today 64 percent of U.S. adults age 20 and over are overweight or obese, with 30 percent meeting criteria for obesity.[1] Weight gain occurs whenever a person's energy intake exceeds his or her energy expenditure; however, it is challenging to tease out what distinguishes people who gain weight from those who do not. It is surprisingly difficult to precisely track every calorie a person consumes and every calorie he or she expends. Recent work has taken a major step in addressing the latter problem with a novel approach to assessing activity level. Researchers recruited 20 volunteers, 10 of whom were lean and 10 of whom were mildly obese, but all of whom were self-described "couch potatoes." For two weeks, the volunteers, who were wearing sensors that monitored their activity, followed their usual day-to-day activities and did not adopt any new exercise routines. During this time, the scientists collected data twice per second to determine

whether the volunteers were sitting, standing, or lying down. They found that the lean subjects stood and/or moved, on average, two hours longer per day than those in the obese group. This type of energy expenditure is called "non-exercise activity thermogenesis," or NEAT. Thus, an important factor in maintaining leanness appears to be the expenditure of energy through movements that are not a component of intentional exercise.

[1]National Center for Health Statistics, http://www.cdc.gov/nchs/fastats/overwt.htm.

Identification of Genetic Mutations Associated with Obesity and Risk for Type 2 Diabetes in Children and Adults—The complexity of the genetics of obesity and type 2 diabetes poses significant challenges to the identification of genes associated with these conditions, as variations in many genes likely contribute to susceptibility. Recently, a group of researchers used a genetic approach to identify a specific region of a human chromosome as the likely location of a gene associated with childhood obesity (chromosomes are the large genetic structures that contain genes). The researchers subsequently pinpointed mutations in a gene within this region as associated with both obesity and type 2 diabetes in children and adults. This gene, called *ENPP1*, was previously known to encode a protein that disrupts signaling by the hormone insulin; it does this by inhibiting actions of a critical cellular partner for insulin, the insulin receptor. Importantly, reduced responsiveness to insulin signaling (insulin resistance) can lead to type 2 diabetes. Further experimental analysis indicated that ENPP1 protein levels are higher in children with obesity-associated mutations in the *ENPP1* gene. The scientists also found that one form of the *ENPP1* gene is "turned on" specifically in cells with particular relevance to obesity and diabetes: fat cells, pancreatic beta cells (which produce insulin), and liver cells. This study suggests a genetic mechanism for the link between childhood obesity and the high risk of type 2 diabetes in adolescence and early adulthood, and may help in the search for additional predisposing genes. Furthermore, these findings present new opportunities for strategies to prevent and treat obesity and diabetes.

A Possible Role for Gut Bacteria in Fat Storage—While the underlying cause of obesity is excess energy intake compared to energy expenditure, genetic and environmental factors influence obesity as well. One factor is the presence of an enormous number of microorganisms in the digestive tract, known as the gut microbiota, which help break down the otherwise indigestible components of the diet. Researchers have proposed that differences in the microbes present in the digestive system play a role in fat storage. They studied the differences in the microbiota between normal mice and mice with a genetic mutation that makes them obese. They found that obesity changes the abundance of different microorganism populations residing in the intestine. In another study, introduction of gut microbiota from normal mice into mice raised in a germ-free environment initially increased the percentage of body fat in the formerly germ-free mice. The scientists then found that these mice also developed insulin resistance, a condition often associated with obesity and that can lead to the development of type 2 diabetes. The increase in body fat resulted from the influence of the microbiota on the metabolic rate and the production and storage of fatty acids in fat tissue of the mouse. Further investigation revealed that the presence of microorganisms in the intestine reduced the expression of a protein called Fiaf. Fiaf has previously been shown to block the uptake of fatty acids into fat tissue. From these studies, the scientists suggested that the gut microbiota is an important "environmental" factor that influences dietary energy acquisition and fat storage. Altering the microbial environment of the human digestive system may be useful for regulating energy intake. This research avenue may offer new opportunities for addressing the public health problem of obesity.

Obesity and Insulin Resistance Linked by a Circulating Protein—Researchers have identified a circulating protein that seems to contribute to insulin resistance in obese people and those with type 2 diabetes. Retinol binding protein 4, RBP4, is a protein secreted by fat cells, and its suppression may have therapeutic benefits. The researchers found that engineering mice to lack *RBP4* showed improved insulin sensitivity, whereas inducing high levels of RBP4 protein expression, or administering purified RBP4 protein, resulted in insulin resistance. The putative negative effects of elevated RBP4 protein levels in mice have been reinforced by the observation that RBP4 is also elevated in humans with obesity and type 2 diabetes. Thus, RBP4 is a factor that may play a causative role in the development of insulin resistance and type 2 diabetes, and it may be a valuable clinical target for new drug therapies. Laboratory studies have already shown that a drug that promotes excretion of RBP4 in urine can improve insulin sensitivity in obese mice. With further investigations, it may be possible to translate these promising results of basic research into clinically-oriented studies that may benefit obese, insulin-resistant individuals who are prone to or affected by type 2 diabetes.

Kidney, Urologic, and Hematologic Diseases

Cardiovascular Mortality Risk in People with Chronic Kidney Disease—Elderly people with chronic kidney disease have a substantial risk of dying from cardiovascular disease (CVD). The Cardiovascular Health Study, involving a group of elderly men and women with a high prevalence of chronic kidney disease, has underscored the importance of combating "traditional" risk factors among this population. These factors include high blood pressure, diabetes, obesity, smoking, and left ventricular hypertrophy (enlargement of the lower left chamber of the heart, usually caused by high blood pressure). In contrast, the study showed that "novel" risk factors for CVD do not play as harmful a role. The novel factors include elevated markers of inflammation such as C-reactive protein and prothrombotic factors (which promote blood clotting), such as fibrinogen and factor VIII. Examining six traditional risk factors and six novel risk factors for CVD, researchers found that, in patients with chronic kidney disease, traditional risk factors were associated with the largest increases in CVD death and that the increases associated with the novel factors were smaller and not statistically significant. These findings suggest that interventions that target traditional risk factors—such as blood pressure control, blood sugar control, smoking cessation, and increased physical activity—may have the greatest potential to reduce CVD mortality in this high-risk population.

Story of Discovery: Helping Women Have a Safer Pregnancy—Advances in Detecting Preeclampsia

A series of research findings may help women avoid a common and sometimes serious complication of pregnancy called toxemia or preeclampsia. This condition usually involves a combination of high blood pressure and persistent swelling, as well as protein in the urine—a sign of impaired kidney function. Preeclampsia can impede blood flow to the baby and result in low birth weight and even graver problems for mother and child. Insights into this condition have been gained by recruiting patients as research partners and combining cutting-edge technology with careful laboratory studies. Moving from the "bench to bedside and back," investigators used patient samples to design laboratory studies, and then returned to patient data to confirm hypotheses. In doing so, they identified a perturbation in a signaling pathway that may play a central role in preeclampsia. In addition, they developed an assay that may predict preeclampsia with a greater degree of precision than previously. This research has also identified potential targets for new prevention-oriented strategies.

Preeclampsia is a relatively common complication of pregnancy, especially in first pregnancies or in twin pregnancies. The central lesion in preeclampsia is the failure of maternal arteries at the uterus/placenta interface to

remodel appropriately. This results in diminished blood supply to the placenta and fetus. Preeclampsia is characterized by high blood pressure and kidney damage resulting in proteinuria, or protein in the urine. It appears in 2.5 to 3.0 percent of pregnancies.[a] Unaddressed, it may progress to eclampsia—violent seizures that can result in the death of the mother and developing child. Children of mothers with preeclampsia may be born prematurely and/or may be small for their age. Treatment for preeclampsia is often not satisfactory. It is managed by close observation of the mother and the administration of anti-hypertensive drugs to lower blood pressure. If the condition progresses, the only effective therapy is urgent delivery of the fetus. Doctors have long believed that placental factors are central to the development of preeclampsia, because the presence of a placenta is an absolute requirement for preeclampsia, and the condition markedly and rapidly improves after delivery.

To investigate possible genetic factors involved in preeclampsia, a research team looked for changes in gene expression in the placentas of women with this condition. They found increased expression of the gene *sFlt-1*, a finding that was interesting for a number of reasons. First, the protein encoded by the *sFlt-1* gene can bind two important growth factors, placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). VEGF and PlGF are powerful promoters of new blood vessel growth, and they play an important role in ensuring the maintenance and survival of the endothelial cells lining blood vessels. Swollen, damaged endothelial cells are one consequence of preeclampsia. Second, the sFlt-1 protein is not anchored in the cell membrane, but circulates in the blood. Although this protein is produced locally in the placenta, it has the potential to act systemically throughout the body. Thus, this protein's ability to bind VEGF and PlGF diminishes the amount of VEGF and PlGF available to endothelial cells. The scientists hypothesized that depletion of VEGF and PlGF due to *sFlt-1* overexpression by the placenta in affected women is a potential explanation for the systemic blood vessel dysfunction that is a hallmark of preeclampsia.

In order to determine whether excessive *sFlt-1* expression might contribute to the vascular derangement seen in preeclampsia, the investigators used laboratory studies to determine the effect of serum from normal and preeclamptic women on the growth of blood vessel cells. Serum from normal women promoted the development of vessel-like tubules in culture, but serum collected from preeclamptic women before delivery inhibited formation of these structures. Intriguingly, when incubated with serum collected from preeclamptic women 48 hours after delivery tubules did form. This rapid loss of the unknown factors causing inhibition of tubule formation strongly suggested the involvement of circulating, placenta-derived factors. Furthermore, when researchers induced overexpression of the *sFlt-1* gene in pregnant and non-pregnant rats, both developed hypertension and proteinuria, and their kidneys showed damage remarkably similar to that seen in humans with preeclampsia. Together, these observations pointed strongly toward the involvement of the sFlt-1/VEGF/PlGF signaling pathway in the vascular and kidney complications of preeclampsia.

Going from the "bench to the bedside," the scientists next compared their laboratory results with patient data. They analyzed blood samples from 120 preeclamptic women and 120 normal controls, which had been collected as part of an earlier study. They found that circulating levels of the sFlt-1 protein increased and PlGF levels decreased late in pregnancy in normal women. These changes occurred earlier and were greater in the women in whom preeclampsia developed, and the increase in levels of the sFlt-1 protein preceded the onset of preeclampsia by about five weeks. Building on this finding, researchers turned to urine samples from the same patients. The sFlt-1 protein cannot be measured in urine because the molecule is too large to be excreted intact. Moreover, deducing circulating levels of VEGF in urine is problematic because kidney cells normally secrete VEGF. The researchers therefore measured PlGF protein levels as a surrogate marker of sFlt-1 and VEGF signaling activity because all three share the same pathway. They reported that PlGF protein levels in urine were similar and rising in both groups early in pregnancy. Women who would go on to develop preeclampsia saw this increase slow at around 25 weeks. After the onset of preeclampsia, PlGF protein levels in affected women plummeted to just one-seventh those seen in normal women. Thus, low urinary PlGF protein levels early in pregnancy may be an early warning sign of subsequent preeclampsia.

The ability to measure a factor in urine that may predict preeclampsia represents a significant advance as a diagnostic tool, because no such previous test existed and because urine can be sampled more easily than blood. The VEGF/PlGF signaling pathway also presents multiple potential new targets for developing therapies aimed at preventing or treating preeclampsia. The rapid pace of recent progress in this area gives hope to at-risk women and their children that, through continued research, they may be able to avoid the perils of preeclampsia.

[a] Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 308: 1592-1594, 2005.

An Ion Channel Plays a Role in Kidney Disease—Focal segmental glomerular sclerosis (FSGS) damages the filtering units of the kidneys, thereby allowing protein and sometimes red blood cells to leak into the urine. Most patients with FSGS progress to end-stage renal disease. The ion channel encoded by the *TRPC6* gene is thought to be an important contributor to the kidney damage seen in this disease, but its role has been unclear. In one recent study, researchers described in fine detail the subcellular localization of the normal protein encoded by the gene within the kidney filters and identified a number of signaling proteins with which the gene interacts. They then identified five families with hereditary kidney disease, and found each had a different mutation in this gene. When expressed in cultured cells, two of these five mutants resulted in increased ion flow across the cell membrane—suggesting that the mutant proteins may alter normal functions in the kidney filters. In another study, researchers studying a large family with hereditary kidney disease identified yet another mutation in the *TRPC6* gene. This mutation results in a protein with altered subcellular distribution that is hypersensitive to stimulation. These two advances identify a novel mechanism for the kidney damage seen in FSGS. The development of agents that target the mutated TRPC6 protein may be a useful strategy in the treatment of chronic kidney disease.

Signaling Pathways in Kidney Fibrosis—New research clues could lead to prevention strategies for a major cause of kidney damage—the scarring of kidney tissue (fibrosis). Insights are emerging about bone morphogenic proteins (BMPs), which not only induce bone formation, but also play an important role in embryonic development. One of these proteins, BMP-7, is key to the development of the kidney. Signaling by BMPs is mediated through cell surface receptors. Their activity is known to be inhibited by proteins, such as chordin and noggin, that prevent them from binding to their receptors. Scientists have now identified another BMP-binding protein called KCP, which is similar in structure to chordin, but which *enhances* BMP-7 activity. Found in embryonic brain, limb buds, and kidney, this protein seems to have its enhancing effect by promoting the binding of BMP-7 to its receptor. Using two animal models of kidney damage, researchers found that mice lacking KCP were more susceptible to kidney damage. In one model, these mice also had a significantly higher death rate and a more problematic recovery compared to normal mice. Kidney fibrosis is a common clinical feature of chronic kidney disease, which can, in turn, lead to irreversible kidney failure. Thus, enhancing BMP signaling with KCP-like agents may have important clinical implications.

Kidney Stones: A Growing Health and Economic Burden—Researchers are gathering data about the natural history and economic impacts of kidney stones, also known as urolithiasis, which are solid masses formed from minerals that are dissolved in urine. Kidney stones are an increasing problem in the United States, and the recurrence rate of kidney stones has been estimated to be as high as 50 percent at 5 years.[1] Treatment of kidney stones may require physician visits, hospitalizations or surgical interventions. Between 1994 and 2000, the number of hospitalizations and the average length of hospital stays for urolithiasis decreased 15 percent.[2] However, due to the emergence of less invasive treatment options, the number of outpatient visits increased by 40 percent and physician office visits increased 43 percent between 1992 and 2000. Overall, kidney stone-related expenditures rose 50 percent from 1994 to 2000, with an

annual total cost of $2.1 billion,[3] despite a shift from costly inpatient procedures to less expensive outpatient procedures. As the number of diagnoses increases, the economic impact of kidney stones in the U.S. is likely to continue to rise.

[1]Coe FL, Keck J, Norton ER. The natural history of calcium urolithiasis. JAMA 238: 1519-1523, 1977.
[2]Pearle MS, Calhoun EA. Curhan GC, et al. Urologic Diseases in America Project: Urolithiasis. J Urol 173: 848-857. 2005.
[3]Ibid.

Insights into the Development of the Urinary Tract—Congenital malformations of the urinary tract are among the most common of all birth defects, and—untreated—can lead to end-stage kidney disease. Researchers have identified a previously unknown key event in urinary tract development that will aid in understanding the developmental process. Complete and efficient removal of toxic substances from the blood depends on tight connections among the kidneys, bladder, and interconnecting tubules called ureters. During embryonic development, one end of the ureter is attached to the nascent kidney and the other end is joined to the developing bladder through a structure called the common nephric duct (CND). The CND disappears during development. Previous models of ureter development posited that the CND underwent tissue remodeling and became a different structure. Scientists have now found that the CND is in fact lost during urinary tract development through a process of programmed cell death. The death of CND cells is dependent on signaling by vitamin A. Loss of the CND is critical for the formation of the essential tight connection between the ureter and the bladder. This novel finding, which differs from the previous model of ureter development, provides a new way to approach the biology of urogenital tract formation.

Insights into Hereditary Hemochromatosis—An important connection has been identified between two molecules involved in maintaining the delicately balanced metabolism of iron. Hemochromatosis is a disease in which abnormal iron metabolism results in the accumulation of toxic iron levels—termed iron overload—that eventually damage the liver, heart and other organs. Recent studies to combat this problem have focused on the hormone hepcidin, which is known to be a key player in the regulation of iron metabolism. Although deficiency in hepcidin has been implicated in some forms of hereditary hemochromatosis, the precise mechanism for hepcidin regulation of iron levels was not known. Scientists recently identified the protein ferroportin (Fpn), an iron exporter on the surface of some cells, as a receptor for hepcidin. In cell cultures, the binding of hepcidin to Fpn resulted in internalization and degradation of the complex, thereby preventing iron export by Fpn. Because Fpn exports iron absorbed by intestinal cells into the circulation, hepcidin-mediated destruction of Fpn may be key to regulating the dietary iron equilibrium. Researchers then studied several mutations in the *Fpn* gene that are linked to one type of hereditary hemochromatosis, and found that they either produced a protein that never arrives at the cell surface or one that does not internalize and degrade in the presence of hepcidin. Taken together, these findings suggest that loss of hepcidin regulation of Fpn levels—caused either by *Fpn* mutations or by deficiency in hepcidin—could explain the abnormal iron accumulation observed in hemochromatosis patients. A fuller understanding of the hepcidin-Fpn pathway in iron regulation will help to provide the foundation for future research aimed at treating or preventing iron overload disorders.

Cardiovascular Disease Risk in HIV-Infected Women—New findings may help researchers overcome the metabolic complications sometimes associated with HIV infection and the highly active antiretroviral therapy used to treat the infection. It is not clear whether these complications arise from HIV infection *per se*, components of the antiretroviral therapy, or a combination of the two. These metabolic complications include lipid (fat) abnormalities, insulin resistance, and abnormal distribution of body fat. They are major risk factors for the development of serious diseases, such as diabetes and cardiovascular disease. A recent study shed light on cardiovascular risk factors in HIV-infected women relative to HIV-negative women. The infected women had higher levels of C-reactive protein (a marker of inflammation) and triglycerides (circulating fat levels); showed elevated 2-hour oral glucose levels after a glucose tolerance test; and had increased fasting insulin levels. Additionally, HIV-infected women had more abdominal visceral fat and less extremity fat than HIV-negative controls. Thus, the HIV-infected women had significantly increased risk factors for cardiovascular disease and abnormal fat distribution. These findings are expanding the knowledge base on which future studies may be framed for devising HIV treatment regimens that address metabolic complications of HIV infection and/or antiretroviral therapy.

Roadmap

The NIDDK has played a major leadership role in the Building Blocks, Biological Pathways, and Networks (BBPN) Roadmap Implementation Working Group. The NIDDK Director is one of four Co-Chairs of the group, and the NIDDK has made significant contributions to implementation of BBPN initiatives on proteomics and metabolomics technology development. These efforts have included international scientific workshops to develop and promote information standards and resource sharing in these rapidly growing fields. Improved tools in proteomics—the study of all proteins within cells—and metabolomics—the study of all metabolites, such as salts, sugars, and fats—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.

The NIDDK has taken a leadership role in a Roadmap pilot program to make available, on a competitive basis, certain governmental contractual resources for the pre-clinical development of small molecules. The NIH-RAID (Rapid Access to Intervention Development) Pilot is intended to reduce some of the common barriers that impede the translation of laboratory discoveries, and clinical trials of new therapeutic entities. During the pilot phase, proposals are limited to small molecule development, but it is anticipated that eventually the program may be expanded to include other therapeutic agents. At present, the program is managed by NIDDK staff. While the program is designed to benefit researchers in any NIH-supported research area, it should prove particularly helpful to NIDDK-supported investigators, many of whom are actively involved in the development of new treatment approaches.

The NIDDK serves as the lead institute in administering the NIH Roadmap Interdisciplinary Research Short Training Programs initiative, which was intended to provide training for investigators at all levels of their careers. The NIDDK also participates in the administration of

the Training for a New Interdisciplinary Research Workforce initiative, through which institutional training grants have been developed.

The NIDDK Director has served as a Member of the Roadmap Implementation Coordinating Committee, providing leadership to the structuring of Roadmap initiatives; their funding, progress review, and evaluation; and means of staff recognition. The NIDDK has also furthered the Roadmap goal of "Re-engineering the Clinical Research Enterprise" within the Institute by: (1) developing central repositories for patient biosamples and data from NIDDK-funded clinical studies and trials, and (2) developing and implementing policies for, and funding of, ancillary studies to specific large clinical trials.

Highlights of Ongoing and Planned Activities

FY 2007 Initiatives

Proteomic and Metabolomic Approaches to the Diagnosis of Diabetes—The NIDDK supports an ongoing initiative to identify new biomarkers related to type 2 diabetes and pre-diabetes. Early diagnosis is crucial for reducing the overall burden of type 2 diabetes in the U.S. Many proteins and metabolites such as peptides, lipids and sugars may be modified in individuals with elevated glucose, a feature of pre-diabetes and diabetes. Disease-related changes in the protein profile of a cell (the proteome) and the metabolite profile (the metabolome) are ideal targets for new diagnostic techniques. Several novel proteomic and metabolomic technologies will be used to analyze plasma samples of pre-diabetic and diabetic patients. A simplified and less burdensome approach to the diagnosis of diabetes and pre-diabetes would facilitate increased recognition and improved care of these conditions.

Collaborative Research between Basic and Clinical Researchers in Obesity—The NIDDK plans to solicit research applications to foster synergistic progress in understanding the biological underpinnings of overweight and obesity and to promote bench-to-bedside-and-back translation by bringing together basic and clinical investigators in the field. The development of close collaborations between basic and clinical researchers holds great promise for the advancement of the study of obesity and associated conditions. In order to help maximize the interest in the initiative and to identify scientific opportunities to be highlighted in a research solicitation, the NIDDK will hold a workshop in Spring, 2006.

Collaborative Research in Proteomics of Obesity: A Search for Co-Morbidity Biomarkers—The NIDDK is encouraging scientific collaboration among its grantees, as well as with other members of the scientific community, who are interested in using proteomics technology to study obesity. This initiative will invite applications for collaborative research to employ proteomics to identify biomarkers that link obesity to type 2 diabetes, heart disease, and other co-morbid conditions. Proteomics—which seeks to highlight the array of proteins involved in a given physiological situation—is particularly valuable for studying complex disease states, identifying biomarkers, and pinpointing potential therapeutic targets.

HALT-C Follow-up Study—The NIDDK currently supports the *Hepatitis C Antiviral Long-term Treatment against Cirrhosis* (HALT-C) trial. This ongoing trial addresses a common cause of liver disease in the U.S., infection with hepatitis C virus (HCV). In some individuals, chronic hepatitis C leads to cirrhosis, liver cancer, and liver failure requiring a liver transplant. HALT-C

is a randomized clinical trial to determine whether patients with HCV infection who have not responded to interferon-based therapy in the past can benefit from long-term treatment with pegylated interferon—a longer-acting form of interferon. The trial began recruitment in 2000, completed randomization in 2004, and will conclude in 2007. In FY 2007, the NIDDK plans to solicit applications for the *HALT-C Follow-up Study*, which will follow the participants in the randomized HALT-C trial in order to assess progression of liver disease after the study ends; use patient samples of serum, tissue, and DNA and clinical information to examine risk factors for chronic hepatitis C progression, and guide plans to enroll patients in additional studies of treatment or screening to prevent the complications of hepatitis C-related liver disease.

New Imaging Methods for Hepatic and Renal Fibrosis—A common problem faced by those studying diseases of the liver and kidney is how to monitor disease progression, particularly how to assess the fibrosis that occurs in these organs as part of the disease process. In FY 2007, the NIDDK plans to solicit research applications to develop non-invasive imaging methods that will allow early detection of renal and hepatic fibrosis and will facilitate monitoring of disease progression. An essential component will be cooperation between investigators who develop cutting-edge imaging methods and investigators who are familiar with the disease issues relevant to fibrosis. This effort will have significant impact on the ability of investigators to pursue novel therapies for many kidney and liver diseases, because it promises to provide a cheaper and more reliable measure of outcomes than current methods. The NIDDK also has plans to pursue a Program Announcement, to be addressed through the Small Business Innovation Research program, that will reinforce and complement the studies funded through the research solicitation on fibrosis imaging.

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 HIV- and HAART-related lipid dysregulation, insulin resistance, and abnormal body fat distribution. These complications are risk factors for serious diseases, such as diabetes and cardiovascular disease. The NIDDK also supports research to define the causes of liver disease associated with HIV. Areas of interest include the delineation of interactions between HIV and hepatitis B and C viruses, and the development of 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 also maintains a highly productive intramural program on structural biology. Scientists seek to determine the structures of biologically significant proteins relative to HIV infection, replication, and integration.

Other Areas of Interest

Digestive Diseases Commission The NIH Director has established a National Commission on Digestive Diseases, based on the shared interest of the NIH and the Congress in advancing research in this area. The Commission will develop a Long-Range Research Plan for Digestive Diseases to assess the state-of-the-science and the related NIH research portfolio, with a view toward identifying areas of research challenge and opportunity. The Commission's Research Plan will then guide the NIH—along with the investigative and lay communities—in pursuing

important research avenues. The Commission will have a diverse membership representing the academic and medical research and practice communities, patients and members of the patient advocacy community, and the NIH and other Federal health agencies. Within the NIH, the NIDDK will provide leadership and support for the Commission. The Director of the Division of Digestive Diseases and Nutrition, NIDDK, will serve as Commission chair.

DETS Type 2 diabetes is a serious, growing problem in minority groups, including American Indians. The Diabetes Based Science Education in Tribal Schools (DETS) program is developing a national, science-based diabetes prevention education curriculum for Native American students in grades K-12. One goal of the program is to enhance awareness and understanding of diabetes among students, families, community members, and teachers in order to prevent the disease and to help affected Tribal members better manage their diabetes. A second goal of the program is to increase the numbers of Native Americans entering the health research professions. The program is sponsored by the NIDDK in close collaboration with American Indian tribal schools, and the Indian Health Service, the Centers for Disease Control and Prevention, and the Office of Science Education of the NIH.

Programs To Increase Diversity in Biomedical Research in NIDDK Mission Areas Many diseases and disorders that disproportionately affect the health of minority populations in the U.S. are NIDDK research areas, including diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder diseases, *H. Pylori* infection, sickle cell disease, kidney diseases, and complications from infection with HIV. The NIDDK supports research to encourage specific efforts in these areas of health disparity to advance the foundation of knowledge in the biomedical sciences.

Because racial and ethnic minorities are under-represented among investigators carrying out the NIDDK mission, the Institute has a number of efforts to address this problem. These efforts are aimed at ensuring an adequate cadre of future minority researchers by supporting current investigators and encouraging junior scientists and students to pursue research careers. The *Network of Minority Research Investigators,* comprised of current and potential biomedical research investigators, is designed to help minority investigators achieve career success while working on issues concerning health-related racial and ethnic disparities. *Pre-doctoral Fellowship Awards for Minority Students (F31)* provide support for research training leading to a Ph.D., M.D./Ph.D., or other professional degree in the biomedical sciences, behavioral sciences, or health services research. These fellowships are designed to enhance the racial and ethnic diversity of the research labor force in the U.S. Under the *Minority Supplement Program to Institutional National Research Service Award (T32)* program, the NIDDK awards an extra position, designated specifically for a selected under-represented minority trainee—either pre-doctoral or post-doctoral—to an existing T32 award. That position then remains a part of the award for as long as the named individual is a member of the training program. Undergraduate students are eligible for a number of NIDDK programs designed to encourage minorities to pursue a research career. Awards through the *Short Term Educational Program for Under-represented Persons (STEP UP)* offer research-education opportunities for minority students in an effort to encourage them to pursue a research career in an area of science relevant to the research mission of the NIDDK. The ten-week *Summer Internship Program* provides an

opportunity for students to participate in research under the direction of preceptors in NIDDK laboratories. This program advances the state of biomedical knowledge and introduces the students to state-of-the-art laboratory methods.

Management and Administration

Enhancing Results-Oriented Management—The NIDDK furthered the establishment of meaningful, results-oriented performance contracts for senior Institute managers to ensure that NIDDK staff achieves agreed-upon goals. The NIDDK also developed a detailed plan for implementing the recommendations of the Blue Ribbon Panel (BRP) review of the NIDDK Intramural Research Program, submitted in March, 2005. The BRP commended the many accomplishments of the NIDDK Intramural Research Program and provided specific recommendations for strengthening and enhancing it, particularly in the areas of clinical investigation and research training. The Implementation Plan was submitted to the NIH Director and shared with the BRP in July 2005, and is currently being executed.

The NIDDK also contributed to the "Effective" rating the NIH received on the OMB's application of the Program Assessment and Rating Tool (PART) to the agency's Intramural Program. As a contributor to a NHGRI-led goal under the Government Performance and Results Act (GPRA), the NIDDK provided extensive documentation about the planning and productivity of genetics studies of diabetes in the Pima Indians, which are conducted by its Phoenix Epidemiology and Clinical Research Branch.

Since May, 2005, the NIDDK Director has provided leadership to the NIH Research Infrastructure *Ad Hoc* Committee in efforts to provide an analysis and recommendations to the NIH Steering Committee for improving efficiencies in the area of research infrastructure.

Improvements in Grants Management Operation and Oversight—The NIDDK Director is a member of the NIH Steering Committee (2004-present), a new governance committee of IC Directors established by the NIH Director to help develop and oversee policies across the NIH. He has also Co-chaired the Steering Committee Extramural Activities Work Group (EAWG) (2005). This Work Group considers all issues broadly impacting NIH extramural activities irrespective of their organizational origin, and provides governance for efforts aimed at restructuring and consolidating key administrative components associated with extramural research and research training. The NIDDK has also provided appropriate outreach and support to encourage electronic submission of applications to NIH programs available through www.grants.gov.

Consolidation of Management Functions and Achievement of Administrative Efficiencies—The NIDDK is the lead institute for a Consolidated Operational Acquisition Centers (COAC) and has made decisions regarding the organizational structure and the recruitment of vacant positions. The NIDDK has led meetings with IC Directors, Deputy Directors, and Executive Officers within the COAC to resolve issues and plan for future changes. As the lead IC, the NIDDK has developed Service Level Agreements and Intra-agency Agreements that will be used in the COAC. In addition, the NIDDK is supporting the development of an integrated, Department-wide financial system that consistently produces relevant, reliable and timely financial information to support decision-making and cost-effective business operations.

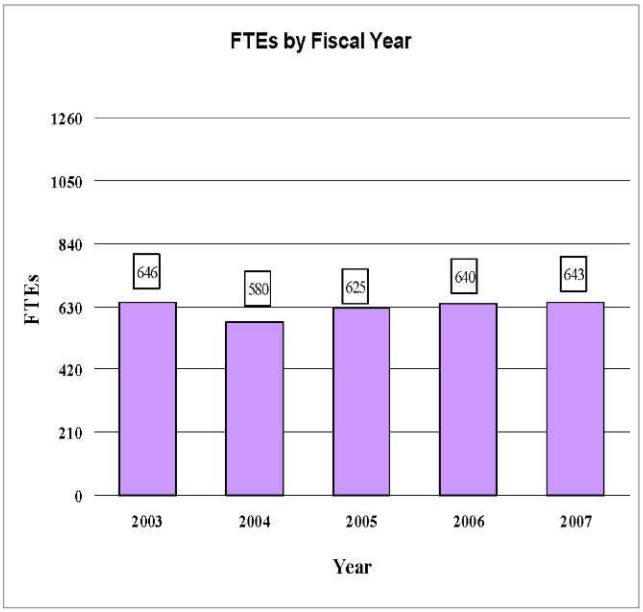
Improvements in Financial Management—The NIDDK provides leadership and oversight for the Special Statutory Funding Program for Type 1 Diabetes Research, which is vested in the Secretary, HHS, in Sec. 330B of the PHS Act, and which involves multiple NIH Institutes and Centers, along with the CDC. Efforts include a January, 2005, mid-course assessment and planning meeting focused on the program's research consortia and networks; progress in developing a mandatory evaluation of the Special Funding Program, which will culminate in an evaluation report due to the Congress in January 2007; and efforts to promote and enhance coordination among the various consortia and networks supported by the Special Funding Program in order to maximize this significant investment in type 1 diabetes research. For example, the NIDDK has expanded the type 1 diabetes website to facilitate and promote the sharing of information and research resources among consortia investigators.

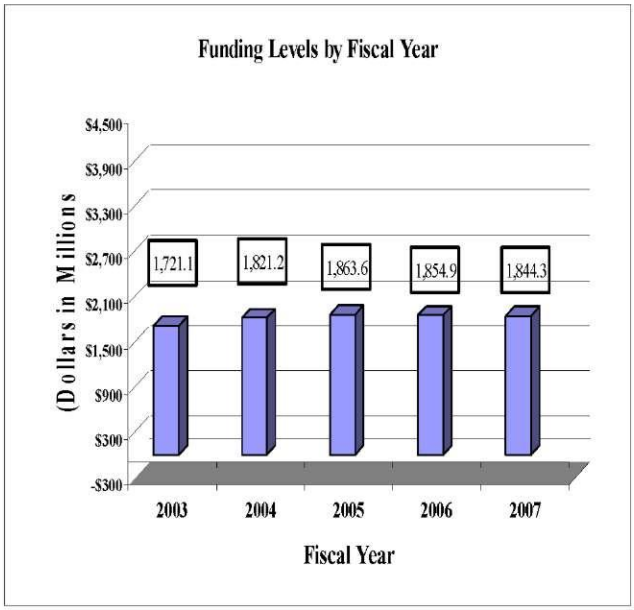
The NIDDK also initiated a review of Institute-wide budget processes by a group of senior financial management experts from several other ICs. Recommendations are currently being considered for implementation in order to strengthen internal systems of financial planning, execution, and accountability.

Budget Policy

The Fiscal Year 2007 budget request for the NIDDK is $1,844,298,000, a decrease of $10,627,000 and 0.6 percent over the FY 2006 Appropriation. Included in the FY 2007 request is NIDDK's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIDDK are shown in the graphs below. Note that as the result of several administrative restructurings in recent years, FTE data is non-comparable.





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 $344,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIDDK has committed to a programmatic increase for an award, such increases will be provided.

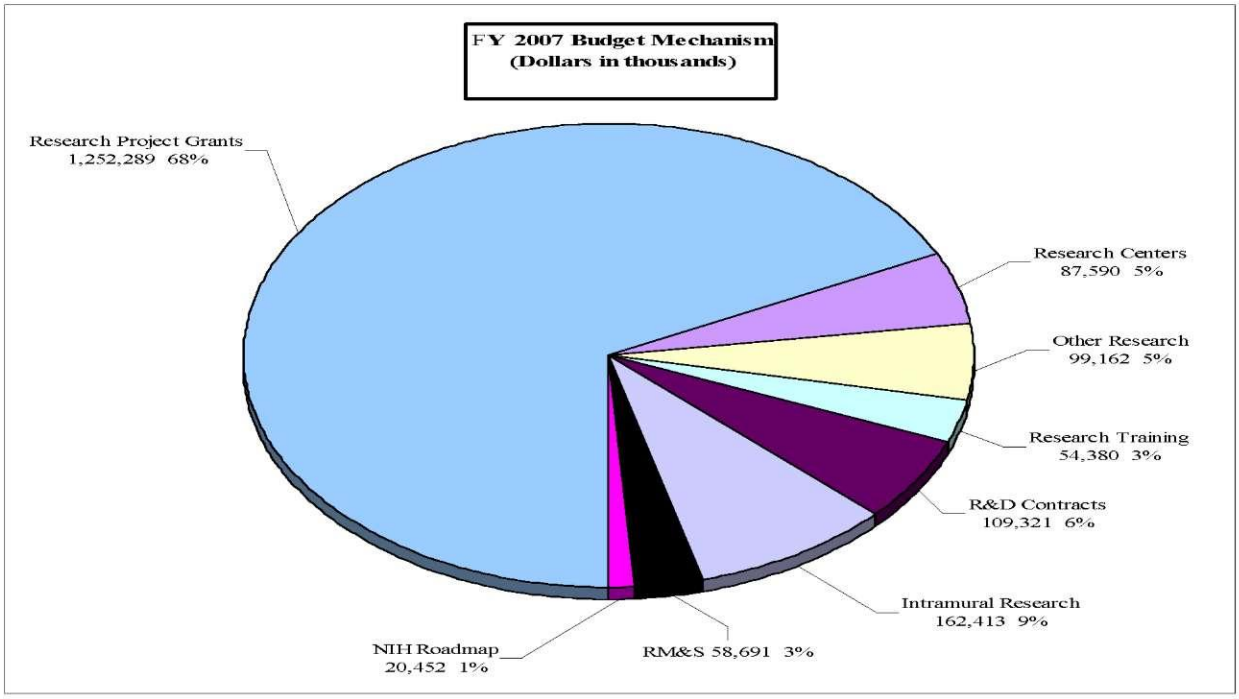
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIDDK, $1.350 million will be used to support 7 awards for the new K/R "Bridges to Independence" program.

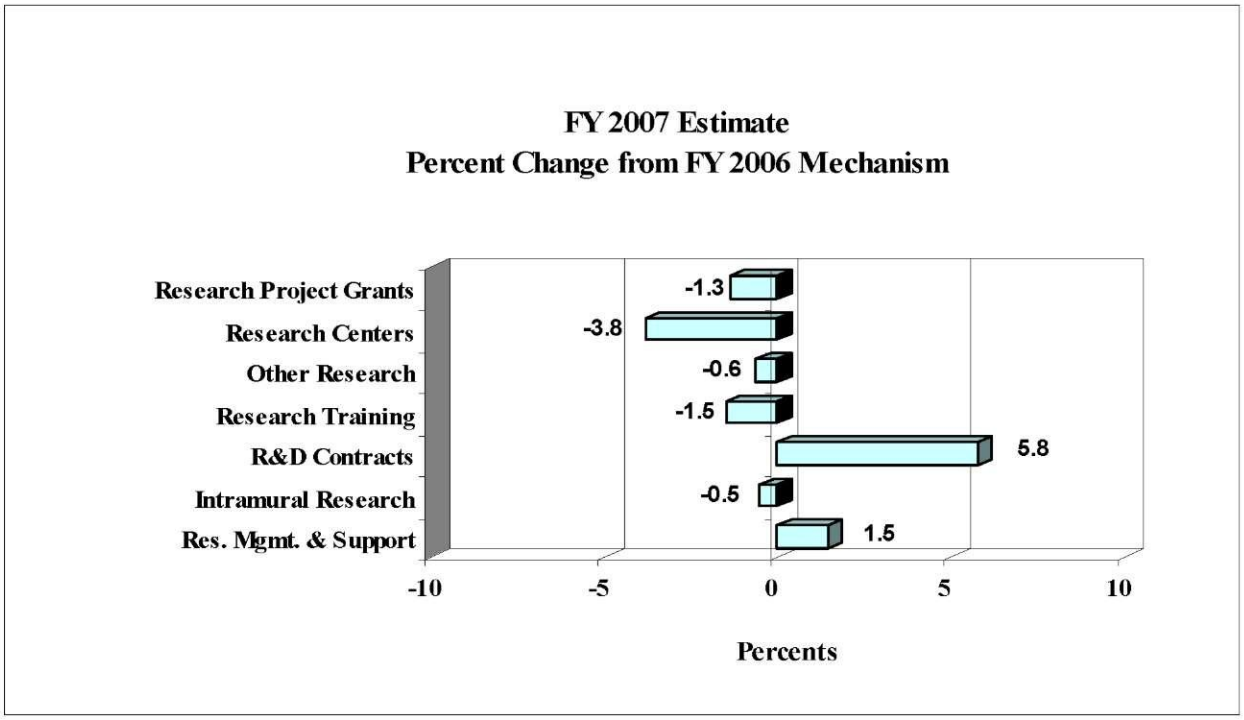
NIDDK will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $2,872,000 to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 77 research centers, 608 other research grants, including 520 career awards, and 417 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

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 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	2,496	$952,023,000	2,398	$947,168,000	2,301	$923,679,000
Administrative supplements	(197)	20,389,000	(200)	19,000,000	(200)	19,000,000
Competing:						
Renewal	284	110,210,000	260	105,987,000	267	108,764,000
New	540	159,006,000	493	152,913,000	506	156,919,000
Supplements	0	0	0	0	0	0
Subtotal, competing	824	269,216,000	753	258,900,000	773	265,683,000
Subtotal, RPGs	3,320	1,241,628,000	3,151	1,225,068,000	3,074	1,208,362,000
SBIR/STTR	146	44,840,000	140	44,212,000	139	43,927,000
Subtotal, RPGs	3,466	1,286,468,000	3,291	1,269,280,000	3,213	1,252,289,000
Research Centers:						
Specialized/comprehensive	80	89,666,000	77	87,787,000	77	87,348,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	250,000	0	0	0	0
Comparative medicine	0	5,150,000	0	3,243,000	0	242,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	80	95,066,000	77	91,030,000	77	87,590,000
Other Research:						
Research careers	496	63,861,000	518	67,583,000	520	67,122,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	3	2,698,000	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	1,521,000	0	1,521,000	0	1,521,000
Other	91	31,233,000	88	30,672,000	88	30,519,000
Subtotal, Other Research	590	99,313,000	606	99,776,000	608	99,162,000
Total Research Grants	4,136	1,480,847,000	3,974	1,460,086,000	3,898	1,439,041,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	170	8,027,000	168	8,028,000	168	8,028,000
Institutional awards	951	45,552,000	945	47,167,000	931	46,352,000
Total, Training	1,121	53,579,000	1,113	55,195,000	1,099	54,380,000
Research & development contracts	411	96,556,000	416	103,340,000	417	109,321,000
(SBIR/STTR)	(2)	(100)	(2)	(100)	(2)	(100)
	FTEs		FTEs		FTEs	
Intramural research	437	164,716,000	428	163,229,000	428	162,413,000
Research management and support	184	57,053,000	209	57,839,000	212	58,691,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	4	10,833,000	3	15,236,000	3	20,452,000
Total, NIDDK	625	1,863,584,000	640	1,854,925,000	643	1,844,298,000
(Clinical Trials)		(188,000,000)		(188,000,000)		(188,000,000)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism - Type 1 Diabetes Only

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	122	$101,643,000	68	$75,536,000	114	$81,910,000
Administrative supplements	(4)	1,551,000	(0)	0	(0)	0
Competing:						
Renewal	4	500,000	10	1,451,000	9	1,315,000
New	22	13,714,000	56	39,785,000	49	36,064,000
Supplements	0	0	0	0	0	0
Subtotal, competing	26	14,214,000	66	41,236,000	58	37,379,000
Subtotal, RPGs	148	117,408,000	134	116,772,000	172	119,289,000
SBIR/STTR	6	4,167,000	6	4,167,000	6	4,167,000
Subtotal, RPGs	154	121,575,000	140	120,939,000	178	123,456,000
Research Centers:						
Specialized/comprehensive	0	0	0	0	0	0
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	5,000,000	0	3,000,000	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	0	5,000,000	0	3,000,000	0	0
Other Research:						
Research careers	7	2,384,000	7	2,398,000	2	587,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	3	2,698,000	0	0	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	10	5,082,000	7	2,398,000	2	587,000
Total Research Grants	164	131,657,000	147	126,337,000	180	124,043,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	0	0	0	0	0	0
Institutional awards	19	785,000	20	1,137,000	6	322,000
Total, Training	19	785,000	20	1,137,000	6	322,000
Research & development contracts	11	17,022,000	16	21,487,000	15	24,596,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	0	0	0	0	0	0
Research management and support	0	536,000	0	1,039,000	0	1,039,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	0	0	0	0	0	0
Total, NIDDK	0	150,000,000	0	150,000,000	0	150,000,000
(Clinical Trials)		(0)		(0)		(0)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

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

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Endocrinology and Metabolic Diseases		826,047		819,786		811,744		(8,042)
Division of Digestive Diseases and Nutrition		415,117		411,971		407,929		(4,042)
Division of Kidney, Urologic and Hematologic Diseases		389,818		386,864		383,069		(3,795)
Subtotal, Extramural research		1,630,982		1,618,621		1,602,742		(15,879)
Intramural research	437	164,716	428	163,229	428	162,413	0	(816)
Res. management & support	184	57,053	209	57,839	212	58,691	3	852
Cancer Control & Prevention	0	0	0	0	0	0	0	0
NIH Roadmap for Medical Research	4	10,833	3	15,236	3	20,452	0	5,216
Total	625	1,863,584	640	1,854,925	643	1,844,298	3	(10,627)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

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

Summary of Changes

FY 2006 Estimate				$1,854,925,000
FY 2007 Estimated Budget Authority				1,844,298,000
Net change				(10,627,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$62,885,000		$882,000
b. Annualization of January 2006 pay increase		62,885,000		1,189,000
c. January 2007 pay increase		62,885,000		906,000
d. Payment for centrally furnished services		30,157,000		452,000
e. Increased cost of laboratory supplies, materials, and other expenses		70,187,000		1,412,000
Subtotal				4,841,000
2. Research Management and Support:				
a. Within grade increase		24,813,000		343,000
b. Annualization of January 2006 pay increase		24,813,000		463,000
c. January 2007 pay increase		24,813,000		352,000
d. Payment for centrally furnished services		8,495,000		127,000
e. Increased cost of laboratory supplies, materials, and other expenses		23,850,000		493,000
Subtotal				1,778,000
Subtotal, Built-in				6,619,000

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

Summary of Changes--continued

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,398	$966,168,000	(97)	($23,489,000)
b. Competing	753	258,900,000	20	6,783,000
c. SBIR/STTR	140	44,212,000	(1)	(285,000)
Total	3,291	1,269,280,000	(78)	(16,991,000)
2. Research centers	77	91,030,000	0	(3,440,000)
3. Other research	606	99,776,000	2	(614,000)
4. Research training	1,113	55,195,000	(14)	(815,000)
5. Research and development contracts	416	103,340,000	417	5,981,000
Subtotal, extramural				(15,879,000)
	FTEs		FTEs	
6. Intramural research	428	163,229,000	0	(5,657,000)
7. Research management and support	209	57,839,000	3	(926,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Buildings and Facilities		0		0
11. NIH Roadmap for Medical Research	3	15,236,000	0	5,216,000
Subtotal, program		1,854,925,000		(17,246,000)
Total changes	640		3	(10,627,000)

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

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	640	643	3
Full-time equivalent of overtime & holiday hours	2	2	0
Average ES salary	$139,146	$141,511	$2,365
Average GM/GS grade	11.9	12.0	0.1
Average GM/GS salary	$80,765	$82,138	$1,373
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$82,850	$84,258	$1,408
Average salary of ungraded positions	114,927	116,881	1,954

	OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$29,369,000	$30,396,000	$1,027,000
11.3	Other than Full-Time Permanent	26,548,000	27,474,000	926,000
11.5	Other Personnel Compensation	1,117,000	1,136,000	19,000
11.7	Military Personnel	1,438,000	1,462,000	24,000
11.8	Special Personnel Services Payments	12,288,000	12,497,000	209,000
	Total, Personnel Compensation	70,760,000	72,965,000	2,205,000
12.0	Personnel Benefits	15,580,000	16,125,000	545,000
12.2	Military Personnel Benefits	1,358,000	1,381,000	23,000
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**87,698,000**	**90,471,000**	**2,773,000**
21.0	Travel & Transportation of Persons	2,598,000	2,592,000	(6,000)
22.0	Transportation of Things	137,000	130,000	(7,000)
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	15,000	15,000	0
23.3	Communications, Utilities & Miscellaneous Charges	860,000	870,000	10,000
24.0	Printing & Reproduction	740,000	750,000	10,000
25.1	Consulting Services	1,468,000	1,472,000	4,000
25.2	Other Services	8,132,000	5,652,000	(2,480,000)
25.3	Purchase of Goods & Services from Government Accounts	136,204,000	139,102,000	2,898,000
25.4	Operation & Maintenance of Facilities	4,682,000	3,750,000	(932,000)
25.5	Research & Development Contracts	55,975,000	59,586,000	3,611,000
25.6	Medical Care	1,482,000	1,400,000	(82,000)
25.7	Operation & Maintenance of Equipment	2,026,000	2,019,000	(7,000)
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**209,969,000**	**212,981,000**	**3,012,000**
26.0	Supplies & Materials	14,216,000	14,358,000	142,000
31.0	Equipment	8,145,000	8,226,000	81,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,515,281,000	1,493,421,000	(21,860,000)
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	30,000	32,000	2,000
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,751,991,000**	**1,733,375,000**	**(18,616,000)**
	NIH Roadmap for Medical Research	**15,236,000**	**20,452,000**	**5,216,000**
	Total Budget Authority by Object	**1,854,925,000**	**1,844,298,000**	**(10,627,000)**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

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

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$29,369,000	$30,396,000	$1,027,000
Other Than Full-Time Permanent (11.3)	26,548,000	27,474,000	926,000
Other Personnel Compensation (11.5)	1,117,000	1,136,000	19,000
Military Personnel (11.7)	1,438,000	1,462,000	24,000
Special Personnel Services Payments (11.8)	12,288,000	12,497,000	209,000
Total Personnel Compensation (11.9)	**70,760,000**	**72,965,000**	**2,205,000**
Civilian Personnel Benefits (12.1)	15,580,000	16,125,000	545,000
Military Personnel Benefits (12.2)	1,358,000	1,381,000	
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**87,698,000**	**90,471,000**	**2,773,000**
Travel (21.0)	2,598,000	2,592,000	(6,000)
Transportation of Things (22.0)	137,000	130,000	(7,000)
Rental Payments to Others (23.2)	15,000	15,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	860,000	870,000	10,000
Printing and Reproduction (24.0)	740,000	750,000	10,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	1,468,000	1,472,000	4,000
Other Services (25.2)	8,132,000	5,652,000	(2,480,000)
Purchases from Govt. Accounts (25.3)	64,358,000	66,445,000	2,087,000
Operation & Maintenance of Facilities (25.4)	4,682,000	3,750,000	(932,000)
Operation & Maintenance of Equipment (25.7)	2,026,000	2,019,000	(7,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**80,666,000**	**79,338,000**	**(1,328,000)**
Supplies and Materials (26.0)	14,161,000	14,303,000	142,000
Subtotal, Non-Pay Costs	99,177,000	97,998,000	(1,179,000)
Total, Administrative Costs	**186,875,000**	**188,469,000**	**1,594,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

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

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Islet Transplantation - The Committee commends NIDDK and NIAID for the establishment of the Clinical Islet Transplantation Consortium and the islet transplantation clinical trial that will include Medicare-eligible individuals whose transplant and related costs will be covered by Medicare. Cooperation between the NIDDK and NIAID and members of the Consortium is urged to ensure the timely launch of these clinical trials. (p. 66)

Action taken or to be taken

The Clinical Islet Transplantation Consortium (CIT) plans to build on and optimize the successful "Edmonton Protocol" for pancreatic islet transplantation to treat type 1 diabetes by performing pivotal islet transplantation trials using state of the art methodologies, as well as developing innovative approaches. The CIT Steering Committee is responsible for overall consortium operations and includes representation from the NIDDK, the NIAID, and the principal investigators from the five clinical research centers and the coordinating center. The Steering Committee is one important means of fostering cooperation among the participating organizations, especially the two key institutes—NIDDK and NIAID.

The CIT is responsive to the Medicare Modernization Act of 2003 (P.L. 108-173; §733), which directs the NIDDK to "...conduct a clinical investigation of pancreatic islet cell transplantation which includes Medicare beneficiaries." The Diabetes Mellitus Interagency Coordinating Committee (DMICC) provides an important venue for coordination of islet transplantation efforts of NIDDK, NIAID, and other partners, as mandated by the Pancreatic Islet Cell Transplantation Act of 2004. The DMICC devoted a full meeting in November 2004 to discussion of coordination of efforts among the many agencies involved. The NIDDK and NIAID convened an advisory panel of experts in pancreas, kidney, and islet transplantation in February 2005 to consider optimal design of CIT studies. The NIDDK and NIAID have followed the panel's recommendation on developing a protocol for islet transplantation following kidney transplantation in Medicare recipients.

Clinical protocols designed by the CIT build on research performed by related NIH consortia such as the Non-Human Primate Cooperative Study Group, a joint effort of the NIAID and NIDDK; the Type 1 Diabetes TrialNet, a joint effort of the NIDDK, NIAID, and NICHD; the Immune Tolerance Network, a joint effort of the NIAID and NIDDK; the Collaborative Islet Transplantation Registry managed by the NIDDK; and the Islet Cell Resource Centers managed by the NCRR in cooperation with the NIDDK. The CIT has also held multiple meetings to establish a standard manufacturing process to be used in all of the initial consortium clinical studies. This detailed manufacturing information is being formally submitted to the FDA.

The CIT is taking steps to expedite launching the trials. Approval from the Data Safety Monitoring Board (DSMB), the FDA and Institutional Review Boards (IRBs) is required prior to trial initiation. For regulatory affairs, the NIAID assumes principal leadership; for management of the Data Safety Monitoring Board (DSMB), the NIDDK provides the lead. The DSMB for the consortium met in September 2005, and approved the pivotal protocols. CIT representatives, including NIAID and NIDDK staff, met with the FDA on three occasions in late 2005 to discuss the overall plan to develop islet transplantation therapy and the proposed pivotal trials using islets-alone and islet-after-kidney transplantation. Although agreement was reached in these discussions, it is anticipated that it will take additional time to collect data requested by the FDA before the trials can begin. A future meeting with the FDA is planned to discuss four pilot studies of islet-alone transplantation that are being developed by the CIT. IRB submissions are planned to coincide with the final FDA submission.

Item

Drug screening – The Committee applauds NIDDK for convening an exploratory workshop to investigate the potential of conducting a screen of FDA-approved pharmaceutical drugs for hyperglycemia-induced cellular injury leading to diabetic complications. Screens of this type have the potential to lead to the identification of new treatment strategies that can be rapidly translated into clinical applicability. The Committee urges the Institute to continue to promote research in this promising area. (p. 66)

Action taken or to be taken

The NIDDK remains committed to the goal of combating hyperglycemia-induced cellular injury (HCI), a diabetes complication that leads to devastating health complications affecting nearly every organ system in the body. The Institute convened a workshop in February 2005, to explore approaches for expediting identification of potential compounds to treat HCI as a means to alleviate diabetic complications. Subsequently, the NIDDK, along with the National Heart, Lung, and Blood Institute, National Cancer Institute, National Eye Institute, and National Institute of Neurological Disorders and Stroke and in partnership with the Juvenile Diabetes Research Foundation International, actively encouraged investigators to participate in a collaborative effort to screen approximately 1,000 compounds, which have previously been approved for use in humans, in laboratory HCI tests. This approach, based on a successful NINDS drug screening program for neurodegeneration, has the potential to rapidly translate compounds that test successfully in the lab into clinical applications because it builds upon what is already known about these clinically approved compounds.

This collaborative program is designed to encourage laboratory scientists to participate in translational research. To ensure objectivity, the identity of the compounds will be masked from the researchers; data will be collected and analyzed centrally by the NIH. In addition to potentially discovering new drugs for diabetic complications and uncovering new metabolic or signaling pathways involved in the cellular injury of diabetes, this research paradigm will enable participants to compare existing laboratory tests for hyperglycemia-induced cellular injury. The NIH expects to award supplements to grants in 2006.

Item

Rapid access to intervention development – The Committee commends NIDDK and NCI for extending the rapid access to intervention development (RAID) pre-clinical resources to researchers working in the field of type 1 diabetes and its complications. The Committee encourages NIDDK to release to the public information on compounds to be produced for projects supported by RAID, much like the NCI releases for cancer-related projects on its public website. (p.66)

Action taken or to be taken

The NIDDK has created a public website for the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program (http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID/), which includes information on the projects that have been approved for support through the program (the projects can be accessed at: http://www.niddk.nih.gov/fund/diabetesspecialfunds/t1d-raid/T1D-RAID-Proj-info.htm). Similar to the NCI's RAID website, after which the T1D-RAID website was modeled, the publicly available information includes the project name and summary, the agent category (e.g., small molecule, biologic), and the name of the investigator in charge of the project. The NIDDK plans to continue posting information on projects supported by T1D-RAID on this publicly available website.

Item

Pediatric Kidney Disease – Kidney disease remains a persistent and poorly understood problem among infants, children and adolescents, impairing normal growth and development and often resulting in learning disabilities and mental retardation. Of urgent concern today is the explosion in the incidence of obesity among children and adolescents, a morbidity that places more than 15 percent of America's children at risk for developing type 2 diabetes, hypertension, and chronic kidney disease (CKD). These morbidities not only represent a significant financial burden to the health care system but also are important risk factors for the development of cardiovascular disease. The Committee encourages NIDDK to continue to support research focused on the pathogenesis, prevention, and treatment of kidney disease in children. The Committee recommends that emphasis be placed on exploring the contributions of obesity, type 2 diabetes, and hypertension to progression of disease, and interventions that may limit cardiovascular morbidity in patients with CKD. (p.67)

Action taken or to be taken

Chronic kidney disease (CKD) and its accompanying metabolic complications substantially affect the well-being of children. When CKD develops during the neonatal period or in early infancy, significant problems in brain development occur that can impair the child's ability to think, reason, and concentrate. However, little is known regarding the impact of a decrease in renal function that develops later in childhood. To address this gap in knowledge, the NIDDK has launched The Prospective Study of Chronic Kidney Disease in Children (C-KiD), a longitudinal, observational study of 540 children, ages 1-16, who have mildly to moderately impaired kidney function. The goals of the study are to determine: (1) risk factors for accelerated decline in renal function; (2) incidence, nature, magnitude and temporal evolution of impaired brain function and structure; (3) prevalence of risk factors for cardiovascular disease; and (4) implications with respect to morbidity of growth failure, and its treatment. As part of the study, researchers will measure blood pressure, growth and nutritional/metabolic status, and

protein in the urine. By studying this new, important cohort of children with CKD, researchers will be able to explore the associated cardiovascular morbidity and mortality, and a number of risk factors for worsening kidney disease, including obesity, type 2 diabetes, and hypertension. The information obtained from this study will establish natural history and outcome measures for future intervention and prevention trials.

Item

Polycystic Kidney Disease – The Committee recognizes that NIH research combined with grants from the private sector and the involvement of industry has produced the first clinical drug trial for PKD in humans, and has fostered the development of additional, innovative PKD therapies. The Committee recognizes that the four PKD centers of excellence have engendered a broad range of alternative model research systems and reagents shared worldwide among PKD investigators and have drawn a host of investigators from other disciplines into the PKD field. The Committee encourages NIDDK to facilitate PKD clinical trials by strengthening studies of pathophysiology and cellular pathobiology. (p.67)

Action taken or to be taken

The NIDDK is committed to research that will pursue opportunities to combat polycystic kidney disease (PKD)—a serious, burdensome, and costly disorder characterized by the growth of numerous cysts in the kidneys. The NIDDK supports a diverse portfolio of basic and clinical research into the underlying biology of and possible therapies for PKD. The Interdisciplinary Centers for Polycystic Kidney Disease Research are important components of this research portfolio. The NIDDK has recently renewed funding for four Centers for 5 more years. Three of these Centers focus on the more common autosomal dominant PKD (ADPKD) and will explore extensively the basic and clinical functional changes seen in ADPKD. The fourth center focuses on autosomal recessive PKD (ARPKD) and will make available to investigators in the field a broad range of model research systems and reagents for the study of ARPKD.

The Institute also has two other major research projects related to PKD--the HALT-PKD trial network, and the Consortium for Radiologic Imaging Studies of PKD (CRISP) cohort study. 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, in combination with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, will slow the progression of PKD. These drugs are used to treat the high blood pressure that often accompanies PKD. Left untreated, high blood pressure can cause further damage to the kidneys and increase the risk for stroke and other cardiovascular events. The HALT-PKD studies began in late 2005. A partnership with industry to provide medications for testing in these studies has been negotiated.

CRISP was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for ADPKD. This 4-year study has followed 240 PKD patients with annual glomerular filtration rate evaluation (a measure of kidney function), and magnetic resonance imaging to assess changes in kidney volume over time. The first phase of CRISP was recently completed, and the primary study results will soon be analyzed and submitted for publication. The NIDDK anticipates funding an extension of CRISP in early 2006.

Item

Interstitial cystitis (IC) – The Committee believes that the 2003 NIDDK-sponsored scientific symposium on IC was very successful and encourages NIDDK to convene a similar symposium on IC in 2006, collaborating with appropriate voluntary organizations. The Committee also encourages NIDDK to hold a separate meeting of leading international researchers involved in IC research to seek clarity on the definition of IC. The absence of a uniform definition which accurately captures the condition and the affected population is negatively affecting patients in terms of diagnosis and treatment as well as researchers in terms of literature review. The Committee was encouraged to learn that NIDDK is launching an IC awareness campaign and hopes that NIDDK will continue to work closely with the IC patient community on both developing the content and executing the campaign. (p.67)

Action taken or to be taken

The NIDDK is pursuing multiple efforts to combat IC, a condition that results in recurring discomfort or pain in the bladder and the surrounding pelvic region. These include its IC Clinical Research Network and basic science to help further understanding of underlying causes and symptoms and thus speed new interventions. An NIDDK-planned international scientific meeting for FY 2006 will focus on "Frontiers in Painful Bladder Syndrome and Interstitial Cystitis." Participating in the planning are extramural researchers; the Interstitial Cystitis Association (ICA), a major patient advocacy group; and the NIH Office of Research on Women's Health. In conjunction with this meeting, the NIDDK plans to hold its second meeting of grantees funded through an FY2003 Requests for Applications.

The NIDDK shares the Committee's concern about the lack of a consensus definition, and hopes to build upon progress that has been made in identifying common clinical symptoms among some patients. Emerging scientific data could be key in developing an evidence-based, clinically useful diagnostic definition. For example, clinical studies of a promising biomarker for IC, antiproliferative factor (APF), may yield a new diagnostic tool. This research is rapidly evolving, as is experience with questionnaire based instruments for diagnosis, and there is some concern that it may be premature to harden diagnostic criteria without the results of this on-going work. The diagnostic issue will be discussed with members of the IC Clinical Research Network and the external advisory committees for each of our IC studies. Discussion of the diagnostic issues will also be a major topic at the 2006 international meeting. While a consensus definition is still under development, awareness needs to be increased so that individuals exhibiting symptoms can receive a timely diagnosis and currently available treatments for pain and urinary frequency. In fall 2004, the NIDDK initiated an IC Awareness Campaign to reach out to urologists and to increase general public awareness. Its National Kidney and Urologic Diseases Information Clearinghouse is the primary distribution channel for outreach materials, which include information on therapeutic options for patients. In developing this campaign, the NIDDK received input from the ICA through its participation in an *ad hoc* coordinating panel for the Clearinghouse, and through discussions with the group's president and founder. Approaches were targeted to three audiences; for example, to reach the general public, the Clearinghouse developed a feature article about IC and achieved nationwide distribution. The NIDDK is currently completing its information campaign for urologists, and will collaborate with the CDC's new public campaign on IC.

Item

Hepatitis C – The Committee is pleased to learn that there have been 50 patient applications filed for new therapies for hepatitis C and there are at least 6 drugs currently in early human trials. In addition to developing new drugs, the Committee encourages NIDDK to study the improvement of existing drugs to reduce their toxicity and negative side effects. The Committee applauds NIDDK for formally adopting the goal of 90% treatment effectiveness rate for hepatitis C within ten years. (p. 68)

Action taken or to be taken

The NIDDK supports several clinical trials in which therapies for hepatitis C are being assessed in specific patient populations, in terms of both their effectiveness and side effects, including toxicity. For example, in the "Hepatitis C Antiviral Long-term Treatment Against Cirrhosis" (HALT-C) clinical trial of patients with hepatitis C who did not previously respond to treatment with antiviral therapy, one outcome being evaluated is patient quality of life and adverse events in response to long-term treatment with peginterferon, a drug used to treat hepatitis C. In a similar clinical trial in children with hepatitis C, the "Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C" trial (Peds-C), response to therapy with these drugs is being evaluated in terms of short- and long-term risks. The study of "Viral Resistance to Antiviral Therapy of Chronic Hepatitis C" (Virahep-C) is investigating reasons for the lower response rate to interferon-based therapy in African Americans with hepatitis C, and will monitor response to this therapy, including any side effects, so that therapy in these patients can be improved. Additionally, the NIDDK has established the "Drug-Induced Liver Injury Network" (DILIN) to help develop means to prevent, detect, and treat liver disease due to toxicity caused by medications. This Network includes a prospective study of prescription drugs, over-the-counter medications, and herbal medications, as well as the development of instruments to improve diagnosis. These issues are also addressed in the ten-year trans-NIH "Action Plan for Liver Disease Research." Research goals include: identifying genetic factors that contribute to liver toxicity; improving the response rate to available treatments for chronic hepatitis C so that more than 90 percent of patients can be effectively treated; and defining the efficacy of interferon and ribavirin in subgroups of patients with hepatitis C.

Item

Fatty liver disease – The Committee notes that there is an emerging obesity-related chronic liver disease, which may affect as many as one in four adults and a significant number of obese children. 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 is pleased that NIDDK is funding a fatty liver disease clinical trial that includes both adult and pediatric populations. The Committee encourages NIDDK to focus research on the progression of fatty liver disease to cirrhosis and the impact of alcohol on the progression of fatty liver disease. (p.68)

Action taken or to be taken

The NIDDK continues to vigorously support research on fatty liver disease, which occurs in two forms: alcoholic and non-alcoholic. Non-alcoholic liver disease--when accompanied by liver injury, liver cell death, inflammation, and scarring--is referred to as non-alcoholic steatohepatitis

(NASH). The NIDDK's research efforts include studies of the natural history, development, and treatment of non-alcoholic steatohepatitis (NASH)--including studies through the NASH Clinical Research Network. The Network has initiated two randomized controlled trials of promising therapies of NASH, one in adults and one in children.

The Institute recently funded a research program to develop a model to identify patients with more severe grades of non-alcoholic fatty liver disease--which can lead to NASH--and to better define the biological basis of its progression. The NIDDK has recently undertaken an initiative to encourage research targeted at preventing mitochondrial injury in diabetes, a disease that can be a precursor to NASH. In addition, the NIDDK, together with the National Institute on Alcohol Abuse and Alcoholism and the NIH Office of Dietary Supplements, is actively encouraging research to understand the molecular and biochemical mechanisms of both alcoholic and non-alcoholic forms of fatty liver disease.

As a first step toward understanding the impact of alcohol consumption by individuals with fatty liver disease, the NIDDK recently supported a large, national, population-based study. The findings of the study indicated that consumption of more than two alcoholic drinks per day for overweight persons or one alcoholic drink per day for obese person increased the risk of an elevated marker (the enzyme alanine aminotransferase or ALT) of liver damage or disease, compared to normal-weight persons. This study concluded that the risk of alcohol-related abnormal ALT activity was limited to overweight and obese individuals.

To spearhead future research, the NIDDK Liver Disease Branch and the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee recently developed the ten-year trans-NIH "Action Plan for Liver Disease Research," (http://liverplan.niddk.nih.gov). The Plan includes research objectives related to fatty liver disease, including: (1) to more fully characterize the clinical, metabolic, and molecular abnormalities during disease progression, and (2) to better define the safe level of alcohol intake in different populations, including the overweight and obese, minority populations, and patients with diabetes and chronic viral hepatitis or other forms of non-alcoholic liver disease.

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 of this disorder and encourages NIDDK to collaborate with NHLBI and other institutes to enhance its research portfolio, encourage detection, raise public awareness about alpha-1 and provide appropriate information to health professionals. (p.68)

Action taken or to be taken

The NIDDK supports basic and clinical research aimed at understanding the mechanisms of liver injury and translational efforts to develop treatment options for liver disease associated with alpha-1 antitrypsin (AAT) deficiency. AAT is a protein that is produced in the liver and maintains healthy lungs by preventing emphysema. Mutant AAT genes produce abnormal protein molecules that combine and form polymers. The polymers cannot be secreted and accumulate in the liver cells, eventually becoming toxic and causing liver disease. AAT deficiency is one of five liver conditions that affect children to be included in the recently

established Cholestatic Liver Disease Consortium. This Consortium provides an opportunity to gather clinical and biochemical data and an adequate number of biosamples collected in a prospective manner to enable research on the development and optimal diagnosis of this disease, as well as its prevention and treatment.

The NIDDK also supports a toxicity study of an adeno-associated virus/AAT agent used to deliver genetic material to the liver of hepatitis C-infected chimpanzees through the NIH-supported National Gene Vector Laboratories. In addition, the NIDDK and the National Heart, Lung, and Blood Institute consult regularly on the application of gene therapy to AAT deficiency diseases, which can damage both the liver and the heart. The two Institutes support initiatives jointly and independently to encourage research in response to emerging scientific opportunities.

To advance future research on diseases such as AAT deficiency, the NIDDK Liver Disease Research Branch and the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee spearheaded the ten-year trans-NIH "Action Plan for Liver Disease Research" (http://liverplan.niddk.nih.gov), published in December 2004. The NHLBI and other NIH Institutes and Centers contributed to the development of the Plan, and will continue to participate in its implementation, which includes research goals relevant to better understanding and managing ATT deficiency.

The NIDDK is also making efforts to raise awareness about AAT deficiency. For example, the NIDDK-supported National Digestive Diseases Information Clearinghouse website has a link to the Alpha-1 Foundation website, accessible at: 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

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 strengthen this important program with an increased emphasis on irritable bowel syndrome. (p.68)

Action Taken or to be Taken

To combat the wide range of digestive diseases, the NIDDK supports multi-pronged research programs, such as its Digestive Diseases Research Centers Program, which includes a center with a research focus on irritable bowel syndrome (IBS). This center is the Specialized Center of Research on Sex and Gender, at the University of California, Los Angeles. The Center has brought together experts in the areas of women's health and brain-gut interactions. This investigative network is applying functional brain imaging, such as functional magnetic resonance imaging (MRI), to elucidate the differences in brain-gut interactions in IBS patients. Through their imaging studies, these scientists have discovered that central stress responses are altered in patients with IBS, especially among female patients.

The NIDDK also supports the Gastrointestinal Biopsychosocial Research Center at the University of North Carolina, Chapel Hill. The center, consisting of seven cores, provides infrastructure for research studies conducted by the Center for Functional GI and Motility Disorders. Researchers are examining the psychological role of the perception and modulation of pain, the mechanisms of the central nervous system's role in modulating pain, the effects of reproductive hormones, and the role of stress and other factors on IBS.

In addition, NIDDK Digestive Disease Research Centers support studies relating to liver development and disease, peptic ulcer disease, Crohn's disease, hepatitis B, hepatitis C, and gastrointestinal cancers.

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. The Committee encourages NIDDK to provide adequate funding for irritable bowel syndrome/functional bowel disorders research and to give high priority to funding grants that will continue to increase the IBS portfolio. The Committee requests NIDDK to report to the Committee by March 15, 2006 its views on the appropriateness of developing a strategic plan for IBS research. (p.69)

Action taken or to be taken

The NIDDK continues to take steps to strengthen research on irritable bowel syndrome (IBS). Among the studies supported are those aimed at understanding the development of pathways that control motility mechanisms in the gut; integration of pain, motility and behavior within the central nervous system; the relationship of gut inflammation to these pathways; translational research aimed at moving discoveries in animal models into studies in humans; and clinical studies. IBS is a focus of research at the NIDDK-supported Center for Neurovisceral Science and Women's Health at the University of California, Los Angeles. This center includes studies of the sex-based differences responsible for the greater vulnerability of women for chronic functional pain syndromes. Experts in the area of women's health and brain-gut interactions form a network that is applying functional brain imaging, such as functional MRI, to elucidate these differences.

With respect to strategic planning, the NIH is in the process of establishing a new National Commission on Digestive Diseases, which will develop a long-range research plan for the field, including IBS. It is expected that the report of the Commission will recommend promising research directions in IBS that will help guide the NIDDK, the NIH and the investigative and lay community in the pursuit of the most productive research avenues.

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 5 years after diagnosis. More research is needed in order to develop safe and effective treatments and to identify the causes of the complications of scleroderma. (p.69)

Action taken or to be taken

Scleroderma is an autoimmune disease characterized by abnormal growth of connective tissue in many organs of the body. With respect to altered functioning of the digestive system, the NIDDK supports research programs to address fundamental scientific properties of the cells and organs of the gastrointestinal tract in complications that can be caused by scleroderma—Barrett's esophagus, gastroesophageal reflux disease (GERD), gastroparesis, motility disorders, and fibrosis of the gut in inflammatory diseases. Insights obtained from these research areas may lead to improved treatment for the complications of scleroderma. For example, better treatments for patients with irritable bowel syndrome (a collection of motility disorders including gastroparesis or constipation) may lead to better treatments that will also benefit patients with scleroderma. In addition to basic research, the NIDDK supports significant translational research—translating the findings of basic research to clinical practice—on GERD.

With respect to kidney disease, patients with scleroderma who develop progressive kidney failure have over-activation of the renin-angiotensin system and increased levels of renin in their blood. When present in excessive amounts, renin, a hormone produced by the kidneys that helps regulate the volume of fluid in the body and blood pressure, may cause kidney failure. To better understand how renin levels are regulated in the blood, the NIDDK is supporting research to determine the normal and abnormal physiology of the renin-angiotensin system, as well as to elucidate specific mediators of blood vessel injury in the kidney.

The NIDDK participates in several NIH-wide activities that serve to promote research on scleroderma. The Institute is represented on the National Institute of Allergy and Infectious Diseases-led NIH Autoimmune Disease Coordinating Committee, which facilitates collaboration among the NIH institutes, other federal agencies such as the CDC and FDA, and non-Federal organizations. The NIDDK coordinates research efforts with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the lead institute with regard to scleroderma research at NIH. The NIDDK will continue to support meritorious research that targets specific organs within the Institute's mission that can be affected by scleroderma.

Item

Glomerular disease research – The Committee continues to be pleased with the work of NIDDK in the area of glomerular disease research, particularly as it relates to focal segmental glomerulosclerosis. The Committee commends NIDDK for conducting the recent glomerular disease workshop and encourages NIDDK to use a program announcement or other appropriate mechanism to ensure the initiation of grant proposals, training positions, and other activities to expand the NIDDK portfolio in this important area of research. (p.69)

Action taken or to be taken

The NIDDK is furthering research to understand, treat and prevent diseases that arise from damage to the glomeruli—the tiny filtering units of the kidney. Damage to these filtering units can allow protein and sometimes red blood cells to leak into the urine. In severe cases, glomerular disease can impair the clearance of waste products from the blood by the kidney.

There are a number of causes of glomerular disease; it may be the direct result of an infection or a drug toxic to the kidneys, or it may result from a disease that affects the entire body. In January, 2005, the NIDDK convened a two-day workshop on glomerular disease. Experts from around the world and NIH staff discussed the pathobiology of glomerular disease, the identification of biomarkers of glomerular disease, resources from existing sample banks and cooperative studies, and ways to implement clinical trials more effectively. A summary of the meeting was recently accepted for publication in the *Journal of the American Society of Nephrology* and is also available on the NIDDK website (http://www.niddk.nih.gov/fund/other/glomerular/Summary-Report.pdf). The Institute has observed an increase in grant applications focusing on glomerular disease, and has recently funded several glomerular disease clinical projects. The Institute anticipates issuing a program announcement in FY 2006 to encourage basic science proposals in areas highlighted in this report. In addition NIDDK will give priority to investigator-initiated clinical projects that are responsive to the overall goals discussed at the workshop, as it continues the Kidney Disease Clinical Studies Initiative (KDCSI). KDCSI aims to improve the quality and quantity of clinical studies encouraging the full and effective use of resources, including data and biological samples, from NIDDK-supported clinical trials and epidemiological studies in kidney disease. The KDCSI also hopes to increase the number of investigator-initiated clinical studies, including small-scale, interventional studies; observational studies; and feasibility studies that could lead to potential, large-scale interventional trials that are adequately powered and efficient.

One kind of glomerular disease, focal segmental glomerulosclerosis (FSGS), is a relatively common, irreversible kidney disease characterized by the presence of areas of scarring in some of the glomeruli. Although it can be associated with other disorders, such as HIV infection or certain cancers, FSGS can also appear as a primary condition. No current treatment for FSGS is completely satisfactory. The NIDDK has formed a collaborative network of research centers to study possible new therapies for FSGS. The FSGS Clinical Trial is comparing the effectiveness of two treatment regimens in children and young adults with steroid-resistant FSGS. Although the trial has experienced an unexpected difficulty in recruiting substantial numbers of patients, the Institute is actively working with the researchers to address this impediment to this important trial's progress.

Item

Osteoporosis – The Committee encourages NIDDK to support research targeting new technologies and therapies to increase bone mass and combat osteoporosis through focus on: (1) genetics, environmental and lifestyle factors, and (2) the effects of disease, in order to address the research questions highlighted in the Surgeon General's Report on Bone Health and Osteoporosis. (p.70)

Action taken or to be taken

The NIDDK funds important research on the factors affecting bone health, with particular emphasis on the effects of hormones and metabolic processes on bone formation and integrity. The NIDDK's research efforts will help to address some of the key questions in the 2004 Surgeon General's Report on Bone Health and Osteoporosis related to bone remodeling and the importance of hormones and calcium in maintaining bone health. In osteoporosis, bone strength is compromised, resulting in increased risk for fracture. Bone strength, which depends on the mineral and matrix composition of the bone, is affected by nutritional factors such as calcium

intake, phosphorous, or vitamin D deficiency; lifestyle factors such as smoking or lack of weight-bearing exercise; and genetic factors, including the control of parathyroid hormone (PTH). An example of relevant NIDDK research is the Institute's support of extensive research on leptin, a hormone involved in bone formation and on bone-specific anabolic (growth-promoting) factors. Other important NIDDK research focuses on hyperparathyroidism, a calcium-regulation hormone disorder, and reduced bone mineral density (osteopenia). These are the most common conditions associated with osteoporosis and fractures. NIDDK-supported research on parathyroid hormone (PTH) has led to development of a form of PTH (a fragment of the complete peptide) as a therapeutic agent for osteoporosis. Furthermore, studies of nuclear receptors may be particularly helpful in understanding glucocorticoid-induced osteoporosis, caused when cortisone-type medications both interfere with bone-formation and increase bone loss.

The NIDDK continues to work in concert with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the institute with the primary role of supporting work on the genetics and cell biology of bone cell function, as well as with the National Institute on Aging, which plays a key role in research on age-related changes in bone health. Cooperative research efforts address the effects of body composition on the skeleton both in adults and children, and in those affected by chronic conditions such as kidney disease, obesity, and type 2 diabetes. Furthermore, the NIDDK promotes research on technologies and therapies to increase bone mass, as well as mechanistic studies designed to better understand the molecular processes that control bone remodeling in health and disease.

Item

Paget's disease – The Committee encourages NIDDK to study the functional consequences of the recently identified gene mutations in Paget's disease as a means of identifying new therapeutic treatments for the disease. (p.70)

Action taken or to be taken

The NIDDK supports research in a number of areas that contribute to the understanding of common and convergent metabolic and signaling pathways that may impact bone metabolism in genetically susceptible individuals—including patients with Paget's disease. It is clearly important to understand the mechanisms underlying Paget's disease, a bone remodeling disorder that affects bones in the skull, hip, pelvis, legs, and back. Research has shown that the disease has strong genetic components, particularly mutations of proteins involving a specific molecular signaling pathway called NF-kappa-B. This pathway relays cues from outside the cell to effect changes in gene expression, usually inducing an inflammation response. The defect in Paget's disease primarily affects osteoclasts, the cells that break down bone tissue. Recent NIDDK-supported research on the NF-kappa-B pathway in closely related cells (macrophages) has identified and characterized components that may be amenable to therapeutic treatment. In a related effort, the NIDDK has supported research to understand the basis of drug-induced osteopenia, reduced bone mineral density. These efforts may lead to the development of new targeted anabolic (growth-promoting) agents for the treatment of multiple bone disorders.

Item

Mucopolysaccharidosis (MPS) – The Committee recognizes the efforts of 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 efforts by NIDDK to reach out to NIAMS to improve collaborative bone and joint disease research in MPS disorders. Research focused on the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored, and potential therapeutic approaches continue to be of significant interest of the Committee. The Committee commends NIDDK on its collaborations with NINDS, NICHD, NCRR, and ORD in advancing broad-based MPS-related research. (p.70)

Action taken or to be taken

The NIDDK remains committed to supporting research on MPS disorders, so that new therapeutic approaches can be developed. Among the many deleterious effects of MPS are bone and joint abnormalities, resulting from the toxic accumulation of substances called glycosaminoglycans (GAGs) in cells. A recently-funded research project is exploring a new hypothesis as to how, at the molecular level, GAG accumulation leads to bone and cartilage abnormalities. The NIDDK also supports other research to investigate the pathogenesis of MPS-related bone and joint lesions, as well as other MPS-related problems. Knowledge gained from this research may inform the development of new treatment approaches, and the NIDDK has met with the National Institute of Arthritis and Musculoskeletal and Skin Diseases to discuss potential future efforts relevant to MPS research. The NIDDK also supports Molecular Therapy Core Centers (MTCC) that are pursuing MPS research. The NIDDK supports research on gene therapy for MPS in animal models, including studies associated with MTCCs and other studies. For example, this past year, a researcher reported promising results of gene therapy in mice to prevent cardiac, bone, ear, and eye disease. A treatment in clinical use for MPS I disease is enzyme replacement therapy: administration of the enzyme that patients lack. A limitation of this strategy is the body's natural "blood-brain barrier," which impedes the penetration into the brain of therapeutic agents that are circulating in the blood. This biologic barrier thus limits the effectiveness of therapeutic agents on the serious brain-related symptoms of MPS. However, in recent NIDDK-supported research on a mouse model of MPS VII, scientists reported a potential strategy for overcoming the blood-brain barrier; these results may have implications for enzyme replacement therapy in humans. Among the genetic mutations in MPS patients, several affect protein processing, resulting in defects in the normal degradation of GAGs. Research addressing abnormalities in protein processing and folding may lead to new therapies for some MPS patients and people with other inherited diseases with similar underlying protein defects. The NIDDK is encouraging research to identify and optimize small molecule reagents that ameliorate disease-causing defects in protein folding or processing. Finally, the NIDDK supports research on newborn screening tests for MPS. For example, this past year, scientists reported new progress in screening newborn blood spots for MPS I. The severe infantile form of MPS I is a progressive degenerative disease; newborn screening would identify infants with this disease, permitting therapy initiation prior to irreversible tissue damage. Therapies could include transplantation of bone marrow (previously the only effective therapy) or umbilical cord blood (which recently showed promise in studies in children), and/or the recently-developed enzyme therapy.

Item

Fragile X – Fragile X mental retardation is a single-gene disorder that results from an unusual kind of mutation. Study of the chain of events set in motion by this mutation may lead to the identification of points in the process at which interventions may ameliorate symptoms. The Committee encourages NIDDK to enhance its research activities on fragile X and to coordinate these efforts with other Institutes working on related activities, including NIMH and NICHD. (p.70)

Action Taken or to be Taken

Fragile X is a genetic, developmental disorder that most dramatically affects the central nervous system. Thus, other components of the NIH—National Institute of Child Health and Human Development, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke—are primarily responsible for research on this disease. However, NIDDK scientists are studying the etiology of Fragile X through analysis of the gene that is mutated in this disorder. More generally, the NIDDK supports four Molecular Therapy Core Centers that are pursuing the goal of gene therapy, which would be of potential benefit to patients with Fragile X, as well as those with other genetic diseases.

Item

Cooley's anemia – The Committee continues to support the high quality research being conducted by 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.70)

Action taken or to be taken

The NIDDK is pursuing research to develop less burdensome therapies for removing toxic iron levels that result from the chronic blood transfusions Cooley's anemia patients need for survival. Cooley's anemia is a genetic blood disease that results in an inadequate production of hemoglobin, the essential oxygen-carrying substance in blood. A specific focus of the research program is the development of effective and more easily administered iron-removing drugs—known as iron chelating agents. The NIDDK is seeking alternatives to the injected drug, desferrioxamine, whose administration regimen is difficult and painful for patients. Another chelator (HBED) has entered an industry-supported clinical trial; while this chelator must be injected, the procedure is much less onerous than conventional therapy, and patients are expected to show improved adherence to therapy when using this drug. NIDDK-supported studies have also resulted in successful preclinical evaluation of a re-engineered version of the oral chelator, desferrithiocin – a substance that binds to the iron. This new compound is currently being tested in an industry-supported clinical study. The NIDDK is supporting additional studies on other chelators, and has emphasized the importance of this area by providing an expedited "MERIT" award to an investigator in the field. Two new chelators have entered the NIDDK toxicology contract program for preclinical toxicity testing. Finally, through studies supported by NIDDK, researchers have a better understanding of how the different iron chelating drugs remove iron from body tissues. Researchers are now testing whether "smart" combinations of chelators may both maximize iron removal and enable use of lower doses of the drugs; early results are encouraging.

Current methods for non-invasive measurement of body iron in patients with iron overload are costly and not widely available. The NIDDK and National Institute of Biomedical Imaging and Bioengineering are collaborating in support of projects that may improve the utility of magnetic resonance imaging (MRI) in this area. 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 Cooley's anemia and sickle cell disease patients. In October 2005, the NIDDK and the NIBIB hosted a second 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. Several groups reported progress regarding the ability to obtain clinically-useful information via MRI technology, and to advise patients concerning their iron burden. Building upon this progress, researchers can continue to refine MRI technology as applied to measuring iron burden so that it may become an important tool in tailoring treatment for individual patients.

Item

Cystic fibrosis (CF) – The Committee commends NIDDK for supporting cystic fibrosis research and translational centers. When awarded later this year, they will provide resources for communication and collaboration between basic and clinical researchers to enhance the efficiency of research and foster cooperation within and among institutions with strong existing bases of cystic fibrosis (CF) research. The Committee also commends NIDDK for its support of the EPIC study, a longitudinal assessment of risk factors for and impact of Pseudomonas aeruginosa acquisition and early antipseudomonal treatment in children with CF. This study holds the promise of yielding critically important information about the optimal treatment of initial lung infections in children with CF. The Committee encourages NIDDK to continue its support of CF research efforts, including proteomics research. CF researchers are looking at the many proteins that play a role in CF, in hopes of identifying new drug targets to treat CF. The Committee commends NIDDK for its support of the program announcement for research proposals focusing on discovery and development of compounds that will correct protein misfolding. The Committee encourages NIDDK to further support this especially promising area of research. (p.70)

Action taken or to be taken

The NIH is pursuing multiple avenues to bolster research toward understanding and finding therapies for cystic fibrosis (CF), including studies of protein misfolding or misprocessing, which underlies this disease and many others. With a Program Announcement in 2005, the NIDDK is fostering research to identify and optimize small molecule reagents that ameliorate a protein misfolding or misprocessing defect that would cause diseases such as CF. As a result of another Program Announcement, the NIDDK recently funded a new project to develop a high throughput screen to facilitate identification of potentially therapeutic agents for CF. The type of agents targeted by this screen would work by helping a mutant protein (caused by a mutation termed "deltaF508") get from the interior of a cell to its proper location at the cell surface. The deltaF508 mutation is involved in most cases of CF. The NIDDK also funded two Cystic Fibrosis Research and Translational Core Centers in 2005, and is partnering with the National Heart, Lung, and Blood Institute to support a new trial, begun this past year, on Early Pseudomonas Infection Control (EPIC). CF research may also benefit from research emanating

from the initiatives of the NIH Roadmap for Medical Research. For example, the Molecular Libraries component of the NIH Roadmap aims to develop and make available small molecules as research tools, and to accelerate development of advanced screening technologies.

Item

Hepatitis C virus (HCV) and bleeding disorders – The Committee encourages NIDDK to work with appropriate voluntary organizations in developing and advancing research initiatives for addressing HCV within the bleeding disorders community. (p.70)

Action taken or to be taken

Research issues relevant to particular populations of patients with hepatitis C, such as those with bleeding disorders, are addressed in the trans-NIH "Action Plan for Liver Disease Research." This Plan was recently developed with broad stakeholder input from across the NIH and other Federal agencies, academic research and medical practice communities, and professional and patient advocacy groups. Leadership for the Action Plan was provided by the NIDDK under the auspices of the statutory Digestive Diseases Interagency Coordinating Committee. Research goals identified in this ten-year Action Plan include improving the response rate to available treatments for chronic hepatitis C so that more than 90 percent of patients can be effectively treated, and defining the effectiveness of interferon and ribavirin in subgroups of patients with hepatitis C. To pursue important research goals identified in this Plan, the NIDDK will continue to collaborate with all stakeholders, including representatives of professional and patient advocacy organizations focusing on bleeding disorders, in order to advance liver disease research relevant to these communities.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Cystic Fibrosis [CF] – The Committee encourages NIDDK to continue its support of CF research efforts, including proteomics research. CF researchers are looking at the many proteins that play a role in CF, in hopes of identifying new drug targets to treat CF. The Committee commends the NIDDK for its support of the program announcement for research proposals focusing on discovery and development of compounds that will correct protein misfolding. The Committee encourages NIDDK to further support this especially promising area of research. (p.104)

Action taken or to be taken

Please refer to pages 48-49 of this document for the NIDDK's response to this significant item regarding cystic fibrosis.

Item

Diamond-Blackfan Anemia – The Committee is pleased that NIDDK will be hosting a workshop to understand the state of the science of Diamond-Blackfan Anemia [DBA] as it relates to research important to NIDDK, including red cell formation, ribosomal proteins, DBA animal models, gene therapy, mechanisms of iron overload and the development of treatment options for patients with iron overload. The Committee strongly encourages NIDDK to develop grant opportunities to support DBA research initiatives in these areas. (p.104)

Action taken or to be taken
The NIDDK is currently planning to host the scientific workshop in Spring 2006 on Diamond Blackfan Anemia (DBA), a rare congenital anemia that usually presents early in infancy. The workshop will focus on a number of scientific research areas within the NIDDK mission that are critical for making progress regarding the causes and treatment of DBA. The NIDDK intends to develop a research solicitation for DBA based upon scientific research opportunities identified through the workshop. The NIDDK will seek collaborations with other NIH ICs that support research important to understanding DBA when planning the workshop and subsequent efforts, in order to build synergy in this area.

Item
Digestive Diseases – 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 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.104)

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 digestive diseases.

Item
Diabetes in Native Hawaiians – The Committee commends the NIDDK for its focused research on diabetes in Native American, Native Alaskan, and Native Hawaiian populations. The Committee is pleased with the innovative multicultural diabetes prevention campaign tailored specifically for native populations and the collaboration with CDC in the SEARCH epidemiological study. Additionally, the Committee requests an update in the fiscal year 2007 appropriations justification on recommendations resulting from the NIDDK and IHS conference scheduled to convene in 2005, and looks forward to similar conferences addressing prevention and treatment strategies in Native Hawaiian communities. (p.104)

Action taken or to be taken
Native Hawaiians, American Indians, and Alaska Natives are at increased risk for type 2 diabetes, and the NIDDK is continuing its strong support of diabetes research and education efforts for these populations. The NIDDK provided scientific advice to the Indian Health Service (IHS) during the planning of the IHS's 2005 conference on "Prevention of Cardiovascular Disease and Diabetes among American Indians and Alaska Natives." At this meeting, the NIDDK- and CDC-supported National Diabetes Education Program (NDEP) introduced its new materials tailored for American Indians and Alaska Natives, for the campaign "Take Care of Your Heart: Manage Your Diabetes for Future Generations." These new materials were adapted from the NDEP's nationwide "Be Smart About Your Heart" campaign. The IHS conference participants assessed options for prevention and treatment of cardiovascular disease (CVD) and type 2 diabetes; reviewed health disparities issues affecting American Indians

and Alaska Natives; explored the vital role of American Indian and Alaska Native Tribal and health leaders in the development of health interventions; and obtained tools, skills, and ideas to help promote the prevention of diabetes and CVD in these populations.

Examples of other efforts include the following. The NIDDK is supporting the NDEP's "Small Steps. Big Rewards. Prevent Type 2 Diabetes" campaign, with materials tailored specifically for American Indians and Alaska Natives and for Asian Americans and Pacific Islanders. This campaign is based on the results of the Diabetes Prevention Program (DPP), a landmark NIH-supported multicenter clinical trial that demonstrated that people at increased risk for type 2 diabetes can prevent or delay disease onset through relatively modest changes in diet and moderate physical activity. The DPP included American Indian and Native Hawaiian participants. Researchers are continuing to follow the DPP participants, in Hawaii and the other locations, in the DPP Outcomes Study. The NIDDK also supports studies to develop a curriculum for teaching American Indian middle and high school students about biology in the context of diabetes, in order to convey the benefits of lifestyle changes to reduce diabetes risk and to encourage the students to prepare for biomedical careers. To determine the prevalence and incidence of both type 1 and type 2 diabetes in children, the NIDDK is supporting the CDC-led SEARCH epidemiological study. One of the six nationwide SEARCH centers is in Hawaii, and another is specifically recruiting American Indians.

Item

Fatty Liver Disease – The Committee notes that there is an emerging obesity-related chronic liver disease, which may affect as many as one in four adults and a significant number of obese children. 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 is pleased that NIDDK is funding a fatty liver disease clinical trial that includes both adult and pediatric populations. The Committee urges NIDDK to focus research on the progression of fatty liver disease to cirrhosis and the impact of alcohol on the progression of fatty liver disease. The Committee notes that the recently published new USDA nutrition guidelines regarding alcohol consumption may not be appropriate for individuals with fatty liver disease, and therefore urges NIDDK to focus research on this matter to support a clarification of the USDA guidelines. (p.105)

Action taken or to be taken

Non-alcoholic steatohepatitis (NASH) is a form of non-alcoholic fatty liver disease accompanied by liver injury, hepatocellular necrosis, inflammation, and scarring. Research addressing the natural history, development, and treatment of NASH continues to be an active area of research for the Institute. In addition to the NASH Clinical Research Network, the NIDDK has recently funded a research program to better define the biological progression of non-alcoholic fatty liver disease and to develop a model to identify patients with more severe grades of the disease. The Institute has recently undertaken an initiative to encourage research targeted at preventing mitochondrial injury in diabetes, which can be a precursor disease. To gain insights into the

molecular and biochemical mechanisms of alcoholic and non-alcoholic fatty liver disease, the NIDDK, together with the National Institute on Alcohol Abuse and Alcoholism and the NIH Office of Dietary Supplements, has released a research solicitation to encourage research in this area.

As a first step toward understanding the impact of alcohol consumption by individuals with fatty liver disease, the NIDDK recently supported a large, national, population-based study. The findings of the study indicated that consumption of more than two alcoholic drinks per day for overweight persons or one alcoholic drink per day for obese person increased the risk of an elevated marker (the enzyme alanine aminotransferase or ALT) of liver damage or disease, compared to normal-weight persons. This study concluded that the risk of alcohol-related abnormal ALT activity was limited to overweight and obese individuals. Consistent with these findings, the USDA guidelines recommend that persons with other diseases not drink alcohol and this is particularly apropos to fatty liver disease. The NIDDK Liver Disease Branch and the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee recently developed the ten-year trans-NIH "Action Plan for Liver Disease Research," (http://liverplan.niddk.nih.gov) to guide future research in liver diseases. The Plan includes research objectives related to fatty liver disease, including : (1) to more fully characterize progression of non-alcoholic and alcoholic liver disease, and (2) to better define the safe level of alcohol intake in different populations. NIH-funded research will continue to be an important source of input to the USDA in the development of nutrition guidelines for Americans.

Item

Hepatitis B – The Committee is concerned that a consensus treatment protocol for hepatitis B does not yet exist, but is pleased to learn that NIDDK is actively supporting preliminary research to convene a research workshop to plan a Hepatitis B Consensus Development Conference. The Committee is pleased that NIDDK is taking all necessary steps to plan a successful conference, and urges that this conference be convened as soon as possible. (p.105)

Action taken or to be taken

Hepatitis B is a major cause of chronic hepatitis, cirrhosis, and liver cancer in the United States. A 3-day NIH workshop is planned on the topic of "Management of Hepatitis B" for April 6-8, 2006. This workshop will help to address several research challenges, including drug development for this disease. Several drugs are currently available to treat hepatitis B, and work by directly inhibiting replication of the virus or modulating the patient's immune system. Some of these agents were only recently approved, and consensus has not yet been reached on which treatment protocols are most effective in patients, particularly in certain subgroups. The workshop will also assess current understanding of the hepatitis B virus, the disease that it causes, and its optimal management, including a consideration of up-to-date results of clinical trials of new treatments. Recommendations for future directions in basic and clinical research will also emerge from this workshop. The workshop proceedings and recommendations will be submitted for publication in order to disseminate them for use by the wider medical practice community. The workshop will be sponsored by the NIDDK in collaboration with the American Association for the Study of Liver Diseases (AASLD).

Item

Hepatitis C – The Committee is pleased to learn that there have been 50 patent applications filed for new therapies for hepatitis C and there are at least six drugs currently in early human trials. In addition to developing new drugs, the Committee urges NIDDK to encourage the improvement of existing drugs to reduce their toxicity and negative side effects. The Committee applauds NIDDK for formally adopting the goal of a 90 percent treatment effectiveness rate for hepatitis C within 10 years. The Committee encourages NIDDK to work with the National Hemophilia Foundation in developing and advancing research initiatives for addressing HCV within the bleeding disorders community. (p. 105-106)

Action taken or to be taken

The NIDDK supports several clinical trials in which therapies for hepatitis C are being assessed in specific patient populations, in terms of both their effectiveness and side effects, including toxicity. For example, in the "Hepatitis C Antiviral Long-term Treatment Against Cirrhosis" (HALT-C) clinical trial of patients with hepatitis C who did not previously respond to treatment with antiviral therapy, one outcome being evaluated is patient quality of life and adverse events in response to long-term treatment with peginterferon, a drug used to treat hepatitis C. In a similar clinical trial in children with hepatitis C, the "Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C" trial (Peds-C), response to therapy with these drugs is being evaluated in terms of short- and long-term risks. The study of "Viral Resistance to Antiviral Therapy of Chronic Hepatitis C" (Virahep-C) is investigating reasons for the lower response rate to interferon-based therapy in African Americans with hepatitis C, and will monitor response to this therapy, including any side effects, so that therapy in these patients can be improved. Additionally, the NIDDK has established the "Drug-Induced Liver Injury Network" (DILIN) to help develop means to prevent, detect, and treat liver disease due to toxicity caused by medications. This Network includes a prospective study of prescription drugs, over-the-counter medications, and herbal medications, as well as the development of instruments to improve diagnosis.

These issues are also addressed in the ten-year trans-NIH "Action Plan for Liver Disease Research." Research goals include: identifying genetic factors that contribute to liver toxicity; improving the response rate to available treatments for chronic hepatitis C so that more than 90 percent of patients can be effectively treated; and defining the efficacy of interferon and ribavirin in subgroups of patients with hepatitis C. In order to pursue these and other important research goals and issues identified in this Action Plan, the NIDDK will continue to collaborate with all stakeholders, including representatives of patient advocacy organizations such as the National Hemophilia Foundation, to advance liver disease research relevant to these communities.

Item

Hematology – The Committee is aware of the high-quality hematology research in iron metabolism, gene regulation, and stem cell plasticity currently funded by the Institute. The Committee encourages NIDDK to set priorities for future research in these and new areas that significantly impact a broad array of blood disorders, such as erythroid differentiation, oxidant injury, and metabolomics. (p. 106)

Action taken or to be taken

The NIDDK has taken a number of steps to enhance and build its fundamental research programs in hematology. In March 2005, the Institute convened an external group of researchers to review its hematology program and to provide guidance on future program development. The group assessed existing gaps in the research portfolio and made recommendations on how to address them, providing input in such areas as hematopoietic stem cell development, and the use of the red blood cell as a model system for studying cellular damage, the nature and interrelationships of metabolites (small molecules having important functions in development, aging, and disease), and gene regulation. The NIDDK will implement the reviewers' recommendations as it pursues these research areas. To accelerate these efforts, the NIDDK recruited and hired a new co-director for its hematology research program. The new co-director--a clinical research scientist with extensive hematology expertise--joined the Institute in October 2005. The NIDDK also has a leadership role for an NIH-wide Roadmap Initiative on metabolomics. By enhancing technology, this cross-cutting, technology-development initiative is expected to benefit research on many diseases, including blood diseases.

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 is pleased that NIDDK is contributing to the development of standardized approaches to measure incontinence and urges NIDDK to continue collaborating with NICHD on the incontinence state-of-the-science conference and on appropriate follow-up to this conference. (p. 106)

Action taken or to be taken

The NIDDK has initiated steps to co-sponsor, with the National Institute of Child Health and Human Development and the NIH Office of Medical Applications of Research (OMAR), a state-of-the-science conference on "Prevention and Treatment of Fecal and Urinary Incontinence." OMAR has the responsibility for planning and coordinating the conference. The NIDDK and the OMAR plan to convene a group of representatives from interested Institutes and Centers of the NIH to discuss key aspects of the conference, to identify extramural scientific experts to serve on the OMAR Planning Committee, and to consider suggestions for a conference chair. The proceedings and recommendations from this conference will help to guide the NIH in its pursuit of future research directions in this important area.

Item

Inflammatory Bowel Disease – The Committee has been encouraged in recent years by discoveries related to Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease [IBD]. These extremely complex disorders represent the major cause of morbidity from intestinal illness. The Committee commends NIDDK for its strong leadership in this area and encourages the Institute to increase funding for research focused on: (1) 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 titled ''Challenges in Inflammatory Bowel Disease.'' The Committee also encourages NIDDK to continue to strengthen its partnership with the IBD community and increase funding for its successful Digestive Disease Centers program with an emphasis on IBD. (p. 106)

Action taken or to be taken

The NIDDK will continue to intensify its research efforts to understand, treat and prevent inflammatory bowel disease (IBD), including studies in the areas noted by the Committee. With respect to genetics, the NIDDK is exploiting research findings that have demonstrated a strong correlation between mutations in the *Nod2* gene and Crohn's disease. These findings suggest that the Nod2 protein plays a role in innate immunity in the intestine. Nod2 normally acts as an intracellular sensor for components of the bacterial cell wall, termed peptidoglycans. When Nod2 is mutated, it is no longer effective at detecting intracellular bacteria, which may contribute to Crohn's disease. Recent NIDDK-supported studies have shown that animal models of Crohn's disease have increased concentrations of an inflammatory mediator, IL-1β, and diminished capability to mount an innate immune response against bacterial infection in the intestine. These results provide greater insights into the causes and mechanisms of Crohn's disease and offer new targets for developing therapeutic strategies to treat this disease.

The NIDDK continues to fund translational research in IBD, including a multi-center clinical trial to evaluate rosiglitazone, a drug previously shown to contain anti-inflammatory effects in an animal model of IBD. The Institute also continues to support a multi-center Genetics Consortium to speed the search for additional genes which, when mutated, may be implicated in IBD.

In developing the NIDDK's digestive diseases research portfolio, the Institute requests and welcomes recommendations from the external scientific and lay community, including the research agenda developed by the scientific community titled: ''Challenges in Inflammatory Bowel Disease." Such stakeholder input has been useful in advancing research on the two major forms of IBD--Crohn's disease and ulcerative colitis. The NIDDK continues to work closely with the Crohn's and Colitis Foundation of America (CCFA). The Institute recently participated in the CCFA Workshop on "Colorectal Cancer Screening and Surveillance in Inflammatory Bowel Disease," and in the CCFA-sponsored meeting on "Pediatric Challenges in IBD Research."

Item

Integration of Type 1 Diabetes Research – The Committee urges the NIH to facilitate the effective integration of the various research programs funded by the special funding for Type 1 Diabetes Research. (p. 106)

Action taken or to be taken

The NIDDK has taken numerous steps to enhance ongoing coordination efforts among the research consortia and networks supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which the Institute administers on behalf of the Secretary and which involves multiple NIH ICs and the CDC. For example, the NIDDK has taken a leadership role in

standardizing the measurement of autoantibodies that are predictive of the development of type 1 diabetes across multiple consortia that are studying type 1 diabetes. These efforts will facilitate clinical trials of type 1 diabetes, as well as clinical trials of type 2 diabetes and children.

The NIDDK has also established a "Type 1 Diabetes Consortia Coordination Committee," which is chaired by a scientist external to the NIH and has representatives from numerous type 1 diabetes research consortia and networks. The NIDDK convened a meeting of the Committee in May 2005, with scientific representatives from 20 consortia and networks supported by the *Special Program* to promote increased collaboration. The NIDDK has responded to a recommendation emanating from that meeting by expanding its website dedicated to the *Special Program*, so that it can be used as the primary means for information sharing among the research consortia and also be useful to patients and researchers (http://T1Diabetes.nih.gov/). The major diabetes voluntary organizations, the American Diabetes Association (ADA) and the Juvenile Diabetes Research Foundation International (JDRF) have posted links to the website on their organizational websites. These links serve to direct type 1 diabetes patients directly to the NIH. To further coordinate clinical trial recruitment, the NIDDK has established a toll-free telephone number (1-800-HALT-DM1) to provide information on clinical trials to type 1 diabetes patients. In addition to the larger meeting on type 1 diabetes coordination, the NIDDK has also facilitated more focused meetings among consortia that share common interests. For example, in July 2005, the NIDDK convened a meeting of consortia whose investigators are studying the genetics of type 1 diabetes or its complications to discuss interoperability of databases and coordination of genotyping efforts. In addition, NIH staff and investigators involved in Type 1 Diabetes TrialNet and the Immune Tolerance Network have had a series of meetings to coordinate efforts.

More broadly, the NIDDK is coordinating its type 1 diabetes research efforts with other NIH-supported autoimmune disease efforts. The Institute is also considering approaches to integrate bioinformatics issues across multiple type 1 diabetes consortia in order to facilitate data sharing and analysis. Through focused meetings of consortia with common interests, as well as through broader coordination efforts, the NIDDK plans to continue promoting the integration of NIH type 1 diabetes research programs. These efforts will also be facilitated by a Strategic Plan for Type 1 Diabetes Research, which is currently under development by the statutory Diabetes Mellitus Interagency Coordinating Committee.

Item

Interstitial Cystitis – The Committee notes that RFAs have been very helpful in stimulating scientific interest in interstitial cystitis [IC]. Therefore, the Committee urges the NIDDK to continue using this funding mechanism when investing in IC-specific basic science research, particularly in the area of urinary markers. The Committee also encourages the NIDDK to sponsor a scientific symposium on IC in 2006 to follow up on the very successful 2003 symposium. The Committee also urges the NIDDK to hold a separate meeting of leading international opinion leaders involved in IC research to seek clarity 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 encouraged to learn that the NIDDK is launching an IC awareness campaign, and it hopes the NIDDK will continue to work closely with the IC patient community on both developing the content and executing the campaign. (p. 106-107)

Action taken or to be taken

The NIDDK is using multiple approaches to stimulate research on IC that could increase understanding of the cause(s) of IC and its symptoms--knowledge that will enable development of better treatments and possible a cure. For example, over 20 grantees were funded through an FY 2003 Request for Applications (RFA), "Basic Research in Interstitial Cystitis." A current Program Announcement is encouraging pilot and feasibility studies in urology, including studies in IC. A recently launched initiative to stimulate ancillary studies to NIDDK-supported clinical trials includes the Interstitial Cystitis Clinical Research Network (ICCRN), and will thus provide more opportunities for study of IC using patient samples and data collected (in accordance with policies that will be developed by the Network). The NIDDK also plans to support another meeting, in 2006, of the investigators funded under the FY 2003 RFA, in conjunction with an international symposium on IC and painful bladder syndrome. Both of these meetings will help continue the critically important cross-fertilization of ideas among researchers in the field. They will also provide forums at which investigators can provide feedback to the Institute on areas in which a future research solicitation, such as an RFA, may help to stimulate scientific pursuit in IC.

Please refer to page 38 of this document for the NIDDK's response to the remainder of this significant item regarding interstitial cystitis.

Item

Kidney Disease – Kidney disease is a rapidly growing health problem in the United States, where an estimated 15 million people have lost 50 percent of their kidney function and another 20 million more Americans are at increased risk of developing kidney disease. The marked increase in the end-stage renal disease [ESRD] population is fueled by the large number of patients with diabetes. Diabetes is the most common cause of kidney disease and accounts for 34 percent of patients on dialysis. Chronic kidney disease has emerged as a major contributing factor to cardiovascular disease. The Committee therefore encourages NIDDK to assign priority to expand the kidney disease research infrastructure through a robust program of kidney research core centers to promulgate collaborative research on a local, regional and national level. In addition, the Committee recommends expanded support for investigator-initiated research projects in five priority areas of greatest clinical importance: acute renal failure, diabetic nephropathy, hypertension, transplantation, and uremic cardiovascular toxicity. Research grant applications in these areas should be encouraged with appropriate program announcements and requests for proposals. Continued funding of grants to support development of investigator-initiated clinical and basic studies in these areas of high priority is essential. The Committee wishes to commend NIDDK for moving forward with the Clinical Trials Cooperative Group and supports collaboration with the renal community to seek new strategies and energize KUH clinical investigation in the above mentioned areas. (p. 107)

Action taken or to be taken

The NIDDK supports a diverse portfolio of research into the causes of and treatments for a number of kidney diseases. The Institute has worked to expand its portfolio of investigator-initiated clinical research studies, and has undertaken initiatives designed to encourage ancillary studies to ongoing clinical trials. The Kidney Disease Clinical Studies Initiative (KDCSI) aims to improve the quality and quantity of clinical studies by maximizing outcomes and reducing costs through sharing of resources obtained in previous studies, such as samples, specimens, and

data, and through innovative funding mechanisms. Launched in 2003 with a solicitation for "Concept Development Administrative Supplements" to existing NIDDK clinical projects, this Initiative was followed by three Program Announcements for "Ancillary Studies of Kidney Disease Accessing Information from Clinical Trials, Epidemiological Studies, and Databases," "Research Grants for Clinical Studies of Kidney Disease," and "Ancillary Studies to Major Ongoing NIDDK Clinical Research Studies." The main goals are: (1) to encourage the full and effective use of resources, including data and biological samples, from NIDDK-supported clinical trials and epidemiological studies in kidney disease, and (2) to increase the number of investigator-initiated clinical studies, including small-scale, interventional studies; observational studies; and feasibility studies that could lead to potential, large-scale, adequately powered, and efficient interventional trials. A Program Announcement is encouraging a "Pilot and Feasibility Program Related to the Kidney," which could include pre-clinical projects. In addition, the NIDDK and National Heart, Lung, and Blood Institute are issuing a Program Announcement to encourage ancillary studies to major ongoing clinical efforts, including clinical trials, epidemiological studies and databases. This initiative provides an opportunity to use well-described patient cohorts to address outstanding scientific questions. In moving forward, the Institute will continue to work closely with professional and voluntary organizations, including the American Society of Nephrology.

Item
Osteoporosis – NIDDK is encouraged to support research targeting new technologies and therapies to increase bone mass and combat osteoporosis, through focus on: (1) genetics, environmental and lifestyle factors, and (2) the effects of disease, in order to address the critical research questions highlighted in the Surgeon General's Report on Bone Health and Osteoporosis. (p.108)

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 osteoporosis.

Item
Paget's Disease – NIDDK is urged to study the functional consequences of the recently identified gene mutations in Paget's disease as a means of identifying new therapeutic treatments for the disease. (p. 108)

Action taken or to be taken
Please refer to page 45 of this document for the NIDDK's response to this significant item regarding Paget's Disease.

Item
Pediatric Kidney Disease – Kidney disease remains a persistent and poorly understood problem among infants, children and adolescents, impairing normal growth and development and often resulting in learning disabilities and mental retardation. Of urgent concern today is the explosion in the incidence of obesity among children and adolescents, a morbidity that places more than 15 percent of America's children at risk for developing type 2 diabetes, hypertension, and chronic kidney disease [CKD]. These morbidities not only represent a significant financial burden to the health care system but also are important risk factors for the development of cardiovascular

disease. The Committee urges NIDDK to continue to support research focused on the pathogenesis, prevention, and treatment of kidney disease in children. The Committee recommends that emphasis be placed on exploring the contributions of obesity, type 2 diabetes, and hypertension to progression of disease, and interventions that may limit cardiovascular morbidity in patients with CKD. (p. 108)

Action taken or to be taken
Please refer to pages 36-37 of this document for the NIDDK's response to this significant item regarding pediatric kidney disease.

Item
Polycystic Kidney Disease – The Committee is pleased to learn of the first clinical drug trial for PKD in humans and the development of additional, innovative PKD therapies. This progress directly benefits more than 600,000 Americans suffering from PKD and could potentially save billions of Medicare and Medicaid dollars for renal replacement therapy and free up thousands of spots on the kidney transplant waiting list. These discoveries have produced a cohesive, interdisciplinary body of scientific work benefiting PKD research; engendered a broad range of alternative model research systems and reagents shared worldwide among PKD investigators; and drawn a host of talented investigators from other disciplines into the PKD field. The Committee urges NIDDK to pursue fulfillment of its PKD Strategic Plan by facilitating PKD clinical trials, expanding studies of pathophysiology and cellular pathobiology, expanding the PKD research infrastructure, and enhancing resources to create a supportive environment for PKD investigators to develop new interventional strategies and pursue long-range planning. (p. 108-109)

Action taken or to be taken
Please refer to page 37 of this document for the NIDDK's response to this significant item regarding polycystic kidney disease.

Item
Primary Biliary Cirrhosis [PBC] – PBC is a rare, chronic and progressive liver disease that causes irreversible destruction of the bile ducts. The cause of PBC is still unknown, but current studies suggest it may involve autoimmunity, infection, or genetic predisposition, and does seem to appear more often in certain families. Women are affected 10 times more than men, and PBC is usually diagnosed in patients between the ages of 35 to 60 years. The Committee encourages NIDDK to further study this rare disease to determine among other things, why women are predominantly affected and whether there are successful treatment options other than liver transplantation. (p. 109)

Action taken or to be taken
NIDDK-funded research on primary biliary cirrhosis (PBC) is generating new knowledge about this disease, which can pave the way to better treatment and prevention strategies. For example, NIDDK-supported investigators recently reported that patients with PBC not only have elevated levels of peripheral blood monocytes (a type of white blood cell), but that the monocytes produce increased amounts of inflammatory proteins in the presence of molecules resembling a "mock" pathogen infection, compared to normal controls. These findings indicate that monocytes from patients with PBC respond in an exaggerated fashion when confronted with pathogens and this

response may be critical to the collapse of the body's ability to recognize "self" and to its subsequent misguided autoimmune attack on its own tissues. The NIDDK continues to support research designed to advance clinical, epidemiologic, and translational knowledge in the field of PBC. To encourage research on animal models of PBC, the NIDDK recently released a Program Announcement entitled "Animal Models of NIDDK-relevant Diseases."

With respect to current treatment, the drug ursodiol is effective in decreasing liver injury due to the blockage of bile excretion from the liver, and in retarding the progression of early-stage disease. The NIDDK continues to support pilot studies of therapy for PBC to identify agents that are safe and that can prevent progression to liver failure. One example is a pilot study that is evaluating the safety and efficacy of sertraline to decrease severe itching associated with PBC.

To help guide future research in PBC, the recently released ten-year trans-NIH "Action Plan for Liver Disease Research" contains several research goals, including the identification of genetic linkages and the development of sensitive and specific biomarkers for disease activity and stage. In addition, the Digestive Diseases and Nutrition Division of NIDDK expects to be supporting a review of the burden of digestive diseases in America, including differential impacts on subpopulations such as women and minorities. This review will help to further studies into the disproportionate impact of some digestive diseases on women--such as PBC and irritable bowel syndrome. With respect to strategic planning, the NIH is in the process of establishing a new National Commission on Digestive Diseases, which will develop a long-range plan for the field with a view toward identifying research challenges and opportunities.

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 for prostatitis. 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. The Committee applauds the work the Chronic Prostatitis Collaborative Research Network [CPCRN] has undertaken. The genetic and other possibilities linking prostate diseases are virtually unexplored. The Committee encourages microscopic studies of the prostatic fluid and tissue by infectious disease specialists, pathologists, immunologists and others. The Committee further encourages the NIDDK to increase research, public awareness, and public education to erase the stigma attached to this affliction that attacks young men. (p. 109)

Action taken or to be taken

The NIDDK is taking steps to encourage research to improve the understanding, management, and treatment of chronic prostatitis (CP), including using approaches that encourage the application of expertise from diverse medical specialties to such studies. For example, from October 19-21, 2005, the NIDDK convened a major scientific workshop on chronic pelvic pain and chronic prostatitis (http://www.niddk.nih.gov/fund/other/cpp/index.html). This meeting gathered experts in a variety of fields important to understanding and treating CP and other chronic pelvic pain syndromes, including pain and pain management, depression, neurology, interstitial cystitis, inflammation, and microbial infection. The topics and issues discussed at the workshop will help guide future NIDDK efforts in advancing research in this area.

The NIDDK is also continuing its support for the CP Collaborative Research Network (CPCRN). The Network was established in 1997 as part of an effort to standardize and evaluate various methods of diagnosing and treating CP, with the long-term goal of preventing and effectively treating this condition. A new, expanded Network was organized in FY 2003. This Network is currently conducting a randomized, double-blind placebo-controlled clinical trial of a drug, alfuzosin, that has shown promise to ameliorate urinary symptoms in men with CP/chronic pelvic pain syndrome. This trial will be conducted in recently diagnosed and/or newly symptomatic men who have not been previously treated with a drug of this type. This trial will enable evaluation of the potential benefit of treatment in men earlier in the course of their disease. To enhance trial development, the NIDDK has fostered collaboration between Network investigators and chronic pelvic pain experts in the NIDDK-supported Interstitial Cystitis Clinical Research Network. The NIDDK also continues to encourage the Network to investigate novel pathogens that may be contributing to the cause or course of prostatitis in the absence of bacteria. These efforts complement the Institute's ongoing support for investigator-initiated basic research projects in prostate biology and prostatitis. As a better understanding of CP is gained, and improved therapeutic options are developed, updated information will be made available to patients and the public through the NIDDK's National Kidney and Urologic Diseases Information Clearinghouse. Current information on the prevalence, incidence, treatment, and economic impact of CP in the United States will also be included in the final version of the Urologic Diseases in America compendium, publicly available on the NIDDK website (http://kidney.niddk.nih.gov/statistics/uda/index.htm).

Item

TEDDY – The Committee commends the NIDDK for launching TEDDY, a long-term study to identify the environmental causes of autoimmune diabetes. The Committee urges the NIDDK to communicate details of the study to the research community, to provide access to study materials and data, and to develop mechanisms to integrate new technologies into the study design. (p. 109)

Action Taken or to be Taken

The primary aim of TEDDY (The Environmental Determinants of Diabetes in the Young) is to identify infectious agents, dietary factors, or other environmental factors including psychosocial events, which may trigger the autoimmune attack on insulin-producing cells in people who are genetically susceptible to type 1 diabetes. Other aims include developing novel approaches to identifying environmental influences that may contribute to the onset of type 1 diabetes, and new strategies to prevent, delay and reverse the disease.

Among the most important of the explicit accessory aims of the study is to create a central repository with data and biological samples for use by the scientific community, thereby maximizing the scientific benefit that will come from this ambitious project. Indeed, samples are already being deposited by the NIDDK in a central repository.

Details of the study are being communicated to the public and to the research community in a variety of ways. In addition to the materials available on the NIDDK website (http://www.niddk.nih.gov/fund/diabetesspecialfunds/consortia-networks/teddy.htm), the study has its own public website (http://teddy.epi.usf.edu/). The TEDDY design report has been submitted for publication. Likewise, the data from the full study, when available, will be

submitted for publication. In the meantime, the methods and information about the study and opportunities for scientific participation via ancillary studies will be available on the websites, and in presentations at scientific meetings.

The NIDDK and TEDDY study coordinators have been proactive in their approach to ensuring that new technologies and novel methods for detecting disease-causing agents are brought to bear in the study of TEDDY biosamples. In close consultation and collaboration with the NIAID, the NIDDK held two workshops on the topic, bringing together a wide range of experts in the field. The samples from study cohorts will be available for use in ancillary studies in successfully competing research proposals.

Item

TrialNet – The Committee commends the NIDDK for its support of the Type 1 Diabetes TrialNet, which has launched a natural history study and a clinical intervention trial for juvenile diabetes. The Committee encourages the NIDDK to continue its efforts to translate basic and preclinical research on juvenile diabetes into a pipeline of new therapeutic strategies that can be evaluated through the TrialNet clinical trials network. The Committee urges the NIDDK to develop biomarkers for the evaluation of efficacy and the efficient operation of clinical trials and to develop more efficient approaches to subject recruitment for clinical trials. (p. 109)

Action Taken or to be Taken

TrialNet is being enhanced in ways noted by the Committee. TrialNet is committed to the development of biomarkers in support of clinical trials and it contributes to this effort in several important ways. First, TrialNet is directly engaged in an attempt to validate measurements of T cell autoimmunity in type 1 diabetes patients compared to controls (T Cell Validation Study, currently under way). Second, TrialNet is undertaking concurrent measurement of changes in the characteristics of immune cells that occur in response to therapy in ongoing trials (MMF/DZB Trial), and both phenotypic and functional studies in interventional trials under development (AntiCD20 and Oral Insulin). Third, NIDDK is planning to stimulate the discovery and development of biomarkers of autoimmunity in type 1 diabetes by offering a new research solicitation, with special emphasis on biomarkers able to track responses to therapy in clinical trials. TrialNet is also committed to partnering with the Immune Tolerance Network to collect and store samples from all individuals in phase 2 and phase 3 trials in the Natural History study, and from patients enrolled in all interventional trials. These samples will be stored in the NIDDK central repository and made available, by a peer-reviewed competitive process, to the type 1 diabetes research community to support the development of biomarkers.

With respect to patient recruitment, efforts are under way in TrialNet to meet this key challenge, which is present in any clinical study. The TrialNet Data Safety and Monitoring Board (DSMB) has addressed the issue of maximizing recruitment through a multi-pronged approach. Informational videotapes, CDs and DVDs are being prepared for prospective patients and their parents to explain the studies; consent forms are being improved for readability; advertisements and feature articles will run in the patient-oriented publications of the American Diabetes Association (*Forecast*) and the Juvenile Diabetes Research Foundation International (*Countdown*); a direct mail campaign, print advertisements, slides, and web-based promotions will be part of an outreach campaign to bring TrialNet to the attention of health care providers; and research is being conducted to determine which outreach methods are the most effective.

As part of the continuing effort to translate basic and preclinical research on type 1 diabetes into practical use, the NIDDK has expanded the T1D-RAID (Type 1 Diabetes-Rapid Access to Intervention Development) program to not only produce biological materials for testing, but also to make mouse models available for use in the tests. T1D-RAID, a program that is not part of TrialNet, is designed to facilitate translation to the clinic of novel, scientifically meritorious therapeutic interventions.

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 know as angiomyolipoma that can result in kidney failure. The Committee is encouraged that NIDDK is participating in a Trans-NIH Tuberous Sclerosis Coordinating Committee, and urges NIDDK's continued involvement in this process. The Committee also urges NIDDK to collaborate with NCI on a conference on nutrient sensing and insulin-signaling in cells with inclusion of TSC research. (p. 110)

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). Mutations in either the *TSC1* or *TSC2* tumor suppressor genes are responsible for the development of TSC. Recent studies show that the proteins encoded by these genes are negative regulators of insulin signaling. A workshop, co-sponsored by NIDDK and NCI, is planned for May, 2006, to bring together the communities of people studying insulin signaling and cell growth, and to focus their attention on the tuberous sclerosis complex. Sessions will include clinical and basic research presentations that are relevant to hamartoma syndromes, the collective term for diseases characterized by widespread development of benign tumors.

The NIDDK also supports a number of research projects to address the molecular and cellular mechanisms underlying TSC. 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 interferon gamma, a key immune system regulator, as a prevention or treatment agent. The NIDDK will continue to participate in the inter-Institute TSC Research Coordination Committee, which works to implement the NIH Tuberous Sclerosis Research Agenda.

FY 2006 Congressional Appropriations Committee Conference Report Language

Item

The conferees urge NIDDK to continue to support and develop the "Urologic Diseases in America" report and to include urological complications as well as diabetes and obesity research initiatives. The conferees further encourage the Institute to continue the Urinary Incontinence Treatment Network and to convene an external strategic planning group to develop future

urology clinical trials. The conferees also encourage the Institute to convene a Strategic Planning Group to make recommendations on basic and clinical research in men's health, including the development of biomarkers to distinguish benign prostatic hyperplasia from prostate cancer. (p. 1-2)

Action Taken or to be Taken

The Urologic Diseases in America report (URL: http://kidney.niddk.nih.gov/statistics/uda) has provided significant information related to major urologic diseases, and NIDDK is strongly committed to maintaining this program. A research solicitation is being developed for the next phase of Urologic Diseases in America that will include assessment of the impact of diabetes and obesity on urologic diseases.

The Urinary Incontinence Treatment Network has successfully shown that multicenter, randomized clinical trials of surgical techniques can be designed and successfully completed. The NIDDK plans to continue funding the Network, and will design and conduct other multi-center surgical and non-surgical clinical studies on urinary incontinence in women. A research solicitation will be issued shortly to enlist investigators in the next phase of the Network. It is anticipated that applications from this solicitation will be reviewed in the summer of 2006.

The NIDDK is currently developing three urology strategic planning groups. One group will meet in spring 2006 and will focus on urinary tract stone disease. The other two groups are in the planning stage. One will focus on women's urologic health issues. The other will focus on men's urologic health issues, emphasizing issues related to benign prostate diseases. All three groups will identify research needs and approaches. Each will develop a strategic plan for research. The development of concepts for clinical trials identified in each of these areas will be an integral part of each planning meeting.

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

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,799,730,000	Indefinite	$1,789,918,000
Digestive and Kidney Diseases	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	55,195,000		54,380,000
Total, Budget Authority				1,854,925,000		1,844,298,000

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/
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/,12/
Rescission				(10,617,000)
2004	1,820,000,000	1,820,007,000	1,833,007,000	1,821,240,000 9/,12/
Rescission				(10,654,000)
2005	1,877,696,000	1,876,196,000	1,889,100,000	1,863,584,000 10/,12/
Rescission				(14,112,000)
2006	1,872,146,000	1,872,146,000	1,917,919,000	1,854,925,000 11/,12/
Rescission				(17,221,000)
2007	1,844,298,000 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/ Excludes enacted administrative reductions of $17,221,000.
12/ Includes Type 1 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 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	60	70	72
Division of Diabetes, Endocrinology and Metabolic Diseases	26	28	28
Division of Digestive Diseases and Nutrition	19	20	20
Division of Kidney, Urologic and Hematologic Diseases	17	19	19
Division of Nutrition Research Coordination	8	8	8
Division of Extramural Activities	58	67	68
Division of Intramural Research	437	428	428
Total	625	640	643
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(4)	(4)	(4)

FISCAL YEAR	Average GM/GS Grade
2003	11.0
2004	11.3
2005	11.8
2006	11.9
2007	12.0

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

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	1	1	1
Total - ES Salary	$135,984	$139,146	$141,511
GM/GS-15	43	45	45
GM/GS-14	55	55	55
GM/GS-13	63	65	66
GS-12	55	60	60
GS-11	46	48	50
GS-10	1	1	1
GS-9	36	38	40
GS-8	26	28	28
GS-7	17	20	22
GS-6	3	3	3
GS-5	2	4	4
GS-4	0	0	1
GS-3	1	2	2
GS-2	0	0	0
GS-1	0	1	2
Subtotal	348	370	379
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	10	12	13
Senior Grade	6	7	8
Full Grade	3	3	3
Senior Assistant Grade			
Assistant Grade			
Subtotal	19	22	24
Ungraded	284	286	287
Total permanent positions	393	401	404
Total positions, end of year	652	672	680
Total full-time equivalent (FTE) employment,end of year	625	640	643
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$135,984	$139,146	$141,511
Average GM/GS grade	11.8	11.9	12.0
Average GM/GS salary	$78,949	$80,765	$82,138

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research