60 years 1950 2010

NIDDK

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

60 Years of Advancing Research to Improve Health

2010

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Director's Message

CELEBRATING 60 YEARS OF RESEARCH DISCOVERY AT THE NIDDK

As the ninth Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), it is my great honor to present this compendium, in which we celebrate the Institute's accomplishments over the past 60 years in supporting and conducting research on some of the most common, chronic, and costly diseases affecting people in this country and around the world, as well as on diseases and disorders which are less widespread but nonetheless devastating in their impacts.

Diseases and disorders within the NIDDK's mission include diabetes and other endocrine and metabolic diseases, digestive and liver diseases, nutritional disorders, obesity, kidney and urologic diseases, and diseases of the blood. Many of the NIDDK's research programs cut across boundaries of disease and discipline through their applicability to multiple areas of biomedical inquiry and a range of diseases.

Throughout its history, the NIDDK has remained committed to supporting vigorous basic, clinical, and translational research efforts by extramural scientists at academic and other medical research institutions throughout the country, as well as by scientists in the Institute's Intramural Research Program. The NIDDK also maintains strong support for research training and career development for the next generation of scientists who will carry forth these efforts into the future. To identify key research challenges and opportunities and maximize the health return on research investments, the Institute engages in strategic planning with broad stakeholder input. Through our education and outreach programs, the NIDDK disseminates science-based health information to patients, healthcare providers, and the public.

Ground-breaking scientific research has been driven forward by the efforts of dedicated investigators, as well as the participation of patients in clinical research. The Institute is deeply grateful to the patients and families who participate in NIDDK research studies to benefit others affected by disease. The perspectives of some of these patients are highlighted in this compendium.

The research highlighted here represents just a sampling of the Institute's past and current efforts and future plans. For additional information, I encourage you to visit our web site at: *www.niddk.nih.gov.*

We hope that you enjoy this retrospective tour of NIDDK-supported research achievements as we look forward to building on this progress to propel scientific discovery in the years ahead toward improving the nation's health.

Griffin P. Rodgers, M.D., M.A.C.P.
Director
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
U.S. Department of Health and Human Services

Overview

MISSION AND ORGANIZATION OF THE INSTITUTE: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports research on many serious, chronic diseases: diabetes and other endocrine and metabolic diseases and disorders; digestive diseases; nutritional disorders; and kidney, urologic, and hematologic (blood) diseases.

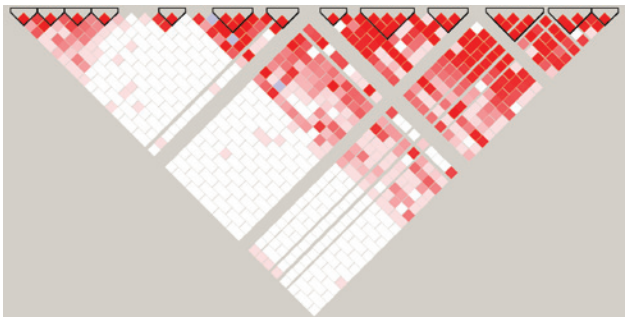
The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases (DEM) supports basic and clinical research in the areas of diabetes; obesity; cystic fibrosis; osteoporosis; and other, often rare, endocrine and genetic metabolic diseases. The Division of Digestive Diseases and Nutrition (DDN) supports research toward understanding, preventing, and treating diseases of the esophagus, stomach, intestines, liver and biliary system, and pancreas, as well as research on obesity and basic nutrition research. The Division of Kidney, Urologic, and Hematologic Diseases (KUH) supports research into chronic kidney disease and kidney failure, urologic diseases, the development of the genitourinary tract, and hematologic diseases. The DEM, DDN, and KUH Divisions all support extramural research—research by scientists at universities and other medical research institutions throughout the country. The Institute's Division of Extramural Activities provides leadership, oversight, tools, and guidance to manage the Institute's grants policies and operations, including efforts related to the scientific peer-review process for assessing grant applications. The NIDDK is also home to the National Institutes of Health (NIH) Division of Nutrition Research Coordination, which provides advice and coordination for nutrition research. The NIDDK's Division of Intramural Research consists of government scientists who conduct research across a broad spectrum of basic and clinical topics. With respect to clinical research, extramural and intramural, the research progress since the Institute's establishment reflects the contributions both of NIDDK-supported investigators and of the patient volunteers in clinical studies. The Institute also supports research training for students and scientists at various stages of their careers, and a range of education and outreach programs that aim to bring science-based information to patients and their families, healthcare professionals, and the public.

ESTABLISHMENT AND HISTORY OF THE INSTITUTE: On August 15, 1950, President Harry S. Truman signed the Omnibus Medical Research Act (P.L. 81-692) into law, establishing the National Institute of Arthritis and Metabolic Diseases, the forerunner to the NIDDK. In the ensuing years, the Institute was renamed several times. In 1986, one of the Institute's former Divisions became the core of a new, separate NIH component focused on arthritis and other diseases, and the Institute acquired its current name: the National Institute of Diabetes and Digestive and Kidney Diseases—the NIDDK.

Cross-Cutting Research

Advances in medicine are largely dependent upon the accumulation of new knowledge about biologic processes, often at the smallest levels of an organism—its genes, the proteins they encode, and the workings of and communications between cells. In many cases, major strides in fighting disease can be traced back to laboratory studies whose immediate relevance to health could not have been fully known or appreciated at the time they were conducted. Opportunities to make exciting new discoveries and advances are arising ever more rapidly with the development of new technologies, new approaches, and even new scientific disciplines. Described here are studies that span scientific boundaries, including research on fundamental biologic processes as well as the development of new technologies that make such studies possible. The insights gained through this type of research can be expected to propel disease-oriented research, not only within the NIDDK mission, but also in many other fields, for today's cross-cutting advances may lead to tomorrow's new treatments.

Genome-wide Association and Other Genetic Studies: NIDDK-supported scientists have discovered many genetic variants that influence a person's likelihood of developing different diseases. Genetic findings have greatly accelerated in recent years as a result of the Human Genome Project and related efforts, including the development of the HapMap, a collection of many thousands of common genetic variants, called "SNPs," throughout the genome. Genome-wide association studies (GWAS) rely on these research tools and advanced technologies to identify genetic differences between people with specific illnesses and healthy individuals. In some cases, the genetic association maps to a chromosomal region that had not been thought to play a role in biological processes involved in the disease under study. Researchers have thus far identified over 40 genetic variants that are associated with an increased risk of type 1 diabetes, and over 30 genetic variants associated with increased risk of type 2 diabetes. One genetic region previously found to be strongly associated with type 2 diabetes has recently been implicated in a very different condition: prostate cancer. Scientists in the NIDDK-supported Inflammatory Bowel Disease (IBD) Genetics Consortium, together with other research teams, have identified over 30 genes and chromosomal regions



Data from a genome-wide association study of inflammatory bowel disease, which identified genetic variations associated with disease susceptibility. *Image credit:* Rioux J. et al. Reprinted by permission from Macmillan Publishers Ltd: *Nat Genet*, 39: 596-604, copyright 2007.

associated with Crohn's disease. Through another advanced approach to genetic analysis, also based on the HapMap and SNP data, researchers recently identified variations around the *MYH9* gene that may account for much of the increased burden of idiopathic focal segmental glomerulosclerosis (a type of kidney disease) and other non-diabetic kidney disease among African Americans. Other types of genetic studies over the past several decades have identified genes that influence diseases such as cystic fibrosis, pancreatitis, and forms of monogenic diabetes. These discoveries open up new avenues of research for disease prevention and treatment.

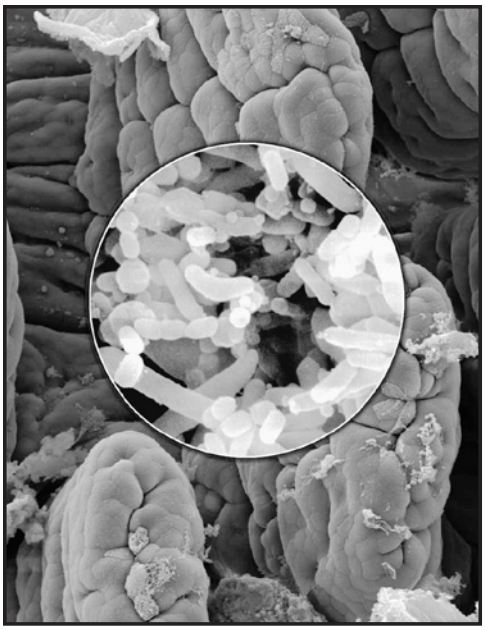
Nuclear Hormone Receptors: A broad range of metabolic, reproductive, developmental, and immune processes are regulated by a family of proteins called nuclear hormone receptors. These proteins respond to a variety of hormones by turning genes on or off, to modulate cell functions. The Nuclear Receptor Signaling Atlas (NURSA) is a trans-NIH initiative, led by the NIDDK, that funds scientists to develop a comprehensive understanding of the structure, function, and role in disease of nuclear hormone receptors. NURSA is focused on metabolism and the development of a number of metabolic disorders, including obesity, lipid dysregulation, and type 2 diabetes, as well as on processes of aging and hormone-dependent cancers. Researchers in the NURSA consortium have made key discoveries in the role of nuclear receptors in physiology and mechanisms of disease.

Pegylation: The addition of polyethylene glycol—"pegylation"—has emerged as a favored way to improve the staying power, and hence the effectiveness, of a variety of compounds used to treat conditions such as adenosine deaminase deficiency, hepatitis C, and other NIDDK-relevant diseases. Studies are under way to examine the possible benefits of pegylating insulin, to prolong its circulation time; antibodies for targeting of tumors; and other enzymes to aid in recovery from injury.

Regulating Cellular Traffic: NIDDK-supported studies have yielded important insights into the exquisitely organized transport of nutrients, hormones, and other molecules from within a cell to the cell's outer membrane, and between a cell and its surroundings. Scientists discovered how small cellular structures called vesicles carry this cargo and dock at the correct target locations. This research has improved our understanding of diverse biologic processes and illuminated the role of vesicle transport in diseases such as type 2 diabetes and cystic fibrosis.

Role of "Autophagy" in NIDDK-related Diseases: Autophagy is a process that cells use to degrade and recycle components that are damaged or no longer needed, as well as to eliminate harmful bacteria. NIDDK-supported research on this cellular degradation pathway has wide-reaching implications for understanding diseases within the Institute's mission. For example, the IBD Genetics Consortium identified mutations in an autophagy-related gene called *ATG16L1* that are associated with Crohn's disease. Further research showed that the protein encoded by this gene is important for intestinal cell secretion of granules containing antimicrobial agents, shedding light on how immune defenses are compromised in Crohn's disease. Studies of alpha-1 antitrypsin deficiency have shown that autophagy is important for degrading the mutant proteins that accumulate in the livers of individuals with this genetic disorder. Researchers have also found that red blood cell maturation relies on autophagy of mitochondria, and that disorders such as anemia can result when this process is compromised.

Gut Microbes in Health and Disease: The human digestive system is host to an enormous ecosystem of microorganisms, which is mostly beneficial but may occasionally be harmful. Bolstered by recent technological advances, NIDDK-supported researchers have been examining the composition of the microbial community in our intestines. By analyzing the bacterial genomes, collectively called the microbiome, scientists have uncovered a genomic view of the beneficial human-bacterial relationship that exists in the normal, healthy intestine. Scientists have also discovered that changes in the normal composition of the gut microbial community are associated with obesity, and that abnormal functioning of the human immune system in response to otherwise harmless gut microbes is

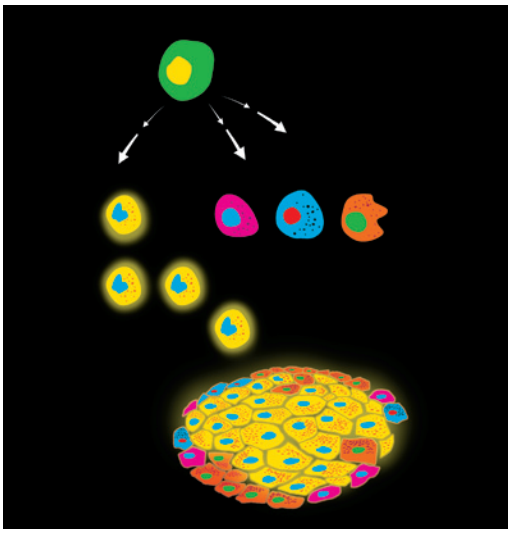


The human gut is home to a broad array of microscopic organisms that play an important role in human health and disease.
Image credit: Gross L. Human Gut Hosts a Dynamically Evolving Microbial Ecosystem. *PLoS Biology,* July 2007, vol. 5, issue 7, e199.

associated with inflammatory bowel diseases. NIDDK researchers have also discovered additional protective benefits of the normal gut microbial community in reducing infection by harmful bacteria and are investigating a possible role for gut microbes in reducing risk for type 1 diabetes. In addition to investigating bacteria in the intestines, NIDDK investigators have also studied *Helicobacter pylori* infection of the stomach. Recent advances have shown how the bacterium interacts with cells lining the stomach to alter their function, and how changes in the *H. pylori* genome are associated with progression from stomach inflammation to more serious inflammatory conditions and stomach cancer. Further NIDDK research efforts will continue to reveal new roles for gut microbial communities in normal health and disease.

RNAi-based Strategies for Metabolic and Inflammatory Diseases: Understanding the process by which the body can become resistant to the hormone insulin and the link between insulin resistance and the inflammatory response of the immune system is critical to developing effective therapeutics. NIDDK-supported scientists are utilizing a technique based on the phenomenon of ribonucleic acid interference (RNAi) both to identify factors involved in insulin resistance and the inflammatory response as well as for use as a potential therapy. In RNAi, molecules called "small interfering RNAs" reduce levels of specific proteins. Recently, investigators targeted a small interfering RNA to an inflammatory protein and administered this RNA to mice, using an innovative delivery vehicle. In doing so, they were able both to block the inflammatory response and alter the insulin resistance in obese mice. This research reveals the exciting potential for a new method of therapy for numerous diseases, including type 2 diabetes.

Stem Cells: Stem cells have the potential to develop into many different cell types in the body, and NIDDK-supported scientists continue to characterize their properties and seek potential new ways of using them to benefit patients. For example, researchers discovered a novel group of adult pancreatic progenitor cells that can generate insulin-producing beta cells, a finding with implications for future diabetes treatments. Scientists have also demonstrated that purified rat fetal stem cells transplanted into animals missing two-thirds of their livers are capable of fully repopulating this organ, lending support for the consideration of stem cell transplantation as an alternative to whole or partial liver



Stem cells can differentiate into a number of different cell types, a characteristic that may allow researchers to develop therapies for diseases in which tissues are damaged or malfunctioning.
Image credit: Donald Bliss, Medical Arts and Photography Branch, National Institutes of Health.

transplantation. Pursuing another avenue of research, and building on a landmark study on mouse cells by scientists in Japan, NIDDK-supported researchers showed that the insertion of just four defined genes into adult human skin cells could cause the cells to revert to a stem cell-like state, with characteristics closely resembling those of embryonic stem cells. Scientists have used this approach to generate stem cell lines from patients with different genetic diseases and disorders. These cells, known as induced pluripotent stem cells, or iPS cells, may provide insights into disease development, facilitate screening of candidate therapeutic agents, and, with further research progress, may one day yield cells for use in transplantation. These and other developments have the potential to lead to new cell-based therapies for a broad range of disorders.

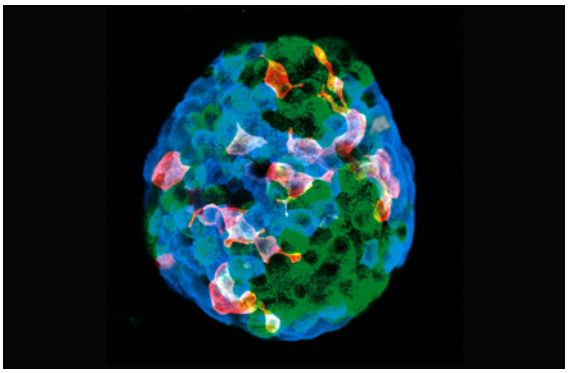
Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK's support of research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, obesity, osteoporosis, cystic fibrosis, lysosomal storage disorders, and thyroid and other endocrine disorders. Together, they affect many millions of Americans. As highlighted in this chapter, the past 60 years have brought about significant research progress and led to dramatic improvements in the health and quality of life of people affected by these diseases and disorders.

DIABETES OVERVIEW

Diabetes is characterized by the body's inability to produce and/or respond appropriately to the hormone insulin. Produced by beta cells in the islets of the pancreas, insulin is needed for the body to absorb and use glucose (sugar) as a cellular fuel. Defects in insulin production or action result in persistent elevation of glucose levels and other metabolic abnormalities, which can lead to development of debilitating disease complications. The most common forms of the disease are type 1 diabetes, in which the body loses its ability to produce insulin; and type 2 diabetes, which is due to a combination of insulin resistance and insufficient insulin production. Women can also develop gestational diabetes, a risk factor for type 2 diabetes, during pregnancy. Rarer forms of diabetes also exist. Diabetes affects about 23.6 million people in the U.S.; another 57 million Americans are estimated to be at increased risk for the disease.[1]

Insights gained from research over the past 60 years have contributed to a knowledge base leading to improvements in survival and quality of life for people with diabetes. Doctors now use simple blood tests to diagnose diabetes and to assess long-term blood glucose control. People at high risk for type 2 diabetes can prevent or delay disease onset by losing a modest amount of weight through dietary changes and moderate exercise. People with type 1 diabetes can reduce their risk for complications by intensively controlling blood glucose levels. Doctors can prescribe new classes of oral drugs and combinations of drugs to treat people with type 2 diabetes. Patients can use new technologies, such as continuous glucose monitors, to manage their diabetes. As a result of these improvements, people with diabetes are living longer and healthier lives than ever before.



In this pancreatic islet, beta cells, which produce insulin, are stained green; alpha cells, which produce glucagon, are blue; and delta cells, which produce somatostatin, are red.
Image credit: Dr. Todd C. Brelje and Dr. Robert L. Sorenson, Islet Biology Laboratory, Department of Genetics, Cell Biology and Development, University of Minnesota.

[1] *http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf*

HIGHLIGHTS OF DIABETES SCIENTIFIC ADVANCES SUPPORTED BY NIDDK OVER THE PAST 60 YEARS

IN THE 1960s AND 1970s, NIDDK-SUPPORTED RESEARCHERS:

1960: Recognized a rare form of diabetes later called "maturity-onset diabetes of the young" or MODY. MODY and neonatal diabetes mellitus are the two main forms of monogenic diabetes, which arise from a mutation in a single gene.

1965: Began research with Pima Indians, a community with the highest prevalence of type 2 diabetes in the world. Studies with the Pima Indians led to insights including identification of obesity and high levels of insulin in the blood as strong risk factors for the disease, and demonstration that children of mothers who are diabetic during pregnancy are at higher risk for obesity and diabetes than the children of nondiabetic mothers.

1967: Discovered pro-insulin. Pro-insulin is split into the hormone insulin and a molecule called C-peptide, a marker used to measure beta cell function. This discovery led to the production of biosynthetic insulin, which was the first hormone to be produced by biotechnology.

1969-1971: Identified the insulin receptor and described diseases associated with it.

1972: Reported that islet transplantation cures diabetes in rats.

IN THE 1980s, NIDDK-SUPPORTED RESEARCHERS:

1980-1989: Discovered glucose transporters and subsequently the genes that control glucose transport. Found defective glucose transport systems in people with diabetes.

IN THE 1990s, NIDDK-SUPPORTED RESEARCHERS:

1993: Proved that intensive blood glucose control reduces risk of complications of the eyes, kidneys, and nerves in people with type 1 diabetes, in the Diabetes Control and Complications Trial (DCCT). The DCCT validated the use of HbA1c tests for assessing blood glucose control.

1998: Demonstrated, through the United Kingdom Prospective Diabetes Study (UKPDS), that intensive blood glucose control reduces risk of eye and kidney complications in people with type 2 diabetes.

IN THE 2000s, NIDDK-SUPPORTED RESEARCHERS:

2002: Demonstrated, through the Diabetes Prevention Program (DPP) clinical trial, that people at risk of developing type 2 diabetes can prevent or delay disease onset and improve their blood sugar through modest improvements in diet and exercise or through the diabetes drug metformin.

2002: Determined, in a key component of the Diabetes Prevention Trial-Type 1 (DPT-1), that accurate assessment of risk for type 1 diabetes is feasible in relatives of people with the disease. DPT-1 was the prototype for the NIDDK's current-day Type 1 Diabetes TrialNet.

2005: Showed, in the Diabetes Autoimmunity Study of the Young (DAISY), that newborns genetically vulnerable to type 1 diabetes can be identified and followed to prevent diabetic ketoacidosis.

2005: Reported, after long-term follow-up of DCCT participants, that intensive blood glucose control reduces cardiovascular complications of type 1 diabetes.

2006: With industry-supported scientists, realized the fruits of many years of research with the Food and Drug Administration (FDA) approval of the first generation of continuous glucose monitors paired with insulin pumps.

2008: Demonstrated, after 10-year follow-up of UKPDS participants, persistent reductions in eye and kidney complications, and decreased risk of heart attack and death due to any cause.

2008: Learned, from the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, supported by the National Heart, Lung, and Blood Institute and the NIDDK, that there is not a "one-size-fits-all" approach to treating people with type 2 diabetes.

2009: Identified genes or gene regions commonly associated with diabetes in large-scale studies. Scientists have found over 40 genes for type 1 diabetes and over 30 for type 2 diabetes.

2009: Demonstrated remarkable improvements in long-term outcomes achieved with intensive glucose control in people with type 1 diabetes.

2009: Showed, with 10-year follow-up of DPP participants, that the lifestyle intervention yields long-term health rewards by reducing risk for type 2 diabetes and other heart disease risk factors.

UNDERSTANDING, PREDICTING, AND PREVENTING DIABETES

Different Forms of Diabetes and Common Links:

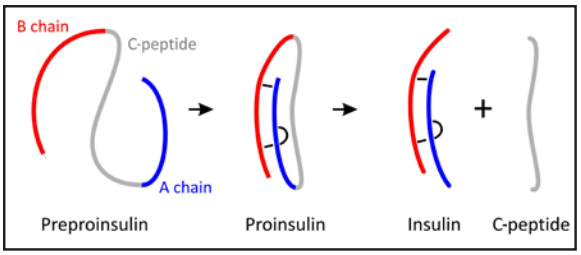
The most common forms of diabetes are type 1 and type 2 diabetes. However, there is increasing recognition of other forms of diabetes, as well as emerging evidence about common links between the two most common forms:

Monogenic forms of diabetes: Some forms of diabetes result from mutations in a single gene, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus.

Gestational diabetes: A form of diabetes that is first diagnosed in women during pregnancy, gestational diabetes generally goes away after the baby is born, but leaves both mother and child at increased risk for developing type 2 diabetes.

Secondary diabetes: Secondary diabetes develops as a result of another disease or disease treatment. For example, diabetes is the most common secondary disease in people with cystic fibrosis. HIV-infected patients are at increased risk of developing diabetes when taking antiretroviral drugs. Some psychiatric medications, especially antipsychotic agents associated with substantial weight gain risk, can increase risk for obesity and diabetes.

Type 1 and type 2 diabetes—common links: Scientists are recognizing commonalities between type 1 and type 2 diabetes. Some people with type 2 diabetes have autoantibodies characteristic of type 1 diabetes. Some people with type 1 diabetes have insulin resistance, which is a hallmark of type 2 diabetes. A better understanding of these common links could inform the development of improved therapies for both forms of the disease.



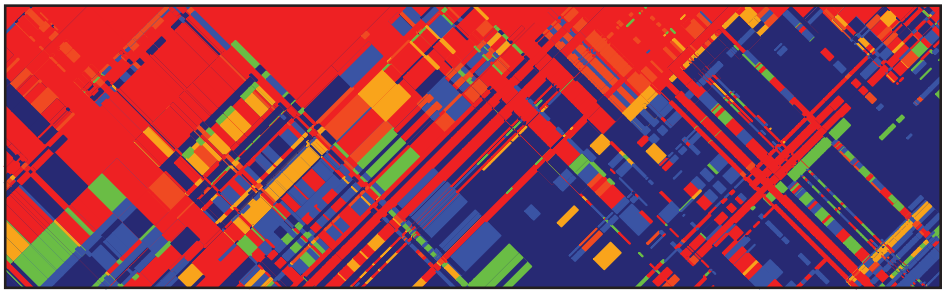
The hormone insulin is formed by chemical modification and cleavage of a precursor molecule. The cleaved "C-peptide" is useful for monitoring residual beta cell function in patients with diabetes who are on insulin therapy.

Ability to Predict Type 1 Diabetes Offers Hope for Prevention: NIDDK-supported research on the autoimmune destruction of pancreatic beta cells in type 1 diabetes and the genetics of the disease have combined to create a powerful tool for assessing type 1 diabetes risk. Dozens of genes have now been linked to diabetes risk, most within the last 2 years, but the most important of these is *HLA*, which was linked to type 1 diabetes in the 1970s. Two of the many *HLA* variants cause substantially increased risk of the disease. Certain *HLA* variants lower risk, while others are neutral in their impact. In the 1960s, research showed that people's antibodies target their own proteins in the run-up to type 1 diabetes, signaling a high likelihood of the disease. Type 1 diabetes is an autoimmune disease, because the body attacks its own proteins and cells, so these antibodies are called autoantibodies.

With the knowledge of *HLA* and antibody associations with type 1 diabetes, NIDDK-supported scientists designed a prevention trial in the 1990s, called DPT-1, which successfully used genetic and antibody tests to predict risk for developing type 1 diabetes in people who have a close relative with the disease. Although the DPT-1 prevention strategies did not prove effective, the researchers' estimates of risk for disease based on these tests proved to be remarkably accurate. DPT-1 thus demonstrated that it is possible to identify people at risk for type 1 diabetes. Physician-scientists are now building on this knowledge and offering people with diabetes risk factors the option of participating in clinical trials to test new prevention strategies. The ability to predict risk for type 1 diabetes can speed the process of such trials by reducing the number of participants needed for the studies. In the future, clinicians will be able to use these same techniques to identify people who might benefit from any prevention approach that turns out to be effective.

Diabetes Genetics: Recent advances in genetic methods have led to an explosion in the number of genes known to be linked to the disease processes that lead to type 1 and type 2 diabetes. This diabetes genetics renaissance was made possible by the Human Genome Project, which sequenced the 3 billion nucleotide base pairs of the human genome, and began to uncover the nature and extent of human genetic variation. The HapMap, a collection of many thousands of common genetic variants throughout the genome, has been used with great success to compare people with and without different diseases and discover genes that individually may have only a modest impact on the likelihood of developing complex diseases like type 1 and type 2 diabetes. These analyses are known as genome-wide association studies (GWAS). As recently as 2003, just three type 1 diabetes genes and two type 2 diabetes genes were known. Just 6 years later, over 40 type 1 and over 30 type 2 diabetes genes or genetic regions have been identified, as a result of genome-wide studies.

As one example of a successful diabetes genetics effort, the international Type 1 Diabetes Genetics Consortium (T1DGC) has made remarkable progress in uncovering the genetic underpinnings of type 1 diabetes. With NIDDK support, the T1DGC recruited 2,800 families who have at least two siblings with type 1 diabetes and found at least 40 genetic regions associated with the disease, many of which contain genes involved in the immune system. New research is building on these exciting findings to pinpoint the exact genes that are associated with type 1 diabetes and to understand how the genes may play a role in disease.



Data from a genome-wide association study of type 2 diabetes, which identified genetic sequences associated with the disease.
Image credit: From Scott LJ, et al: *Science* 316: 1341-1345, 2007. Reprinted with permission from AAAS.

Two of **Toni and Rob Berg**'s three children have type 1 diabetes, which made the family eligible to participate in the Type 1 Diabetes Genetics Consortium study. Toni encourages other families to participate in type 1 diabetes clinical research studies, saying, "The larger the pool of people they have to study, the more they can learn about combating the disease."

Researchers have also found genes related to rarer forms of diabetes. While the risk for developing type 1 or type 2 diabetes, both common forms of the disease, is related to combinations of variants in multiple genes (as well as environmental factors), some rare forms of diabetes are "monogenic"—that is, a mutation in just a single gene can lead to the disease. In the 1990s and 2000s, NIDDK-supported researchers discovered a number of genes associated with these "monogenic" forms of diabetes, including different types of maturity-onset diabetes of the young and neonatal diabetes mellitus.

Knowledge of genes and genetic variants that contribute to different types of diabetes can lead to improved ways to predict risk for disease. Understanding the genetic contributors to diabetes can inform the development of new prevention and treatment strategies.

Environmental Contributors to Type 1 Diabetes: Although many genes associated with type 1 diabetes have been identified, much less is known about the environmental factors that increase a person's risk of developing the disease. Thus, the NIDDK supports research in this area. For example, since 1993, NIDDK has supported the Diabetes Autoimmunity Study of the Young (DAISY) to investigate environmental triggers of type 1 diabetes in children. As part of this study, researchers first screened blood samples to try to identify newborns at high genetic risk for the disease, as a way to facilitate subsequent analysis of potential contributing environmental factors. The DAISY study found that genetically vulnerable newborns can be identified and then followed to reduce their chances of developing a life-threatening condition called diabetic ketoacidosis and requiring hospitalization at disease onset. In 2002, NIDDK launched a large-scale study, The Environmental Determinants of Diabetes in the Young (TEDDY). This ongoing study is the first to bring together and coordinate researchers from around the world to identify triggers of type 1 diabetes. TEDDY is completing its recruitment of over 7,000 newborns at high genetic risk for the disease and will follow them until age 15. By collecting dietary and health data, and stool, blood, and other samples, scientists hope to identify a factor or factors that lead some genetically predisposed children to develop the disease while others do not. Identification of these factors will lead to a better understanding of the causes of type 1 diabetes, and may result in new strategies to prevent, delay, or reverse the disease.

Jodie Distel enrolled her son, **Dillon**, into the DAISY study shortly after his birth. Dillon was diagnosed with type 1 diabetes at age 7, but Jodie and Dillon were prepared for the diagnosis because of their participation in DAISY. Jodie says, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

Having volunteered for the DPP clinical trial and now participating in the DPP Outcomes Study, **Irish Stovall** says she would advise anyone interested in his or her health to take part in studies like these. Although she was at high risk for type 2 diabetes at the time she enrolled in the DPP, she says "I didn't have diabetes at that time and, thanks to the study, I still don't."

Type 2 Diabetes Can Be Prevented or Delayed: Spearheaded by the NIDDK, the landmark Diabetes Prevention Program (DPP) was the first major, randomized, multisite clinical trial to demonstrate that type 2 diabetes could be prevented or delayed in a diverse American population at high risk for developing the disease. At sites throughout the country, researchers enrolled 3,234 overweight people who had impaired glucose tolerance (a condition in which blood glucose levels are elevated but not yet in the diabetic range). Nearly one-half of the participants were from minority groups disproportionately burdened by diabetes. The trial compared three preventive approaches: standard medical advice; intensive lifestyle modification aimed at losing 5 to 7 percent of body weight through diet and moderate exercise (*e.g.*, walking 5 days a week for 30 minutes a day); and treatment with the drug metformin. The duration of the intervention was approximately 3 years. The DPP results, announced in 2002, showed that the lifestyle intervention reduced risk for type 2 diabetes by a dramatic 58 percent, while metformin reduced risk by 31 percent. The interventions worked in all ethnic and racial groups studied, in both men and women, and in women with a history of gestational diabetes; and the lifestyle intervention was particularly effective in older adults. To inform the public and healthcare providers about these exciting results, the National Diabetes Education Program (NDEP) launched the "*Small Steps. Big Rewards. Prevent Type 2 Diabetes*" educational campaign (described later in this chapter). Translational research efforts have also been initiated to develop cost-effective ways to achieve the lifestyle change that delayed or prevented type 2 diabetes (see the translational research section in this chapter).

Diabetes Prevention Program

The Diabetes Prevention Program (DPP) and the DPP Outcomes Study (DPPOS) demonstrated that people at risk of developing type 2 diabetes can prevent or delay disease onset and improve their blood sugar levels through a lifestyle intervention of modest changes in diet and exercise, and that the drug metformin also reduces risk, compared to standard therapy. In 2009, DPPOS researchers reported that, in addition to reduced risk of type 2 diabetes, people in the lifestyle group also had fewer heart disease risk factors, including improvements in blood pressure and blood lipids.

Most people who participated in the DPP continue to be followed in the DPP Outcomes Study (DPPOS). The DPPOS is examining the durability of the DPP interventions on development of type 2 diabetes and its cardiovascular complications. In 2009, DPPOS researchers reported that, after a 10-year period of following participants, long-term benefits of the interventions emerged: the lifestyle and metformin

Like many other Native Americans, **Monica Boone** has a family history of type 2 diabetes, and she was at high risk. Since participating in the DPP study, she no longer has pre-diabetes, and she says "I have more energy; I'm quicker in my movements; and I enjoy going here and there."

interventions reduced development of diabetes by 34 percent and 18 percent, respectively. People in the lifestyle group also had fewer heart disease risk factors, despite taking fewer drugs to control their heart disease risk. Thus, even though sustaining weight loss with lifestyle changes is challenging, it produces long-term health rewards by lowering people's risk for type 2 diabetes and reducing other heart disease risk factors.

HEALTHY: The HEALTHY multicenter clinical study is collecting data on risk factors for type 2 diabetes in youth, and providing the most intensive school-based intervention to date to address the question of whether an intervention delivered only in schools can reduce overweight and obesity and other type 2 diabetes risk factors. The students in the participating middle schools are largely from minority groups disproportionately burdened by type 2 diabetes. The researchers measured risk factors for type 2 diabetes at the beginning of the study, when the children were in sixth grade. Nearly half of the students were overweight or obese, 16 percent had elevated fasting blood glucose levels, and almost 7 percent had elevated fasting insulin levels. These findings of high levels of risk factors for type 2 diabetes in middle-school age children, particularly those from minority groups, highlight the importance of focusing on this population to try to reduce these risk factors.

Diabetes During Pregnancy: Diabetes that is present during pregnancy can adversely affect both mother and child, not only during delivery and infancy, but also later in life. Among the studies the Institute has funded in this area, the University of Southern California Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational diabetes and identified metabolic factors that may predict future development of type 2 diabetes in the mother. In a groundbreaking study on the effects of the intrauterine environment on offspring, NIDDK intramural scientists, in partnership with Pima Indian volunteers, found that maternal type 2 diabetes during pregnancy increases risk for obesity and type 2 diabetes in the offspring. A similar association between maternal diabetes during pregnancy and increased risk for type 2 diabetes in the offspring was subsequently observed in a racially and ethnically diverse population by another research team, in the SEARCH for Diabetes in Youth study. As described in this chapter, the Diabetes Prevention Program (DPP) showed that there is hope for preventing or delaying type 2 diabetes in those at high risk, including women who have had gestational diabetes.

The Gestational Diabetes Mellitus (GDM) Cohort Study focused on Hispanic women who had gestational, or pregnancy-related, diabetes. This research has increased understanding of GDM and risk for subsequent type 2 diabetes. **Modesta Solórzano** participated in the study, and says, "It's been very helpful to me and my family." ("Ha sido muy útil para mí y para mi familia.")

Deepening the Understanding of Insulin Action and Metabolism: Every cell in the body requires energy to perform its functions, so a key requirement for all living things is to ensure an appropriate energy supply to their tissues. The hormone insulin has long been known to regulate the body's use of glucose for energy. Secreted by the pancreas, insulin induces cells in muscle and adipose (fat) tissue to take up glucose from the blood and halts production of extra glucose by the liver; it also influences other cellular processes. In the last two decades, NIDDK-supported researchers have advanced understanding of the molecular pathways through which insulin acts and have made enormous strides in elucidating the complex network of signaling pathways through which many tissues and organs throughout the body communicate to regulate metabolism. For example, scientists have discovered that cells of the gut secrete small protein hormones in

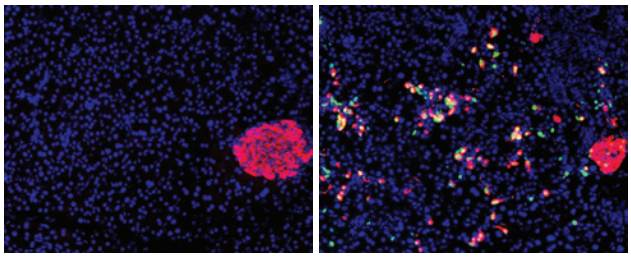
response to the presence and absence of food. Adipose tissue is itself now recognized as an endocrine organ, releasing hormones with important effects on hunger, satiety, and metabolism. The brain, particularly a region called the hypothalamus, integrates signals from other organs and tissues to control metabolism. Indeed, the body's control of energy use and storage is becoming better understood in its remarkable subtlety and complexity.

Mouse Metabolic Phenotyping Centers (MMPCs): The MMPCs provide phenotyping services to the research community who use mice to study diabetes, obesity, diabetes complications, and other metabolic diseases. The MMPCs use state-of-the-art technologies to offer a variety of tests that require specialized expertise or equipment and thus cannot easily be performed in individual laboratories. The Centers also support a pilot and feasibility program to develop new technologies for performing metabolic tests in mice, and several annual courses to introduce students to important techniques and theory. The MMPCs collaborate in exciting research areas, and are currently developing bariatric surgical procedures in the mouse in order to facilitate our understanding of how these surgeries benefit metabolic health as well as facilitate weight loss.

The Role of Inflammation in Diabetes: Inflammation—tissue swelling usually accompanied by pain and heat—is the body's generic response to a host of insults, such as infection. When associated with an infection, inflammation is acute, ending when the infection is controlled. However, it is becoming increasingly clear that metabolic conditions, including diabetes and obesity, are associated with chronic inflammation in which the immune response is present but at a low and persistent level. Chronic inflammation has also been linked to insulin resistance and the development of diabetes complications. Understanding how inflammation links obesity, insulin resistance, and diabetes may lead to new therapeutic approaches. A recent multicenter, NIDDK-supported clinical trial, called Targeting Inflammation with Salsalate in Type 2 Diabetes, is testing whether an anti-inflammatory drug, called salsalate, can reduce blood glucose levels in people with type 2 diabetes. Salsalate is approved by the FDA to relieve mild to moderate pain, fever, arthritis, and other conditions. If successful, the trial could lead to an effective, inexpensive way to treat people with type 2 diabetes.

ADVANCES IN TREATING DIABETES

Advances in Beta Cell Research: The beta cells of the pancreas produce insulin, a hormone that regulates the body's levels of blood glucose. Understanding biology of beta cells is critical for both type 1 and type 2 diabetes, as the beta cells are damaged in both forms of the disease. The Beta Cell Biology Consortium (BCBC) was established by NIDDK to promote collaborative basic research on beta cells toward the development of therapies for diabetes. BCBC investigators are studying pancreatic development, exploring the potential of stem cells as a source for making islets (clusters of cells that include beta cells) for transplantation, and determining methods to restore insulin production by regenerating a patient's beta cells. Exciting recent advances from the BCBC and from other NIDDK-supported scientists include the identification of beta cell progenitor cells and key progenitor cell proteins in the adult mouse pancreas, demonstration that some adult cells in the mouse pancreas can be reprogrammed into beta cells and that embryonic-like progenitor cells can regenerate beta cells in mice, discovery of factors important in expanding beta cell mass during pregnancy, discovery of a new marker for pre-clinical type 1 diabetes, and development of a mouse model for studying beta cell regeneration.



Increasing beta cell mass is critically important for both type 1 and type 2 diabetes. Left: Insulin-producing beta cells (pink) in a mouse pancreas. Right: Injection of an engineered virus containing regulators of pancreatic development results in additional insulin-producing cells.
Image credit: Zhou Q et al. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 455: 627-632, copyright 2008.

TREATING DIABETES—YESTERDAY AND TODAY

Since the establishment of the NIDDK in 1950, there have been major improvements in the treatment of diabetes. People with diabetes now have options for treatments that are safer and more effective, resulting in improved health outcomes. Research supported by the Institute contributed to the identification, development, and testing of many of these treatments.

TREATING DIABETES 60 YEARS AGO:

People monitored their blood glucose levels with urine tests, which recognized high but not dangerously low glucose levels and reflected past, not current, glucose levels.

People with type 1 diabetes relied on painful injections of animal-derived insulin.

People with type 2 diabetes had limited options: injections of insulin or drugs that stimulate insulin release from the beta cells of the pancreas (sulfonylureas). Both of these therapies can cause dangerously low blood glucose reactions and weight gain.

No proven strategies existed to prevent disease complications, such as blindness, kidney disease, nerve damage, and heart disease.

Physicians did not recognize the existence of rare forms of diabetes, such as maturity-onset diabetes of the young and neonatal diabetes mellitus, for which there now are specific therapies.

TREATING DIABETES TODAY:

People monitor their blood glucose with precise, less painful methods, sometimes including a continuous glucose monitor. The hemoglobin A1c (HbA1c) test is also used by patients and healthcare providers to assess average blood glucose control over the past 3 months.

People with type 1 diabetes have a choice of genetically-engineered human insulin formulations suitable for injection or use in pumps. Intensive glucose control is now possible, combining improved insulin administration with improved glucose monitoring techniques.

People with type 1 diabetes know that intensive control of blood glucose can dramatically delay or prevent eye, nerve, kidney, and cardiovascular complications, leading to improvements in long-term outcomes, as demonstrated in the landmark, NIDDK-supported DCCT. In each successive decade, people diagnosed with type 1 diabetes are living longer than those diagnosed the decade before.

People with type 2 diabetes benefit from improved forms of insulin, a range of oral medications to control blood glucose levels and reduce the need for insulin, and drugs that may not only control blood glucose, but also strengthen the activity of a person's own insulin-producing cells.

People with type 2 diabetes benefit from intensive blood glucose control early in the course of the disease and reduce their risk of long-term complications, demonstrated by the NIDDK-supported United Kingdom Prospective Diabetes Study. However, people with type 2 diabetes at high risk of heart disease do not benefit from intensive blood glucose control below current recommendations, as shown in the NIDDK-supported ACCORD clinical trial. Thus, rather than a one-size-fits-all approach, recommendations for treating people with type 2 diabetes can be personalized.

People with diabetes can prevent many of the debilitating complications of the disease. They can reduce their risk of cardiovascular disease by controlling their blood pressure and level of low-density lipoproteins (LDL). People with nerve damage can reduce the likelihood of limb amputation with improved methods of foot care. Progression of kidney disease can be prevented with specific drugs. Laser therapy can stop progression of eye complications to blindness.

Scientists have identified rarer, specific genetic forms of diabetes, permitting improved management. For example, infants with neonatal diabetes mellitus, a disease formerly treated with insulin injections, can be better treated with oral sulfonylurea drugs, a finding based on NIDDK-supported basic research on the biology of insulin secretion.

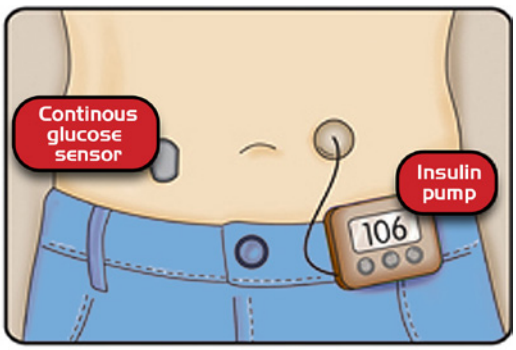
Some people with type 1 diabetes can undergo an islet transplant to reverse insulin dependency. NIDDK supports research to improve the safety and efficacy of this treatment approach, as well as to develop an artificial pancreas that would link glucose monitoring and insulin delivery.

Metabolic Research Yields New Therapies for Type 2 Diabetes: NIDDK research has led to the development of a remarkable new class of medications for treating type 2 diabetes. Glucose levels in the blood are controlled by a variety of factors, but two key hormones are critical. During fasting, glucagon keeps glucose levels up by signaling the liver to release stored energy. After meals, insulin has the dual effect of attenuating the glucagon effect and signaling cells to take up glucose, thus lowering its level in blood. Surprisingly, when NIDDK-supported scientists discovered the gene for glucagon in 1982, they found it was next to a gene for a different hormone—called glucagon-like peptide 1 or GLP-1—that actually acts to stimulate the insulin response after meals. GLP-1 is produced by cells of the small intestine when food is present in the digestive tract. People with type 2 diabetes do not produce enough insulin, so the capacity of GLP-1 to stimulate insulin production suggested that it might be helpful for people with the disease, but because the protein lasts just a few minutes in blood after it is produced, its potential as a therapeutic seemed limited. In the 1980s, scientists in the NIDDK Intramural Research Program discovered that saliva from a lizard known as the Gila monster contains a related but longer-lasting protein. This finding led to the development and 2005 approval of exenatide, an injected medication that boosts a person's own insulin production. Exenatide also slows digestion and makes people feel full longer after meals, leading to weight loss, a major benefit as the majority of people with type 2 diabetes are overweight or obese. However, exenatide has been found to cause acute pancreatitis (reversible but dangerous inflammation of the pancreas) in rare cases, so patients and prescribing physicians are cautioned to watch for symptoms of this complication. More recent developments include oral medications that act to extend the life of GLP-1 in the blood, yielding a similar net effect to that of exenatide without the need for injection.

Exenatide, a synthetic form of a protein derived from the saliva of the venomous Gila monster, is currently being used to help manage type 2 diabetes.
Photo credit: ©2009 Photos.com.

Casey Burkhalter's parents used to check her blood sugar every 2 hours at night, but they've been able to sleep better since Casey began testing a continuous glucose monitor as a participant in the DirecNet study. Says her mother, **Leslie**, "This technology is unbelievably helpful."

Continuous Glucose Monitors (CGMs)—Helping To Manage the Highs and Lows of Diabetes: For people with type 1 diabetes, undetected high or low blood glucose levels can have severe health consequences—including heart disease, blindness, and coma. As a result of decades of research, people with type 1 diabetes can now monitor their glucose levels continuously, so as to better adjust their insulin administration and take other steps to improve glucose control. Scientists invented the first device to measure blood glucose levels in the 1960s, and by the 1980s, blood glucose meters were widely used. In the 1990s, the landmark NIDDK-supported Diabetes Control and Complications Trial demonstrated the tremendous health benefits of intensive blood glucose control. This trial, which was possible because of the availability of glucose-monitoring devices, showed that intensive glucose control greatly reduced the development of diabetic eye disease, kidney disease, and nerve damage. The ongoing follow-up study recently demonstrated reduced risk for heart disease and stroke. However,



Continuous glucose monitoring can identify variations and trends in blood sugar levels over time with much greater detail than traditional finger sticks.

intensive control required multiple painful finger sticks each day to test blood glucose, and increased risk for dangerously low blood sugar. Because glucose in the blood cannot be measured continuously to detect highs and lows, scientists pursued the development of a sensor for glucose in the interstitial fluid in tissues under the skin. This research, with NIDDK, industry, and other support, led to the FDA approval of the first continuous monitor in 1999.

More advanced CGMs were approved in 2006 and 2007 for adults and children. These wearable monitors report glucose levels every 5 minutes; transmit data to an insulin pump to display real-time trend data on how levels are fluctuating; and sound alarms when levels are too high or low—especially important during sleep. Although patients still must be actively involved in determining their insulin doses, this pairing of a continuous monitor and pump has major implications. Scientists currently seek to integrate a CGM with an insulin pump so as to create an "artificial pancreas" that would automate insulin delivery in response to the body's needs. For now, patients can improve their glucose control, with likely future health benefits, using the unprecedented knowledge from continuous glucose monitors.

Treating Type 2 Diabetes in Children:
Type 2 diabetes is increasingly being diagnosed in children, particularly minority youth. Because the disease was previously rare in children, there is little information on how best to treat it. To address this gap in knowledge, the NIDDK launched the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial at centers around the country, to test three different treatment regimens for type 2 diabetes in children 10-17 years of age. Through TODAY and other studies, the NIDDK hopes to ameliorate type 2 diabetes and its complications in this most vulnerable population.

After realizing from his own Internet search that he had symptoms of type 2 diabetes, **Todd Hutchinson**, a Cherokee descendant, was officially diagnosed with the disease at age 13. He then joined the TODAY study. "I enjoy being in the study," he says. "It's a little bit of work, but it's well worth it." His mother, **Lisa**, adds, "The TODAY study has really changed Todd's life."

Studies of the Biology of Insulin Secretion Pave Way to New Treatment for Neonatal Diabetes:
In the 1950s, little did scientists know that new drugs to treat type 2 diabetes in adults would be used half a century later to treat a rare form of diabetes in babies. In the mid-1950s, sulfonylurea compounds were found to be effective for treating type 2 diabetes by stimulating insulin secretion. However, it was unknown for many decades *how* sulfonylureas worked. A clue came in 1985, when NIDDK-supported scientists demonstrated that the drug inhibited a potassium ion channel. The composition of the ion channel was revealed in 1995, when NIDDK-supported scientists discovered that the channel was made up of two proteins: the sulfonylurea receptor (SUR) and Kir6.2. Sulfonylureas bound directly to the SUR subunit of the channel to inhibit it and stimulate insulin release from the beta cell (mimicking the effects of glucose). This pioneering research contributed to a model of the regulation of insulin secretion by glucose.

In 2004, researchers in Europe found that people with permanent neonatal diabetes had mutations in their gene encoding Kir6.2. Neonatal diabetes is rare, usually occurring within the first 6 months of life, and may be permanent or transient. The same scientists discovered that 90 percent of people with permanent neonatal diabetes who had mutations in that gene could be treated with oral sulfonylurea rather than insulin—an exciting result because oral therapy is less burdensome and more effective than insulin administration for controlling blood glucose in this form of diabetes. NIDDK-supported scientists have also shown that some people with neonatal diabetes have mutations in their gene encoding SUR, and NIH-supported researchers confirmed that the gene for Kir6.2 is also linked to type 2 diabetes. Thus, the NIDDK-supported discovery of SUR/Kir6.2 informed key genetic studies and provided a greater understanding of the biology of insulin secretion. It also elegantly demonstrates how long-term NIDDK-supported basic research led to an improved treatment option for patients.

RESEARCH ON THE COMPLICATIONS OF DIABETES

The DCCT/EDIC Study Group—Improving Lives of People with Type 1 Diabetes: Impressive research progress toward combating diabetes complications was achieved through a large clinical trial launched by the NIDDK in 1983. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial in 1,441 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of small blood vessel (microvascular) complications affecting the eyes, kidneys, and nerves. The DCCT proved that intensive therapy reduces the risk of microvascular complications by 35 to 76 percent compared with conventional therapy.

Upon completion of the DCCT, the participants who had received conventional treatment were taught intensive treatment, and all of the patients were encouraged to use intensive treatment. Nearly all of the DCCT participants volunteered for the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to assess long-term outcomes of reducing the body's exposure to high blood glucose levels. In 2002 and 2003, EDIC investigators found that, 7 to 8 years after the end of DCCT, the period of intensive glucose control during the DCCT continued to reduce risk for microvascular complications. These long-term benefits were observed despite the fact that patients from the original intensive and conventional treatment groups had nearly identical blood glucose control during EDIC. While DCCT proved that glucose control could prevent small vessel damage, the effect of glucose on cardiovascular disease (CVD) was unknown. In 2005, DCCT/EDIC researchers found that, during an average follow-up time of 17 years, people in the former intensive treatment group had fewer than half the number of CVD events than those in the conventional group. These results showed for the first time that intensive control has long-term beneficial effects on CVD risk in people with type 1 diabetes.

The discovery that intensive glucose control reduced risk of disease complications revolutionized medical care for type 1 diabetes. Physicians now recommend that patients control their diabetes as early and intensively as possible. Intensive treatment is being translated into improved health, as recently reported by scientists from the DCCT/EDIC and the NIDDK-supported Pittsburgh Epidemiology of Diabetes Complications (EDC) study. The researchers found that the outlook for people with longstanding type 1 diabetes has greatly improved in the past 20 years. This exciting finding, due in large part to the fruits of DCCT/EDIC research, is further motivation for patients to implement early and intensive blood glucose control.

Diabetes and Cardiovascular Disease: Cardiovascular disease (CVD) is the leading cause of death for people with diabetes. Finding ways to reduce the risk of CVD in people with diabetes is a long-standing goal of NIDDK research programs, often pursued in collaboration with the National Heart,

Lung, and Blood Institute (NHLBI). There is very strong evidence that blood pressure and cholesterol control can markedly reduce CVD in people with diabetes. However, while NIDDK-supported research has clearly established the benefits of good control of blood glucose early during the course of diabetes to reduce later risk for eye, kidney, and nerve complications, the relationship of glucose control to CVD risk—particularly for people with type 2 diabetes—has proven more complex. In 2008, new insights emerged from several clinical trials. One trial, called ACCORD (supported by NHLBI with additional funding from NIDDK), showed that more intensive control than currently recommended can be dangerous in people with long-duration type 2 diabetes who also either have CVD or are at high risk of developing it. Two other non-NIH clinical trials found neither cardiovascular harm nor benefit from moving from "good" to near-normal glucose levels. However, another study, the UKPDS, which was supported in part by NIDDK, found that targeting good glucose control early in the course of disease can reduce CVD risks decades later for many people with type 2 diabetes—similar to what was seen in the NIDDK's DCCT/EDIC study for people with type 1 diabetes. Taken together, the new results refine the approach to treating diabetes and demonstrate the importance of tailoring therapy to individual patients. Genetics also plays an important role in determining susceptibility to diabetes and its complications, and future research will continue to integrate new genetic findings into efforts to tailor therapies. Additional insights should be forthcoming from another NIDDK-supported clinical trial, called Look AHEAD (Action for Health in Diabetes), which is examining the long-term effects of sustained weight loss on CVD in obese persons with type 2 diabetes (described in the Obesity chapter).

TRANSLATIONAL RESEARCH

From Bench to Bedside: "Bench to bedside" research aims to move discoveries from a laboratory (bench) setting to a pre-clinical or clinical (bedside) setting to test new therapies. One example of a program that has fostered bench to bedside translation is the Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) program, which provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. When NIDDK-supported scientists demonstrated that an anti-inflammatory drug, lisofylline, prevented the recurrence of type 1 diabetes after islet transplantation in a mouse model, T1D-RAID supported the manufacture of lisofylline for human trials undertaken through the Clinical Islet Transplantation Consortium, which is co-supported by NIDDK and the National Institute of Allergy and Infectious Diseases. Fostering bench to bedside research helps to ensure a pipeline of new therapies for clinical testing.

From Clinical Study to Community and Medical Practice: Another step in the translational research spectrum is to move therapies found to be efficacious in clinical trials to the broader community. For example, the NIDDK's Diabetes Prevention Program (DPP) clinical trial found that modest weight loss through diet and exercise reduced risk for type 2 diabetes in overweight adults with pre-diabetes. The NIDDK supports research to translate these results from a controlled clinical setting to "real world" conditions. Most of these studies involve communities with minority populations overly burdened by type 2 diabetes. Data from a recent pilot study suggest that using the YMCA to deliver a DPP

Dan Lamb enrolled in the DCCT clinical trial in 1983, and participates in the EDIC study to this day. He says, "Had I not been part of the DCCT, I probably would not have paid attention to my diabetes as closely as I have, nor possess the same understanding of the disease and its complications that I have now. The study has been a huge part of my life, and has contributed greatly to my success as a person with diabetes."

lifestyle intervention may be a low cost way to reach large numbers of people.

SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

The Special Statutory Funding Program for Type 1 Diabetes Research, or Special Diabetes Program, supports research on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. It is administered by the NIDDK on behalf of the Secretary of the U.S. Department of Health and Human Services and in collaboration with multiple other Institutes and Centers of the NIH and the Centers for Disease Control and Prevention (CDC). The Special Diabetes Program supports collaborative research that spans a continuum from basic research on underlying causes of disease, to pre-clinical drug development and testing, to clinical trials testing new therapies in people. The Special Diabetes Program has been extremely successful in promoting this "bench to bedside" research paradigm, which is important for moving promising therapies from the laboratory to the people who could benefit from them.

Since the Program's inception in 1998, significant progress has been achieved. For example, an international clinical trials network, called Type 1 Diabetes TrialNet, is conducting trials testing strategies for disease prevention and early treatment. In 2009, TrialNet found that the drug rituximab preserved function of insulin-producing beta cells in people newly-diagnosed with type 1 diabetes. Rituximab targets the antibody-producing B cells of the immune system and has been approved by the FDA for treatment of B cell non-Hodgkin's lymphoma and some autoimmune disorders. Several other trials testing novel therapies are under way through TrialNet.

Type 1 diabetes results from a complex interplay between genes and the environment, and the Special Diabetes Program supports research in these key areas. The Type 1 Diabetes Genetics Consortium (T1DGC) has identified at least 40 genetic regions associated with disease. The long-term TEDDY study has nearly completed recruitment and is following genetically-susceptible newborns to identify environmental factors that trigger type 1 diabetes. (For information on T1DGC and TEDDY, see section on Understanding, Predicting, and Preventing Diabetes.)

Research supported by the Special Diabetes Program also contributed to the development of new continuous glucose monitoring technology. The Diabetes Research in Children Network (DirecNet) is studying the use of this technology in children. Other research supported by the Program is building on this new technology and aims to "close the loop" to link glucose monitoring and insulin delivery, toward the development of an artificial pancreas. The Special Diabetes Program also supports research on islet transplantation, beta cell biology, islet imaging, immune tolerance, diabetes complications, and other areas, toward the goals of improving the health of people with type 1 diabetes and ultimately curing the disease.

PROMOTING DIABETES EDUCATION AND INFORMATION FOR THE PUBLIC

Translating research discoveries in diabetes into education campaigns and health information that can improve public health is an important part of the NIDDK mission. The National Diabetes Education Program (NDEP), jointly sponsored by NIDDK and CDC, works in partnership with public and private organizations on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. NDEP also works to reduce health disparities in diabetes by reaching out to diverse audiences. Established in 1997 to disseminate the good news from the DCCT that improved control of blood glucose levels can reduce risk for serious diabetes health complications, the NDEP has continued to evolve in response to major research findings. Currently, NDEP runs a national multicultural campaign for type 2 diabetes prevention—the first in the Nation—with tailored materials and messages for high-risk audiences. This campaign, "*Small Steps. Big Rewards. Prevent Type 2 Diabetes*," builds on the research results of the landmark Diabetes Prevention Program, encouraging moderate weight loss through exercise and healthful

diet among people at risk for type 2 diabetes. Campaign materials include motivational tip sheets as well as print and radio public-service ads. Another national NDEP campaign, "*Control Your Diabetes. For Life,*" emphasizes the key elements of diabetes management to help prevent heart attack, stroke, and other diabetes complications. Many materials for both campaigns are available in up to 15 different languages. The NDEP has also developed special materials to help children with diabetes, their families, and school personnel deal with the daily demands of diabetes during the school year. Through its many partners, the NDEP is able to effectively develop, tailor, and disseminate materials that can help save the lives and protect the health of people with and at risk for diabetes. (For more information, visit http://ndep.nih.gov.)

Among the populations hardest hit by type 2 diabetes in the United States are American Indians/Alaska Natives. NIDDK, CDC, and the Indian Health Service have worked in concert with Tribal Colleges and Universities to support researchers in the development of a K-12 diabetes-related science curriculum for Tribal schools to reduce diabetes health disparities and to increase interest in the biomedical sciences and in science careers related to diabetes among American Indian children. The curriculum development was completed in 2008, and its launch was celebrated at a special ceremony at the Smithsonian's National Museum of the American Indian.

NIDDK also provides a comprehensive diabetes resource for patients, healthcare professionals, and the general public through the National Diabetes Information Clearinghouse (NDIC). Established in 1978, the Clearinghouse develops science-based materials about diabetes and its complications, from basic information about the different forms of the disease, to easy-to-read information about signs, symptoms, prevention, management, and treatment. In carrying out its mission, NDIC works closely with NIDDK's Diabetes Research and Training Centers; the NDEP; professional, patient, and voluntary associations; government agencies; and state health departments to identify and respond to informational needs about diabetes. To reach diverse audiences, Clearinghouse publications are increasingly made available in Spanish. Recently, the Clearinghouse developed a special "Awareness and Prevention" series for diabetes. Part of a larger NIDDK effort designed to raise awareness of common health problems among people not yet diagnosed, the diabetes series provides brief overviews of diabetes and pre-diabetes in English and Spanish for distribution at health fairs and similar venues. As communication technology advances, NIDDK is exploring new outlets such as podcasts, vodcasts, and other approaches to increase awareness of diabetes to improve public health.

The National Diabetes Education Program includes over 200 partners at the Federal, state, and local levels working to disseminate science-based information—such as the materials shown here—to health care providers, patients, and the general public.

ENDOCRINE AND METABOLIC DISORDERS

Dramatic Advances in the Understanding and Treatment of Cystic Fibrosis: In the early 1960s, the life expectancy of a child born with cystic fibrosis (CF) was just 10 years: the disease leads to accumulation of mucus in the lungs, creating an ideal breeding ground for bacteria like *Pseudomonas aeruginosa*, that cause severe lung damage—damage that led invariably to childhood death. Research has improved prospects for people with CF tremendously since then, almost quadrupling life expectancy to 37 years in the U.S., and improving quality of life.

The landmark 1989 discovery of the CF gene, called *CFTR*, by researchers including then NIDDK-supported scientist Dr. Francis Collins (now Director

The September 8, 1989 issue of *Science* magazine featured a cover picture of then-five-year-old **Danny Bessette**, who has cystic fibrosis (CF), and a report of the historic discovery of the CF gene. Danny has since grown and thrived, and recently graduated from college. Remarking on the progress of CF research since he was a child, he says that "the advancements they've made since then are incredible and help me big time."

Photo credit: Cystic Fibrosis Foundation.
The quote from Danny Bessette is reprinted, with permission, from the Fall 2006 issue of the Cystic Fibrosis Foundation's publication *Commitment*.

of the NIH), opened important windows into understanding of the CF disease process, which originates with mutations in the *CFTR* gene. It also suggested potential therapeutic approaches, including some, like gene therapy, that have not yet been realized. But routine newborn screening now catches cases of CF early so that therapy can begin almost from birth, thus alleviating the malnutrition and growth delays once associated with the disease. Powerful new antibiotics, like inhaled tobramycin, are effective against *P. aeruginosa*, reducing lung scarring and prolonging life. Other medications now slow the progression of lung disease, while mechanical chest physical therapy helps people with CF loosen and clear mucus from their bodies.

Life expectancy for people with CF continues to climb, but as much progress as has been made, there is still no cure. Effective treatment requires hours of demanding daily therapy. But ongoing research provides real hope for continued improvement of medical care for CF. NIDDK-supported scientists recently developed a pig model of the disease, which provides a key tool for testing therapeutic strategies. New medications are currently in development, some of which may provide a functional CFTR protein in patients with some versions of the gene, potentially eliminating many disease complications and allowing people with the disease to live essentially normal lives. Researchers are also working to develop other new therapies with the hope of one day dramatically improving the water-salt balance in people with CF, to enable them to clear mucus from their lungs and experience fewer infections.

Strides in the Treatment of Lysosomal Storage Disorders: The body's cells recycle many of the substances they no longer need by digesting them with enzymes inside cellular compartments called lysosomes. Rare genetic mutations can lead to missing or defective enzymes resulting in the build-up of toxic waste products in the lysosomes. These "lysosomal storage disorders" can cause severe organ damage. In the 1960s, scientists in the NIDDK's Intramural Research Program found that normal cells secrete lysosomal enzymes, and that cells from patients with these disorders can take them up and use them in their lysosomes. The discovery suggested the possibility that one day, people with lysosomal storage disorders could be treated with purified enzymes.

The genes for many of these enzymes were discovered in the 1980s. When dogs were found that lack some of the same enzymes, and have many of the same symptoms observed in people with these diseases, it became possible to test the enzyme replacement therapeutic strategy in an animal model. On the basis of this work, clinical trials then led to the FDA approval of enzyme replacement therapy for several lysosomal storage disorders, including mucopolysaccharidosis types I and VI, and Fabry, Gaucher, and Pompe diseases. The approach is not a cure, requires ongoing injections of replacement enzymes, and does not alleviate all symptoms, but it greatly improves quality of life for people with these diseases. NIDDK-supported researchers continue to test other treatment approaches, such as stabilizing mutant forms of the enzymes found in some patients. If shown to be safe and effective, enzyme stabilization may one day alleviate more

symptoms than enzyme replacement in people with some forms of lysosomal storage disorders.

Parathyroid, Bone, and Kidney Disease—the Calcium Connection: Through research to understand how the body regulates calcium levels, scientists have developed novel medical therapies and gained important understanding of multiple diseases. Insights into calcium regulation began in the 1960s and earlier, when scientists noticed a connection between blood calcium levels and parathyroid hormone secretion. Scientists in NIDDK's Intramural Research Program and elsewhere built on this research; among their findings was that parathyroid hormone raises calcium levels in the blood, in part by releasing calcium from bones. In 1993, with NIDDK and other support, scientists identified the gene for the master regulator of calcium levels—the calcium-sensing receptor protein, or CaSR. This protein maintains constant surveillance of blood calcium levels to regulate release of parathyroid hormone. NIDDK-supported scientists then discovered that mutations in the CaSR gene cause rare diseases in which excess parathyroid hormone plunders calcium from the skeleton, leading to bone fractures and other health problems. Another condition, severe kidney disease, is associated with low blood calcium levels, which trigger an increase in parathyroid hormone that weakens bones. Therapies for these conditions include surgery and other approaches—one of which was based on research on the CaSR. Scientists at a biotechnology company developed a novel type of drug, called a calcimimetic because it "mimics" calcium's effect on the CaSR. In 2004, an industry-sponsored clinical trial demonstrated the drug's effectiveness in kidney disease patients on dialysis. It is now FDA-approved as a treatment for excess parathyroid hormone resulting from kidney disease and also for parathyroid cancer. Patients are thus benefitting from years of basic and clinical research.

Research on parathyroid hormone has also led to a treatment for the devastating disease osteoporosis. The skeleton contains different types of living cells that routinely break down and re-build bone. Dietary nutrients, including calcium and vitamin D, and exercise help maintain and strengthen bones, and several medical interventions are available that can help reduce bone loss and increase bone density. One of these interventions resulted from decades of research on parathyroid hormone. Paradoxically, chronic excesses of this hormone render bones weak from loss of calcium, while short bursts stimulate new bone growth. Building on pioneering research by NIDDK intramural scientists on parathyroid hormone, researchers at other institutions—supported by NIDDK, industry, and other sources—assessed the potential of this hormone for treating osteoporosis in clinical studies. This research culminated in the FDA approval, in 2002, of a synthetic version of parathyroid hormone for treating certain patients at particularly high risk for bone fractures.

Surprises from Research on Bones: Research continues to reveal how bones not only support the body, but also contribute to other biological processes. In recent research, NIDDK-funded scientists studying mice discovered that bone formation is inhibited by gut-derived serotonin. Altered serotonin levels have also been observed in people with a rare bone disease. Thus, serotonin action may be a target for developing new therapeutic strategies to treat osteoporosis. Another recent NIDDK-funded study brought to light an unexpected additional function for the skeleton, beyond its critical structural support for the body. In research in mice, a hormone produced by bone cells, osteocalcin, was found to regulate metabolic processes relevant to obesity and type 2 diabetes. This surprising finding may open new avenues for intervention approaches for metabolic conditions. Insights from research on bone biology and metabolism thus hold promise for continued benefits to health.

LOOKING TO THE FUTURE

As the NIDDK reflects on the past 60 years of supporting and conducting research on diabetes, endocrinology, and metabolic diseases, it is clear that the scientific progress achieved during that time period has been remarkable. Looking to the future, the NIDDK will continue to build on the landmark scientific discoveries of the past to foster new research breakthroughs. Paramount to this effort is the continued vigorous support of basic, pre-clinical, and clinical

research, as well as the development of educational materials to disseminate important new research findings to patients, their families, and healthcare providers. To inform research directions in diabetes, endocrinology, and metabolic diseases, the NIDDK will continue to solicit input from the broad scientific community through forums such as scientific workshops and conferences. In addition, strategic planning, with broad external input, will continue to guide future research directions. For example, *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan* was released by NIDDK in 2006, and the Institute has recently undertaken a new strategic planning process to identify opportunities for all forms of diabetes. Through these efforts, the NIDDK remains steadfast in its mission to support and conduct research to improve people's health and quality of life.

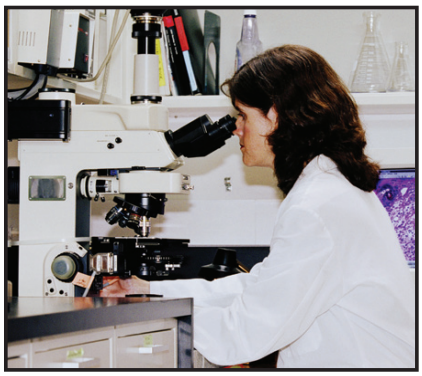


Photo credit: Getty Images.

Digestive Diseases and Nutrition

The NIDDK supports a broad portfolio of basic, translational, and clinical research and training programs related to digestive diseases, which affect the gastrointestinal (GI) tract, pancreas, liver and biliary system, as well as nutritional disorders. They encompass some of the most common, severe, and disabling conditions afflicting Americans today. As illustrated in this chapter, past research supported by the NIDDK has enhanced our understanding of digestive system biology and function, and led to improvements in the health and well-being of people suffering from digestive and nutrition-related conditions. Given the impact on public health, the National Commission on Digestive Diseases recently assessed the state-of-the-science on digestive diseases and developed a long-range research plan, which was informed by a recent report on the current burden of digestive diseases in the U.S. The NIDDK will continue to foster new discoveries that advance the understanding, prevention, and treatment of digestive diseases and nutritional disorders.

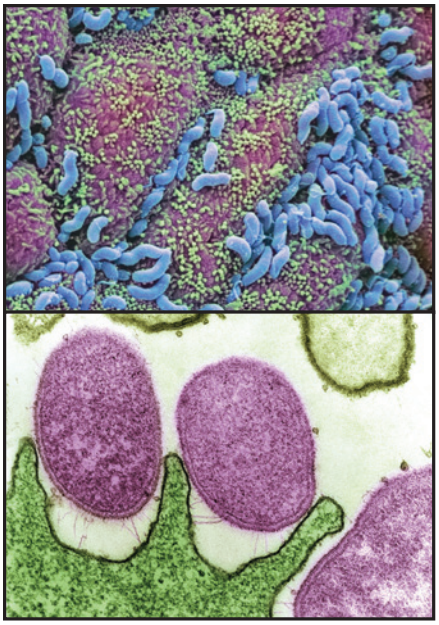
DISEASES OF THE GI TRACT

Targeting Acid Reflux and Related Diseases of the Esophagus: Gastroesophageal reflux disease (GERD), more commonly known as acid reflux or "heartburn," occurs when the stomach acid normally used to digest food flows backwards into the esophagus, resulting in inflammation, tissue damage, and associated conditions. The NIDDK has made significant investments over the years in research aimed at understanding the basic biology of acid production and secretion in the stomach. Nearly four decades ago, NIDDK-supported scientists discovered a "proton pump" on the surface of specialized cells responsible for the final step of acid secretion in the stomach. The methods developed to isolate the proton pump and study its biochemistry were critical for the design of new pharmacological agents that turn off the pump and block acid secretion. These so-called "proton pump inhibitors" are now the standard of care for the treatment of acid reflux and are amongst the most widely prescribed drugs on the market today.

GERD is associated with Barrett's Esophagus (BE), a condition in which cells lining the esophagus change in shape, organization, and function. BE puts patients at greater risk for developing esophageal adenocarcinoma, the predominant form of esophageal cancer in the U.S. The NIDDK supports research to identify risk factors and improve the treatment of BE. For example, in 2009, a landmark study conducted by a team of researchers throughout the country demonstrated the use of a new endoscopic procedure for the treatment of BE. In addition, NIDDK-supported studies identified behavioral risk factors associated with this condition. Researchers found that obesity, in particular an increased waist size, places individuals at greater risk of developing BE. However, a healthier diet that

includes more fruits and vegetables may help to reduce this risk. These studies and other continued efforts to identify genetic and epigenetic markers associated with BE will help to identify patients at risk, guide treatment protocols, and reduce the burden of diseases such as esophageal cancer.

Bacterial Contributions to Diseases of the Stomach: The discovery in the 1980s that the bacteria *Helicobacter pylori* resides in the human stomach and plays a role in the development of stomach inflammation, peptic ulcer disease, and gastric cancer revolutionized the understanding, management, and treatment of stomach diseases. In 1994, NIDDK convened an NIH Consensus Development Conference to assess the relationship between *H. pylori* and gastric malignancies. Following an evaluation of the state-of-the-science, the Consensus Development Panel made recommendations for the use of antimicrobial agents to target *H. pylori* infection, changing the standard of care for peptic ulcer disease. In response to this recommendation, novel antimicrobial treatment protocols have been developed to effectively eradicate the bacteria from the harsh environment of the stomach and virtually eliminate subsequent risk of developing peptic ulcers caused by this microbe.



Colorized electron micrographs of *Helicobacter pylori* bacteria (on top in blue; on bottom in purple) in the human stomach. *Image credits:* Top image: David McCarthy/ Photo Researchers, Inc; bottom image: SPL/ Photo Researchers, Inc.

Related to this seminal advance, researchers have been intensely interested in understanding the molecular basis for how *H. pylori* infection leads from stomach inflammation to the development of peptic ulcers and stomach cancer. NIDDK-supported scientists uncovered the key molecules that allow *H. pylori* to attach to the surface of stomach cells to mediate infection and determined how particular bacterial proteins, or virulence factors, disrupt the normal shape and structure of cells lining the stomach. In other breakthroughs, researchers studying the genetic diversity of *H. pylori* strains have identified different bacterial genes associated with the transition from simple inflammation to more serious pre-cancerous conditions and gastric cancer. Ongoing research will address how these genetic variations and virulence factors lead to the development of severe gastric disease and offer new avenues for the design of therapeutic interventions.

Intestinal Health and Disease: NIDDK research has illuminated the workings, in health and disease, of the body's "inner tube"—the intestines—where life-sustaining nutrients from foods are digested by enzymes secreted by the GI tract, pancreas, and beneficial resident bacteria into molecules that can be absorbed. Intestinal health problems, such as acute diarrhea, can be caused by "bad" bacteria or viruses that invade the intestines, and the NIDDK has supported research elucidating the mechanisms by which certain types of foodborne *Escherichia coli* cause severe diarrhea. Diarrhea can also be a symptom of intestinal diseases and functional bowel disorders.

Irritable bowel syndrome (IBS) causes severe, sometimes debilitating, intestinal pain, and occurs more often in women than in men. While diet and stress contribute to this disorder, the underlying causes are unknown. NIDDK-supported researchers are studying the interplay of gut and brain pathways in these disorders. For example, investigators found that women with IBS perceive visceral pain associated with this disorder differently than do healthy volunteers. They also found that a history of physical abuse heightens visceral pain responses in women with IBS. Additionally, researchers identified sex/gender-specific

differences in brain activity in female and male IBS patients. These findings may lead to the development of improved treatment strategies.

Celiac disease—an intolerance of the gluten proteins in many grains—causes intestinal damage and often goes undetected, which can result in malnutrition and impaired growth in children. Scientists have recently developed a test for proteins made by patients with celiac disease that permits earlier diagnosis.

In celiac disease, intestinal damage results from an intolerance to the gluten protein found in grains. *Image credit:* Illustration courtesy of the NIH Office of Medical Applications of Research.

Based on research findings, inflammatory bowel diseases (IBD) are thought to arise from genetic factors that cause inappropriate immune responses to otherwise harmless gut microbes. The two major types of IBD are Crohn's disease, which can occur in the small intestine and colon, and ulcerative colitis (discussed below), which occurs only in the colon. More than 30 IBD susceptibility genes have now been identified by research groups such as the NIDDK-supported IBD Genetics Consortium, a team of researchers from several sites in the U.S. and Canada. Many of the genes affect both forms of IBD, and their identification provides insights into disease processes and potential therapeutic targets. A timeline of NIDDK's major scientific advances in IBD research appears later in this chapter.

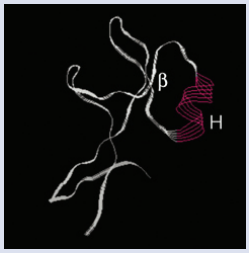
Diseases of the Colon: A common form of digestive disease in the U.S., colon cancer can be avoided if pre-cancerous polyps are identified during colorectal screening and removed. A 2008 NIDDK-supported study matching polyp size with pre-cancerous or cancerous states informed the development of updated guidelines for screening and management of colon cancer in the U.S. Another recent study focused on racial disparities in colon cancer and showed that African Americans had greater numbers of pre-cancerous polyps than Caucasians. Additionally, older adults were more likely to have polyps in the upper (proximal) colon, a region that can be evaluated by colonoscopy but not by sigmoidoscopy. These results may lead to further consideration of screening guidelines. In another area of research, a study of ulcerative colitis showed that the drug rosiglitazone reduced disease—first in mice, then in humans—and led to its being the first effective drug specifically indicated for this disease.

HIGHLIGHTS OF NIDDK-SUPPORTED IBD RESEARCH ADVANCES

1979: In the landmark National Cooperative Crohn's Disease Study conducted with principal support by the NIDDK, two pharmaceutical agents—prednisone and sulfasalazine—are each shown to be effective as treatments for Crohn's disease.

1994: Genetically engineered rats raised in a germ-free environment are found to be resistant to developing IBD in an NIDDK-supported study, suggesting that both microbes and genetic factors contribute to this disease.

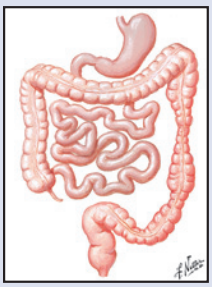
1994: In NIDDK-supported research, trefoil peptides are associated with wound healing in the intestine. More continues to be discovered about their key roles in mucosal tissue protection and repair, advancing understanding of IBD.



Trefoil factor 1 peptide
Image credit: Taupin D. and Podolsky D.K. Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Mol Cell Biol*, 4: 721-732, copyright 2003.

1999: TNF-alpha blocker infliximab approved for treating IBD. Research on using this new-generation drug to treat Crohn's disease was propelled by model mouse studies sponsored by the Institute.

2001: Discovery of first Crohn's disease susceptibility gene, *NOD2*. This landmark finding, by NIDDK-supported scientists, also identifies one of the first genes associated with a complex genetic disease and provides evidence linking IBD to an inflammatory response to bacteria.



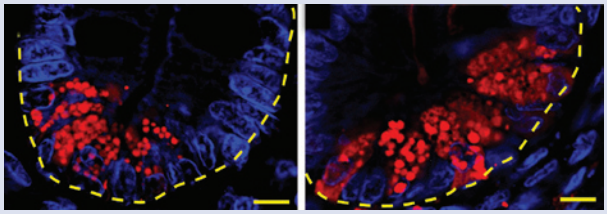
Artistic representation of the human digestive tract.
Image credit: Netter medical illustration used with permission of Elsevier. All rights reserved. http://www.netterimages.com.

2005: Two new mouse models developed with NIDDK support shed light on the protective role that the Crohn's disease susceptibility gene *NOD2* normally plays in fighting bacterial infection in the gut.

2006: NIDDK-funded researchers identify the *IL23 receptor* gene as a major Crohn's disease susceptibility gene.

2007: A subset of immune cells (T_H17 cells) is identified by NIDDK-supported researchers as inducing intestinal inflammation in Crohn's disease.

2007: In further NIDDK-supported genetic studies, the *ATG16L1* gene is associated with Crohn's disease, linking the cellular process of "autophagy" to IBD.



Autophagy gene *ATG16L1* expression in human intestinal cells
Image credit: Cadwell K et al. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 456: 259-263, copyright 2008.

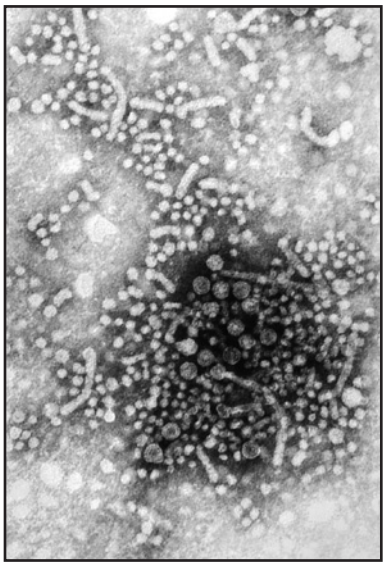
2008: NIDDK-funded trial of the diabetes drug rosiglitazone for ulcerative colitis demonstrates the short-term effectiveness of this treatment.

PRESENT: More than 30 IBD susceptibility genes have now been identified through collaborative studies conducted by international research groups, including the NIDDK-funded IBD Genetics Consortium.

Image credit: Image courtesy of Dr. Judy Cho, Yale School of Medicine, IBD Genetics Consortium.

HEPATOBILIARY DISEASES

Viral Hepatitis: Viral hepatitis is the most common cause of liver disease in the U.S. and worldwide. The NIDDK supports research to characterize and develop means of prevention, treatment, and control of the five major forms of viral hepatitis (hepatitis A, B, C, D, and E)—efforts which have led to direct health benefits for individuals affected by these diseases. Many past studies have focused on chronic hepatitis B and C, which are major causes of cirrhosis and liver cancer. Building on the Institute's basic research efforts to characterize the hepatitis B virus, including the Nobel-winning discovery of the virus by an NIDDK scientist in 1963, vaccination and blood screening programs have significantly reduced transmission of hepatitis B in the U.S. (See also the feature on Nobel laureates in this book.) The NIDDK has also sponsored long-term clinical trials to test the safety and compare the effectiveness of multiple drugs currently available to treat chronic hepatitis B. With centers throughout the country, the NIDDK-funded Hepatitis B Clinical Research Network will further advance understanding of disease processes and effective approaches to treating and controlling hepatitis B. Research on hepatitis C has also led to significant breakthroughs. Clinical studies by NIDDK intramural scientists in the 1980s tested the first effective treatment for chronic hepatitis C—long-term interferon therapy—which remains a standard treatment for the disease today. Additional clinical trials over the past decade have assessed the effectiveness of long-term hepatitis C treatment in preventing liver disease progression, tested therapies for chronic hepatitis C in children, and investigated different treatment responses in African Americans compared to Caucasians with chronic hepatitis C. NIDDK researchers also developed some of the first cell culture systems for studying the hepatitis C virus in the laboratory, enabling an expanded range of studies on viral life cycle and response to new antiviral agents.



Transmission electron micrograph showing particles of the virus that causes hepatitis B, a major form of liver disease. *Image credit:* CDC/ Betty Partin.

"God, I'm lucky," says **Howard Klein**, a musician who participated in several NIDDK clinical trials over the years to test various treatments against hepatitis B. A treatment stemming from these trials has allowed him to avoid serious disease and continue his music career.

Advances in Nonalcoholic Fatty Liver Disease (NAFLD) Research: NAFLD results from the inappropriate accumulation of fat in the liver, which can lead to more serious complications of liver injury, steatohepatitis (inflammation), and cirrhosis. NIDDK is pursuing research to understand basic mechanisms of fat metabolism in the liver and to develop ways to prevent and treat NAFLD. In recent years, NIDDK-supported scientists discovered how a cellular protein unexpectedly regulates production of fat in the liver and also uncovered a gene variant that may help to identify patients at risk for developing NAFLD. To combat the rise in NAFLD associated with increasing overweight and obesity in U.S. adults and children, NIDDK is conducting clinical trials of potential treatments for NAFLD within its multi-center Nonalcoholic Steatohepatitis Clinical Research Network. The

ongoing efforts of the Network's investigators are expected to uncover new information about disease development, broaden treatment options, and improve patient outcomes.

Gallstones: Gallstones are among the most common digestive disorders in the U.S., exacting high healthcare costs from their surgical treatment through gallbladder removal. From the 1960s to 1980s, NIDDK-supported investigators demonstrated how the normal physical and chemical properties of bile rely on maintaining cholesterol and calcium dissolved in the bile and described how alterations in this process led to gallstone formation. Animal models of cholesterol gallstones have been created, including strains of inbred mice that enabled the identification of several genetic factors that contribute to the disorder; some of these factors have been identified in humans as conferring increased susceptibility. Research also found that infection with several species of *Helicobacter* bacteria is associated with gallstone formation. Population studies showed that American Indian populations in several parts of the U.S. suffer from gallstones at a much higher rate than other racial or ethnic groups in this country.

Iron Metabolism and Hemochromatosis: Iron is essential for good health, but too much iron—a condition called iron overload—can threaten health by damaging organs, such as the liver and heart. Unfortunately, the human body does not have a natural way to rid itself of excess iron. Iron overload occurs in a disease called hemochromatosis, in which genetic mutations alter mechanisms that would otherwise precisely regulate iron absorption. NIDDK-sponsored research has advanced understanding of the causes of hemochromatosis and is contributing to improvements in its diagnosis and treatment. In the mid-1990s, scientists achieved a major advance in understanding hemochromatosis: they identified mutations in a gene called *HFE* that underlie the most common form of the disease in humans. Through further exploration, the scientists found that most of the people with mutant *HFE* genes do not develop clinical symptoms or signs of organ toxicity—indicating that additional mutations or environmental factors likely contribute to the development of hereditary hemochromatosis.

Joe Crossan has a disease called hemochromatosis, which causes a build-up of iron in his body. Fortunately, a treatment called phlebotomy helps people like Joe by removing excess iron from the circulation. Joe states "Thirty years ago, when my father died, very little was known about hemochromatosis. Thanks to research, a lot is known today about the disease."

Other insights into hemochromatosis emerged from studies showing the significance of the protein hepcidin in controlling iron balance in the body. The NIDDK continues to pursue these studies of iron metabolism, as well as to seek new diagnostic and therapeutic options for hemochromatosis, such as a non-invasive test to measure body iron and better iron chelators to remove excess iron from the blood.

Rare Genetic and Metabolic Liver Diseases: Alpha-1 antitrypsin deficiency is a rare genetic disease affecting children and adults. NIDDK-supported research has led to greater understanding of this disease, which is caused by mutations in the alpha-1 antitrypsin protein. These mutations cause the protein to be misshapen (or "misfolded") and to accumulate in the liver. Through experiments with mice and cells grown in the laboratory, researchers gained insights into which cellular processes are involved in the degradation and disposal of the mutant proteins, implicating pathways known as the "autophagy" pathway and the "ER overload response." By studying genes that were turned on or off to regulate disposal of mutant proteins, they also identified a gene activated in response to the aggregation of mutant alpha-1 antitrypsin proteins. This gene may be a new biomarker for research on disease development and progression and a potential target for new therapeutic strategies. Recently, researchers developed a new model for studying the

disease: a tiny transparent worm with mutant alpha-1 antitrypsin genes fused to a green fluorescent protein gene. The green proteins made from these genes can be observed aggregating within the liver or being secreted into the intestine. The scientists are currently adapting this little worm model for research to identify potential genetic modifiers of disease severity and for screening potential therapies for the disease.

Allen Russell's liver and lungs were being destroyed by alpha-1 antitrypsin deficiency when a liver transplant saved his life. Allen says, "I remain extremely grateful to my donor for my second chance in life." NIDDK is dedicated to improving the care of people with this disease by supporting research to advance liver transplantation and develop new treatments.

Liver Transplantation-related Topics: Since the first human liver transplantation was performed in 1967 by an NIDDK grantee, the Institute has supported research to improve outcomes of this potentially life-saving procedure for those with severe liver disease and/or acute liver failure. For example, NIDDK research contributed to surgical and organ preservation techniques that reduce patient blood loss, preserve the donor organ, and lengthen the time available for organ transportation and surgery. Research has also provided evidence for development of effective post-operative immunosuppressive therapy to prevent liver transplant rejection. The NIDDK played a key role in organizing an NIH Consensus Development Conference on liver transplantation held in 1983 that supported the use of this procedure for end-stage liver disease, prompting a dramatic increase in the number of liver transplants performed in the U.S. The Institute continues to support research efforts to enhance liver transplantation through such programs as the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), conducted by a group of researchers throughout the country. In the last few years, A2ALL has characterized the benefits and risks of the living donor liver transplantation procedure for donors and for recipients, including specific patient populations such as those with hepatitis C. Another NIDDK-supported program called Studies of Pediatric Liver Transplantation conducts research to improve the success of liver transplants in children.

The NIDDK also supports research on some of the conditions that commonly lead to liver transplantation, such as drug-induced liver injury and resulting acute liver failure, through programs such as the Drug-Induced Liver Injury Network and both the adult and pediatric Acute Liver Failure Study Groups, all conducted at multiple sites across the country. These programs are assessing ways to better detect, treat, and prevent severe liver injury due to drugs (prescription and over-the-counter) or complementary and alternative medicines, so that individuals do not reach the point of requiring a liver transplantation.

HIGHLIGHTS OF NIDDK-SUPPORTED LIVER RESEARCH ADVANCES

1963: An NIDDK intramural scientist discovers hepatitis B virus or "Australia antigen" while conducting research at the Institute, for which he is subsequently awarded the Nobel Prize in Physiology or Medicine. This finding represents a scientific and clinical breakthrough in detection and control of viral hepatitis and leads to the development of measures to prevent viral hepatitis and liver cancer.

1967: The first human liver transplantation is performed by an NIDDK grantee. This surgical breakthrough opens the door for use of this life-saving procedure in cases of severe liver disease and acute liver failure.

1983: NIH Consensus Development Conference on liver transplantation, sponsored by the NIDDK and NIH Office of Medical Applications of Research, supports use of this procedure for end-stage liver disease, prompting a dramatic increase in the number of liver transplants performed in the U.S.

1986: Clinical research conducted by intramural scientists in the NIDDK Liver Diseases Section provides evidence for the first effective treatment for chronic hepatitis C in the form of long-term interferon therapy.

1998: NIDDK-supported researchers develop a mouse model of hereditary hemochromatosis by knocking out the *HFE* gene. This animal model also confirms the importance of *HFE* to the development of hepatic iron overload in this disease.

2002: The NIDDK-supported Adult Acute Liver Failure Study Group reports that liver injury is increasing in the U.S. due to overdose of the painkiller acetaminophen, which is now the leading cause of acute liver failure.

2005: NIDDK intramural researchers develop some of the first cell culture systems to study hepatitis C virus *in vitro*, enabling direct laboratory investigation of viral life cycle and response to antiviral agents.

2007: A mouse model is developed with a "humanized" liver by replacing the livers of immunodeficient mice with human liver cells. This animal model can be used in the future to facilitate new drug development and research in such areas as drug-induced liver disease, viral hepatitis, and liver regeneration.

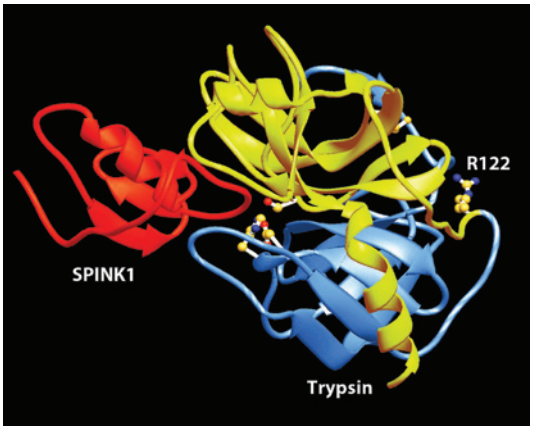
2007-2008: The NIDDK-supported Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) characterizes the benefits and risks of the living donor liver transplantation procedure for both recipients and donors.

2008: Results of the NIDDK-funded clinical trial called Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) demonstrate that, in people who do not respond to initial therapy, longer-term interferon treatment is ineffective in preventing chronic hepatitis C progression to conditions such as cirrhosis and liver cancer, emphasizing the importance of developing other long-term therapeutic approaches.

2008: NIDDK provides leadership for the NIH Consensus Development Conference on Management of Hepatitis B and launches the Hepatitis B Clinical Research Network.

DISEASES OF THE PANCREAS

Genetic Insights into Pancreatitis: Pancreatitis, or inflammation of the pancreas, is believed to result from destruction of the pancreas from the inside, by the digestive enzymes that it produces. In 1996, NIDDK-supported scientists reported the discovery of a genetic variant in patients suffering from hereditary pancreatitis. The mutation is in the gene encoding a form of trypsin, a digestive enzyme which is normally inactive in the pancreas, and which self-destructs if prematurely activated to avoid pancreatic damage. The mutation disables this defense mechanism. Subsequent studies identified other genetic variants associated with pancreatitis, including mutations in a gene that helps protect the pancreas from trypsin activity, and in the *CFTR* gene, originally identified in association with cystic fibrosis. In an ongoing study with participants from the North American Pancreatic Study Group, researchers are scanning entire genomes to uncover other genetic markers that may help to identify susceptible individuals and prevent pancreatitis.



Ribbon diagram of the trypsinogen-trypsinogen inhibitor complex; a mutation in the trypsinogen gene is associated with hereditary pancreatitis.
Image credit: Image courtesy of Dr. David Whitcomb.

Uncovering a Genetic Cause of Zollinger-Ellison Syndrome (ZES): Patients with ZES have tumors in the pancreas and small intestine, which release hormones that trigger overproduction of stomach acid and formation of peptic ulcers. Some of these tumors are caused by an inherited genetic disorder called multiple endocrine neoplasia type 1 (MEN1). Scientists at the NIDDK, including former NIDDK Director Dr. Allen Spiegel, in collaboration with a team of scientists at the National Human Genome Research Institute led by Dr. Francis Collins, now the NIH Director, were the first to clone the *MEN1* gene and identify several mutations associated with this inherited disorder (see also Intramural chapter). Subsequently, researchers discovered that *MEN1* produces a protein that acts as a "tumor suppressor" to suppress cell growth. As these landmark studies uncovered the molecular basis of ZES caused by MEN1, the NIDDK continues to lead innovative studies aimed at improving approaches to the diagnosis and management of ZES.

NUTRITION AND METABOLISM

Many health conditions are affected by nutrients in the foods we consume, and how well our bodies metabolize these nutrients. In addition to research on diabetes, metabolic disorders, and obesity, which are described in greater detail in other chapters of this book, the NIDDK supports studies related to other specific nutritional and metabolic alterations. For example, researchers investigating metabolism of the nutrient copper, which plays an essential role in many biological processes as an enzyme component, uncovered some of the mechanisms and potential therapeutic targets associated with an inherited form of copper deficiency called Menkes disease. Children with this disease suffer from seizures, poor muscle tone, neurodegeneration, and failure-to-thrive starting a few weeks after birth. NIDDK-supported research using a zebrafish model has enhanced knowledge of how Menkes disease develops and can best be treated.

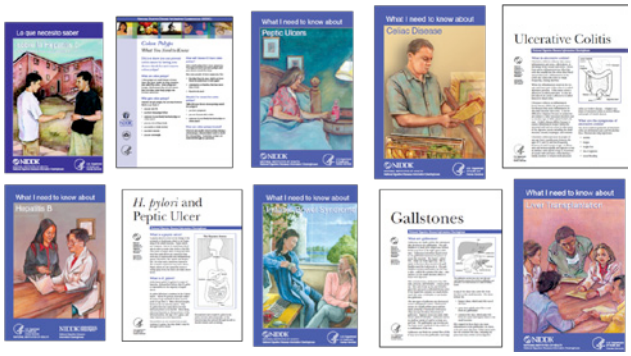
CROSS-CUTTING DIGESTIVE DISEASES AND NUTRITION-RELATED RESEARCH

Many areas of NIDDK-supported research cut across multiple digestive diseases and nutritional disorders. For example, through genomic studies, researchers have uncovered genetic variants associated with several digestive diseases, such as hereditary pancreatitis, celiac disease, Crohn's disease, and nonalcoholic fatty liver disease. Scientists are also studying, through programs

such as the NIH Human Microbiome Project, how the composition of bacteria that reside in the gut influences digestive health. NIDDK-supported studies have led to important discoveries of how the gut microbial community contributes to conditions such as IBD and potentially to obesity. NIDDK-funded researchers are also investigating other factors in the gut that contribute to obesity, and uncovering, for example, how a hormone released in the gut increases the feeling of hunger in the brain. Investigators in the multi-center Longitudinal Assessment of Bariatric Surgery (LABS) and related Teen-LABS studies are assessing long-term risks and benefits of bariatric surgery in adults and adolescents. Many other avenues of obesity research are described in the Obesity chapter.

Mariah Watts suffered from sleep apnea, a dangerous condition associated with obesity, had pre-diabetes, and tried many weight loss approaches that didn't work. As a last resort, she underwent bariatric surgery, after assessment by a multidisciplinary pediatric clinical team to determine her eligibility, and her health has improved. Having researched the procedure on her own on the internet, she suggests that others "do their homework first" too, before deciding on surgery. Mariah is participating in Teen-LABS, an observational study collecting data from just before surgery to two years after, to evaluate the surgery's risks and benefits — information that will help others. Her mother says, "We thought it was important for us to get involved so that other parents and their teenage children could make more informed decisions." Mariah agrees.

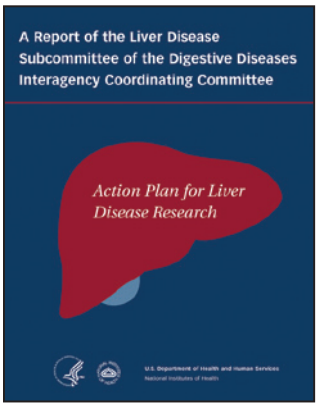
EDUCATION PROGRAMS



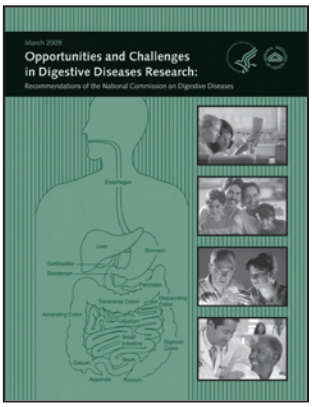
Information from the National Digestive Diseases Information Clearinghouse.

The NIDDK supports education programs for patients, their families, healthcare providers, and the public to enhance knowledge of digestive and nutrition-related conditions and prevention and treatment approaches. For example, many people are unaware they have celiac disease, an intolerance to the protein gluten found in some grains, which can result in intestinal injury and reduced nutrient absorption. Although an effective treatment exists in the form of a gluten-free diet, celiac disease often goes undiagnosed and thus untreated. The Celiac Disease Awareness Campaign was launched by the NIDDK in 2006 in response to recommendations from a 2004 NIH Consensus Development Conference to provide a variety of informational materials. Another educational campaign is being developed to address the rising rate of fecal incontinence in the aging U.S. population. This campaign to educate professionals and the public stems from recommendations of a 2007 NIH State-of-the-Science Conference. The National Digestive Diseases Information Clearinghouse, established in 1980, provides a variety of user-friendly educational materials about digestive diseases to patients, their families, health professionals, and the public, including clinical trial information, print and web-based publications, listings of patient organizations, and interactive health features and tools. Clearinghouse materials, in English and Spanish, can be accessed electronically or ordered in hard copy at http://digestive.niddk.nih.gov/.

LOOKING TO THE FUTURE



Trans-NIH *Action Plan for Liver Disease Research*
U.S. Department of Health and Human Services, National Institutes of Health, December 2004, NIH Publication No. 04-5491.



Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases
U.S. Department of Health and Human Services, National Institutes of Health, March 2009, NIH Publication No. 08-6514.

Tomorrow's research directions for digestive and nutrition-related diseases are informed by a combination of ongoing efforts, including strategic plans, workshops, broad external input from stakeholders—along with the fruits of current research—with the ultimate aim of improving the lives of patients and their families. The NIDDK has provided substantial leadership and support for important trans-NIH research planning efforts related to digestive diseases. The trans-NIH *Action Plan for Liver Disease Research*, released in 2004, identifies areas of scientific opportunity leading to research goals in the prevention and control of liver and biliary diseases. Another research plan, entitled *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*, released in 2009, is the culmination of a rigorous 4-year planning process to identify research challenges and opportunities spanning the wide range of digestive conditions. Within the Commission's research plan, a chapter on liver and biliary diseases references and updates research goals from the *Action Plan*. Both the liver disease-focused and the broader digestive diseases research plans feature a 10-year time horizon and represent the broad external input of individuals committed to advancing digestive diseases research, including those from the NIH and other Federal agencies, intramural and extramural researchers, physicians, and representatives of professional and patient advocacy groups. These research plans can be accessed in electronic form or ordered in hard copy through the following web sites: http://liverplan.niddk.nih.gov and http://NCDD.niddk.nih.gov.

Photo credit: Richard Nowitz, for NIDDK.

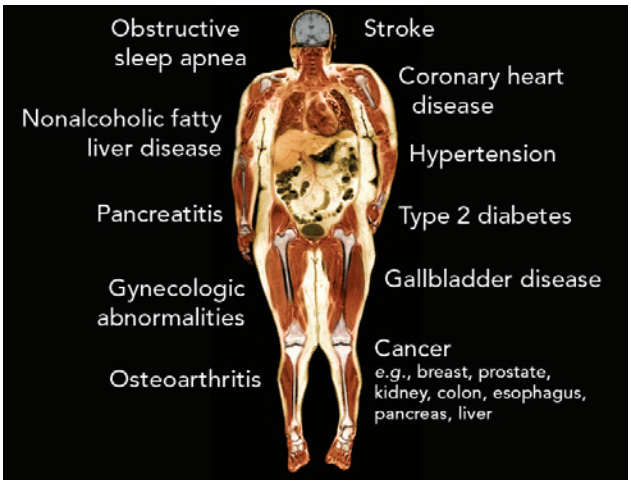
Obesity

Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders. A common, chronic, and costly condition, obesity affects more than one-third of adults in the U.S. and 16 percent of children—who are at risk for developing serious diseases both during their youth and later in adulthood.[2] Obesity also disproportionately affects racial and ethnic minority populations, and those who are socioeconomically disadvantaged. Thus, NIDDK supports a broad spectrum of obesity research to understand the factors that influence body weight, illuminate how obesity leads to disease, and develop and test prevention and treatment strategies in the clinic and community settings.

A CONVERGENCE OF BIOLOGY AND THE ENVIRONMENT

The Discovery of Leptin, and Molecular Regulation of Body Weight: The body's adipose tissue—or fat—sustains life in times of famine and fuels physical activity and vital biological processes, but too much fat is a recipe for metabolic disaster. Although scientists had recognized for decades that obesity, or excess fat, is linked to type 2 diabetes and other diseases, it wasn't clear why. However, there were hints that not all fat tissue is the same, and that the amount of body fat is regulated.

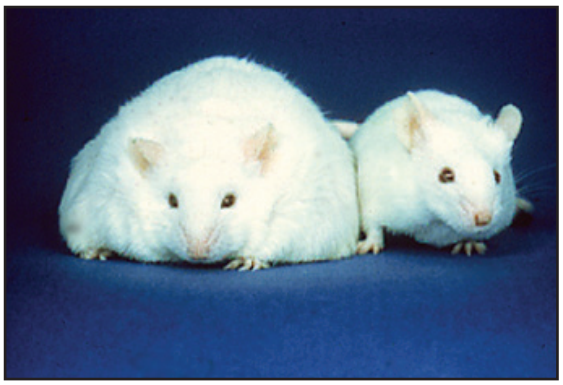
In 1994, NIDDK-supported scientists studying obese mice identified the gene for the hormone leptin—a discovery that would ignite an explosion of research into the control of appetite and body weight, shine a spotlight on the role of adipose tissue in regulating metabolism, and change perceptions about obesity. Subsequent research showed that leptin, which is produced by fat cells, travels to a key control center



Whole-body scan of an individual who is obese. Potential obesity-associated health complications are indicated.
Image credit: Adapted from image created by Dr. Wei Shen and Dr. Steven Heymsfield, New York Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University, New York.

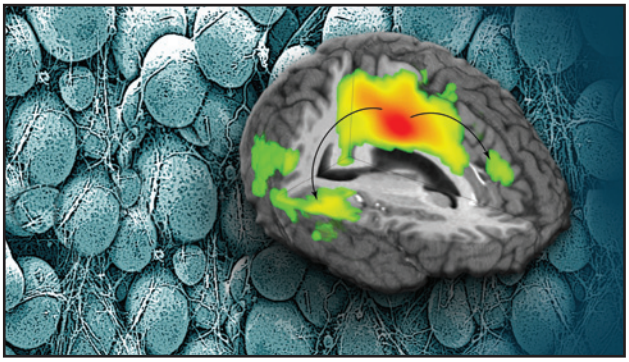
[2] *National Center for Health Statistics, CDC, Data Brief Number 1, 2007; and* JAMA *299: 2401-5, 2008. Obesity in adults is defined as a body mass index (BMI, a measure of weight relative to height) of 30 or greater. For children, this document uses the term obesity to refer to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).*

in the brain to report on the body's energy stores and reduce appetite. For people who lack leptin due to very rare genetic mutations, administration of this hormone effectively treats their extreme obesity. Demonstrating a genetic and hormonal basis for excess body weight, this research also underscored that appetite control could no longer be viewed as solely a "willpower" issue. Most people who are obese do not have leptin deficiency, and in fact, have very high levels of leptin, but in obesity, the body appears to become resistant to this hormone's actions. Years of research have shown that genetic factors nevertheless strongly influence common forms of obesity as well. As many as 5 percent of individuals with early onset severe obesity may have a defect in a brain molecule known as the melanocortin-4 receptor. With advanced genome-wide analyses, scientists are identifying additional genes associated with common forms of obesity.



Mutation of the receptor for the hormone leptin causes obesity in the mouse on left, compared to a normal mouse on the right.
Image credit: Image courtesy of the Jackson Laboratory.

Since the discovery of leptin, NIDDK-funded researchers have elucidated an extraordinarily complex regulatory system of hormones and other molecular signals that not only sense the body's energy stores (in the form of fat) to modulate appetite and satiety, but also respond to the rewarding nature of tasty food. Signaling factors produced in the brain as well as those secreted by fat tissue and other parts of the body converge in the brain to regulate body weight. Just a few examples are the hormone ghrelin, which is released from the gut and acts on the brain to stimulate appetite; apo A-IV, which reduces food intake after a high-fat meal; and factors such as mTOR, serotonin, and others. Other research has advanced knowledge of the many biologic processes that contribute to regain of lost weight and body fat, including hormonal and other changes that affect hunger and energy expenditure (calorie burning). Very recently, neuroimaging studies revealed that the sight of food elicits different patterns of brain activity in obese people before and after weight loss; leptin administration reversed many of these changes. The exciting insights from these and other studies are providing potential targets for new drug development and may inform other treatment approaches with the goal of helping people lose excess body fat and maintain the weight loss long-term.



Neuroimaging, with such methods as a brain scan (foreground image) can reveal aspects of brain activity associated with obesity (represented by the fat cells in the background).
Image credit: Brain scan of cingulate functional connectivity, courtesy of Dr. Elliot Hong (Maryland Psychiatric Research Center), and Drs. Elliot Stein and Thomas Ross (National Institute on Drug Abuse).

"Brown" Fat Tissue: Not all body fat, or adipose tissue, is the same. White adipose tissue stores extra calories as fat for later use; obesity is an excess of this type of fat tissue. Another type of fat, "brown" adipose tissue, burns fat molecules to dissipate heat and helps keep babies and small animals warm. In humans, brown fat tissue was previously thought to disappear after infancy, but in 2009, NIDDK-supported scientists and other research teams discovered that brown fat is present in adult humans and appears metabolically active with exposure to cooler temperatures. They also found that people who are overweight or obese seem to have less active brown fat. NIDDK-funded scientists are also elucidating how brown fat cells develop, and have discovered that some brown fat arises from the same precursor cells as another energy-burning tissue—muscle—while other brown fat cells may share a lineage

with white adipose cells. These findings suggest a novel strategy for treating obesity: generating more brown fat cells to burn more excess calories.

Food, Physical Activity, and Fidgeting: Beyond the biologic factors within us, aspects of our environment can also contribute to obesity: the availability of healthy foods and beverages; opportunities for physical activity; and the pervasive lure, or necessity, of sedentary behaviors. In research on eating behaviors, for example, NIDDK-supported scientists have shown that larger portion sizes lead to greater food consumption. In the realm of activity, an NIDDK-funded study of thousands of women found that sedentary behavior, particularly sitting while watching television, is predictive of greater risk for obesity and type 2 diabetes. Another team of NIDDK-funded scientists discovered that among self-described "couch potatoes," people who are lean tend to stand and move far more than those who are obese. Fidgeting—technically "non-exercise activity thermogenesis"—may thus burn a substantial number of calories.

Gut Bacteria and Obesity: A surprising contributor to obesity may be the bacteria and other microbes that reside in the gut. NIDDK-funded scientists recently discovered that gut microbes differ between lean and obese individuals: microbes associated with obesity may be better at harvesting extra calories from food. Gut microbes also influence the body's storage of calories as fat. Manipulation of gut microbes may thus be a novel approach to prevent or treat obesity.

Linking Excess Fat to Disease: NIDDK-supported research on obesity has advanced understanding of how excess fat leads to disease. Earlier research had shown that fat in certain areas of the body confers heightened risk for type 2 diabetes, especially tissue now referred to as "visceral" fat, or fat around the organs deep within the abdomen. Within the past decade, scientists have identified molecular links between obesity and associated health problems. For example, a hormone produced in adipose tissue, adiponectin, helps the body respond to insulin. In obesity, abnormally low levels of adiponectin are associated with insulin resistance, which is a risk factor for and hallmark of type 2 diabetes. Scientists have also found that elevated levels of another factor, called RBP4, are associated with insulin resistance, as well as type 2 diabetes and cardiovascular disease risk, and thus may be a potential diagnostic marker and therapeutic target. RBP4 is produced by visceral fat cells. Several other factors secreted by adipose tissue promote chronic inflammation, which has been linked to type 2 diabetes and cardiovascular disease risk. In 2003, researchers made the surprising discovery that some of these factors, such as TNF-alpha, are produced by cells of the immune system, called macrophages, which infiltrate fat tissue. Levels of another hormone, resistin, also contribute to insulin resistance. Originally identified as a fat cell-derived factor in mice, resistin interestingly is secreted by macrophages in humans. In an emerging area of research, scientists are learning that the link between fat and disease can begin early in life. NIDDK intramural researchers have shown that maternal type 2 diabetes during pregnancy leads to increased risk for the offspring to develop diabetes and obesity later in life. Focusing on another disease, researchers studying non-human primates observed that maternal consumption of a high-fat (and high-calorie) diet during pregnancy—similar to a typical American diet—results in extensive fatty liver disease in the offspring. Although the mechanisms for these effects are not yet clear, they may involve epigenetics—molecular modifications that affect gene activity without changing the DNA sequence.

PREVENTION AND TREATMENT STRATEGIES

Lifestyle and Medical Interventions: The NIDDK has sponsored numerous studies of approaches to prevent or treat excess weight gain and lower risk for obesity-associated disease. For example, one recent study showed that a strategy to reduce television and computer use beneficially affects body mass index (BMI, a measure of weight relative to height) in young children, particularly those from a socioeconomically disadvantaged background. Other researchers found that an intervention to reduce consumption of sugar-sweetened beverages in teens had a beneficial effect on body weight in those who, at the beginning of the study, had very high body weights compared to

their peers. In a study with obese adults, researchers showed that treatment with a lifestyle modification program of diet, exercise, and behavioral therapy, when used in combination with the weight-loss medication sibutramine, resulted in significantly greater weight loss than treatment with the medication alone. Exploring the challenging task of maintaining weight loss, scientists leading the Study to Prevent Regain (STOP Regain) clinical trial discovered that a face-to-face intervention incorporating daily self-weighing can help adults maintain a desired weight following weight loss. Many other studies are ongoing to investigate a variety of approaches to prevent or manage overweight and obesity in children and adults, in diverse populations, and in a variety of settings, such as the home, school, and other community sites.

Lifestyle factors such as physical activity and healthy eating can help kids to avoid obesity and its complications.
Photo credit: Jupiterimages.

A major study focused on a disease associated with obesity, type 2 diabetes, was the Diabetes Prevention Program (DPP). This landmark clinical trial, which was conducted at sites throughout the country, demonstrated that people who are overweight or obese and at high risk for type 2 diabetes can dramatically reduce their chances of developing the disease through modest weight loss, achieved with moderate exercise and reduced dietary fat and calories. The lifestyle intervention, which was based on extensive prior behavioral research, worked in both men and women, and in all ages and racial and ethnic groups studied. The DPP results were announced in 2002, and a follow-up study has recently shown that the health benefits have continued. (See additional information in the Diabetes, Endocrinology, and Metabolic Diseases chapter.)

Another large clinical trial, Look AHEAD (Action for Health in Diabetes), is focused on overweight and obese adults who already have type 2 diabetes. Currently ongoing at research centers around the country, Look AHEAD is examining the health effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term, through exercise and decreased caloric intake. The study will assess the impact of the intensive lifestyle intervention on the incidence of heart attack, stroke, and cardiovascular-related death, along with other outcomes. Over 5,000 participants have enrolled, including both men and women, and members of minority groups disproportionately affected by obesity and diabetes. Encouraging results from the first year of the trial, reported in 2007, showed that clinically significant weight loss could be achieved through the lifestyle intervention, and led to improvements in health-related quality of life, cardiovascular fitness, blood pressure, cholesterol, and blood glucose. These results are particularly important in light of the fact that previous research had suggested that weight loss and maintenance might be more difficult in obese individuals with type 2 diabetes.

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) study demonstrated another health benefit of weight loss. In 2009, researchers reported that women who are overweight or obese can significantly reduce their episodes of urinary incontinence through modest weight loss.

Surgical Treatment for Extreme Obesity: For people who are extremely obese, bariatric surgical procedures are being increasingly performed and can have dramatic health benefits, such as improved control of blood sugar or even reversal of type 2 diabetes, but also carry serious health risks. Thus, the NIDDK supports a multi-center observational study, the Longitudinal Assessment of Bariatric Surgery (LABS), to advance understanding of the risks and benefits of these procedures. Recently, LABS researchers found that short-term complications and death rates were low following bariatric surgery; the study is continuing to assess longer-term outcomes. The NIDDK is additionally supporting the Teen-LABS observational study to evaluate the surgery's risks and benefits in

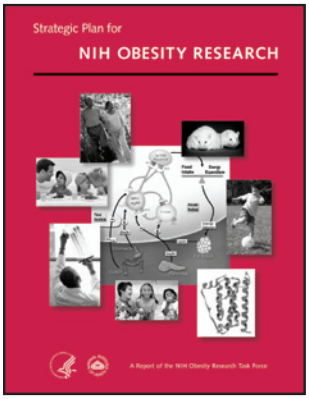
adolescents. (Additional information is presented in the Digestive Diseases and Nutrition chapter.)

EDUCATION AND OUTREACH PROGRAMS

Information from NIDDK's Weight-control Information Network.

In addition to funding basic and clinical research, the NIDDK also sponsors educational and outreach programs to disseminate science-based information. The Institute established the Weight-control Information Network (WIN) in 1994 to provide the general public and health professionals with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues (http://win.niddk.nih.gov/index.htm). Among WIN's many publications is a series of booklets, in English and Spanish, on "Healthy Eating and Activity Across Your Lifespan." WIN also developed a national initiative, *Sisters Together: Move More, Eat Better*, to encourage Black women to maintain a healthy weight by becoming more physically active and eating healthier foods. A recently-published WIN brochure is designed to help men get fit and lose weight. The NIDDK also co-sponsors *We Can!* (Ways to Enhance Children's Activity and Nutrition), a national education program led by the National Heart, Lung, and Blood Institute. *We Can!* is designed for families and communities to help children 8-13 years old maintain a healthy weight (http://wecan.nhlbi.nih.gov).

LOOKING TO THE FUTURE



Strategic Plan for NIH Obesity Research U.S. Department of Health and Human Services, National Institutes of Health, August 2004, NIH Publication No. 04-5493.

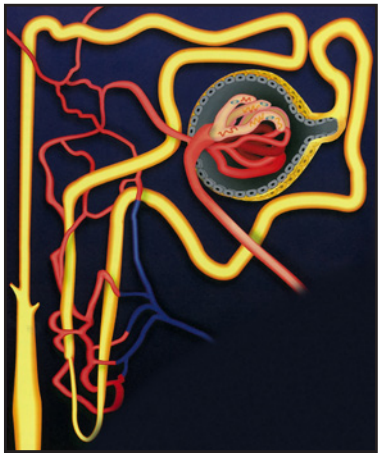
Building on the discoveries and opportunities emanating from past research, the NIDDK—and the scientists it supports—will continue to pursue new insights into the complex problem of obesity, develop and test prevention and treatment strategies, and expand the scientific evidence base that can be used to inform policy making and other community efforts. These multidimensional research efforts will continue to be informed by input from external scientists and clinicians at universities and other institutions and members of the broader public through the NIDDK Clinical Obesity Research Panel, scientific workshops, and other venues. Additionally, the Institute has a leadership role on the NIH Obesity Research Task Force, which in 2004 developed a *Strategic Plan for NIH Obesity Research* with extensive external input. The Task Force is currently updating this *Plan*. Through continued advances in obesity research, the NIDDK aims to improve people's lives and public health.

Photo credit: Getty Images.

Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the U.S. They afflict millions of Americans, including children and adults. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease, in which case patients require dialysis or a kidney transplant to live. The NIDDK supports a significant portfolio of research on the biology underlying chronic kidney disease. Urologic diseases affect men, women, and children; result in significant health care expenditures; and may lead to substantial disability and impaired quality of life. The NIDDK's urology research effort includes basic, clinical, and epidemiologic research on the genitourinary tract. The NIDDK's hematology research efforts are advancing knowledge of the normal and abnormal function of blood cells and the blood-forming system. These programs seek to increase our understanding of the causes of kidney, urologic, and hematologic diseases and to enhance prevention and treatment approaches in order to lessen the burden faced by people living with these diseases.

Chronic Kidney Disease: An estimated 23 million Americans have chronic kidney disease.[3] A significant burden of chronic kidney disease is the high risk of cardiovascular disease faced by these patients. The Chronic Renal Insufficiency Cohort (CRIC) study, funded by NIDDK, aims to elucidate the relationship between chronic kidney disease and cardiovascular disease. CRIC has enrolled almost 4,000 adults with chronic kidney disease; it is the largest such study. In another NIDDK-supported effort, the African American Study of Kidney Disease and Hypertension (AASK) clinical trial, researchers assessed different interventions for kidney disease progression at over 20 academic and community medical centers throughout the country. This trial, the largest and longest study of chronic kidney disease in African Americans, found that



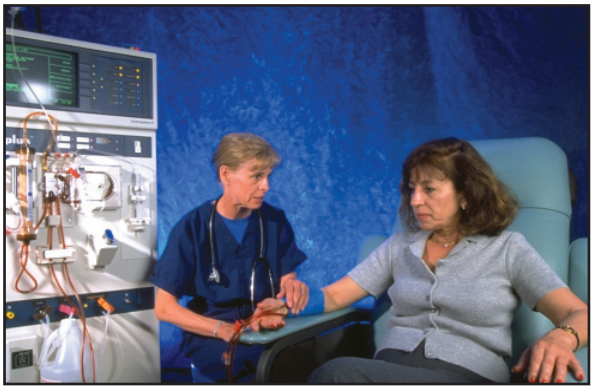
Each kidney contains about 1 million nephrons, such as the one illustrated here, which are the working units of the kidneys. Nephrons remove waste and excess fluids from the blood. *Image credit:* Maryetta Lancaster, for NIH Medical Arts and Photography Branch.

[3] *Levey AJ et al. A New Equation to Estimate Glomerular Filtration Rate.* Ann Intern Med *150: 604-612, 2009.*

an angiotensin-converting enzyme inhibitor was more effective than either a calcium channel blocker or beta-blocker in slowing kidney disease progression in African Americans with kidney disease attributed to high blood pressure. Unfortunately, this optimal treatment did not keep the disease from substantially worsening in about one-fourth of study participants. Other NIDDK-supported research suggests that interventions that target traditional risk factors—blood pressure control, blood sugar control, smoking cessation, and increased physical activity—may have the greatest potential to reduce mortality in some high-risk populations, such as the elderly.

Genetic factors likely contribute to a person's risk of developing chronic kidney disease as well. The NIDDK-supported Family Investigation of Nephropathy and Diabetes (FIND) consortium has identified four chromosomal regions that are correlated with elevated protein in the urine (a sign of impaired kidney function) or an increased risk of diabetic kidney disease.

Children and adolescents with chronic kidney disease are particularly vulnerable to its adverse effects. The CKiD study is an ongoing prospective, observational study of children with mild to moderate chronic kidney disease, taking place at over 40 medical centers. Supported by NIDDK, CKiD has enrolled several hundred children to identify the risk factors for decline in kidney function and to define how decline in kidney function impacts neurocognitive function, behavior, and other factors.



Dialysis to remove waste products and excess fluid represents a life-saving treatment for people with end-stage renal disease or kidney failure.
Photo credit: Richard Nowitz, for NIDDK.

End-stage Renal Disease: Over half a million Americans have kidney failure, also called end-stage renal disease or ESRD, and require either dialysis or a kidney transplant to live.[4] Diabetes and high blood pressure are the two leading causes of ESRD, and rates of kidney failure had been rising. After 20 years of 5 to 10 percent annual increases, however, rates of new cases of kidney failure seem to have stabilized in recent years, as reported by the U.S. Renal Data System (see sidebar). The reasons for improvement may be attributable, at least in part, to better prevention-oriented care. Unfortunately, racial disparities in ESRD rates persist, highlighting the importance of continued efforts to improve prevention and treatment approaches for kidney disease.

For patients with ESRD who are undergoing dialysis, the Dialysis Access Consortium has examined ways to improve the longevity and usefulness of two main types of vascular access sites, surgically-created sites on the body where blood is removed for cleansing and returned during dialysis. Established by the NIDDK, the Consortium is a team of researchers from universities and medical centers across the country. In one study, the anti-platelet drug clopidogrel did not improve the long-term usability of an access site called a fistula. However, in 2008, a second study by the Consortium demonstrated that a combination of aspirin and the anti-platelet drug

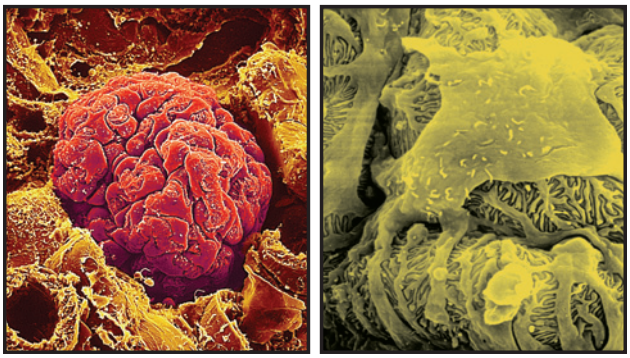
The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) and chronic kidney disease (CKD) in the U.S. Launched in 1988, it facilitates epidemiological and clinical research, leading to improved management of chronic kidney disease and end-stage renal disease. The USRDS is funded by the NIDDK in conjunction with the Centers for Medicare and Medicaid Services. Along with producing an Annual Data Report on CKD and ESRD in the U.S., the USRDS also publishes the Researcher's Guide, fulfills data requests, provides standard analysis files and specialized datasets to researchers, and presents the results of its research at national conferences and in peer-reviewed journals.

[4] *U.S. Renal Data System, USRDS 2009 Annual Data Report, 2009.*

dipyridamole could modestly prolong the durability of another type of access site called an AV graft.

James Willingham's kidney failure was diagnosed when he was hospitalized five years ago for an unrelated cause. James volunteered to participate in a Dialysis Access Consortium study of ways to improve access to blood vessels in patients undergoing dialysis. "It is studies like these that help people like me," James says. "The study was a very good experience."

For many years, it was unclear whether higher doses of dialysis—either prolonged dialysis or the use of high-flux filters—provided a benefit to patients. In 2002, the NIDDK-supported, multi-center HEMO Study confirmed that the minimum dialysis dose recommended by treatment guidelines is adequate and that, in general, a higher dose and special filters provide no added benefit to ESRD patients. It was the first major NIH clinical trial of dialysis in over 20 years. The ongoing Frequent Hemodialysis Network is supporting two studies comparing dialysis regimens: one will compare traditional thrice-weekly, in-center dialysis treatments with six shorter, daily treatments; a second will compare thrice weekly, in-home dialysis to six overnight treatments a week.

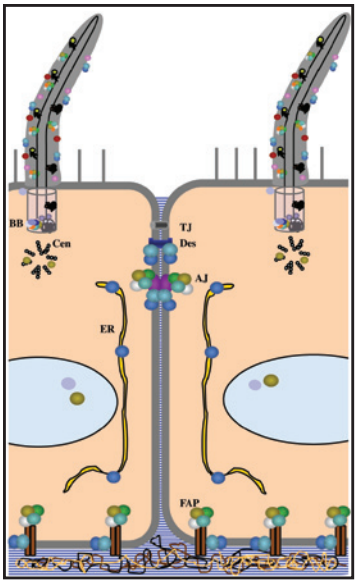


The glomerulus (left) is a small ball of capillaries that, together with surrounding cells, comprises the basic filtering unit of the kidney. The glomerulus is composed of several cell types, including podocytes (right). *Image credits:* Susumu Nishinaga/Photo Researchers, Inc. (left) and Dr. Tobias B. Huber, University Hospital Freiburg (right).

Acute Kidney Injury: Acute renal failure or acute kidney injury is a serious medical condition characterized by a relatively rapid loss of kidney function. The Veterans Affairs (VA)/NIH Acute Renal Failure Trial Network Study was conducted at 27 VA and university-affiliated medical centers, and enrolled over 1,100 critically ill patients with acute kidney injury, and compared higher-dose dialysis with less intensive, conventional dialysis. After 60 days, no significant difference in death rates was found between the two groups of patients. These results may spare patients from unnecessarily-intensive medical interventions. They also underscore the need for research into other approaches to treating acute kidney injury. Toward this end, the NIDDK has launched a study of the natural history of patients with acute kidney injury, ASSESS AKI. This study will provide important information about the natural history of acute kidney injury and recovery.

Polycystic Kidney Disease: In people with polycystic kidney disease, or PKD, fluid-filled cysts form in the kidneys and other organs and can, as they grow over time, compromise kidney function. Symptoms and complications of PKD include high blood pressure, urinary tract infections, and chronic pain. NIDDK-funded scientists have played an important role in illuminating the mechanisms underlying the two main forms of polycystic kidney disease: autosomal dominant PKD (ADPKD), the most common form, and autosomal recessive PKD (ARPKD). They found that ADPKD results from mutation of either of two genes, *PKD1* or *PKD2*, whose encoded proteins form a cell surface receptor-ion channel complex that plays a key role in kidney cell signaling and function. They also determined that ARPKD results from mutation of a single gene, *PKHD1*, which encodes a large membrane protein that localizes to the primary cilium—a tiny, hair-like projection on the cell surface. NIDDK-supported scientists have also provided important insights into the mechanisms of disease, including the discovery that cilia play an important role in sensing and cell signaling; this, in turn, sparked a new field of study into the role of cilia-mediated signaling in

other cell types. NIDDK has also supported the generation of rodent models of PKD, which have become valuable tools to study the natural history of and possible treatments for this disease. Furthermore, the identification of intracellular mediators of cell signaling has helped to identify important targets for drug development and treatment.



Proteins that are thought to play a role in polycystic kidney disease (colored spheres in this image) are involved in the assembly and function of cilia—tiny, hairlike projections on the surface of many types of cells. Research into signaling by cilia in the kidney, and its potential disruption in people with PKD, has provided new insights into possible mechanisms of disease initiation and progression and novel targets for future therapy. *Image credit*: Reprinted from *Methods in Cell Biology*, Volume 94; LF Menezes and GG Germino, Polycystic Kidney Disease, Cilia, and Planar Polarity; Copyright 2009, with permission from Elsevier.

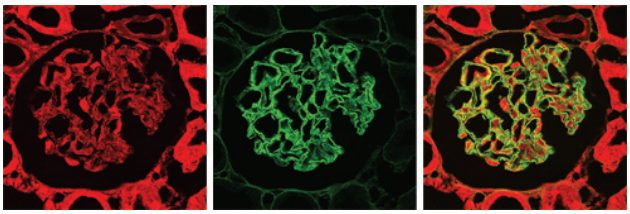
In addition to a robust portfolio of basic research projects, the NIDDK supports clinical studies aimed at furthering our knowledge about the origins, progression, and treatment of this disease. In 2006, the Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys, which may predict functional changes earlier than standard blood and urine tests in people with ADPKD. This valuable cohort of patients is being monitored through an extension of the original study. With co-funding from the PKD Foundation, the NIDDK is also supporting two clinical trials of people with ADPKD. These two trials, conducted at six sites around the country, are the largest multi-center studies of PKD conducted to date, and are collectively termed HALT-PKD. The NIDDK is also funding an interventional trial of blood pressure and cholesterol-lowering medications in children and young adults with autosomal dominant PKD to lower the risk of both heart disease and kidney failure.

In addition to these efforts, in 1999 the NIDDK established Interdisciplinary Centers for PKD Research, a partnership of scientific investigators from various disciplines who use complementary and integrated approaches in PKD research.

Focal Segmental Glomerulosclerosis: Focal segmental glomerulosclerosis (FSGS) damages the filtering units of the kidneys, thereby allowing protein and sometimes red blood cells to leak into the urine. Many patients with FSGS progress to kidney failure. Most FSGS arises from unknown causes and is termed "idiopathic" FSGS. African Americans are approximately five times more likely to develop idiopathic FSGS compared to individuals of other racial backgrounds. NIDDK intramural scientists and colleagues in the FIND consortium have found variants in the genetic region near the *MYH9* gene that seem to account for much of the increased risk for idiopathic FSGS and HIV-associated FSGS among African Americans compared to European Americans, and a portion of the increased risk for kidney disease associated with high blood pressure. Surprisingly, however, these variants were not associated with kidney failure arising from diabetes. Variation in another gene, *TRPC6*, which encodes an ion channel, is also thought to be an important

Six-year-old **Frankie Cervantes** received a kidney transplant from his mother, after his own kidneys had shut down due to the severe disease, FSGS. "I could not have been happier to learn that we matched," his mother says. The day of the transplant, Frankie was very joyful. "It's kidney day. It's kidney day," he told his parents. Because the disease could still recur, his parents are counting on medical research to help their son and others like him.

contributor to the kidney damage seen in this disease. Recent studies have found that, in some families with FSGS, the *TRPC6* gene is mutated, suggesting altered signaling by this protein may lead to kidney damage. The NIDDK is supporting a number of clinical trials aimed at improving therapy for FSGS. Many patients with FSGS do not respond to standard therapy or relapse after an initial response. The FSGS Clinical Trial is comparing two different immunosuppressive treatments for FSGS, while an NIDDK intramural trial is testing an anti-fibrotic agent in patients with FSGS. These trials seek to improve outcomes in patients with FSGS.



Kidney cells expressing the TRPC6 protein (left, red) and specialized cells called podocytes (center, green) are identified by fluorescent staining. When the images are merged (right), localization of TRPC6 to the podocytes is seen in yellow.
Image credit: Reiser J et al. Reprinted by permission from Macmillan Publishers Ltd: *Nat Genet* 37: 739-744, copyright 2005.

Urinary Tract Biology: The NIDDK supports and conducts both basic and clinical urological research. Experts have been brought together as the GenitoUrinary Development Molecular Anatomy Project (GUDMAP) consortium to assemble a molecular atlas of gene expression for the developing organs of the genitourinary tract and other tools to facilitate research.

Some children develop a condition, called vesicoureteral reflux, in which urine flows backward from the bladder to the kidney during urination. This condition is found in 30 to 50 percent of children who have had a urinary tract infection (UTI), and recurrent UTIs are thought to increase the risk of kidney damage.[5] The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study is designed to determine whether all children with vesicoureteral reflux should be treated with long-term antibiotics.

Andrea Arnold was diagnosed with urinary reflux when she was 6 months old, and at age 12 her damaged kidneys were removed. Andrea hopes to one day receive a kidney transplant. In the meantime, she's made friends with other patients in the dialysis center: "We don't see each other as sick. We're just close friends and we talk about everything." Researchers are striving to advance treatment for kidney disease, so that patients like Andrea and her friends will have improved health and quality of life.

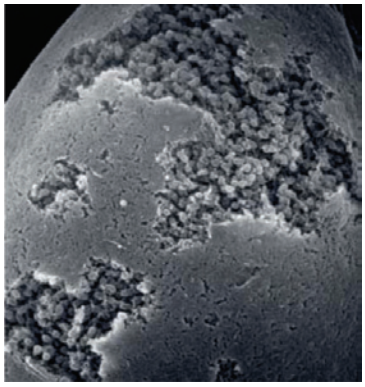
Kidney Stones—Urolithiasis and Urinary Tract Stone Disease: Kidney stone disorders are extremely painful conditions that are frequent causes of visits to health care providers. The NIDDK has a robust interest in this field, ranging from research into the basic mechanisms of stone formation and dissolution to studies of ways to improve the current minimally invasive treatment modalities of laser or ultrasound lithotripsy or extracorporal shock wave lithotripsy (ESWL) to break up stones in the body. The Institute also supports research to identify risk factors for kidney stone formation. In the 1970s and 1980s, an NIDDK-funded investigator identified many separate metabolic causes of stones, and developed several treatments. Recently, NIDDK-supported researchers made the surprising discovery that increased intake of dietary oxalate does not substantially increase risk of kidney stones, despite the fact that a large percentage of kidney stones contain a compound called calcium oxalate. Another recent study reported that the common gut bacterium, *Oxalobacter formigenes*, can break down oxalate in the digestive tract, thereby reducing the likelihood of oxalate entering the body and forming a kidney stone. Unfortunately, administration of *O. formigenes* has not been shown to

[5] *http://www.nih.gov/news/health/jun2008/niddk-20.htm*

reduce the risk of forming kidney stones, indicating that additional research into this condition is needed.

Preeclampsia: A series of research findings, from NIDDK-supported studies, may one day help women avoid a common and serious complication of pregnancy. Preeclampsia usually involves a combination of high blood pressure, swelling, impaired kidney function, and reduced blood flow to the developing fetus. Without intervention, preeclampsia can progress to a condition that is fatal for both mother and child. Placenta-derived factors are believed to be central to its development. Researchers have found increased levels of a placenta-derived protein called sFLT-1 in patients with preeclampsia. This protein can diminish the activity of two growth factors important for the maintenance and survival of blood vessels, VEGF and PlGF. Although sFLT-1 levels cannot be assessed easily for routine screening, PlGF can be measured in urine, and researchers showed that women who developed preeclampsia had abnormally low levels of PlGF several weeks earlier in their pregnancies. The ability to measure a factor in urine that may predict risk for preeclampsia represents a significant advance as a diagnostic tool. The VEGF/PlGF signaling pathway also presents multiple potential new targets for developing therapies aimed at preventing or treating this serious condition.

Research to Improve Women's Urologic Health: Many diseases of the bladder and urinary tract, such as urinary tract infections (UTIs) and urinary incontinence, are more common in women than in men. NIDDK urology research programs have spurred basic and clinical discoveries that, in turn, are leading to new or improved prevention and treatment strategies for these conditions. For example, many women suffer from recurrent UTIs, caused mostly by certain types of *Escherichia coli* (*E. coli*) bacteria. While treatable with antibiotics, the financial costs, health risks, and threat of antibiotic resistance associated with UTI therapy makes understanding these infections very important. In a discovery that could explain many recurrent UTIs, NIDDK-funded researchers have found a novel pathway by which UTI-causing *E. coli* invade, replicate in, and ultimately "hide out" in cells lining the bladder, escaping clearance by antibiotics or the immune system. Clinical



The ability of bacteria to "hide" within a pod on the surface of a mouse bladder cell may allow them to survive antibiotics, resulting in repeated, painful urinary tract infections.
Image credit: Anderson GG et al, *Science* 301: 105-107, 2003. Reprinted with permission from AAAS.

studies in women have uncovered evidence for this so-called intracellular bacterial community (IBC)-pathway in human UTIs, opening up new approaches to assessing, treating, and potentially preventing recurrent UTIs. Likewise, the results of clinical trials supported by the Institute are improving treatment options for urinary incontinence. The NIDDK-supported Urinary Incontinence Treatment Network has compared the benefits and drawbacks of two common surgeries for stress urinary incontinence in women, providing information that can help patients and providers make better informed decisions about treatment. It has also explored the potential for behavioral therapy versus drug treatment for urge incontinence. This multi-site Network is continuing its efforts with a trial to compare minimally invasive treatments for stress urinary incontinence. Independently, another NIDDK-funded clinical trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study, has shown that

Janet Colardo, a participant in the Program to Reduce Incontinence by Diet and Exercise (PRIDE), says she would "absolutely" recommend studies like PRIDE to others. She says that the PRIDE staff made her feel accountable to herself, as well as to them. "And I'll have the knowledge they gave me forever."

modest weight loss significantly reduces episodes of urine leakage in overweight and obese women who experience incontinence—expanding the options physicians and their patients can consider for treating incontinence in women. With NIDDK support, scientists will continue to expand on these robust findings to move urology research forward.

Chronic Urologic Pelvic Pain Syndromes: People with interstitial cystitis/painful bladder syndrome (IC/PBS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) suffer from recurring discomfort or pain in the bladder and lower urinary tract and the surrounding pelvic region, as well as other symptoms. Diagnosis is difficult, and effective therapies remain elusive. Starting with the development of the first consensus research definitions for IC/PBS and CP/CPPS in the late 1980s and mid-1990s, NIDDK has sought to bolster scientific studies that could lead to better understanding, diagnosis, and prevention and treatment for these conditions. A program of basic and clinical research studies and trials has moved the field forward. Still, identifying the potential causes, risk factors, and prevalence of IC/PBS and CP/CPPS has proved challenging. These questions have been a focus of major NIDDK-supported epidemiology studies—including a study that has been conducting a cross-sectional examination of IC/PBS, prostatitis, and several other urological problems in a diverse adult population over the past several years. Another study has developed survey tools to enable researchers to identify likely cases of IC/PBS among women in the U.S. Looking to the future, NIDDK recently established the Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. In this Network, researchers at six "Discovery Sites" will conduct innovative, collaborative studies of IC/PBS and CP/CPPS and the potential relationships between these conditions and other chronic pain disorders, such as fibromyalgia, while scientists at two "Core Sites" will coordinate data collection, analyze tissue samples, and provide technical support. This effort capitalizes on research suggesting that clues to the cause(s) of both IC/PBS and CP/CPPS may lie outside the bladder, a promising new direction that could elucidate these challenging pain conditions.

Richard Gordon

participated in the Medical Therapy of Prostatic Symptoms clinical trial, which found a combination of two drugs to be more effective in treating the symptoms of benign prostatic hyperplasia (BPH) than either drug singly. "I'm grateful that my BPH was treated early," Richard says. "This is a problem that men should take seriously."

Advances in the Treatment of Benign Prostatic Hyperplasia: More than half of men in their sixties and as many as 90 percent in their seventies and eighties have some symptoms of benign prostatic hyperplasia (BPH), including a weak urine stream, frequent urination, and urinary tract infections. In the early 1990s, treatment of BPH generally involved a surgical procedure or one or more drug regimens. Some of these drugs acted by relaxing the smooth muscles in the prostate, allowing urine to flow more freely; others acted by inhibiting the metabolism of the male sex hormone testosterone, thereby limiting growth of the prostate. In 1994, the NIDDK launched the Medical Therapy of Prostatic Symptoms (MTOPS) trial, in which scientists at multiple medical centers compared these two kinds of drugs, used alone or together, with placebo in men with BPH. The study followed participants for an average of five years and monitored them for signs of BPH progression.

Published in 2003, the results of the MTOPS trial were unequivocal: although each drug was somewhat effective when used alone, combination therapy reduced the risk of BPH progression by 66 percent compared to placebo. The findings of the MTOPS trial validated an important nonsurgical option for BPH treatment.

HIGHLIGHTS OF NIDDK-SUPPORTED RESEARCH ADVANCES IN KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

1953: Researchers supported by the U.S. Public Health Service purify a kidney-derived factor, later identified as erythropoietin, that stimulates the production of red blood cells.

1960s: The discovery and characterization of the human leukocyte antigen (HLA) system sheds important light on the immune response and molecular differentiation between "self" and "non-self" cells and tissues.

1990: Urothelial uroplakins, proteins that regulate the permeability of cells lining the urinary tract, are discovered.

1990: The drug hydroxyurea is shown to relieve anemia and pain in patients with sickle cell disease. In 1998, the FDA approves it for use in adults; it remains the only such drug.

1993: Investigators localize a second gene for autosomal dominant polycystic kidney disease.

1994: The Modification of Diet in Renal Disease Study finds that a low-protein diet can slow the decline of kidney function in people with moderate kidney disease, leading to an equation to estimate kidney function.

1994: The gene for thrombopoietin, an important regulator of hematopoiesis, is cloned and characterized.

1999: Mutations in the elastase gene are found to underlie congenital neutropenia syndrome, in which very low levels of infection-fighting white blood cells leave patients vulnerable to infection.

2001: The African American Study of Kidney Disease and Hypertension (AASK) shows that angiotensin converting enzyme (ACE) inhibitors in a treatment regimen are more effective than calcium channel blockers in slowing progression of hypertensive kidney disease.

2002: The HEMO Study, the largest-ever randomized trial of hemodialysis, finds that standard dose dialysis works as well as higher doses, sparing patients unnecessary treatment.

2003: The Medical Therapy of Prostatic Symptoms (MTOPS) trial shows that combination therapy of two drugs is more effective than either drug singly in the treatment of benign prostatic hyperplasia (BPH). MTOPS is the largest and longest trial of BPH to date.

2004: Details of how hepcidin and ferroportin work to regulate the release of iron from cells are elucidated.

2005: After 20 years of annual increases of 5 to 10 percent, rates for new cases of kidney failure stabilize, according to the United States Renal Data System. Treatment strategies proven in the 1990s—such as ACE-inhibitors and angiotensin receptor blockers—and more careful control of diabetes and blood pressure, are largely credited.

2006: MRI is shown to accurately track structural changes that predict functional changes earlier than standard blood and urine tests in people with autosomal dominant PKD, according to the Consortium for Radiological Imaging Studies of PKD (CRISP).

2007: The landmark Boston Area Community Health (BACH) survey provides important data about urologic symptoms in the U.S., including prevalence and risk factors.

2008: The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which will conduct highly collaborative research of the most common urologic chronic pelvic pain syndromes from a broadened systemic perspective, is launched.

2008: The VA/NIH Acute Renal Failure Trial Network (ATN) Study finds that standard dose dialysis works as well as higher doses in patients with acute kidney failure.

2008: Researchers describe genetic variations in the *MYH9* gene, which is thought to contribute to non-diabetic end-stage renal disease in African Americans.

2009: The NIDDK-supported Program to Reduce Incontinence by Diet and Exercise (PRIDE) study finds that modest weight loss results in a reduction of weekly urinary incontinence episodes by nearly one-half in overweight and obese women.

2009: The M-type phospholipase A2 receptor (PLA_2R) is implicated in up to 70 percent of cases of the kidney disease idiopathic membranous nephropathy.

2009: Researchers report success with a modified blood stem-cell transplant regimen to treat adult patients with sickle cell disease.

Hematology Research: The NIDDK's multi-faceted hematology research program focuses on understanding basic cellular and molecular mechanisms that underlie the production and function of blood cells in health and disease, and NIDDK-supported scientists have played an important role in many seminal breakthroughs over the years. NIDDK-funded research in the 1950s and 1960s contributed to the discovery of the human leukocyte antigen (HLA) system, cell-surface proteins that help the immune system differentiate between "self" and "non-self" cells. These findings facilitated improved success rates for organ transplantation, as HLA typing allowed physicians to minimize the risk of rejection. Variations in HLA types are also thought to play a role in the susceptibility of certain individuals to autoimmune diseases such as lupus, rheumatoid arthritis, and type 1 diabetes.

Beginning with research in the 1970s, the molecular and genetic bases of many congenital blood disorders have been elucidated by NIDDK-supported researchers. Advances have included the application of molecular genetic techniques to facilitate diagnosis of hemoglobin disorders such as thalassemia and sickle cell disease. NIDDK researchers contributed to the discovery, purification, and characterization of key hormones that regulate blood cell production, including the purification of erythropoietin in 1977, which led to the subsequent cloning of the gene for this hormone—which controls the production of red blood cells—in 1985, and the gene for thrombopoietin—which regulates the production of platelets by the bone marrow—in 1994. In the late 1990s, NIDDK-supported scientists identified the genetic basis of congenital neutropenias, a family of hereditary disorders characterized by an abnormally low number of an important type of white blood cell that leaves patients susceptible to infection.

Iron is a critical component of hemoglobin, and total body iron must be carefully balanced, as iron overload can damage organs and is potentially fatal, while iron deficiency impairs red blood cell production and causes anemia. Over the past decade, research supported by the NIDDK has led to important insights into how iron levels are maintained within an acceptable range, and how dysregulation of regulatory proteins (such as hepcidin, hemojuvelin, and ferroportin) can lead to too

much or too little available iron for the support of red blood cell production.

EDUCATION PROGRAMS

The NIDDK's National Kidney Disease Education Program (NKDEP) was established to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure. Kidney disease often has no symptoms, but if detected early, it can be treated. Current education efforts for the public include campaigns aimed at individuals with diabetes or high blood pressure, African Americans, and Hispanic audiences, with materials available in both English and Spanish; additional campaigns target health care providers and laboratory professionals (www.nkdep.nih.gov). The NIDDK also supports the National Kidney and Urologic Diseases Information Clearinghouse, which was established in 1987 to increase knowledge and understanding about diseases of the kidneys and urologic system among people with these conditions and their families, health care professionals, and the general public. An awareness campaign has helped to improve public and healthcare provider knowledge about interstitial cystitis/painful bladder syndrome (IC/PBS). The NIDDK's National Hematologic Diseases Information Service provides information and publications and responds to public inquiries.

Information from the National Kidney Disease Education Program.

LOOKING TO THE FUTURE

Photo credit: Getty Images.

Moving forward, the NIDDK is hopeful that its research portfolio will continue to provide scientific insights and improvements in patient care. As always, an important component of the Institute's support for biomedical research is its strategic planning. Often, initiatives and funding solicitations emerge from opportunities identified through this planning process, which reflect both broad scientific review and input from key stakeholders. Planning may occur in an *ad hoc* process, or may be organized under the auspices of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, and sometimes involves partnering with professional and/or patient advocacy groups. Examples of recent plans include a *Research Progress Report and Strategic Plan for Pediatric Urology*, released in 2006, and a *Prostate Research Strategic Plan*, released in 2008. Through these efforts, the NIDDK seeks to steer the research enterprise in a way that follows science while maximizing the return on the Institute's investment in order to improve the lives of patients and their families.

Intramural Research

Scientists in the NIDDK's Intramural Research Program conduct basic, translational, and clinical biomedical research related to the Institute's mission at facilities in Bethesda, Maryland and Phoenix, Arizona. Researchers trained as post-doctoral fellows in the Intramural Research Program have become faculty members at research institutions all over the world. Intramural scientists have achieved national and international recognition for their work, several earning the Nobel Prize (see feature on Nobel laureates in this compendium). A sampling of areas under study includes: biophysics, cell biology, chemical biology and medicinal chemistry, developmental biology, molecular biology, signal transduction, structural biology, genetics and pathogenesis of diseases, and novel therapies. As in other chapters, the examples of discoveries here represent only a subset of the numerous scientific accomplishments from the past 60 years.

SNAPSHOTS OF BASIC RESEARCH DISCOVERIES

Since its inception in 1950, the NIDDK's Intramural Research Program has made a host of seminal contributions to biomedical science. Highlighted here are examples of major basic research discoveries that advanced knowledge of fundamental biologic molecules and processes, as well as the development of research methods that propelled further scientific inquiry.

Receptors: Scientists devised the first successful method to identify and measure cell surface receptors, first for adrenocorticotropic hormone and later for glucagon, insulin, growth hormone, insulin-like growth factor, thyroid-stimulating hormone, adenosine, and a wide range of gastrointestinal hormones.

DNA Gyrase and DNA Ligase: Two enzymes that are key to DNA supercoiling were discovered.

Glycoprotein Turnover: Scientists elucidated the precise conditions necessary for removal of glycoproteins from the circulation by the liver; discovered that the forms of these proteins lacking sialic acid are removed by a receptor-mediated process; and showed how the asialoglycoproteins are dismantled in liver cells. Glycoprotein breakdown products are used by cells for energy and protein synthesis.

Antibody Structure: Using X-ray crystallographic techniques to visualize the three-dimensional molecular architecture of antibodies and

SNAPSHOTS OF BASIC RESEARCH DISCOVERIES (CONTINUED)

antibody-ligand complexes, scientists made important contributions to understanding the basis of antibody recognition of foreign substances.

Gene Regulation: Scientists characterized a DNA-binding protein that regulates expression of the hemoglobin gene.

Enzyme Purification: Affinity chromatography was used to purify enzymes selectively in a single step. The method proves of great value in the isolation and purification of many biologically active proteins and polypeptides.

Pentose Phosphate Pathway: The 6-phospho-gluconate pathway of glucose breakdown, known as the pentose phosphate pathway, was elucidated. This pathway serves primarily as an important source of a coenzyme for the biosynthesis of fatty acids and steroids, and of sugars for the synthesis of nucleic acids.

Amyloid Proteins: Institute scientists were the first to elucidate the structure of an amyloid. Amyloids are abnormal forms of proteins that accumulate in disease states.

Mutagenesis: Initial research was conducted for development of the Ames test, a widely employed biological assay in which bacteria are used to determine the carcinogenicity of chemical compounds.

Biosynthesis and Physiological Effects of Polyamines: Scientists characterized a class of essential molecules known as polyamines, determining how they are synthesized, revealing how their synthesis and degradation are regulated, and uncovering their diverse physiologic functions.

Mechanism of Penicillin Action: Research led to the discovery that penicillin acts by impairing bacterial cell wall synthesis.

Molecular Crowding: The presence of high concentrations of macromolecules in cells and tissues was shown to have enormous effects on biochemical reactions.

Proteins, DNA, and Genes: Intramural researchers have determined the structure of proteins important in health and disease, deciphered the genetic code, and illuminated how segments of DNA can control activity of nearby genes. See descriptions later in this chapter of these and other key discoveries about proteins, DNA, and genes.

CLINICAL RESEARCH

Diabetes: NIDDK intramural scientists have made important contributions to diabetes research. Among their accomplishments was the delineation of the first several steps in the action of the hormone insulin, including the binding of insulin to its receptor (the protein on which it docks on the surface of cells), receptor autophosphorylation, and insulin-mediated phosphorylation of cellular proteins. They also pioneered the line of investigation leading to the principle of "down regulation" of insulin action, a concept that became widely applied to many other cell-hormone systems. Additionally, intramural researchers illuminated the post-translational modification of the insulin receptor, and alterations of the insulin receptor in human disease states—including the novel recognition of diseases associated with extreme insulin resistance. More recently, intramural researchers performed the first islet cell transplant in the United States to achieve prolonged euglycemia. Scientists in the Intramural Research Program also discovered exendin-4, a protein component of Gila lizard venom related to the hormone GLP-1 (see Diabetes, Endocrinology, and Metabolic Diseases chapter). A synthetic version of exendin-4 called exenatide was approved in 2005 as a therapy for type 2 diabetes. The medication promotes release of insulin in response to food and helps slow digestion,

making people feel full longer. NIDDK intramural research is also elucidating the function of dendritic cells and regulatory T cells (Tregs) in mediating immune "tolerance"—preventing the immune system from attacking the body's own tissues. This process goes awry in autoimmune diseases such as type 1 diabetes.

Phoenix Epidemiology and Clinical Research Branch: Established in 1963, the Branch studies the causes of type 2 diabetes as it occurs among Pima Indians of the Gila River Indian Community in Phoenix, Arizona. This population of American Indians has the highest reported prevalence of diabetes of any population in the world. Working closely with Pima Indian volunteers, the Branch has made substantial progress in identifying physiologic and genetic determinants of diabetes risk factors. The Branch also plays a pivotal role in the recruitment of Pima Indians and other American Indian populations in clinical studies that also involve extramural NIDDK-supported sites, such as the Diabetes Prevention Program clinical trial and the ongoing Diabetes Prevention Program Outcomes Study, the Look AHEAD ("Action for Health in Diabetes") clinical trial, and the Family Investigation of Nephropathy and Diabetes study. Studies often are conducted in collaboration with the Indian Health Service.

Parathyroid Hormone and Calcium Metabolism: Intramural scientists have made ground-breaking discoveries in the fields of endocrine and metabolic diseases. For example, one major set of advances by intramural researchers was the isolation of parathyroid hormone; determination of its structure; investigation of the role of this hormone, calcitonin, and vitamin D in calcium metabolism and calcium-related disorders; and characterization of molecular defects associated with pseudohypoparathyroidism. These researchers additionally helped to develop a program that achieved extraordinary success in treating patients with hyperparathyroidism. Research in this area has led to new treatments to correct abnormal calcium levels that are common in patients suffering from rare diseases of the parathyroid glands, including parathyroid cancer (see also the Diabetes, Endocrinology, and Metabolic Diseases chapter).

GTP-binding proteins: Another landmark in biomedical research was the discovery of GTP-binding ("G") proteins—molecules that, when working improperly, play key roles in numerous diseases such as diabetes, cardiovascular defects, and certain forms of cancer. Research to reveal the critical role of guanosine triphosphate (GTP) in regulating the activity of a variety of hormone receptors led to the identification of G proteins—proteins that regulate adenylate cyclase stimulation and inhibition by hormones. Such regulation is central to the transduction of hormone signals across the cell membrane. Further studies by former NIDDK Director Dr. Allen Spiegel and colleagues identified activating and inactivating mutations of G-s-alpha, a subunit of the major human G protein.

Steroid Research: Intramural scientists pioneered several fields of steroid research, including pleiotropic effects of steroid hormones. The rate-limiting step in cortisol metabolism was delineated, and the effects of thyroid hormone on this reaction were explained.

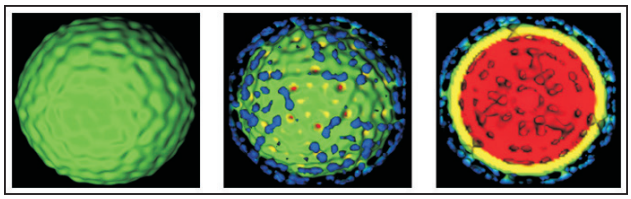
Hormone Treatment for Radiation Exposure: Intramural researchers collaborated on studies that introduced hormone treatment to thwart the development of thyroid nodules and cancer propagated by radiation fallout. The programs for the prevention and treatment of radiation-related cancers developed by these scientists have become standard care procedures for victims exposed to high levels of radiation during nuclear catastrophes such as Three Mile Island and Chernobyl.

Endocrine Tumors: A team of researchers, including current NIH Director Dr. Francis Collins and former NIDDK Director Dr. Allen Spiegel, identified the *MEN1* gene in 1997; mutations in this gene cause multiple endocrine neoplasia, a cancer syndrome marked by tumors in hormone-producing (endocrine) glands, including the parathyroid glands, pancreas, anterior pituitary, and other tissues. The scientists additionally discovered that *MEN1* gene variants are associated with tumor formation in a subset of patients with Zollinger-Ellison syndrome.

Lysosomal Storage Disorders: Critical discoveries over several decades by NIDDK intramural scientists and extramural researchers enabled the development of enzyme replacement therapy for these severe diseases. (See the Diabetes, Endocrinology and Metabolic Diseases chapter.)

Leptin as a Treatment for Lipodystrophy: The hormone leptin is secreted by fat cells and released in proportion to the amount of fat. Mice and people with very rare leptin gene mutations do lose weight when given the hormone, but leptin was not found to be effective in treating the vast majority of cases of human obesity, which are not caused by leptin deficiency. However, scientists in the NIDDK's Intramural Research Program identified another patient population—people with lipodystrophy—who could benefit from leptin treatment. Lipodystrophy is a rare and difficult-to-treat disorder, marked by a lack of normal fat in some areas of the body and excess fat in other areas. The disorder shares some metabolic problems with type 2 diabetes. People with lipodystrophy also have low levels of leptin. Clinical trials conducted since the early 2000s by scientists in the NIDDK Intramural Research Program, led by former NIDDK Director Dr. Phillip Gorden, and their collaborators found that leptin effectively treated all forms of lipodystrophy tested and corrected a broad range of metabolic defects observed in the patients. This research identified a new therapy for a rare disease and also demonstrates how the discovery of leptin has led—and continues to lead—to a cascade of exciting and unexpected findings with broad implications for improving health.

Hepatitis C: The NIDDK supports research to address the many forms of viral hepatitis, including a strong intramural research program that has been at the forefront of hepatitis C research (see also Digestive Diseases and Nutrition chapter). For example, in 1986, before the virus that causes hepatitis C was identified, NIDDK scientists tested the first effective treatment for chronic hepatitis C—long-term interferon therapy—which remains a standard treatment for the disease. Since then, the Institute has continued to perform rigorous clinical research aimed at improving the treatment of chronic hepatitis C.



Reconstructed images of a hepatitis C virus-like particle.
Image credit: Images courtesy of Dr. T. Jake Liang, Liver Diseases Branch, NIDDK Division of Intramural Research.

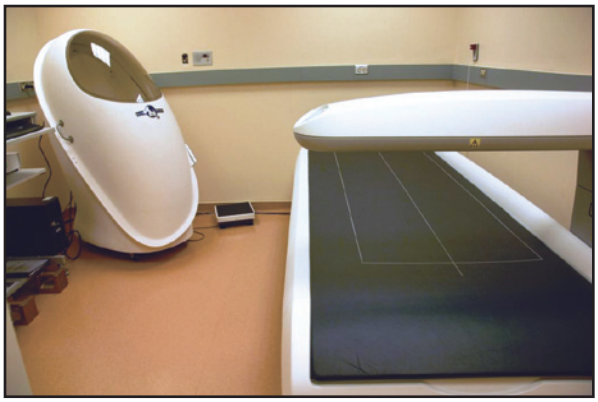
Following the discovery of the hepatitis C virus in 1989, researchers have worked to identify and characterize viral and immunological factors involved in the immune response and ability to clear the virus. A landmark achievement by NIDDK scientists was the development of one of the first cell culture systems available for studying infection by the hepatitis C virus. These cell culture systems enabled previously impossible studies of how the virus infects cells and triggers disease processes, as well as a new means of testing therapeutic antiviral agents.

An important goal for hepatitis C research from a public health standpoint is to develop a vaccine for disease prevention, a strategy that has been extremely successful for the prevention of hepatitis B. Intramural scientists have explored the potential of using hepatitis C virus-like particles as a vaccine, and are continuing this research.

Iron Metabolism: Dysregulated iron metabolism and iron overload are features of a number of human diseases. Although some genes involved in cellular iron uptake and export have been identified, very little is known about iron transport and utilization. NIDDK scientists recently reported that poly-C binding protein 1 (PCBP1) functions in both yeast and human cells as an iron chaperone and enhances the loading of iron into ferritin, a process that is essential for life in mammals.

Kidney Disease Research: Within the NIDDK Intramural Research Program, the Kidney Disease Branch is home to the Institute's research into the role of the kidneys in maintaining fluid and electrolyte balance and the causes of and treatments for kidney disease and kidney failure. Over the years, discoveries

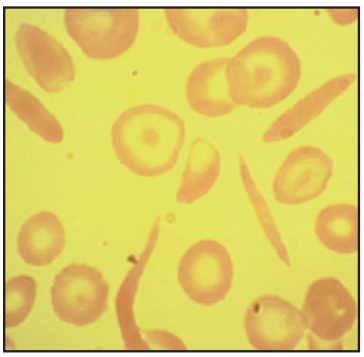
by NIDDK scientists have led to several key advances in our understanding of kidney disease, including important insights into the disease process in lupus nephritis, an inflammatory kidney disease; the identification of potential biomarkers to detect acute renal failure in its early stages and therapies to prevent and treat it; and the discovery, reported in 2008, of the relationship between genetic mutations near the *MYH9* gene locus and non-diabetic kidney disease in African Americans (see also the Kidney, Urologic, and Hematologic Diseases chapter).



The NIDDK's Metabolic Clinical Research Unit includes a body composition room where a BodPod® (left) and DXA scan machine (right) are used to measure total body composition and fat distribution. *Photo credit:* Image courtesy of Dr. Kong Chen, Director, Metabolic Research Core, NIDDK Metabolic Clinical Research Unit.

Metabolic Clinical Research Unit: In 2007, the NIDDK, in collaboration with the NIH Clinical Center, established the NIH Metabolic Clinical Research Unit (MCRU). The MCRU is designed to foster a collaborative research approach, bringing together experts from the fields of metabolism, endocrinology, nutrition, cardiovascular biology, gastroenterology, hepatology, genetics, and the behavioral sciences. The unit includes inpatient rooms, a metabolic kitchen, an exercise room, special vending machines, and a communal dining area. It also includes access to a "BodPod®" and DXA scanner. The BodPod® can measure total body density and lean and fat body mass using air displacement, while the scanner uses small doses of X-rays to calculate how much of a patient's entire body is composed of fat, muscle and bone. A signature feature of the metabolic unit is three "rapid response respiratory suites." These rooms enable researchers to measure patients' energy metabolism over 24 hours using non-invasive means. Located in the NIH Clinical Center, the unit is permitting investigators to conduct cutting-edge research on the physiology, prevention, and treatment of obesity.

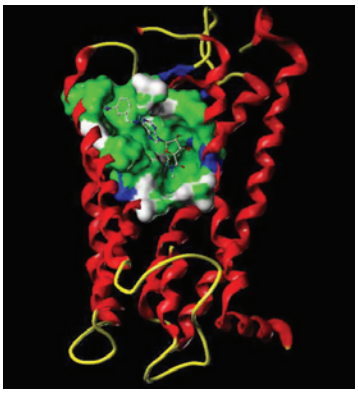
Sickle Cell Disease Research: Sickle cell disease is caused by a mutation in one of the proteins that make up hemoglobin, the oxygen-carrying component of red blood cells. This mutation results in the formation of long polymers of hemoglobin, which causes the red cells to deform into a crescent-like shape. The disease's manifestations involve nerve damage, lung and liver ailments, and periods of extreme and unrelenting bone and joint pain. Several decades of NIH studies have led to important discoveries about causes of and treatments for sickle cell disease and its complications. In studies in the 1980s, Dr. Griffin Rodgers—now NIDDK Director—and his colleagues found that the drug hydroxyurea could moderate the disease's consequences; it was approved by the FDA for this use in 1998. It remains the only drug approved for sickle cell disease. Other studies by NIDDK scientists at the NIH Clinical Center have shown that nitric oxide contributes to complications in sickle cell disease by regulating blood vessel elasticity and inhibiting platelet aggregation and adhesion. In 2009, a team of researchers, including Dr. Rodgers, reported success with a modified blood stem-cell transplant regimen to treat adult patients with sickle cell disease. Although hematopoietic stem cell transplantation represents a potential cure for sickle cell disease, finding a suitable donor remains a challenge for most patients. The NIH will continue ongoing support of research toward improved treatments and a cure for this devastating disease.



In this photograph, "sickle-shaped" cells are shown along with normal, round cells. Individuals with sickle cell disease have a genetic mutation that causes red blood cells to become sickle-shaped, which impairs the cells' ability to fit through tiny blood vessels and thus deprives tissue of oxygen. *Image credit:* Image courtesy of Dr. Griffin P. Rodgers, Director, NIDDK.

CHEMISTRY AND DRUG DEVELOPMENT

Chemistry in Nature: Research on natural products by an intramural scientist and colleagues has led to novel discoveries with major impacts on biomedical science. In one such avenue of research, the amphibian alkaloid epibatidine was found to be 200 times more potent as a painkiller than morphine. Furthermore, the 26 classes of alkaloids identified through this research have had a major impact on our knowledge of how the nervous system functions and how drugs interact with it. Exploration of another natural compound, in the early 1980s, led to the introduction of forskolin, a plant-derived chemical, as an important experimental tool used by the broader scientific community to probe the mechanism of action of drugs that act through cell-surface receptors.

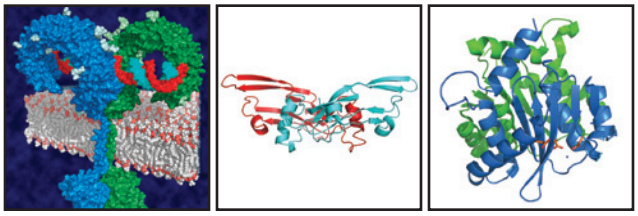


Model of a molecule activating an adenosine receptor. These models are used to study receptor signaling initiated by molecules such as caffeine.
Image credit: Image courtesy of Dr. Ken Jacobson, Chief, Molecular Recognition Section, NIDDK Division of Intramural Research.

Medicinal Chemistry: A team of intramural researchers has taken an interdisciplinary approach to studying the chemical and biological aspects of cell signaling. This research focuses on elucidating the structure and pharmacology of a specific class of cell-surface receptors and in developing drugs that act as activators or inhibitors of these molecules. With both classical chemical approaches as well as computer-aided molecular modeling and template design, these studies have begun to describe the nature of the interactions between the nucleotide and signaling molecule adenosine and its various receptors. The researchers have designed and successfully tested selective, potent activators and inhibitors for all four subtypes of adenosine receptors. These discoveries may allow future therapies to target a specific subtype of adenosine receptor, and to be more effective and have fewer side effects than those currently available, with implications for treating cardiovascular and other diseases.

PROTEINS

Structural Biology: The physical structure of proteins is an important determinant of their biological activity. One fundamental way of determining a protein's structure is a process called X-ray crystallography, in which beams of X-rays are used to develop a three-dimensional picture of the protein. Using X-ray crystallography, scientists in the NIDDK's Intramural Research Program determined the structures of several proteins involved in normal biological and disease processes. Some examples include the "toll-like" receptors, a key component of the immune system; HIV-integrase, one of the proteins of HIV; and transforming growth factor beta, a protein that plays a key part in a wide array of cellular processes. Another method of examining the shape of a protein is nuclear magnetic resonance (NMR), which uses powerful electromagnetic fields to elucidate the protein's structure. NIDDK scientists have also performed pioneering work leading to the development of new NMR-based methods of determining protein structures with great accuracy and complexity at higher resolutions. Some of these protocols have now become the widely accepted standard of carrying out protein NMR studies.

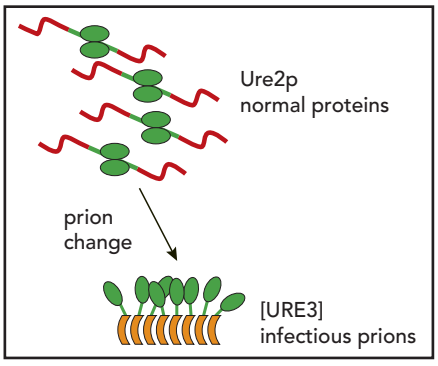


Toll-like receptor 3 | Transforming growth factor-beta | HIV integrase

Image credits: Images courtesy of Dr. David Davies, Laboratory of Molecular Biology, NIDDK Division of Intramural Research.

Protein Turnover: Much of the biochemical work within cells is accomplished by proteins, a group of molecules whose complex chemistry makes them suited to a wide variety of tasks. A protein's presence, absence, and concentration in a cell can have profound consequences. Much work centers on the rate of a protein's synthesis, but NIDDK intramural research established that the rate and timing of protein destruction (turnover) is also key to its biological properties.

Discovery of Yeast Prions: In 1994, a decades-old theory known as the "prion hypothesis" was just becoming widely accepted. In essence the theory is that fatal illnesses like scrapie in sheep, Creutzfeldt-Jakob Disease in humans, and bovine spongiform encephalopathy ("Mad Cow Disease") in cattle are all caused by an infectious "prion" form of a protein encoded by the animal's own genes. However, prions seemed limited to one protein and had been observed only in mammals. NIDDK research demonstrated that the phenomenon was much more widespread in nature, shedding light on the once-puzzling properties of the yeast genetic elements [URE3] and [PSI+]. A series of experiments tested the predictions of the prion hypothesis for [URE3], making a convincing case that it is indeed a prion form of a normal yeast protein called Ure2p. Similar experiments by others later established the same for [PSI+] as a prion form of another protein.



Several fatal diseases in humans and animals are caused by "prions"—infectious proteins that convert normal proteins into abnormal prion forms. Prions typically aggregate into structures called "amyloids." NIDDK research showed that yeast also have prions: [URE3] is a prion of the Ure2p protein. *Image credit:* Adapted with permission from Wickner RB et al. *Bioessays*. 2008; 30:955-964.

Intramural and extramural investigators have since established that three other yeast proteins—Rnq1p, PrB, and Mca1p—also form prions. This research in yeast has provided important insights into the biology and biophysics of prions.

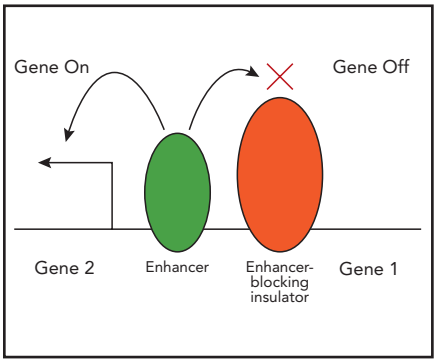
DNA AND GENES

Cracking the Genetic Code: An NIDDK intramural scientist conducted seminal experiments that led to understanding the "genetic code," the relationship between DNA, the genetic material; RNA, the messenger material; and proteins, the building blocks of cells. In 1968, he was awarded the Nobel Prize for deciphering the system used by DNA to code for the synthesis of proteins. (See also the feature on Nobel laureates in this book.)

Synthesizing DNA—and Scientists: By studying DNA replication using the T4 bacteriophage, a virus that infects bacteria, an intramural researcher identified and characterized the biochemical and molecular mechanisms essential for DNA synthesis throughout nature. In 2005, in honor of her memory and commitment to mentoring, the NIDDK established the *Nancy Nossal Fellowship Award* for intramural postdoctoral and clinical fellows.

Establishing Boundaries in the Genome: Studies of "insulator elements"—segments of DNA that mark boundaries in regions of the genome—have provided important insights into how the genome is organized and gene expression (whether a gene is turned on or off) is regulated. Insulator elements have two functions, the first of which is referred to as enhancer-blocking activity. An enhancer is a sequence of DNA that directs the cell to turn on an associated gene. If positioned near an enhancer, an insulator can prevent the enhancer's signal from being broadcast in the wrong direction and thus keep the cell from turning on genes it shouldn't. The second function of insulators is to set up a "barrier" to prevent unwanted silencing—or tight shutting off—of genes. Research in the Intramural Program has led to the identification of proteins involved in these processes and revelations into how insulators perform these two

important activities. Continued study of insulators and genome organization will lead to further insights into the regulation of genes, a process critical for health and development.



One activity of an insulator element (red) is to block another type of DNA element, an enhancer (green) from inappropriately directing a gene to turn on. *Image credit:* Adapted with permission from Gaszner M and Felsenfeld G. *Nat Rev Genet* 7: 703-13, 2006.

BIOLOGICAL MODELING

Using Math to Understand and Predict Biology: Scientists in the Laboratory of Biological Modeling use mathematics to model biological systems and learn how the systems change over time and, in doing so, pioneered the field of computational neuroscience. By investigating the behavior of oscillating signals, these scientists have applied modeling to research fields like neuronal signaling and insulin secretion from the beta cells of the pancreas.

LOOKING TO THE FUTURE

The many discoveries by NIDDK's scientists have impacted biomedical research and clinical practice. Dedicated intramural investigators will continue to pursue a broad spectrum of research to advance knowledge toward improving health.

Photo credit: Richard Nowitz, for NIDDK.

NIDDK and the Nobel Prize

The NIDDK has supported a number of winners of the world's greatest scientific honor—the Nobel Prize. These include extramural scientists at universities and other research institutions across the country who have been supported by NIDDK (Institute grantees), as well as scientists within NIDDK's Intramural Research Program.

1950s

1956
Institute grantee **Dr. Dickinson W. Richards, Jr.** shared the Nobel Prize in Physiology or Medicine with two other scientists. They developed heart catheterization techniques to study and diagnose circulatory disorders.

1959
Dr. Arthur Kornberg, a former Institute intramural researcher, and Institute grantee **Dr. Severo Ochoa** shared the Nobel Prize in Physiology or Medicine for discovering, respectively, the mechanisms of DNA and RNA synthesis.

1960s

1962
Institute grantee **Dr. James D. Watson** received the Nobel Prize in Physiology or Medicine along with two other scientists for discovering that DNA's structure is a double helix. This was a landmark finding of the 20th century, and it opened the field of modern genetics.

Institute grantee **Dr. John Kendrew** shared the Nobel Prize in Chemistry. He discovered the molecular structure of myoglobin, a form of the blood protein hemoglobin found in muscle.

1965
Institute grantee **Dr. Robert B. Woodward** won the Nobel Prize in Chemistry for his contributions to the art of organic synthesis. Among the many compounds he synthesized were quinine, cholesterol, cortisone, and chlorophyll.

1966
Institute grantee **Dr. Charles B. Huggins** shared the Nobel Prize in Physiology or Medicine for discoveries concerning the hormonal treatment of prostate cancer.

1968
Dr. Marshall W. Nirenberg and two other scientists shared the Nobel Prize in Physiology or Medicine for deciphering the genetic code and explaining how it functions in protein synthesis. Nirenberg's code-cracking work was done while he was an Institute intramural scientist.

1970s

1971
Institute grantee **Dr. Earl W. Sutherland, Jr.** won the Nobel Prize in Physiology or Medicine for his findings on the mechanisms of hormone action. His work greatly advanced the field of endocrinology.

1972
Dr. Christian B. Anfinsen shared the Nobel Prize in Chemistry with two other researchers. Anfinsen used the enzyme ribonuclease to show that a protein's amino acid sequence determines its three-dimensional structure, thus demonstrating a basic principle of biology. The award-winning work was done when Anfinsen was in the Institute's Laboratory of Chemical Biology.

Institute grantee **Dr. Gerald M. Edelman** shared the Nobel Prize in Physiology or Medicine for studies of the chemical structure of antibodies that led to a better understanding of the immune system.

1976
Former Institute researcher **Dr. Baruch S. Blumberg** and another NIH scientist received the Nobel Prize in Physiology or Medicine. They were cited for discoveries of new mechanisms for the origin and dissemination of infectious diseases. Blumberg found the hepatitis B virus protein, or "Australia antigen," in 1963 while at the Institute. This advance was a scientific and clinical landmark in the detection and control of hepatitis.

1977
Institute grantees **Dr. Roger C. L. Guillemin** and **Dr. Andrew V. Schally** shared the Nobel Prize in Physiology or Medicine with a third scientist. Guillemin and Schally's prizes were for discoveries related to the brain's production of peptide hormones.

1980s

1980
Institute grantee **Dr. Walter Gilbert** shared the Nobel Prize in Chemistry for his contributions to determining base sequences in DNA.

1984
Institute grantee **Dr. R. Bruce Merrifield** won the Nobel Prize in Chemistry for development of solid-phase peptide synthesis.

1985
Former Institute intramural researcher **Dr. Michael S. Brown** shared the Nobel Prize in Physiology or Medicine with another former NIH scientist for studies on cholesterol metabolism regulation that have led to new treatments for atherosclerosis.

Institute grantee **Dr. Herbert A. Hauptman** shared the Nobel Prize in Chemistry for creating methods to determine crystal structures. The methods advanced the development of practical instruments for learning the three-dimensional shape of molecules.

1989
Former Institute intramural researcher **Dr. Harold E. Varmus** shared the Nobel Prize in Physiology or Medicine with another former NIH scientist. They demonstrated that oncogenes, genes capable of converting normal cells into cancerous ones, can arise from normal cellular genes. Varmus later served as NIH Director.

1990s

1990
Institute grantee **Dr. E. Donnall Thomas** shared the Nobel Prize in Physiology or Medicine with another NIH grantee for pioneering transplant therapy. Thomas' early advances in bone marrow transplantation have aided patients with leukemia and many other diseases.

1992
Institute grantees **Dr. Edmond H. Fischer** and **Dr. Edwin G. Krebs** received the Nobel Prize in Physiology or Medicine for their studies of the regulation of cell activities by enzymes. They discovered protein kinases, enzymes that control basic activities of the cell by adding phosphate groups to proteins.

1994
Dr. Martin Rodbell shared the Nobel Prize in Physiology or Medicine with an NIH grantee for their discovery of G proteins and their role in signal transduction in cells. Rodbell made many of his key findings in the 1970s while an Institute intramural scientist.

1997
Institute grantee **Dr. Paul D. Boyer** shared the Nobel Prize in Chemistry for discovering how the enzyme ATP synthase drives the formation of ATP, the carrier of energy for cells in all living things.

1998
Institute grantee **Dr. Ferid Murad** shared the Nobel Prize in Physiology or Medicine with two other scientists for work demonstrating that the gas nitric oxide plays a role as a signaling molecule in the cardiovascular system.

2000s

2003
Dr. Peter Agre shared the Nobel Prize in Chemistry with another scientist for studies of channels in cell membranes. Agre discovered aquaporins, proteins that move water molecules through the cell membrane.

2004
Long-time grantees **Dr. Irwin A. Rose** and **Dr. Avram Hershko** shared the Nobel Prize in Chemistry with another scientist for the discovery of ubiquitin-mediated protein degradation inside the cell. Later work by this team brought to light insights into the ways that ubiquitin-mediated protein degradation contributes to cellular metabolism in general, as well as other roles of the ubiquitin protein.

Dr. Richard Axel, who was once an intramural research fellow under Dr. Gary Felsenfeld at the NIDDK, shared the Nobel Prize in Physiology or Medicine with another scientist. The pair discovered a large family of receptors selectively expressed in cells that detect specific odors. These receptors were later shown to be the cell surface molecules that bind specific odorants, which is the first step in their detection and identification.

2007
Institute grantee **Dr. Oliver Smithies** shared the Nobel Prize in Physiology or Medicine with two other scientists for the discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells, more commonly referred to as "gene targeting" or "gene knockout."

How NIDDK Supports Research

The NIDDK has employed multiple strategies over the years to support biomedical research relevant to its mission, including the following.

Extramural and Intramural Research Funding: The NIDDK directly funds biomedical research through grants, cooperative agreements, and contracts to advance knowledge in order to extend healthy life and reduce the burden of illness and disability. Many of the research studies supported by these funding awards are investigator-initiated, but some result from solicitations by the Institute. Scientists at universities, medical centers, and companies throughout the country receive funding from the NIDDK to conduct a broad spectrum of basic, clinical, and translational research. In addition to this extramural research, the NIDDK also supports scientists in its Intramural Research Program laboratories in Bethesda, MD and Phoenix, AZ. The NIDDK also supports research centers and research training (described below), as well as scientific conferences and shared resources.

Research Training and Mentoring: NIDDK-funded training programs work to maintain a "pipeline" of new investigators at every career stage. These include summer training programs for high school and college students, with special opportunities for underrepresented minorities; fellowships for medical and graduate students; and support for postdoctoral researchers and physician-scientists. Early career awards are available for newly-independent investigators, while established investigators are encouraged to mentor more junior scientists through mid-career awards.

Research Centers: Through its Research Centers program, the NIDDK supports multi-disciplinary projects, shared research resources, training, and research translation; aims to integrate basic and applied research; promotes research in areas of clinical applications; and facilitates exploration of new research directions through flexible pilot funds. The Institute funds Research Centers focused on diabetes, digestive diseases, kidney diseases, urology, and molecular hematology, as well as molecular therapy and cystic fibrosis. Another group of Centers conducts research on nutrition and obesity.

External Input: To help inform current activities and strategic planning for future research efforts, the NIDDK seeks input from investigators, professional organizations, patient advocates, and the public. The Institute's National Advisory Council provides advice to the Institute from the scientific and lay communities. The NIDDK convenes scientific workshops and *ad hoc* planning groups to help assess the state of the science and to solicit input on research challenges and opportunities. Through Consensus Development Conferences, panels of external experts develop guidelines for the definition and treatment of diseases and identify gaps in knowledge.

Collaboration and Trans-NIH Research Efforts: The NIDDK actively collaborates with other Institutes, Centers, and Offices at the NIH, as well as with other agencies and other partners, to leverage expertise and resources and accelerate research progress. For example, within the NIH, the NIDDK has a leadership role in trans-NIH obesity research efforts and leads collaborative research efforts in diabetes, liver diseases, and other areas. The NIH Common Fund supports cross-cutting, trans-NIH programs, including programs of the NIH Roadmap for Medical

Research, and the NIDDK plays a leadership role in ongoing initiatives related to the microbiome and epigenomics. In a new effort, the NIDDK, along with the other components of the NIH, is deploying funds made available through the American Recovery and Reinvestment Act of 2009 to support highly meritorious research projects; supplements to accelerate the pace of ongoing science and provide for research training; and new NIH activities, such as Challenge Grants.

Research Coordination Across Agencies: The NIDDK leads several key trans-agency coordinating committees. The Diabetes Mellitus Interagency Coordinating Committee coordinates the Federal investment in diabetes programs across the NIH and other Federal agencies, and provides for the communication and information exchange necessary for coordination. The Digestive Diseases Interagency Coordinating Committee promotes the coordination of research efforts across the NIH and Federal agencies. The Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee facilitates the sharing of information about ongoing and planned activities. The Division of Nutrition Research Coordination addresses research and training activities.

Science-based Health Education: The NIDDK supports a number of programs designed to improve health and reduce the burden of disease for patients by disseminating science-based educational information. They include the National Diabetes Education Program, the National Kidney Disease Education Program, the Weight-control Information Network, Information Clearinghouses, and additional disease awareness campaigns.

NIDDK Directors

Dr. William Henry Sebrell, Jr.
Served as Director
August 15, 1950 to October 1, 1950

Dr. Russell M. Wilder
Served as Director
March 6, 1951 to June 30, 1953

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June 17, 1982 to June 30, 1984

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Dr. Phillip Gorden
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September 5, 1986 to November 14, 1999

Dr. Allen M. Spiegel
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November 15, 1999 to March 3, 2006

Dr. Griffin P. Rodgers
Director
April 1, 2007 to present

Acknowledgements

Griffin P. Rodgers, M.D., M.A.C.P.
Director

Gregory G. Germino, M.D.
Deputy Director

Research

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For more information on the NIDDK and its research mission, and links to other sites, please visit: www.niddk.nih.gov.

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