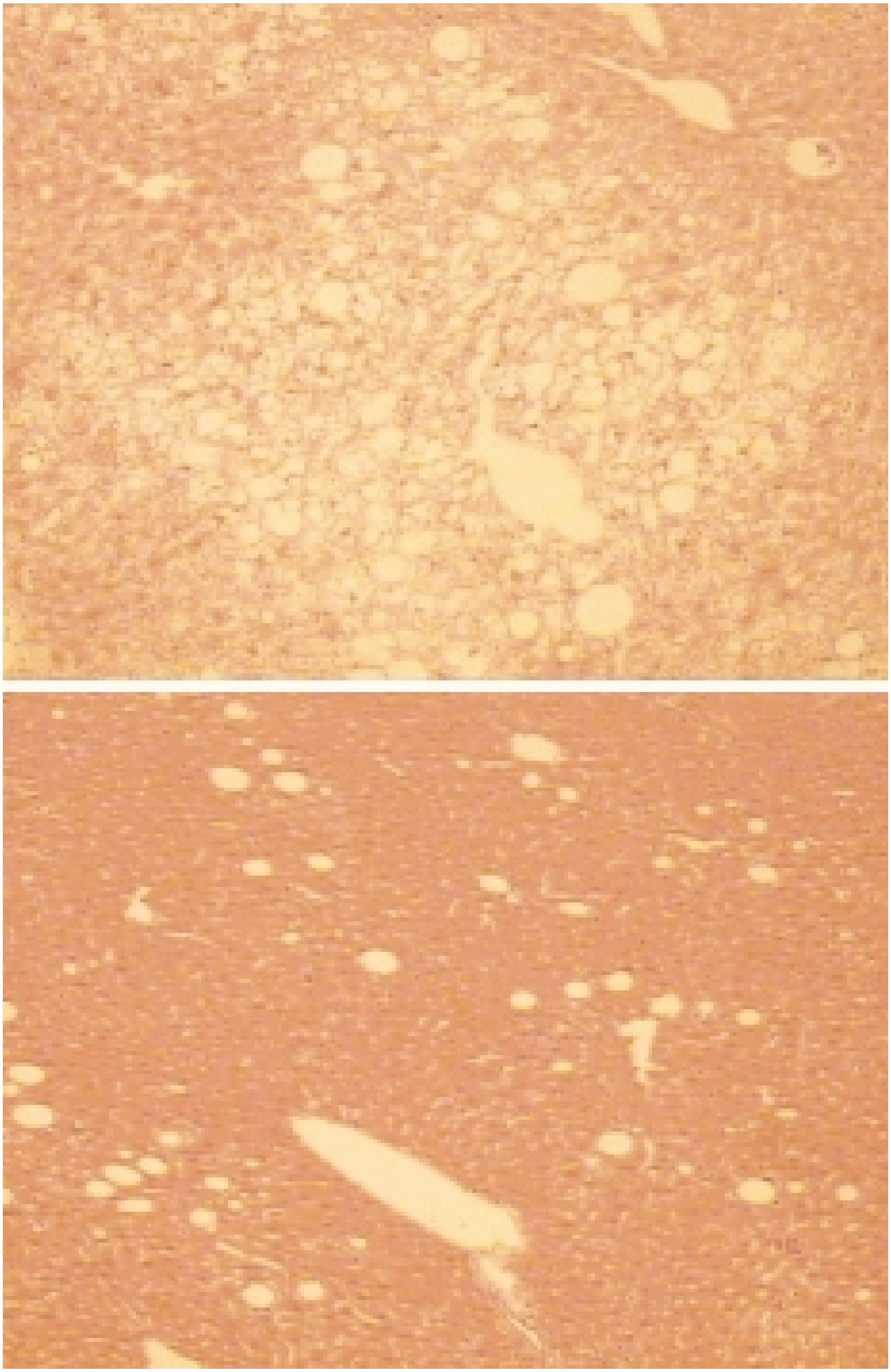

This photograph shows the fat content (white) of the liver from mice deficient for the hormone leptin (top) and those therapeutically treated with the hormone (bottom). Leptin is an important regulator of appetite in the brain, and also alters fat metabolism in the liver and other tissues. Photo: Dr. Ken Ebihara, Kyoto University Graduate School of Medicine. Reprinted with permission from *Diabetes*, Vol. 50, 2001: 1440-1448. Copyright © 2001 American Diabetes Association.

Digestive Diseases and Nutrition

Digestive diseases are among the leading causes of hospitalization, surgery, and disability in the U.S. They include disorders of the gastrointestinal tract, liver, gallbladder, and pancreas. Nutrition research is important to understanding, treating and preventing many diseases such as type 2 diabetes, obesity, chronic renal disease, heart disease and cancer.

Obesity: A National Health Problem

Obesity is the most common and fastest growing health problem in the U.S. Individuals who are overweight or obese are at heightened risk for developing a number of diseases, including type 2 diabetes, heart disease, stroke, and some forms of cancer. The U.S. Surgeon General recently issued a report, "The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity," and publicly identified obesity as the second most common cause of preventable deaths in the U.S. Hence, questions arise regarding the effects of diet and lifestyle changes on quality of life and disease outcomes. Several ways of measuring overweight or obesity exist, including Body Mass Index, or BMI (see the accompanying sidebar on different measures, "Who Should Lose Weight?"). BMI is a ratio derived from a person's weight and height; people with a BMI of 25-30 are considered overweight, while those with a BMI higher than 30 are classified as obese. Based on BMI, more than half of adults in the U.S. are overweight, and nearly one quarter are obese.

Prevention Message of Type 2 Diabetes Trial, the Diabetes Prevention Program (DPP): Long-term studies have already emphasized the importance of diet and lifestyle in the primary prevention of coronary disease. Results that have recently emerged from the Diabetes Prevention Program (DPP), a major clinical trial supported by the NIDDK, vividly illustrate the importance of weight control in preventing another disease, type 2 diabetes. Participants in the DPP were overweight Americans with impaired glucose tolerance; 45 percent of the participants were from minority groups who are disproportionately affected by diabetes. In studying whether type 2 diabetes could be prevented in these individuals at high-risk for the disease, investigators compared the effects of: (1) intensive lifestyle intervention; (2) treatment with the drug metformin; and (3) placebo treatment; patients in the latter two groups also received conventional information about diet and exercise. Participants randomly assigned to intensive lifestyle intervention increased their physical activity by exercising for at least 150 minutes a week, usually with walking or other moderate exercise. They also lost five-to-seven percent of their body weight (an average of 15 pounds). As a result, this group reduced their risk of developing type 2 diabetes by 58 percent. These results demonstrate that even modest weight loss through diet and exercise can prevent a disease that is the main cause of kidney failure, limb amputations, and new onset blindness in adults, and a major cause of heart disease and stroke.

The Biology of Obesity

Obesity is a consequence of greater energy intake in the form of food calories than energy expenditure through metabolic processes and physical activity. The excess energy is most efficiently stored by the body as droplets of fat within specialized cells—adipocytes, or "fat cells"—that develop and grow in different parts of the body. Understanding the biology of fat cells will ultimately lead to improved approaches to managing and preventing obesity. As evidenced by several recent advances, investigators are learning a great deal about how the body regulates energy balance, how normal cellular factors might be manipulated to decrease body fat, and how both the environment and an individual's genetic makeup can affect whether an individual becomes obese in the first place.

Tipping the (Molecular) Scales: How does the body normally know when it has enough energy stored to maintain a healthy weight? Like a car, the body takes in fuel (food), stores the fuel energy (mostly as fat), and burns it (through metabolism and physical activity). Also like a car, the body has gauges and indicators to assess its energy needs. Different tissues in the body release hormones and other molecules during exercise, fat metabolism, feeding, and stress. The brain constantly receives these signals, many of which indicate either an energy surplus or an energy deficit. The brain then responds with signals—also hormones and other molecules—that promote energy balance, usually by modifying behaviors such as feeding and physical activity. Many of these signals are received and generated in a region of the brain called the hypothalamus, considered the brain's "appetite control center." Much recent research has been devoted to identifying the molecules the body uses to gauge and respond to changing energy levels. For example, mice engineered to lack insulin receptors only in their brain eat more and exhibit elevated levels of body fat in contrast to normal mice. This finding indicates that insulin, which is produced by the beta cells of the pancreas, acts on the brain and plays a role in influencing food intake in addition to its better-characterized roles in glucose metabolism. Other hormones, such as the "fat hormone" leptin, target the hypothalamus to regulate body weight by either stimulating or suppressing appetite.

Imbalances in Hormonal Signals: If the fuel gauge fails to register a full tank in a car, the driver can keep adding gas unnecessarily; if the tank could expand, it would take over the car. Not surprisingly, researchers are finding that similar imbalances between the brain and body signals regulating feeding behaviors, energy storage, and energy expenditure can result in the "energy surplus" that leads to obesity. For example, melanin concentrating hormone (MCH) is a peptide hormone produced in the hypothalamus. Levels of MCH go up in mice when they are fasting, because levels of leptin go down; when MCH increases, mice eat more. NIDDK-supported researchers have found that mice genetically engineered to produce just twice as much MCH as normal mice in response to fasting signals eat more than normal mice, become obese, and develop insulin resistance. These results suggest that imbalances in MCH production may contribute to obesity and associated metabolic complications.

Scientists at the NIDDK have also recently found out more about how MCH production is regulated, through research on cellular receptors. Receptor molecules inside and on the surface of a cell act like radio antennae, picking up molecular signals in the cell's environment for translation into useful information. For example, insulin bound to the insulin receptor tells a cell that there is a lot of free glucose in the body. Cells use such information to decide what "molecular activities" they should engage in, such as altering their metabolism or releasing their own signals. Mice that have been genetically engineered to lack the M3 receptor, a specific type of cellular receptor for the signaling molecule acetylcholine, eat less than normal mice and are lean, despite having a normal metabolic rate. Importantly, these lean mice have abnormally low levels of leptin, but, unlike normal mice, their levels of MCH are not increased in response to this fasting signal. As it turns out, the M3 receptor is normally found on the very same cells in the hypothalamus that produce MCH. This finding suggests that acetylcholine may play a pivotal role in stimulating the production of MCH in response to low leptin levels. An exciting new role is thus emerging for acetylcholine, a molecule usually associated with memory, muscle stimulation, and gland secretion. These and future findings about the molecules involved in energy balance could lead to specific interventions for eating disorders that contribute to obesity.

Enhancing Calorie-Burning: Finding ways to enhance the body's burning of calories, called thermogenesis, is another therapeutic approach to obesity. Under normal conditions, the breakdown of fat is "coupled" to the production of chemical energy for use by the cells of the body. Because of this, people who want to lose weight are advised to modify their diets, in order to decrease the amount of food energy they consume, and to exercise, in order to increase the amount of energy they expend. When this happens, the body uses stored fat as an energy source. However, there may be other ways to achieve the dissipation of stored fat. In some fat cells, the presence of "uncoupling proteins" severs the link between fat metabolism and chemical energy production, and the energy that usually drives a series of chemical reactions is instead dissipated as heat. NIDDK-supported researchers have found that mice genetically engineered to overproduce an uncoupling protein in their skeletal muscle have elevated rates of metabolism in both resting and active states, and are leaner than their normal counterparts. Complementing these findings, human genetics researchers in Europe have found a correlation between a genetic variation that increases uncoupling protein production in fat cells and a decreased risk of obesity.

The "uncoupling story" isn't so simple, however: NIDDK-supported researchers recently studied mice that were genetically engineered to under-produce or entirely lack an uncoupling protein that is normally found in a number of tissues, including the insulin-producing pancreatic beta cells. These mice did not gain weight, indicating that removal of the uncoupling protein does not contribute to obesity. Instead, the mice had lower resting blood glucose levels and higher levels of insulin, and they also secreted more insulin than normal mice in response to a "glucose challenge." Beta cells secrete insulin in response to increased chemical energy production, usually initiated by increases in blood glucose. In type 2 diabetes, insulin secretion eventually declines as these cells become insensitive to blood glucose levels. Thus, reducing, rather than increasing, the amount or the activity of the uncoupling protein in beta cells may be important in treating type 2 diabetes, a disease strongly associated with obesity. With better understanding of uncoupling proteins, it may be possible to search for drugs that carefully and specifically manipulate levels of these proteins in target tissues so as to shunt excess calories into heat, rather than fat production, while also maintaining or increasing insulin production by beta cells, thereby preventing or controlling both obesity and diabetes.

Role of Genetics and the Environment: Obesity is not a single disorder, but a diverse group of conditions with multiple causes. As some scientists identify the major regulators of energy balance in the body, others are looking for genetic and environmental factors, such as diet and stress, that influence or disrupt the normal pathways affecting fat accumulation.

Whereas some environmental factors, such as a consistently high-fat diet combined with low physical activity, will cause just about anyone to become overweight, some people have pre-existing genetic variations that will exacerbate the effect of environmental factors. For instance, a distinct correlation exists between increasing percentage of Native Hawaiian ancestry and development of obesity and diabetes. In the general population, over 200 genes, genetic "markers," and chromosomal regions have been reported that are possibly linked with BMI, body fat, and other obesity traits and complications. NIDDK-supported researchers recently studied the relationship between heredity and obesity in several hundred Caucasian families, scanning the entire genome for chromosomal locations that influence the development of visceral obesity, overall obesity, and insulin resistance. They identified two regions, or "loci," one on chromosome 3 and one on chromosome 17. One is strongly "linked" to several traits associated with obesity, including BMI and insulin resistance, and the other is strongly linked with levels of leptin. Such genetic linkage studies in large numbers of families can provide researchers with better maps to find the genes that have the most significant influence on obesity.

Identifying the environmental factors that promote obesity in the population is also extremely important in preventing the onset of disease, especially for individuals with a greater genetic susceptibility toward weight gain. Environmental factors may in fact be the single most significant cause of weight gain, as obesity has only become a significant problem in the post-industrialized world. Even more tellingly, the incidence of childhood obesity and type 2 diabetes has increased dramatically in the past decade.

The most obvious environmental factors affecting weight gain are those affecting diet and physical activity, such as access to high fat foods and an increasing number of sedentary occupations. Researchers are also examining other factors, especially ones affecting early development of obesity. For example, NIDDK-supported scientists recently reported that breast-feeding of infants reduces their risk of becoming obese in older childhood and adolescence. Such a finding could result in future recommendations for improved child health.

Obesity usually develops over a number of years, and is a reversible condition; however, its associated complications and diseases, such as diabetes and cancer, can cause permanent damage. Thus, as researchers identify the environmental factors that promote obesity, they are also developing strategies for early intervention. Because of the cultural and socio-economic influence on factors contributing to obesity, different approaches are also being tailored for specific populations and communities. The effectiveness of all of these approaches in preventing obesity and promoting health needs to be evaluated. In collaboration with a number of other institutes at the NIH, the NIDDK is supporting an initiative, "Environmental Approaches to the Prevention of Obesity," a research solicitation that will establish studies of preventive approaches that target environmental factors contributing to inappropriate weight gain in children, adolescents, and adults.

NIDDK Efforts: The NIDDK maintains a strong program of research on and related to obesity, both as a serious risk factor for type 2 diabetes and its complications and as an independent health problem. The Institute established a National Task Force on the Prevention and Treatment of Obesity, which provides science-based guidance to aid research strategies and to generate public health messages. The NIDDK also supports Obesity/ Nutrition Centers and Clinical Nutrition Units. A multicenter clinical trial has just begun that will examine the health effects of voluntary weight loss in obese diabetic patients, with particular emphasis on cardiovascular health. The trial is called "Look AHEAD," Action for Health in Diabetes. The NIDDK's public education efforts related to obesity include the Weight Control Information Network, and the National Diabetes Education Program. The latter is a cooperative initiative with the Centers for Disease Control and Prevention and approximately 200 public and private partnership organizations. Finally, the NIDDK supports all of these programs with a solid base of fundamental research on biologic processes such as nutrient metabolism and how it is influenced by genetic and environmental factors.

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Copper Transport

Copper is an essential nutrient for most living organisms. Catalyzing the movement of electrons within biological molecules, copper works with proteins as a cofactor to facilitate a variety of metabolic functions. These include photosynthesis and respiration, eradication of toxic elements, connective tissue formation, iron metabolism, and neurological function. Although copper is essential, it is also toxic. Only trace amounts of this metal are needed by the body and it is critical that proper levels of copper be maintained to prevent abnormalities and death.

The tragic effects of deficiencies or excesses of copper are demonstrated by two genetic diseases, Menkes disease and Wilson disease. Patients with Menkes are unable to secrete copper from any of their cells. Therefore, the cells lining the intestine, which can still absorb copper from digested food, cannot make it available to the rest of the body, resulting in copper deficiency. Children with Menkes disease suffer from growth retardation, severe neurological impairment, mental retardation, seizures, and hair and bone abnormalities, usually leading to death before age five. Wilson disease, in contrast, is the result of copper excess. Although patients with Wilson disease do not exhibit symptoms early in life, by age 40 most have suffered liver failure and severe brain deterioration associated with copper deposits in those organs. The genes responsible for Menkes and Wilson disease were recently identified. They code for two distinct but nearly identical enzymes, MNK (Menkes) and WND (Wilson), that are required for the proper export of copper from cells.

Insights from Yeast: To elucidate the mechanisms of copper transport by cells, scientists have historically used yeast, which are single-celled organisms, as a "model system." They are now using their findings in yeast to investigate how multi-cellular organisms maintain proper copper balance, or homeostasis, using animal models and state-of-the-art technology. Following the identification of the protein responsible for copper uptake in yeast, Ctr1p, investigators identified a genetically similar, or homologous, protein in plants, mice, and humans. These Ctr1p "homologs" can substitute for the yeast Ctr1p when they are introduced into yeast that have an inactivated *Ctr1* gene, indicating that they do act as copper transporters. To explore the role of the Ctr1 protein in multi-cellular organisms, NIDDK-supported researchers recently used genetic engineering to create mice in which either one or both copies of the murine *Ctr1* gene were "knocked out." Embryos without a functioning *Ctr1* gene died *in utero*, while those with one active copy of the gene seemed normal, but had approximately half the content of copper in their brains as normal mice. This evidence correlates well with the high expression of Ctr1 protein found in the mouse brain. Like the Ctr1 protein, the mouse MNK protein is highly expressed in the brain. The findings of this study suggest that both Ctr1 and MNK may play a crucial role in copper transport in the brain during development and adulthood.

Chaperone Proteins: New insights into copper transport inside cells have been gained through the recent identification of metallochaperones, a family of proteins that play a role in this transport process. The delivery of copper to intracellular targets in mammals appears to require the metallochaperone Atox1. To clarify the specific function of Atox1 in mammalian cells, and its role in copper stability, NIDDK-supported investigators used genetic engineering to create mouse strains in which the *Atox1* gene was knocked out, so that no Atox1 protein was made. Most of these mice could not survive long after birth and those that did exhibited growth failure, flacid skin, and seizures due to copper deficiency. The research team found that copper was delivered normally to the placenta of both mutant embryos and normal control mice, but significantly less copper was then transported into the *Atox1* mutant embryos. Fetal cells line the blood vessels of the placenta and are responsible for transferring copper from the placenta to the embryo. In the case of the *Atox1* mutants, these cells can take up copper but are unable to transfer it to the embryo. Thus, the mouse embryos suffer from copper deficiency during their development, with devastating results. Furthermore, these effects were compounded when the mouse mother also did not make any Atox1 protein. These findings are consistent with previous research demonstrating that mammalian Atox1 protein interacts with both the Menkes and Wilson copper transporting proteins, and they suggest that one important role for Atox1 is to deliver intracellular copper for export.

As demonstrated by these studies, copper homeostasis is essential from embryogenesis through adulthood in most organisms. Each step toward the elucidation of the role of copper and the mechanisms by which homeostasis is attained brings us closer to therapies and cures for devastating diseases involving copper imbalance.

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Hereditary Pancreatitis

Hereditary pancreatitis (HP), a rare genetic form of pancreatitis, was recognized as a distinct disease in 1952. Since its recognition, more than 200 families with HP have been identified. Studies of these HP families led investigators to determine that mutations in the gene coding for the protein, cationic trypsinogen, were responsible for their disease. Three different mutations in the cationic trypsinogen gene that clearly predispose patients to acute and chronic pancreatitis have been identified.

Trypsinogen, which is made by cells in the pancreas, is an inactive form of the digestive enzyme trypsin.

Normally, the pancreas secretes trypsinogen into the small intestine, where it becomes "activated" to trypsin. Trypsin then activates other pancreatic "pre-enzymes" secreted into the small intestine. The cationic trypsinogen gene mutations identified in HP patients interfere with this process by causing premature activation of trypsinogen while it is still in the pancreas. The mutations apparently either make trypsinogen unable to "auto-digest" itself, which it normally does when it is inappropriately activated in the pancreas, or simply enhance its premature activation. The presence of active trypsin in the pancreas results in the activation of the other digestive enzymes, causing destruction of pancreatic cells and subsequent pancreatitis. Inflammation of the pancreas causes severe abdominal pain, nausea, and elevated pancreatic enzymes. Individuals with hereditary pancreatitis have a lifetime risk of pancreatic cancer ranging from 40 to 75 percent.

HP mutations are "dominant," meaning that only one copy of the cationic trypsinogen gene must be changed for the disease to be expressed. However, only 80 percent of individuals who inherit a gene mutation develop the disease. This correlation led researchers to hypothesize that other modifier genes or environmental factors may contribute to the onset of pancreatitis. To explore this possibility, NIDDK-supported researchers used "twin studies." Twin studies offer a powerful tool for teasing out the role of genetic factors from the effects of environment in the development of disease, because identical twins have the same genetic information at the DNA sequence level. In such studies, identical twins are compared to sibling pairs in the same environment and to paired, unrelated individuals in a different environment. In this study, the overall rate of disease development among individuals in 14 separate twin pairs was nearly 80 percent, as is seen in large family studies. However, three pairs of twins were "discordant," meaning that one member of each pair, although carrying a mutation, did not develop disease. Differences in the age of onset in the other groups compared with the twins suggested that environmental factors or modifying genes may be important in disease expression, but these factors alone do not explain why 20 percent of individuals with mutations never develop the disease at all. The results of this study suggest that other, possibly non-heritable factors (such as unique events in an individual's experience that could act as "triggers"), may contribute to an individual's developing pancreatitis.

This research provides a vital analysis of HP patients and the contribution of genetics and the environment to their disease. However, other pieces of this puzzle are required to understand fully the mechanisms of hereditary pancreatitis. Solving the puzzle is expected to lead to new therapies that will minimize the symptoms or prevent the onset of this disease.

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Irritable Bowel Syndrome: Altered Neurological Activity

Irritable bowel syndrome (IBS) is a common disorder of the intestines that leads to pain, intestinal gas, bloating, and changes in bowel habits. People with IBS may have constipation or diarrhea and some people experience both. Other symptoms include the urge to move the bowels but an inability to do so. The cause of IBS is not known, and as yet there is no cure. IBS is classified as a "functional disorder" because there is no sign of disease when the colon is examined. Although it does not cause permanent harm to the intestines and does not lead to intestinal bleeding of the bowel or to a serious disease such as cancer, IBS patients suffer a great deal of discomfort and distress.

The underlying physiologic cause of IBS is unknown. Ordinary events such as eating and distention from gas or other material in the colon can cause the colon to overreact in a person with IBS. Individuals with IBS seem to have a colon that is more reactive and sensitive than usual, so it responds strongly to stimuli that would not bother most people. Researchers have found that the colon muscle of a person with IBS begins to spasm after only mild stimulation. Stress may also be a factor in the manifestation of disease symptoms.

Patients with IBS also seem to have an enhanced awareness of and sensitivity to normal gastrointestinal events, such as muscle contractions and the filling of the viscera following a meal. This has led some researchers to speculate that when the brains of persons with IBS receive information from the visceral nerves in the intestines, they may process the information differently than persons without IBS.

To examine the possible role of information processing by the brain in causing IBS, researchers studied brain activity in affected patients. In the experiment, the scientists recruited twelve people with IBS, as well as twelve healthy volunteers, and inserted a catheter through the rectum and into the volunteers' colons. Each catheter contained two small balloons along its length that could be inflated to a precise pressure by the researchers. Inflation of balloons of this size is designed to produce mild discomfort, but no serious pain or tissue damage. After the catheters were inserted and the patients had a brief recovery period, the researchers initiated a Positron Emission Tomography (PET) scan of the patients' brains. This scan permitted researchers to see relative rates of metabolism—based on energy usage and blood flow—within specific regions of the brain. The researchers then initiated a three-part experimental phase, in which they told patients that the balloons would or would not be inflated, but did not consistently inflate the balloons in the manner stated. This experimental design allowed the researchers to see responses to no inflation (phase 1), an expected and delivered inflation (phase 2), and an expected but undelivered inflation (phase 3). During this procedure brain activity was monitored by PET scans.

When the scientists analyzed the data generated by the PET scans, they found significant similarities between the normal and IBS patients, but also noted important differences. Brain regions activated by actual and simulated balloon inflations were similar in both groups; however, differences in three important areas of the brain could be detected. First, patients with IBS exhibited enhanced activation of right prefrontal cortex in response to actual or expected balloon inflation, whereas in normal patients, both sides of the brain reacted to a similar extent. This region of the brain is thought to be very important for "higher" cognitive functions, including concentration and judgment. Second, within the anterior cingulate—an area deep within the brain thought to be involved in emotions such as sadness—an enhanced reaction was seen in IBS patients in a sub-region associated with the perception of pain and unpleasantness. Third, the IBS patients demonstrated an overall decreased activation of circuits in the brain believed to activate fear and defense responses.

All three of these observations indicate that IBS patients show altered brain responses to rectal stimuli, regardless of whether these stimuli are actually delivered or simply anticipated. This study provides solid evidence of altered brain activity in patients suffering with this syndrome that is of unknown origin. To help foster more research into the causes of IBS—and its possible treatments—the NIDDK is working with members of the IBS community to develop a conference on the topic of fecal and urinary incontinence that is relevant to many of the quality of life issues that have an impact on people with IBS.

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Hepatitis C

It is likely that infection with the hepatitis C virus (HCV) is the major cause of cirrhosis and end-stage liver disease in the U.S., responsible for 8,000 to 10,000 deaths per year and at least 30 percent of all liver transplants performed in adults in the U.S. Several studies have now shown that viral resistance to the current optimal therapy of alpha interferon and ribavirin in patients with chronic hepatitis C is two-to-threefold more common among African Americans than non-Hispanic Caucasians. The reasons for this difference are not clear, and unfortunately, studies of antiviral therapy have included too few African American patients to either measure the response rate to current therapies or analyze the factors responsible for the lack of effect of therapy. The NIDDK held a workshop on "Hepatitis C and African Americans" in December 1999, which confirmed the scant participation of African Americans in clinical studies.

New Clinical Trial To Address Resistance to Current Treatments: To address this issue, the NIDDK recently initiated a multi-center clinical trial that will study viral resistance to interferon alpha therapy in patients with chronic hepatitis C, specifically focusing upon African Americans. The Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C) is intended to administer first-time treatment to 200 Caucasians and 200 African-Americans with chronic hepatitis C who are infected with HCV genotype 1. Patients will undergo an extensive initial medical evaluation and then receive what is judged to be the current optimal therapy of chronic hepatitis C. During treatment, patients will be followed intensively for virological, immunological, cytokine-signaling, and host genetic differences. It is anticipated that the study will help explain the diversity in clinical outcome of therapy for hepatitis C.

HALT-C Trial: Another important hepatitis C trial that has been initiated by the NIDDK is the study of "Hepatitis C Antiviral Long-Term Treatment to Prevent Cirrhosis (HALT-C)." This is a seven year study of therapy for hepatitis C focusing on patients with advanced disease (with severe fibrosis or cirrhosis) who have not responded to conventional therapy and for whom there are no other practical options available. This trial should help to determine whether progression of hepatitis C could be halted or modified in individuals who previously were virologic non-responders to treatment. Patients will initially receive a combination of long-acting (PEGylated) interferon and ribavirin. Those who continue as non-responders, presumed to be about 80 percent of the initial treatment group, will then be randomized to receive either PEGylated interferon alone or a placebo. Patients are being intensively studied for both beneficial and adverse effects. This trial is designed to enroll over 1,200 patients, with enrollment scheduled to be completed by December 2002. To maximize the knowledge that can be gained from this trial, the Institute has also sought the development of ancillary studies that will be co-funded with other NIH components that share a mutual research interest in hepatitis C. Using data collected before, during and after therapy, the ancillary studies will focus on such areas as the non-invasive assessment of liver fibrosis; how the hepatitis C virus replicates; risk factors for progression, including nutrition, obesity, smoking, and alcohol; and the role of genetic diversity in diagnosis and clinical management of hepatitis C.