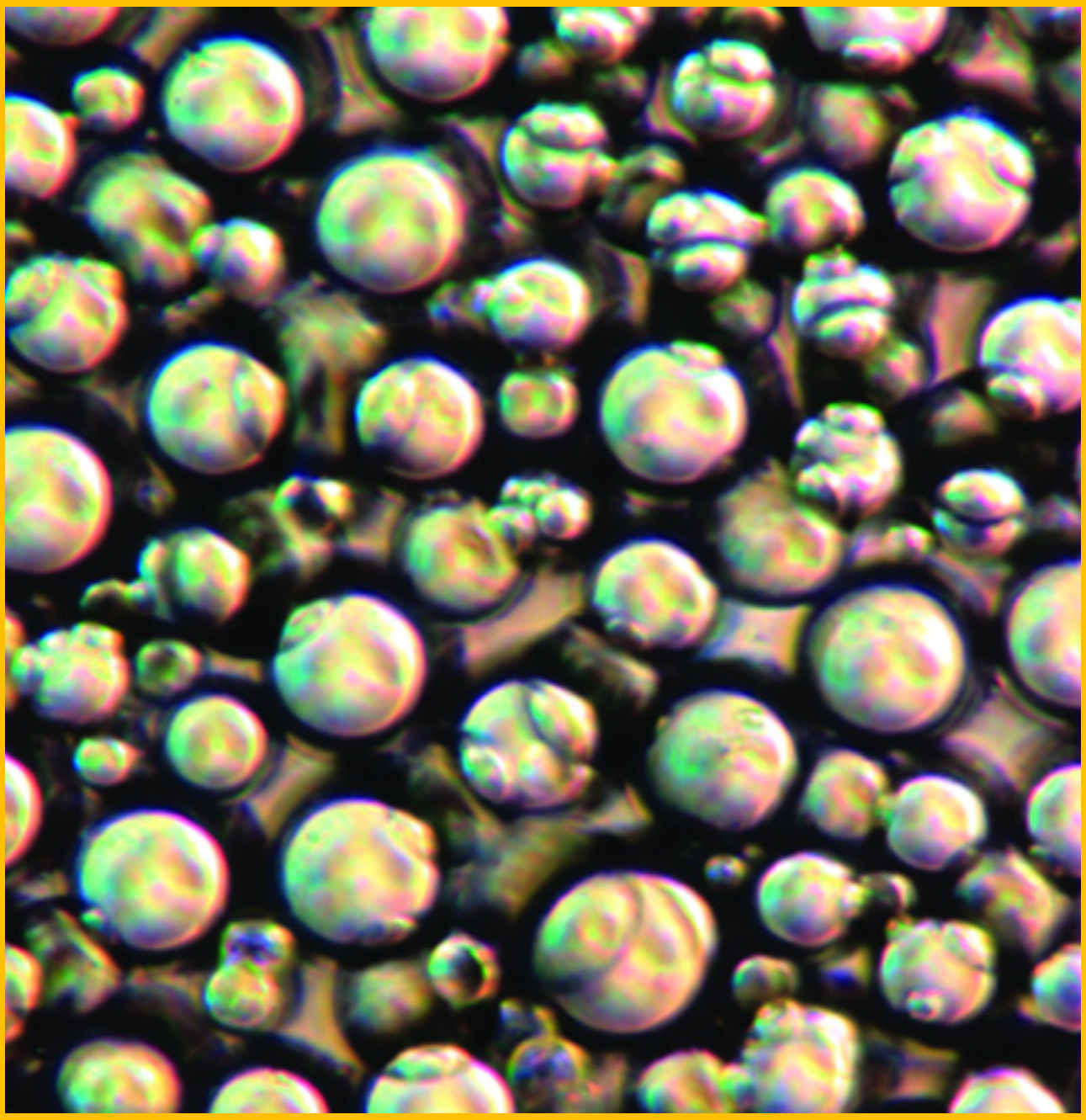

These fat cells were isolated using a method developed by Nobel laureate Dr. Martin Rodbell, whose prizewinning work was supported by NIDDK. In humans, fat cells located in the abdomen secrete hormones believed to be responsible, at least in part, for insulin resistance. Photo: Dr. Joseph Brzostowski and Ms. Mary-Jane Zarnowski, NIDDK.

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, as well as obesity and other nutrition-related disorders. NIDDK-funded scientists are vigorously pursuing research to understand the causes of these diseases and how they progress, and to test pharmacological, surgical, and behavioral interventions for treatment and prevention.

The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels. Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, and cancer. Overweight and obesity also disproportionately affect minority populations, particularly African American, Hispanic, and Native American women and children. As scientists elucidate the molecular factors that control appetite, metabolism, and energy storage, they are identifying potential targets for the development of new pharmacological agents to promote safe, long-term weight loss. Investigators are also continuing behavioral research to help people achieve lifestyle modifications that include increased physical activity and improved diet.

Numerous liver diseases have serious adverse impacts on health and can progress to the need for a liver transplant for survival. Scientists are intensifying research on a variety of liver diseases, from those primarily affecting children, such as biliary atresia, to those commonly affecting adults, such as nonalcoholic steatohepatitis; and from those caused by infection, such as hepatitis C, to those resulting from a variety of other factors, such as autoimmune reactions, genetic mutations, drug toxicity, and as-yet-unknown triggers. Among ongoing and planned clinical research efforts are investigations of treatments for hepatitis C infection and other liver diseases, and studies related to liver transplantation.

The inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, are marked by destructive inflammation in the intestinal tract leading to rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. Surgical treatment is often required. Scientists are dissecting the complex interactions among the genetic and environmental factors that contribute to the development of IBD. The continued identification of predisposing genetic variations and other factors, such as potential autoimmune and microbial influences, will help spur the design of novel therapeutic strategies.

Another intestinal disorder, irritable bowel syndrome, causes pain and constipation or diarrhea and is especially common in women. While diet and stress contribute to this disorder, the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. Scientists are accelerating research to better understand and treat this disorder.

Digestive disease can also be triggered by foods. In individuals with celiac disease, the immune system reacts to a protein called gluten, which is a component of wheat, barley, and rye. This reaction leads to damage to the small intestine, interfering with its ability to absorb nutrients from foods. Celiac disease is associated with a variety of conditions, such as abdominal pain, anemia, osteoporosis, and increased risk of cancer. Following a gluten-free diet is difficult but currently the only treatment; continued scientific research is expected to lead to new therapies.

Among other diseases of the digestive tract are those of the pancreas, including various forms of pancreatitis. Chronic pancreatitis, serious in and of itself, also confers increased risk for pancreatic cancer, one of the deadliest malignancies. Scientists are identifying both genetic and environmental factors associated with pancreatic disease and pancreatic cancer.

Finally, microbes affect digestive health in powerful and sometimes surprising ways. Many foodborne illnesses are caused by bacteria, such as certain strains of *E. coli*, and ulcers and stomach cancer are linked to *H. pylori* infection. Scientists are also gaining insights into how the microorganisms that normally reside in the gut influence the development and function of the digestive tract.

FINDING WAYS TO UNDERSTAND AND TREAT OBESITY

Obesity has emerged as one of the greatest threats to human health and well-being, with the number of those affected continuing to escalate at an alarming rate. Several ways of measuring overweight or obesity exist, including Body Mass Index, or BMI. BMI is a ratio derived from a person's weight and height; people with a BMI of 25 or greater are considered overweight, while those with a BMI 30 or greater are classified as obese. By these measurements, according to the Centers for Disease Control and Prevention, overweight and obesity affect an estimated 64 percent of the U.S. adult population, with serious consequences for the health of the nation. Furthermore, 15 percent of children and teens are also overweight. These individuals are at increased risk for coronary heart disease, diabetes, stroke, and some forms of cancer. Furthermore, data analysis in a recent study suggests that obesity, particularly in young adults, markedly reduces life expectancy.

Obesity occurs when the balance of food intake and energy expenditure is perturbed; excess energy is stored mostly as fat. Maintaining the "energy balance" depends on complicated interactions of many biological and behavioral factors, including genetic predisposition, food intake, and activity level. Although vigorous research has uncovered genes and metabolic pathways that contribute to obesity, a cure remains elusive. Thus, scientists continue to seek answers and look for novel approaches to find means to treat and prevent obesity.

Investigating Leptin's Effects on Metabolism: A significant milestone in our understanding of obesity was the discovery of the fat-cell-derived hormone, leptin. After a meal, fat cells release leptin. The hormone travels to the "appetite-control center" in the hypothalamus, where it binds to leptin receptors (molecules that "see" leptin) on specialized brain cells and signals the brain to "stop!" eating. Scientists found that mice lacking the gene for leptin—*ob/ob* mice—overeat and become obese. When given leptin, these mice lose weight. Unfortunately, administering leptin to humans (except for the few identified with leptin deficiency) does not effectively treat obesity; in fact, most obese humans have high levels of the hormone, indicating that they are resistant to its effects.

However, in addition to acting to repress appetite, leptin also elicits metabolic changes in numerous tissues in order to maintain weight homeostasis. These metabolic changes include increased fat burning (oxidation) and increased glucose uptake. How leptin exerts these effects is still not completely understood. In recent studies, NIDDK-supported scientists set out to determine the effects of leptin in various tissues and the molecular mechanisms and cell signaling pathways involved.

In one study, NIDDK-supported researchers compared the effects of making specific tissues "blind" to leptin. They generated two different groups of mice through genetic engineering, one severely deficient in brain cell leptin receptors and the other severely deficient in liver cell leptin receptors. They found that mice deficient in brain cell receptors for leptin became obese and had enlarged, fatty livers. In contrast, mice deficient in liver cell leptin receptors were lean and appeared to have normal livers. These studies demonstrate that disruption

of the leptin receptor in just the brain can recreate the characteristics of overall leptin deficiency as observed in the *ob/ob* mouse—strongly suggesting that the effects of leptin deficiency on the liver are due to downstream effects of defective leptin signaling in the brain, rather than loss of leptin signaling in the liver itself.

In another study, NIDDK-supported researchers used a technique known as transcription profiling (with microarrays) to identify genes regulated by leptin in the liver of mice. They found that leptin represses the gene that encodes the enzyme SCD-1, decreasing its activity levels. This enzyme catalyzes the synthesis of monounsaturated fatty acids. In order to more fully understand the effect that this enzyme has on obesity, the researchers also studied a mouse strain lacking a functional SCD-1 gene. They observed that these mice are lean, with a higher than normal metabolic rate. The team then used this strain in crosses (matings) to generate a mouse strain that was both SCD-1 deficient and leptin-deficient. They found that leptin-deficient *ob/ob* mice lacking SCD-1 were less obese and had an increased metabolic rate compared to leptin-deficient *ob/ob* mice with a normal SCD-1 gene. Thus, a potential mechanism for leptin's impact on body weight is its inhibition of SCD-1, which may result in a decrease in the synthesis of fat and an increase in its oxidation.

These new studies in mouse models have advanced scientists' understanding of leptin's effects on obesity. They have demonstrated that leptin must bind to receptors on brain cells to have generalized effects on obesity, and that the enzyme SCD-1 is responsive to leptin levels and may be a potential new target for drug intervention in the treatment of human obesity.

Signaling Cells to Burn Energy—An Important Part of Energy Balance: Multiple lines of evidence have led to the current model of energy balance that dictates that, as the brain receives signals of excess calorie intake, it responds by both decreasing appetite and increasing energy expenditure in order to prevent excessive weight gain. The latter phenomenon is known as "diet-induced thermogenesis." Diet-induced thermogenesis is thought to be mediated by the sympathetic nervous system (SNS), *via* stimulation of the beta-adrenergic receptors located on target cells—particularly cells that can "burn off" stored energy in fat by releasing it as heat, rather than using it to power other chemical reactions. When calories are lost as heat energy, they are removed from the total energy balance in the body. However, this hypothesis regarding diet-induced thermogenesis has never been directly tested.

To test this hypothesis, NIDDK-supported researchers generated mice without any active beta-adrenergic receptors and compared them to normal mice. They found that the test mice had a lower metabolic rate and were somewhat fatter than the normal mice when they were fed a typical chow diet and became massively obese when they were fed a high-fat diet. The researchers were also able to demonstrate that the obesity that developed in mice without these receptors was the result of a lower metabolic rate and was not due to a decrease in activity or to an increase in food intake. Thus, beta-adrenergic receptor mediated signaling pathways are indeed necessary for diet-induced thermogenesis, and may represent a possible therapeutic target for preventing or treating obesity.

A Genetic Locus for Severe Obesity: While sedentary lifestyles and unhealthy diets contribute to obesity, heredity also plays a role. However, the search for predisposing genes has been hampered by the genetic complexity of obesity—no single gene is responsible for all human weight gain. Now, in a collaboration between academia and industry, a team of investigators has found a chromosomal region (locus) linked to severe obesity in females.

To design a genetic hunt to circumvent some of the genetic complexity of obesity, the scientists focused on very severely obese individuals. The more extreme a disease, the stronger the genetic influence is likely to be, and the greater the likelihood that it can be pinpointed. They also studied families with very obese members who were closely

related, and thus likely to share the same predisposing genetic variation. Additionally, the scientists incorporated strategies to detect potential gender-specific effects. With DNA samples from hundreds of people and sophisticated computer programs, the scientists pinpointed a locus on chromosome 4 that harbors a gene strongly linked to obesity in females. It is not yet clear whether it affects males. The industrial partner in the collaboration recently announced identification of the predisposing gene within this locus, which they term HOB1. Details about the HOB1 gene have not yet been published in a scientific journal as this document goes to press. However, it is anticipated that understanding how the gene functions could lead to drug development to modulate its effects on obesity.

Exploring Novel Compounds That May Lead to New Obesity Treatments: As indicated by the preceding studies, new opportunities to develop effective, innovative treatments for obesity are emerging from a better understanding of normal weight regulation and how it is disrupted in obesity. Importantly, such studies are complemented by continued experimentation with novel compounds.

One recent research study explored the potential for using a molecule that mimics insulin to control weight. Insulin is a pancreatic hormone that, in addition to stimulating glucose uptake by body cells, interacts with receptors on brain cells in the hypothalamus to modulate energy balance. Through a set of experiments in animals, researchers had already shown that insulin injected into the brain reduces food intake and body weight. In contrast, insulin administered systemically has no effect on curbing obesity, and actually leads to weight gain. An NIDDK-supported research team recently carried out similar experiments, using small molecules that mimic insulin (insulin "mimetics"). When administered to the brain of rodents, an insulin mimetic had the same weight-reducing effect as insulin, but when an insulin mimetic was given orally to rodents, it did not lead to weight gain (as systemic insulin does) and, in fact, reduced diet-induced obesity in these animals. The ability of a small molecule insulin mimetic to control weight when administered orally may give it a significant advantage over natural insulin in terms of its impact on body weight.

Drugs that increase serotonin activity in the brain are frequently used to assist in weight loss, because they suppress appetite. In the mid 1990s, one such drug, fenfluramine, often given in combination with phentermine, was widely prescribed as a weight loss therapy. Although it was prescribed to millions for weight loss because it decreases food intake, fenfluramine and a related drug, dexfenfluramine, were removed from the U.S. market by the FDA due to reports that they caused high blood pressure in the lungs and heart valve damage. Researchers recently studied the activity of dexfenfluramine (d-FEN) in rodents to determine the exact mechanism by which it reduces appetite. Their studies demonstrate that d-FEN stimulates a specific pathway in the brain's appetite control center, the "central melanocortin system," a fundamental regulator of food intake and body weight in rodents and humans. This effect appears to be initiated through the activation of serotonin receptors on certain brain cells, POMC neurons, that are part of the central melanocortin system. Researchers may now be able to develop drugs that act along this pathway in a manner similar to d-FEN, but without producing the damaging side effects that d-FEN and fenfluramine produce.

In other studies, scientists looked at a synthetic compound, C75, which is known to reduce appetite and body weight in mice. In an obese mouse model and normal control mice, a single dose of C75 caused reductions in food intake and body weight. However, when the mice were given lower doses of C75 over a longer time period, the normal mice initially reduced their food intake but became tolerant to C75 after the first day: their food intake returned to near normal and no additional weight was lost. In contrast, the obese mice continued to eat less and lose weight throughout the five-day trial. When researchers gave another group of control mice the same quantity of food as consumed by the C75-treated mice, they lost 25 to 50 percent less

weight than the C75-treated mice. This discrepancy indicates that, in addition to suppressing appetite, C75 may stimulate an increase in the metabolic rate that accounts for the extra weight loss in the C75-treated mice. Future studies may elucidate whether C75 or related compounds will be useful for treating human obesity.

NIDDK Efforts in Obesity: These basic and pre-clinical research studies illustrate the multiple approaches researchers are taking to understand and address weight regulation and obesity at the cellular and molecular level. The hope is that the knowledge gained from these studies will accelerate success in clinical interventions to combat obesity.

To fuel these studies, 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 National Task Force on the Prevention and Treatment of Obesity was established by the NIDDK and includes both NIH scientists and experts from the extramural community. This Task Force provides science-based guidance to aid research strategies. The Task Force also generates public health messages about obesity. The NIDDK also supports Obesity/Nutrition Research Centers and Clinical Nutrition Research Units, which conduct both basic and clinical research studies.

With support from other NIH Institutes, Centers, and Offices, the NIDDK has launched a multi-center clinical trial that will examine the health effects of intentional weight loss in obese diabetic patients, with particular emphasis on cardiovascular health. The trial is called Look AHEAD (Action for Health in Diabetes). In collaboration with a number of other Institutes and Offices at the NIH, the NIDDK is also supporting an initiative, "Environmental Approaches to the Prevention of Obesity," a research solicitation that is establishing studies of preventive approaches targeting environmental factors that contribute to inappropriate weight gain in children, adolescents, and adults—another critical aspect of obesity.

The NIDDK's public education efforts related to obesity include the Weight-control Information Network, and the National Diabetes Education Program (see sidebars here and in the "Diabetes, Endocrinology, and Metabolic Diseases" chapter for further descriptions of both of these efforts). The latter is a partnership among the Centers for Disease Control and Prevention, the NIDDK, and approximately 200 public and private 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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T CELLS AND LIVER DAMAGE IN PRIMARY BILIARY CIRRHOSIS

The liver, the largest organ in the body, is essential for keeping the body functioning properly. It removes or neutralizes poisons from the blood, produces immune agents to control infection, and removes germs and bacteria from the blood. It makes proteins that regulate blood clotting and produces bile to help absorb fats and fat-soluble vitamins. Liver diseases that interfere with these essential functions can therefore severely threaten health (see "Patient Profile: Chris Klug").

Like type 1 diabetes (see "Diabetes, Endocrinology, and Metabolic Diseases" chapter), primary biliary cirrhosis is an autoimmune disease—in this case, one that destroys liver cells. Immune system cells normally protect the body from invaders such as bacteria and viruses, but in the case of primary biliary cirrhosis and other "autoimmune" diseases, some misguided immune system cells attack one of the body's own proteins or cell types. Researchers had previously implicated several different types of immune system cells as having roles in primary biliary cirrhosis and had also identified the target of these autoimmune attacks: a protein called PDC-E2. In experiments designed to elucidate the molecular mechanisms underlying primary biliary cirrhosis, NIDDK-supported scientists have now found evidence that particularly destructive types of immune system cells, called CD8+ T cells, may contribute to the extensive liver damage associated with this disease.

With an advanced technique for detecting particular types of T cells, the NIDDK-supported researchers recently found that CD8+ T cells that recognize the PDC-E2 protein—and that will kill cells that carry PDC-E2—are enriched in the livers of patients with primary biliary cirrhosis. When the scientists compared blood samples with liver tissue from patients, they found that the frequency of these destructive, PDC-E2-reactive T cells in the liver was 10 times higher than that in the blood. This finding was consistent with the greatly enriched number of precursors to CD8+ PDC-E2 reactive T cells that the researchers identified in primary biliary cirrhosis patients as compared to other chronic liver disease patients and normal "control" patients.

These data not only suggest that CD8+T cells are involved in the pathology of primary biliary cirrhosis, but also confirm the importance of the PDC-E2 protein as a central target for the autoimmune attack in this disease. By building upon our knowledge of the types of immune cells involved in liver damage in primary biliary cirrhosis and the target(s) involved, researchers are gaining insights that may ultimately lead to new therapies for this destructive liver disease.

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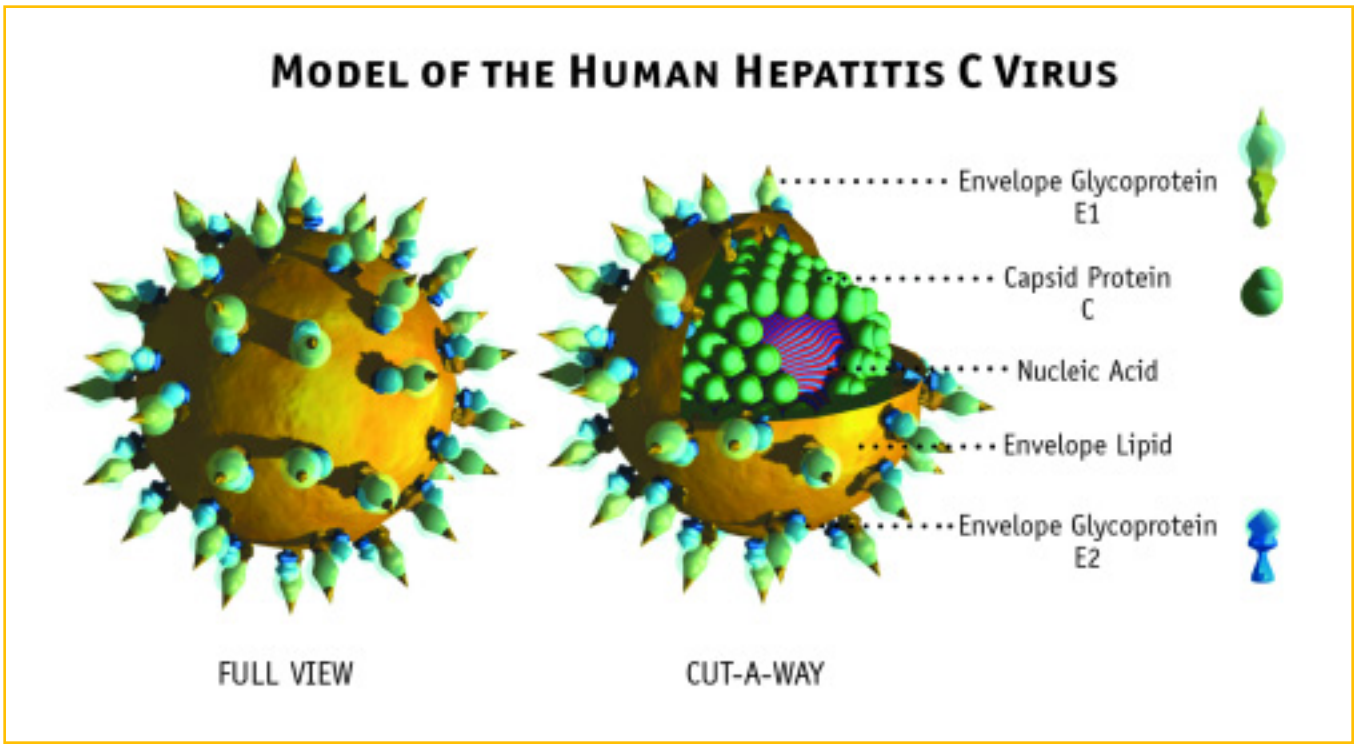
NEW INSIGHTS FROM BASIC AND CLINICAL RESEARCH ON HEPATITIS C

Hepatitis C virus is one of the most common causes of liver disease in the U.S. It accounts for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. An estimated 4 million Americans have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the U.S. alone.

While current drug treatments eliminate the virus in many people, they are totally ineffective or minimally effective in others, and it has not been clear whether a vaccine would be a useful alternative means for protecting against hepatitis C. Additionally, despite its proficiency at human infection, hepatitis C virus has been generally refractory to scientists' efforts to induce infections in small laboratory animals for use as models for



A three-dimensional model of the human hepatitis C virus. Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes 10 to 20 years. After 20 to 40 years, a smaller percentage of patients with chronic disease develop liver cancer. Illustration credit: Three-dimensional model of HCV created by Louis E. Henderson, Ph.D. is reproduced with permission from The PRN Notebook,™ Vol. 6, No. 1, March 2001. Published by Physicians' Research Network, Inc.,® New York, NY, USA. All rights reserved. ©March 2001. For further information visit www.prn.org.

research. One group of NIDDK-supported scientists has now developed a novel mouse model of hepatitis C disease, while another NIDDK-supported research team has investigated whether protection against viral persistence might be possible in humans.

When hepatitis C virus infects humans, it inserts its genetic material into cells, so that the cells will produce viral proteins. Because the virus does not normally infect mice, a group of scientists came up with another way to put viral genes into these animals: they injected the genes into mouse eggs to generate transgenic mice that carried either the entire viral genome or a subset of the genes. The scientists had also linked the viral genes together with a segment of mouse regulatory DNA that turned on the genes in the liver. The genetically engineered mice accumulated excess fat in their livers and developed liver tumors, conditions commonly seen in hepatitis C infections in people. At the same time, because the viral genes were innate to the transgenic mice and not introduced by infection, the potentially injurious inflammation that accompanies infection in humans was absent in these mice. The scientists concluded that viral proteins influence hepatitis C symptoms, although inflammation may also contribute to disease symptoms in human infection.

Vaccines for viral diseases are essentially mock infections with a weakened virus or virus fragment; they train the body to fight off later infections with a real virus. To see whether a vaccine approach might be useful for hepatitis C, scientists recently studied a group of people likely to have multiple exposures to this virus: users of injectable drugs. Some drug users had evidence of an earlier infection from which they had since recovered, while others had not been infected previously. Observations over

the course of two years showed that those who had previous infections were over 10 times less likely to acquire a new persistent infection than those who had not been previously infected. In many of the people, prior infection seemed to confer protection against subsequent, persistent infections. Therefore, the scientists concluded that a vaccine approach to hepatitis C could be beneficial, because the serious liver diseases caused by this virus are associated with its persistence in the liver. This study also revealed that users of injectable drugs have an alarmingly high incidence of hepatitis C virus infection.

These studies provide insights into how hepatitis C wreaks havoc in the liver and how some level of protection against persistence of this virus in the body, and associated disease, might be achieved. This research will likely spur new efforts toward vaccine development.

Providing further support for these research efforts, the NIDDK was one of the primary sponsors of a recent NIH consensus conference on management of hepatitis C (see sidebar, "Hepatitis C Consensus Conference"), to review the current state of knowledge about the disease and treatment options and to identify the most pressing questions for basic and clinical researchers to tackle in the near future.

The NIDDK is also currently supporting two major clinical trials addressing hepatitis C infection. The Hepatitis C Antirviral Long-term Treatment against Cirrhosis (HALT-C) trial is designed to investigate whether long-term treatment of hepatitis C with the drug peginterferon-alfa will prevent progression of liver disease in patients for whom prior treatment did not eliminate the virus. The Virahep-C study will examine resistance to antiviral therapy in patients with chronic hepatitis C, specifically focusing on African Americans, among whom such viral resistance is common. Enrollment for this study has just begun.

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INFLAMMATORY BOWEL DISEASE

The inflammatory bowel diseases (IBD) known as Crohn's disease and ulcerative colitis affect nearly one million Americans. Typical early symptoms of IBD include abdominal pain, fever, watery or bloody diarrhea and weight loss, which can progress to malnutrition and growth retardation, compromise employment and social activities, and increase risk of intestinal cancer (see "Patient Profile: Rachel Hettich—Living with Crohn's Disease"). Although the symptoms are similar, a distinguishing characteristic between Crohn's disease and ulcerative colitis is the location of the inflammation associated with them. The precise cause or causes of IBD are not yet known, but researchers are accumulating new insights into these diseases.

Susceptibility Genes in IBD: One of the theories about the development of IBD is that the patient's immune system reacts inappropriately to bacteria that normally reside in the gut. This reaction initiates a cascade of molecular events that results in inflammation in the gastrointestinal tract. IL-10 is an anti-inflammatory molecule naturally produced in the body that, along with many other molecules, regulates inflammation in IBD. Molecules such as IL-10 that might provide resistance and others that might increase the disease inflammation are the products of individual genes that can be considered "susceptibility" genes. Because of their often small though significant contributions to a disease process, susceptibility genes can be difficult to identify, especially in complex diseases such as IBD. Nonetheless, finding these genes is very important for understanding how a disease develops.

To search for genes that influence IBD severity, NIDDK-supported researchers used a state-of-the-art technique known as quantitative trait locus (QTL) mapping in mice to identify chromosomal regions (loci) in which such genes may be located. For the study, the researchers first selected two strains of IL-10-deficient mice that develop disease that has some similarities to human IBD. One strain of mice is highly susceptible to gut inflammation, while the other is relatively resistant. The scientists then cross-mated mice from each strain and analyzed their hybrid descendants, which carried chromosomal DNA from both original strains.

By quantitating the severity of disease symptoms in the mice and correlating the symptoms with the inheritance of different chromosomal loci, the scientists identified loci that are linked to IBD severity in IL-10-deficient mice. The most significant of these is on chromosome 3. The version of this locus that was inherited from the highly IBD-susceptible strain exacerbated disease, affecting nearly all of the symptoms that were studied. Loci on other chromosomes, including, interestingly, versions of loci from the relatively IBD-resistant strain, also contributed to disease symptoms. Further experiments, in which various combinations of these loci were analyzed, showed that the genetic complexity of IBD arises not only from the multiple loci that control its severity, but also from the different types of effects caused by genetic interactions among these loci.

The complete sequence of the mouse genome is now being assembled, providing sequence information about genes in mice that are homologous to human genes; if the mouse genes on chromosome 3 that contribute to IBD severity can be identified, then it may be possible to identify similar genes which cause disease susceptibility in humans. This study emphasizes the complexity of molecular events leading to IL-10 deficiency-induced IBD in mice. The results provide new knowledge about the genetic underpinnings of IBD, but also emphasize the difficulties to be overcome in finding therapies for patients.

Improving Diagnostics for IBD Lesions: Until now it was not easy to delineate between the two types of colorectal pre-cancerous lesions, ordinary sporadic colorectal adenomas and cancers (SAC) and a type of colon neoplasm associated with IBD, flat inflammatory bowel disease dysplasia (IBDN). The treatments of choice for these two types of lesions are very different when they can be identified. SACs may be removed by a colonoscopy or a surgical procedure, whereas IBDNs may require removal of the entire colon.

In a recent study, NIDDK-supported researchers employed a sophisticated technology known as artificial neural networks (ANN) to distinguish between the two types of lesions. ANNs are mathematical computer models designed to mimic the mammalian brain. They are composed of a large number of processing elements known as "neurons" that are connected by "synapses" that store information. ANNs are unique in their ability to "learn" complex patterns by example. Once information is stored in the synapses, ANNs can apply it to analyze unknowns through pattern recognition.

For this study, researchers used samples of damaged tissue from patients who were diagnosed as having either SAC or IBDN. Gene expression profiling of the tissue generated the data needed to "train" the ANN. After these data were processed and stored in "synapses," the ANN was presented with information derived from 12 new SAC or IBDN patients. The ANN was able to correctly identify all 12 samples as being either SAC or IBDN. This novel system of analyzing data has given clinicians the tools needed to accurately classify SACs and IBDNs and to choose the optimal treatment for their patients. This will prevent SAC patients from unnecessary colonectomies and will ensure that patients with IBDN receive the treatment they require.

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POINTING THE WAY TO ACUTE PANCREATITIS THERAPIES

One of the many functions of the pancreas is to produce the enzymes necessary for digestion. Normally, digestive enzymes are synthesized in the pancreas in an inactive form called a zymogen. They then travel to the small intestine where they are activated and aid digestion by breaking down the fats, proteins, and carbohydrates in food.

Because activated digestive enzymes would start digesting the pancreas if given the opportunity, there are molecular safeguards in place to keep enzyme activation from occurring prematurely. The primary safeguard is that zymogens become activated when an inhibitory piece of protein is clipped off, and this clipping can normally only occur in the chemical conditions present in the small intestine. However, the safeguards sometimes break down, and disease results (see also "Story of Discovery: Genetic Insights into Pancreatitis and Pancreatic Cancer").

Acute pancreatitis is a complex disease that causes inflammation and destruction of pancreatic tissue. In the U.S. there are approximately 80,000 individuals affected each year. In acute pancreatitis, enzymes are activated prematurely in the pancreas and begin to "digest" it. If sufficient damage occurs, active enzymes are released into the bloodstream and transported to other major organs of the body, where they continue their destruction.

The digestive enzyme trypsin is known to be a key player in the events leading to pancreatitis. A recent study has determined that an enzyme called PI3K plays a role in the activation of trypsin. Researchers showed that premature trypsin activation can be reduced, and the severity of acute pancreatitis ameliorated, by inhibitors of PI3K. From this research, it is now clear that PI3K plays a crucial role in trypsin activation and the onset of acute pancreatitis. These studies point the way to the development of potential therapies that can halt this step in the cascade of events responsible for acute pancreatitis.

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A MOLECULAR PROFILE OF MOUSE STOMACH CELLS BEFORE AND AFTER *H. PYLORI* INFECTION

While the stomach has long been known for its role in food digestion, until recently the genes that are active in stomach cells have been elusive. This past year, scientists began a molecular characterization of the different kinds of cells in the stomach to learn which genes are important for stomach function. They also sought to discover genes that are turned on in response to infection with *Helicobacter pylori,* a bacterium linked to ulcers and stomach cancer. The scientists began with the parietal cell, a highly specialized acid-secreting cell of the stomach.

For cataloguing genes expressed (turned on) in the stomach, the choice of the parietal cell arose in part from biomedical considerations: scientists knew that parietal cells secrete acid, and diseases associated with stomach acid are common. Previous studies hinted that these cells may perform other important functions as well. There were also practical considerations: in order to survey genes that are specifically activated in a given type of cell, the researchers needed to be able to separate that cell type from other stomach cells. They were able to do just this for parietal cells by mixing mouse stomach tissue with special magnetic beads. These beads had been coated with a substance that sticks to particular molecules on the surface of parietal cells. The scientists then pulled the magnetic beads—and the attached parietal cells—out of the mixture with a magnet to separate them from the other stomach cells.

Using microarray technology, the researchers then scanned nearly 11,000 mouse genes and identified a set of genes expressed in parietal cells, but not in the other stomach cells. This set not only included genes known to be associated with parietal cell activities, such as acid secretion, but also revealed genes that may play roles in previously unappreciated aspects of parietal cell function, including the regulation of stem cell proliferation in the stomach. To see how parietal cells and other stomach cells react to *H. pylori* infection, the scientists compared the profile of expressed genes in stomach cells of mice before and after infection. While gene expression in the parietal cells remained stable, the other stomach cells commenced a flurry of genetic activity in response to the *H. pylori* infection. The cells turned on genes involved in immune system signaling, genes that help respond to the presence of bacterial molecules, genes that aid in the repair of damaged tissue, and many other genes.

This functional genomics approach to the study of the stomach provides important information not only about normal stomach cell functions, but also about how stomach cells respond to infection. The scientists found a set of genes that were consistently enriched in parietal cells under a variety of conditions. This database of genes provides a molecular signature of parietal cells that will serve as a resource for studying these cells in different disease states and for evaluating how the cells react to different medicines. By identifying the non-parietal cells of the stomach as key responders to *H. pylori* in mice, and by illuminating the repertoire of genes activated in response to this bacterium, the scientists have also opened new avenues of research into this potentially serious infection.

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ONGOING AND NEWLY LAUNCHED NIDDK EFFORTS IN DIGESTIVE DISEASES AND NUTRITION

The NIDDK is currently addressing numerous basic and clinical research challenges and opportunities in order to advance knowledge and therapies for digestive diseases. For example, the NIDDK is intensifying its efforts to combat obesity as a serious health problem and as a risk factor for type 2 diabetes. The Look AHEAD (Action for Health in Diabetes) multi-center clinical trial is under way and has reached approximately the midpoint of its recruitment goal of 5,000 individuals. This long-term clinical trial is designed to answer two major questions. First, do interventions designed to produce voluntary sustained weight loss in obese people with type 2 diabetes improve health, particularly with respect to cardiovascular outcomes? Second, how do these interventions compare with treating obesity-related conditions without weight loss? Results of this study will help guide future patient care.

As noted previously, the NIDDK and other NIH Institutes are co-sponsoring an initiative, "Environmental Approaches to the Prevention of Obesity." Through this research solicitation, the NIH is establishing studies of preventive approaches targeting environmental factors that contribute to inappropriate weight gain in children, adolescents, and adults. Another facet of research on obesity will be to promote clinical research on bariatric surgery, currently used in treating extreme obesity, to better understand the impact of bariatric surgical procedures on obesity and related co-morbid conditions. At the same time, a strong foundation of basic and pre-clinical research is critical for understanding and developing new preventive or interventional therapies for obesity. The continued elucidation of the molecular factors and pathways responsible for appetite regulation, metabolism, and energy storage offers rich prospects for the development of new drugs that will promote safe and effective long-term weight loss.

Through a recent initiative, the NIDDK hopes to support more research to provide new insights into intestinal failure, short gut syndrome, and small bowel transplantation. To strengthen research in inflammatory bowel disease (IBD), the NIDDK will accelerate efforts to identify additional genes or genomic regions associated with increased risk of IBD or with clinical manifestations of IBD through a newly established IBD Genetics Research Consortium.

Research will also be bolstered on hepatitis C virology, epidemiology, natural history, prevention, and therapy—potentially including research on therapy in children. Recently, the Institute launched a new effort to elucidate the clinical features and pathogenesis of drug- and toxin-induced liver injury, common causes of acute liver disease, morbidity, and mortality. As already noted, the NIDDK is continuing enrollment of patients in the multi-center Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) clinical trial. This trial is designed to investigate whether long-term treatment of hepatitis C with peginterferon-alfa will prevent progression of liver disease in patients for whom prior treatment did not eliminate the virus. Enrollment has also begun for the Virahep-C study, which will examine resistance to antiviral therapy in patients with chronic hepatitis C, specifically focusing on African Americans, among whom such viral resistance is common. New clinical research efforts are also now beginning on two other liver diseases, non-alcoholic steatohepatitis and biliary atresia.

Finally, the NIDDK has launched a significant new effort in liver transplantation. Liver transplantation is the only cure for people with end-stage liver disease. Yet, over 17,000 Americans are awaiting transplantation due to the shortage of cadaveric livers available for transplant. The NIDDK, in collaboration with the Federal Health Resources and Service Administration (HRSA) and the American Society of Transplant Surgeons, recently launched the Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL) to carefully evaluate the risks and patient outcomes for donors and patients undergoing this procedure. This procedure enables a patient to receive part of a liver from a living donor, rather than a cadaver; because of the liver's amazing ability to regenerate, the donor's liver eventually regrows to full size, and the transplanted portion also grows in the recipient. The procedure is gaining widespread use, but risks to potential donors need to be comprehensively assessed and uniform criteria for matching donors and recipients are needed. The A2ALL study should provide valuable information to both patients and physicians.

VISION STATEMENT

Rena Wing, Ph.D.

The Diabetes Prevention Program: A Successful Approach to Lifestyle Intervention

Dr. Rena Wing is Professor of Psychiatry and Human Behavior at Brown Medical School—The Miriam Hospital, in Providence, Rhode Island. She was the coordinator of the intensive lifestyle intervention arm of the recently completed Diabetes Prevention Program clinical trial, sponsored by the NIDDK. Dr. Wing's research interests include the development of behavioral treatments for obesity, particularly as it relates to type 2 diabetes. Her research team currently is participating in the Look AHEAD (Action for Health in Diabetes) project, the first major nationwide study to look at the long-term health effects of weight loss in men and women who are overweight and have type 2 diabetes. Dr. Wing is the Chair of the LookAHEAD study. She also is participating in the follow-up study to the Diabetes Prevention Program, the Diabetes Prevention Program Outcomes Study. Both of these studies are sponsored by the NIDDK.

At the May 2002 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council, Dr. Wing presented an overview of the intensive lifestyle intervention arm of the Diabetes Prevention Program (DPP) clinical trial. This aspect of the study yielded remarkable findings about how diet combined with physical activity can reduce the risk of developing type 2 diabetes in individuals who are at high risk for the disease. Trial participants lost an average of 5-to-7 percent of their body weight and performed at least 150 minutes of physical activity per week. These changes reduced their risk of developing diabetes by 58 percent over an average 2.8 year follow-up period. Rigorous, systematic, and controlled testing of the lifestyle hypothesis through the DPP provided definitive proof that prevention of type 2 diabetes is possible through positive lifestyle changes. Dr. Wing emphasized that perhaps the most important factor contributing to the success of the intensive lifestyle intervention was a history of several decades of investment in programmatic basic behavioral intervention research. It was this strong research foundation that enabled DPP investigators to design an effective weight loss program.

Dr. Rena Wing

According to Dr. Wing, the DPP is an example of an extremely effective behavioral intervention. This intervention was based on prior observational studies suggesting that modest changes in weight or physical activity might reduce the risk of developing type 2 diabetes. Clinical trial data from other studies also suggested that modest changes in weight and physical activity could be produced.

Biobehavioral Arm of the DPP

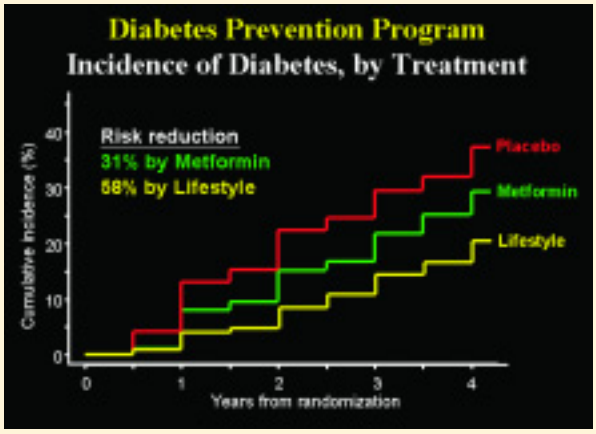
Based on previous behavioral studies, to achieve the weight loss goal, DPP participants were instructed to reduce their dietary fat intake to less than 25 percent of total calories and they were given a calorie intake goal of 1,200 to 2,000 calories daily depending on their initial body weight.

Previous studies also showed that the combination of diet and exercise was particularly effective for long-term maintenance of weight loss. Therefore, the DPP investigators viewed physical activity as important for achieving and maintaining weight loss. The strategy for achieving the physical activity goal was to stress brisk walking and other activities of similar intensity, such as aerobic dance or bicycling. Prior studies also suggested that even short bouts of exercise—as little as 10 minutes—could be very helpful in promoting weight loss and improving fitness. This concept was employed in the DPP, in which participants were encouraged to exercise at least 3 days per week, with at least 10 minutes per session, for a total of at least 150 minutes per week. All of the DPP clinical centers were required to offer two supervised exercise sessions per week to help participants achieve the activity goal.

A key feature of the lifestyle component of the DPP was the use of frequent contact and ongoing intervention. Research has shown that positive reinforcers, contingency contracts, and, in particular, frequent and intensive contact, can help individuals maintain their behavior changes. Thus, in the DPP, all participants were assigned a case manager who worked with them in a one-to-one manner on a weekly to monthly basis throughout the trial. In addition, DPP centers offered three group courses per year during the maintenance phase, usually with courses offered on diet, exercise, and behavior. Three to four motivational campaigns were conducted each year in which participants competed among others in their center or across DPP study centers to see who could achieve the weight loss or exercise goals.

Applicability of DPP Results

In addition to reducing the development of diabetes by 58 percent overall, the DPP intervention yielded consistent results across diverse subgroups. Both men and women and all ethnic/racial groups benefited from the lifestyle intervention. It is important to realize that there are an estimated 16 million Americans with "pre-diabetes" who resemble participants in the DPP with respect to their risk



Cumulative incidence of diabetes according to the Diabetes Prevention Program (DPP) study group.

for developing type 2 diabetes. If they adopt lifestyle changes similar to those in the DPP, their disease risk might be reduced by over 50 percent.

Surprisingly, the lifestyle intervention worked best in older individuals, those over age 60. Contrary to the DPP investigators' concern that many participants over 60 might not be compliant with the lifestyle intervention, this age group actually demonstrated the best adherence to the weight loss and physical activity intervention goals. This result is significant because type 2 diabetes is considerably more prevalent in the over 60 age group.

General Implementation of Lifestyle Intervention

With completion of the DPP, Dr. Wing is turning to the future and to the general implementation of the intensive lifestyle intervention to prevent type 2 diabetes. How is the DPP helping shape the future behavioral research agenda? Dr. Wing notes that the DPP suggests certain areas of particular importance for future research. The one she believes is the highest priority is research on how we can help people maintain their behavior change. "With the most intensive, best program we could develop, our lifestyle participants achieved their best weight losses at 6 months, maintained them through a year, and then gradually regained," she says. "They regained even though we were giving them intensive contact, and were trying everything we could do. Yet, they still

regained. This is the problem we have in the field. I think this is the number one priority for our research, that is, to understand how we can help individuals maintain various types of behavior change and thereby maintain their weight loss long-term."

Dr. Wing believes there are three approaches to the maintenance of behavior change on which research should be encouraged. One is to study people who have successfully changed their behavior long-term. "We need to understand how they do it—how they are able to succeed," she says. A second approach is to understand more fully why maintenance is so difficult. "What happens at six months or a year that makes people start to regain? Is it a physiological change or is it a behavioral problem that leads them to regain?" Lastly, Dr. Wing believes there is a need to encourage investigators to develop innovative strategies for long-term maintenance of behavior change. She notes that: "What we're doing isn't working as well as it should be, and I think we need to encourage creativity and innovative approaches."

Some of Dr. Wing's own research on the maintenance of weight loss indicates that low-calorie diets and, more importantly, low-fat diets are critical to maintaining weight loss long-term. Also important is a relatively high level of physical activity—up to 2,800 calories per week, the equivalent of walking four miles a day, 7 days a week. Dr. Wing stresses, however, that new and innovative approaches to improving long-term maintenance of weight loss must be developed.

Dr. Wing also believes that, to apply the results of the DPP to the general population, it is important to disseminate the DPP message effectively. She is looking at the Internet as one means of disseminating treatments to a large number of people, observing that, "it's increasingly popular, it has no geographic limitations, is convenient to people, and is interactive between a therapist and a participant. There are also opportunities for support among participants." Offering both educational materials and a structured behavioral program on the Internet, Dr. Wing and her colleague Dr. Tate recently reported that, at both the three-month and the six-month point, the Internet behavior therapy program was far more effective than the Internet educational program in changing participants' body weight. The researchers were able to produce a weight loss of about nine pounds through the Internet behavioral program. They are now working to develop an even more effective behavioral program that includes initial weight loss and maintenance of weight loss. "Again, we need to be applying behavioral principles," Dr. Wing says, "carefully looking at how to change the cues and the consequences in the environment so as to maintain the behavior change. I think we really need to be studying how to intervene on the whole environment, particularly the home, where most meals are eaten."

On the impact of the DPP, Dr. Wing says, "I think we have shown that we can conduct studies looking at how behavior change affects health outcomes. I think the DPP has opened the door for further study of the impact of participation in weight loss programs on other health outcomes. I'm thrilled that the NIH has moved to initiate the Look AHEAD study. This is a study examining the long-term health impact of participation in weight loss intervention on cardiovascular morbidity and mortality in 5,000 obese individuals with type 2 diabetes. The study will also be looking at many other health consequences of weight loss, including diabetes complications, changes in cardiovascular risk factors, hospitalizations, and the cost and cost-effectiveness of this lifestyle intervention."

Future Directions in Behavioral Research

Dr. Wing has identified several major topics for future behavioral research as it relates to improving health. These include small-scale basic behavioral studies focused on improving maintenance of behavior change, disseminating the discovery of new treatments, and interventions to change the environment and thereby change behavior. "With knowledge gained from these studies," she says, "investigations can be conducted to examine how lifestyle change affects health outcomes."

WIN: The Weight-Control Information Network

When the Department of Health and Human Services (HHS) released its report entitled, *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity,* HHS Secretary Tommy G. Thompson warned that, "Overweight and obesity are among the most pressing new health challenges we face today." It has been estimated that 300,000 deaths each year in the U.S. are associated with obesity and overweight and the numbers are increasing. Obesity is an epidemic that must be brought under control. The WIN is an NIDDK service directed at reaching this goal.

Established in 1994, the NIDDK's Weight-control Information Network (WIN) is a national information service that produces and provides science-based information on obesity, physical activity, weight control, and nutrition to health professionals, people who are overweight or obese, consumers, the media, and Congress. The WIN has reached out to all age groups and diverse ethnic and racial groups with its materials.

The WIN is publishing a new series of booklets, *Healthy Eating and Physical Activity Across Your Lifespan,* to encourage better eating and physical activity habits. The series contains four booklets entitled, *Tips for Parents, Tips for Adults, Tips for Older Adults,* and the upcoming, *Tips for Pregnant Women*. These booklets are published in both English and Spanish language versions.

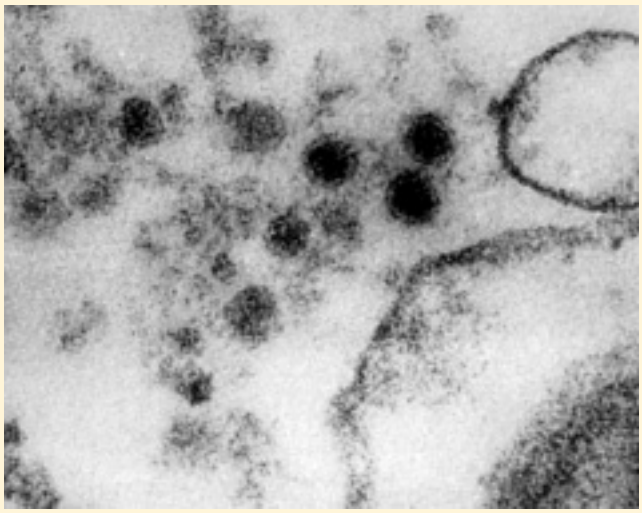
The WIN's "Sisters Together: Move More, Eat Better" initiative encourages African-American women 18 and older, who are disproportionately affected by overweight and obesity, to maintain a healthy weight by increasing physical activity and eating healthier food. A pilot program of "Sisters Together" and its materials was held in Boston in the mid-late 1990's. A planning guide and kit based on the "Sisters Together: Move More, Eat Better" pilot program are available to provide step-by-step instructions for planning, promoting, implementing and evaluating community health awareness programs to prevent African-American women from becoming overweight. "Sisters Together" has also produced other informational brochures.

The WIN is also coordinating with the Institute's Look AHEAD (Action for Health in Diabetes) clinical trial. The Look AHEAD trial is a large scale (anticipated 5,000 participants) multi-center trial that will examine whether a lifestyle intervention designed to achieve voluntary long-term weight loss will improve cardiovascular and other outcomes in obese individuals with type 2 diabetes. The WIN will provide information on physical activity and healthy eating to trial participants.

Hepatitis C Consensus Conference

The NIH's Consensus Development Program brings together scientific experts to consider current evidence and produce consensus statements addressing controversial issues in medicine. NIH Consensus Statements are disseminated widely to healthcare practitioners, healthcare policymakers, patients, the general public, and the media, and serve as a valuable resource to these groups when they make decisions that impact health.

The NIH convened its original Consensus Development Conference on Management of Hepatitis C in March 1997. Because knowledge of hepatitis C has dramatically increased in the past 5 years, a June 2002 conference was convened to revise and reissue the original 1997 Consensus Panel statement. The NIDDK and the NIH's Office of Medical Application of Research (OMAR) were the primary sponsors.



An electron micrograph of Hepatitis C virus particles. Infection with the hepatitis C virus is the most common reason for liver transplantation in the U.S. Photo: Dr. Jake Liang, NIDDK.

The hepatitis C virus (HCV) is one of the most important known causes of chronic liver disease in the U.S. It is a common cause of cirrhosis and hepatocellular carcinoma (HCC, liver cancer), and it is the most common reason for liver transplantation. An estimated 4 million Americans have antibodies to HCV, indicating ongoing or previous infection with the virus. Chronic HCV infection can produce a wide spectrum of outcomes—from little or no liver damage to development of cirrhosis and end-stage liver disease. This wide variability in outcomes makes it particularly challenging for healthcare practitioners deciding how best to diagnose and treat the disease. In such instances, consulting a consensus statement may help them to make informed decisions.

During the first portion of the conference, experts presented the latest hepatitis C research findings to an independent, non-Federal Consensus Development Panel. The panel also considered systematic literature reviews and analyses of controversial hepatitis C topics, presented by the Johns Hopkins University Evidence-Based Practice Center. These included: (1) the role of screening for hepatocellular carcinoma, (2) the role of liver biopsy, and (3) the optimal therapeutic regimens for hepatitis C. After carefully weighing the scientific evidence, the panel drafted a consensus statement targeted at practicing physicians, health care workers, and the general public. On the final day of the conference, the panel chairperson read the draft statement to the audience and invited questions and comments.

The statement provides detailed information and/or recommendations on six major questions:

1. What is the natural history of hepatitis C?
In this section, the authors consider known features of the hepatitis C virus (HCV), the epidemiology of hepatitis C infection, characteristics of both acute and chronic infection, and extrahepatic (or outside the liver) manifestations of hepatitis C infection.

2. What is the most appropriate approach to diagnose and monitor patients?
Here, the authors discuss a variety of possible tests to detect or imply hepatitis C infection, including tests that detect antibodies to HCV, HCV RNA assays, testing for liver enzyme levels suggestive of HCV infection, noninvasive liver scarring tests, liver biopsy, and screening for two diseases commonly associated with HCV, namely hepatocellular carcinoma and HIV/AIDS.

3. What is the most effective therapy for hepatitis C?
The authors discuss improvements in therapy since the original 1997 consensus conference on hepatitis C, including combination therapy with ribavirin and the introduction of pegylated interferons. They describe pros and cons of using these therapies in different patient populations as well as characteristics of patients and of different hepatitis C viral genotypes that influence treatment success. Information on re-treatment of patients, adherence to therapy regimens, and side effects is also included.

4. Which patients with hepatitis C should be treated?
Because of the high cost, variable risk of developing serious liver damage, and complications possible with antiviral therapy, not all HCV-infected patients are recommended for treatment. The authors discuss treatment options for differing liver disease severity (as indicated by liver enzyme levels), recurrence after liver transplantation, HCV-infected children, acute HCV infection, active injection drug users, alcohol abusers, and HIV co-infected individuals.

5. What recommendations can be made to patients to prevent transmission of hepatitis C?
Because injection drug use accounts for two-thirds of all new HCV infections in the U.S., the authors discuss options for reversing this trend. Other risk factors for infection that may be controllable include sexual intercourse with an infected individual, exposure to infected blood or blood products, needlestick injuries, body piercing and tattooing, and transmission to a baby from an infected mother. Suggestions for preventing transmission are made for each situation.

6. What are the most important areas for future research?
The authors identify an extensive list of important research areas, including areas of basic science, clinical research, clinical trials, educational programs, infrastructural support, and statistical research.

The Consensus Development Panel's draft statement was posted online on Wednesday, June 12, 2002. The final statement is now available at this URL: http://consensus.nih.gov/cons/116/ 116cdc_intro.htm. The NIH Consensus Development Program's website is located at: http://consensus.nih.gov/.

This statement reflects the panel's assessment of medical knowledge on management of hepatitis C as of June 2002. Even as the statement is read and used, newer knowledge is constantly accumulating through medical research.

PATIENT PROFILE

Rachel Hettich

Living with Crohn's Disease

Most teenage girls are concerned about gaining weight. Rachel Hettich wishes she had that privilege. At age eight, after undergoing a battery of tests—including a variety of blood tests and a colonoscopy—she was diagnosed with a severe case of Crohn's disease. Crohn's disease is an inflammatory bowel disease (IBD) that causes inflammation in the gastrointestinal tract (it can involve any site from the mouth to the anus).
"In third grade I began losing lots of weight and experiencing excruciating stomach pains that wouldn't go away," says 18-year-old Rachel, a high school senior who, because of Crohn's disease, misses more days of school than she attends.
At the time of her diagnosis, neither Rachel nor her family had any knowledge or understanding of the disease, or of the devastating impact it would exert on all of them. Unfortunately, it wouldn't take long for them to learn.

In Crohn's disease, the immune system attacks cells in the intestines. This causes severe abdominal pain, fever, ulcers and other conditions that can become disabling, including diarrhea and rectal bleeding—all of which Rachel began experiencing early on. By age 14, she had had her gall bladder removed and part of her large intestine taken out. She continues to undergo a number of painful treatments, including gastric-nasal feeding tubes and intravenous feeding methods that automatically exclude her from such normal teenage activities as going out for pizza or sleeping at the homes of friends. "I've tried to adapt as best I can," says this courageous teen, who, despite her Crohn's disease, volunteers to help others. "But it's extremely difficult for me to participate in lots of stuff. Sometimes I feel really separate from everyone else."

Despite suffering from a very severe case of Crohn's disease, 18-year-old Rachel Hettich is a straight "A" student, plays an active role in her community, and is planning her college career. Still, she looks forward to medical breakthroughs that "may not only treat the symptoms...but perhaps even cure the disease." The NIDDK supports a wide variety of research on Crohn's and other IBDs, with the hope of one day finding a cure for these debilitating diseases.

Complications of Crohn's disease include blockage of the intestines, as well as sores, or ulcers that tunnel through affected areas into surrounding tissue such as the bladder or skin. Arthritis, skin problems, inflammation in the eyes or mouth, kidney stones or gallstones, or liver disease also may occur. Currently, there is no cure for Crohn's, and the medications and treatments now available simply treat symptoms, but not the root cause of the disease, which remains elusive.

RACHEL HETTICH

To help the estimated 1 million people in the U.S. who suffer from Crohn's and other IBDs, the NIDDK supports a wide variety of research, with the hope of one day finding a cure for these disabling inflammatory bowel diseases.

NIDDK Crohn's/IBD Research Efforts

- *Funding of a new Inflammatory Bowel Disease Genetics Research Consortium to identify genes or genomic regions associated with increased risk of developing IBD. The consortium also will investigate age of onset, response to therapy, and susceptibility to environmental risk factors, as well as increase molecular understanding of IBD to open new avenues of research towards the development of novel therapies and new diagnostic methods.*
- *Continued funding of NIDDK's Digestive Diseases Research Centers, including support for centers that focus on IBD research and research training.*
- *Conducting workshops to discuss endpoints for clinical research in inflammatory bowel diseases.*
- *Supporting studies on progenitor cells of the gut and research relating to potential autoimmune and microbial influences in the development of IBD.*
- *Encouraging basic and clinical research into intestinal failure, "short gut syndrome," and intestinal transplantation.*

Living with the "Dark Beast"

According to Rachel's father, Bob Hettich, there is no evidence that anyone in either the immediate or extended biological family has ever suffered from Crohn's. "When Rachel was diagnosed 10 years ago, we had no idea what Crohn's disease was," he says. Today, the Hettich family refers to Crohn's as the "dark beast" and is committed to educating others about it. "Crohn's is very poorly understood," adds Mr. Hettich. "Most people don't realize how severe and serious this disease can be. Friends and relatives often say to us, 'Oh, we know someone with Crohn's and they didn't have much of a problem with it.'"

It's true that Crohn's affects people differently. Unfortunately, Rachel suffers from an extremely severe case. As a result, she has undergone every treatment possible over the years, including drugs, nutritional supplements, surgery, or at times a combination of all three. These treatments, however, only help control inflammation, correct nutritional deficiencies, and relieve symptoms like abdominal pain, diarrhea and rectal bleeding—and they come with their own sets of side effects and complications.

Anti-inflammatory drugs, for example, are often the first line of defense for people with Crohn's. However, over time, the body sometimes builds up resistance to these medications. People also can have unique reactions to medications. The medications Rachel takes for her Crohn's appear to result in "weird side effects," she says. "I've had bald spots on the back of my head the size of quarters," says Rachel, who thinks they were the result of one of her medications. "Also, when I perspire, it sometimes causes stains on my clothes that resemble bleach stains." Both of these apparent side effects are temporary, she says.

Many of the anti-inflammatory drugs taken by people with Crohn's also suppress the immune system, making them more susceptible to infection and other illnesses. "When I'm on these medications, I'll catch everything that's going around," says Rachel. "I can't tell if I'm suffering an ordinary stomach virus or an intestinal flare-up as a result of having Crohn's."

RACHEL HETTICH

To "rest" her intestines from these flare-ups, or because at times her intestines cannot absorb enough nutrition from food, Rachel is intravenously fed a special high-calorie liquid formula, called Total Parenteral Nutrition (TPN). Her family has been trained to place the formula into an IV bag. They then insert plastic lines from the bag into an IV line that has been surgically placed in either Rachel's chest or arms for what often amounts to a 10-hour infusion. "I did this for several years when I was in middle school," says Rachel. "Now that my anti-inflammatory medication is no longer working, I'll probably be doing TPN for six months." This will complicate Rachel's life immensely. "The treatment gives me more nutrition, and I have more energy," says Rachel, "but I can't stay out real late or have sleepovers at my friends' houses, and I miss lots of days from school." Even showering is problematic. "I have to put Saran wrap over the insertion, so it doesn't get wet," she adds.

Handling Life with IBD with Humor

In addition to having to endure all of the above, Rachel says that one of the worst things about living with Crohn's is its unpredictability. Intestinal flare-ups can occur at any time. Not only are they extremely painful for Rachel, but as a family the Hettichs are often left homebound until these episodes—which often can go on for weeks, sometimes months—subside.

"My family and I learned that if we did not maintain a positive, even somewhat humorous outlook on life, we would never survive," says Rachel. Over the years, therefore, the Hettich family developed its own version of the "top five ways that you know you have an inflammatory bowel disease." They are:

1. "Having a fever of 101.5 degrees is considered low grade."
2. "You consider the nurses at your doctor's office better friends than your school mates."
3. "Your school measures your absences in weeks rather than days."
4. "You plan all your activities and social life according to how many days it has been since your last infusion of an anti-inflammatory drug."
5. "You seriously consider putting a TV and mini-refrigerator in your bathroom."

Despite her chronic and severe disability, Rachel is a straight "A" student. "My guidance counselor and teachers are amazed at how well I keep up with my work, given the fact that I'm absent from school nearly half the time," she says. She plays an active role in her community by volunteering at a local animal shelter, working with Alzheimer's patients at a retirement home, and serving on the youth council at her church. And she has dreams for her future, as well. After graduating from high school Rachel plans to attend the University of Tennessee and major in anthropology. For all of these reasons, Rachel has been recognized as a "Local Hero" by the Crohn's and Colitis Foundation of America.

"I look forward to the future with great anticipation of medical breakthroughs that may not only treat the symptoms of Crohn's and other IBDs, but perhaps even cure the disease," Rachel says, with much hope of leading a more normal life as an adult.

(For medical information on IBD and ulcerative colitis, see

http://www.niddk.nih.gov/health/digest/pubs/crohns/crohns.htm

http://www.niddk.nih.gov/health/digest/pubs/colitis/colitis.htm)

STORY OF DISCOVERY

Genetic Insights into Pancreatitis and Pancreatic Cancer

When the pancreas produces enzymes to digest food, why don't those enzymes also digest the pancreas? Sometimes, they do—and with painful and potentially fatal consequences—as in the case of the disease hereditary pancreatitis. Several years ago, researchers discovered a mutation that abolishes one of the body's key safeguards against destruction of the pancreas by the very digestive enzymes it manufactures. This scientific breakthrough marked the beginning of a series of genetic discoveries that are providing new insights into hereditary pancreatitis, pancreatitis that arises for unknown reasons (idiopathic), and pancreatic cancer.

Patients with pancreatitis usually experience severe pain. As the pancreas becomes progressively injured and inflamed, in part as a result of infiltrating inflammatory cells, it no longer secretes enough enzymes into the small intestine for digesting food. Eventually, the pancreas cells that produce the vital hormone insulin can become damaged as well, leading to diabetes. Treatments exist to help manage the pain and digestive enzyme deficiency, but currently there are no cures or preventative therapies. Patients suffering long-term from pancreatitis are also at dramatically increased risk for pancreatic cancer. One of the most devastating of all malignancies, pancreatic cancer nearly always kills within a year of diagnosis, and often within six months.

Clinicians had long associated pancreatitis with alcoholism. While excessive alcohol consumption clearly plays a role in many pancreatitis cases, researchers recognized a hereditary form of pancreatitis as early as 1952. An attempt to find a hereditary pancreatitis gene in the 1970s, however, was unsuccessful. The identification of genes associated with pancreatitis awaited the advent of modern molecular and genetic technology.

In 1996, scientists found the first gene linked to a form of pancreatitis called hereditary pancreatitis, which generally strikes in childhood. This gene encodes the protein cationic trypsinogen, an inactive precursor form of the digestive enzyme trypsin. Trypsin helps digest proteins from food essentially by chopping them into pieces. To avoid digestion of the pancreas, trypsinogen normally does not become activated within the pancreas to form trypsin. If it does, the body has what scientists call a "fail-safe" line of defense: for the greater good, the prematurely-active trypsin commits molecular *hara-kiri*, slashing itself. Many people with hereditary pancreatitis have a particular mutation in the trypsinogen gene that disables this defense mechanism. Scientists have also identified other mutations in this gene. The continued identification of mutations that confer susceptibility to hereditary pancreatitis is useful for the design of diagnostic tests.

Among people whose genetic make-up predisposes them to hereditary pancreatitis, about one in five will not actually develop the disease. Surprisingly, researchers have even found pairs of identical twins in which one twin developed hereditary pancreatitis while the other did not, even though identical twins share the same chromosomal gene sequences and most types of environmental factors. These findings clearly suggest that other types of genetic factors (such as "epigenetic factors"), environmental factors, or chance events may also play a part in the development of hereditary pancreatitis. Scientists believe

STORY OF DISCOVERY

that pancreatitis results from a long chain of events activating different enzymes. In addition to known genetic influences, the disease is also precipitated by external factors such as food and alcohol. Gaining a better understanding of the complex interactions between different types of genetic and environmental factors will be a major challenge for future investigations.

Knowledge of genetic influences in hereditary pancreatitis will also help scientists assess environmental risk factors for pancreatic cancer, because people with hereditary pancreatitis are at increased risk for this cancer. Scientists recently found that pancreatic cancer develops an alarming 20 years earlier in hereditary pancreatitis patients who smoke. It is not yet clear whether smoking also has this effect in people who don't have hereditary pancreatitis.

Several years after the discovery that mutations in the trypsinogen gene cause hereditary pancreatitis, scientists identified mutations in a different gene that are associated with idiopathic pancreatitis. This gene encodes a protein called SPINK1, which normally helps protect the pancreas by inhibiting the digestive functions of prematurely-activated trypsin. However, the effects of *SPINK1* mutations are subtle, and dissecting the nature of their association with pancreatitis remains challenging.

The identification of another gene associated with idiopathic pancreatitis had its origins in research on a seemingly unrelated disease, cystic fibrosis, which is caused by mutations in the *CFTR* gene. *CFTR* function is important in many organs, including the pancreas, and scientists recently found that many idiopathic pancreatitis patients harbor a particular pattern of *CFTR* mutations.

With the discovery in 1996 of the link between trypsinogen and hereditary pancreatitis and the findings in 1998 and 2000 that *CFTR* and *SPINK1* are associated with idiopathic pancreatitis, it would seem that another major genetic discovery in pancreatic disease might arrive in 2002. One did. Investigators have now brought to light the first genetic defect specific to pancreatic cancer, pinpointing a region on chromosome 4 as likely to contain a pancreatic cancer susceptibility gene. The future identification of this gene will enhance our understanding of pancreatic cancer and provide a potential tool for early diagnosis.

Screening patients for genetic mutations can have many health benefits, such as alerting patients at risk to seek early medical intervention. However, the results of a genetic test may also influence reproductive choices and the ability to obtain health or life insurance. Deeply concerned about the ethical and social implications of genetic testing for patients and their families, investigators recently surveyed individuals participating in a hereditary pancreatitis genetic research study. The most common reasons the participants gave for joining the study were to help family members and future generations and to obtain genetic testing. The major concern they expressed was the fear of insurance discrimination. The most common reasons for sharing their results were to provide medical information to their families and to improve their own medical care.

These achievements in research on pancreatitis and pancreatic cancer not only illuminate genetic influences underlying these diseases, but also will facilitate research on environmental factors that contribute to disease in genetically-susceptible individuals. Already, the identification of hereditary pancreatitis mutations has led to the development of gene-based methods to evaluate a person's risk for this disease. Further understanding of genetic factors associated with different forms of pancreatitis and pancreatic cancer will undoubtedly lead to new strategies for diagnosis, treatment, and prevention.

VISION STATEMENT

Jeffrey Gordon, M.D.

A Vision of the Future in Digestive Diseases Research: Life in a Microbial World

Dr. Jeffrey Gordon is Professor and Head of the Department of Molecular Biology and Pharmacology at the Washington University School of Medicine in St. Louis. He joined the faculty at Washington University in 1981, after completing his clinical training in internal medicine and gastroenterology and after serving as a research associate in the Laboratory of Biochemistry at the National Cancer Institute. He has remained at Washington University for his entire professional career. In 2001, he was elected to the prestigious National Academy of Sciences. When asked to present his future vision to the NIDDK Advisory Council in September 2002, Dr. Gordon shared his enthusiasm for an emerging field within digestive diseases research that he finds inspiring: the study of "something that is with us all of our lives—our affiliated microbial communities."

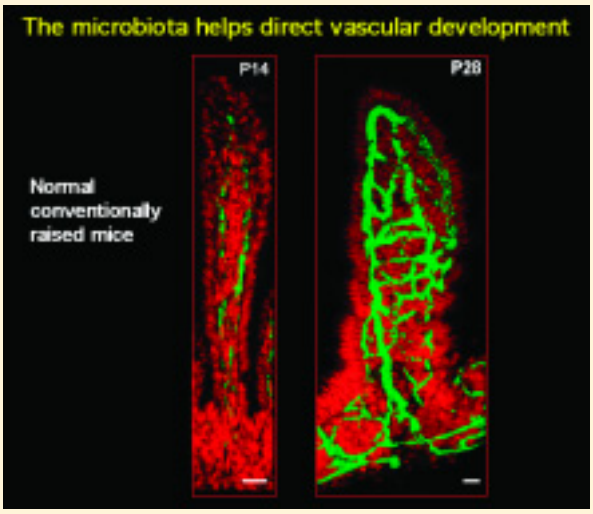
Dr. Jeffrey Gordon

A Transcendent View of Our Genes, Development, and Health

"Beginning at the moment of our birth, we become colonized by a remarkably complex, dynamic, and abundant society of microorganisms," Dr. Gordon explained. In fact, in our intestines we play host to 500 to 1,000 species of bacteria. Dr. Gordon proposed a comprehensive genetic view of ourselves as a life-form that encompasses not only our own genome, but also the "microbiome"—the collective genomes of all of our affiliated microbial partners. We currently know very little about how components of these microbial communities (microbiota) influence our post-natal development and adult physiology—but they do, as scientists like Dr. Gordon are discovering—and in extraordinary and surprising ways. Dr. Gordon depicts these microorganisms as "master physiologic chemists" that, through co-evolution with humans, have developed "very clever chemical strategies for regulating our gene expression (influencing whether genes are active or not) in ways that benefit both them and us." Dr. Gordon's vision of the future of research includes identifying the microbial genes and gene products that modulate the expression of our genes, and determining which of our genes are affected. Additionally, interactions between normal gut bacteria and their hosts may predispose susceptible individuals to a range of diseases both within and outside of the gastrointestinal tract. "Inflammatory bowel disease is one often-cited example of how deranged interactions between indigenous microbes and us can lead to immunopathologic states," Dr. Gordon noted, but he added that other diseases, including irritable bowel syndrome, gastrointestinal cancer, and metabolic disorders such as obesity and diabetes may also arise in part through disruption of normal host-microbial interactions. Research on our intestinal microbiota should provide new molecular targets for drug development and new chemical entities for preventing and treating diseases.

Technologies for Studying the Microorganisms in Our Intestines

Because of the "almost unimaginable degree of complexity" of the interactions between gut microbes and their hosts—and among the microbes themselves—Dr. Gordon's laboratory devised a clever way to simplify these interactions for the purpose of experimental analysis. The scientists first raised mice under germ-free conditions so the animals had no intestinal microorganisms. Then, the scientists added back defined microbial populations to some of these mice, and evaluated the effects, comparing the newly-colonized animals with mice that were maintained in an entirely germ-free environment. As a model microbe, they chose *Bacteroides thetaiotaomicron (B. theta). B. theta* is a prominent member of the normal intestinal microbiota of both mice and humans, and critically for their experiments, *B. theta* can be readily grown in the laboratory and genetically manipulated—unlike many of the other microbes that reside in the gut. Further, Dr. Gordon pointed out, *B. theta* normally colonizes the gut during a critical phase of post-natal gut development, the suckling-weaning transition. This timing affords the scientists an opportunity to see how a component of the microbiota may influence intestinal maturation. To examine gene expression in different cellular components of the intestine, Dr. Gordon's laboratory has employed an advanced technique called laser capture microdissection, which enables them to isolate cells from precise areas of the intestine. Material can then be obtained from the harvested cells to analyze which genes are affected by the presence or absence of *B. theta,* or other gut microbes. His laboratory has used the power of DNA microarray technology and bioinformatic methods to obtain a comprehensive analysis of *in vivo* cellular responses to bacterial colonization.



The indigenous microorganisms (microbiota) in the gut help direct the development of the intestinal blood vessels (vascular system). The photo on the left shows a section of mouse intestine taken 14 days after birth; the vascular system is stained with green fluorescent dye. By the 28th day after birth, as shown in the photo on the right, a very elaborate intestinal vascular system has developed in conventionally-raised mice. This normal vascular developmental program is not completed in mice raised in a special germ-free environment.

Work of the "Master Physiologic Chemists" in the Gut—Influencing Intestinal Biology and Architecture

One of the intriguing lessons learned from the experiments of Dr. Gordon's laboratory is that *B. theta* and other components of the normal microbiota can fortify the mucosal barrier that lines the gut; this barrier prevents intestinal bacteria from escaping into other parts of the body. Moreover, although disease-causing microbes usually elicit an inflammatory response when they infect us, *B. theta* manages to colonize the gut without eliciting such a reaction. From their experiments in mice, Dr. Gordon's laboratory found that *B. theta* does not affect the expression of host genes that would be involved in an inflammatory response—an important feature for an organism that must establish and maintain a long-standing symbiotic

relationship with its host. A deeper understanding of how our indigenous microbes manage to live peacefully in the gut may provide clues as to why, in some circumstances, the immune system aberrantly mounts an inflammatory response to these microorganisms. Interestingly, research from Dr. Gordon's laboratory also revealed that *B. theta* regulates the expression of a host bactericidal protein, angiogenin-4. "In essence," Dr. Gordon said, "components of the microbiota are able to regulate expression of endogenous antibiotics and help define the microbial ecology of their host niche."

The microbiota additionally helps direct post-natal blood vessel development in the intestine. In mice, between about 2-to-4 weeks after birth, the system of tiny blood vessels (microvasculature) in the intestine becomes very elaborate, allowing for growth of the gut and efficient absorption of nutrients. Also during this time interval, components of the microbiota assemble and the composition, complexity and density of the intestinal bacterial community increases dramatically. In mice raised germ-free, the program of intestinal capillary development is arrested at an early stage. Strikingly, when the scientists retrieved gut microbes from a conventionally-raised animal and gave them to mice that had been raised germ-free, the formerly germ-free animals completed their program of blood vessel formation in just 10 days. Administering *B. theta* alone to mice raised germ-free also catalyzed completion of microvasculature development. They went on to show that microbial regulation of blood vessel formation is dependent upon signals that are processed by Paneth cells—a type of intestinal epithelial cell that is a key component of the gut's innate immune system. These findings illustrate the importance of considering features of post-natal mammalian development as manifestations of mutually beneficial collaborations with microbes.

Further Activities of Gut Microbes: The Microbiology of Human Nutrition and Obesity

Another service that components of the microbiota provide their host—in exchange for a place to live and a food supply—is help with processing and uptake of foodstuffs we eat. Dr. Gordon refers to the microbiota as a "multi-cellular symbiont that lives in harmony with us, and facilitates our nutrient processing and uptake." For example, we are not capable of digesting many of the plant polysaccharides that we eat—we don't have the necessary genes. We rely on enzymes manufactured by the bacteria in our intestines for this task. Dr. Gordon's group has recently finished sequencing the entire *B. theta* genome. The results show that this symbiont has a vast repertoire of genes encoding proteins that are able to capture undigested polysaccharides from gut lumen and break them down. It also has an elaborate system for sensing the luminal environment. This well-developed sensory apparatus probably gives it a competitive advantage so that it can become a predominant member of the densely populated intestinal ecosystem. Further, experiments involving *B. theta* colonization of the germ-free intestine showed that it can induce expression of host genes encoding proteins that facilitate absorption of sugars, and that help metabolize fats. As components of the microbiota mediate efficient extraction of nutrients—and associated calories—from food, they may be one determinant of whether their host has a predilection towards obesity. "Germ-free mice must consume 30 percent more chow in order to maintain their body weight compared to their conventionally-raised counterparts," explained Dr. Gordon. He suggested that the capacity to absorb nutrients may vary between individuals as a function of the composition of their microbiota. Thus, the microbiota may be one predisposing environmental factor for obesity." Dr. Gordon hypothesized that the intestinal bioreactor may be more efficient at extracting calories from the diet in obese compared to lean individuals.

VISION STATEMENT

The Future of Research on the Microbial World Within Us

We still know relatively little about the biodiversity within the human intestine—both in healthy individuals and those with diseases. Thus, Dr. Gordon stressed the importance of future research to enumerate the components of the intestinal microbiota. In addition to understanding the activities of the individual microbes, it will be important to learn how the components of the microbiota interact with one another to establish and maintain a microbial community. The knowledge emanating from such research should enable scientists to "explore hypotheses about whether changes in the composition of the microbiota are directly associated with a variety of diseases." Moreover, such knowledge would allow scientists to design and carry out experiments in which microorganisms are administered as potential therapeutic agents (referred to as probiotics). Dr. Gordon further stressed the importance of comparative microbial genomics to identify the genetic features that define the capacity for symbiosis (and distinguish symbionts from pathogens). He called for a "microbiome sequencing project," that would complement the sequencing of the human genome.

A "Transcendent View of a University"

In concluding the presentation of his view of the future of research, Dr. Gordon put forth a perspective about scientific interactions within research institutions. A problem such as the molecular foundations of gut symbiosis and its regulation of postnatal development and adult physiology demands that investigators cross many disciplines. "It is critical that students and their mentors, departments, and universities, together with funding agencies such as the NIH, learn to operate at a number of interfaces." Dr. Gordon described three such interfaces: the biological and physical-computational sciences, the biological and chemical sciences, and the biological and clinical sciences. If we can do this, Dr. Gordon said, "We will be able educate the next generation of leaders in our fields, and attack major problems related to human health."

PATIENT PROFILE

Chris Klug

Liver Transplant Gives Olympian More than Just a Shot at the Gold

For a world-class athlete like 30-year-old Chris Klug, the abbreviation "PSC" should signify "Professional Snowboarding Champion." But the American Olympian who won the bronze medal in the giant slalom event at the 2002 Games in Salt Lake City is well aware that PSC actually stands for "Primary Sclerosing Cholangitis," a rare and potentially deadly liver disease. Had it not been for the liver transplant Chris received in July of 2000, he may never have made it to the Olympics, let alone taken the bronze. "I realize what it's like to receive the gift of life and what it means to have a second chance," says Chris. "I intend to make the most of it, and to continue spreading the life-saving message of organ donation." Chris received a life-sustaining liver transplant only because a family he has never met decided to give the "gift of life" and allowed the liver to be taken from a loved one who had just died.

"Organ donors are heroes. I am here today because a family said 'yes' to a second chance for me to pursue my dreams. I'm forever grateful to the donor and to his or her family."

Chris waited a year-and-a-half before receiving a cadaveric liver for his transplant. "They tell me that 16 people die each day while on the transplant waiting list," says Chris. "I thought I might be one of them." But a new study, sponsored by the NIDDK, called the Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL), may point the way towards reducing the waiting time, as well as the risk of liver transplantation for patients like Chris and the thousands of others in need of a liver transplant.

Thirty-year-old Chris Klug won the bronze medal in the giant slalom event at the 2002 Olympic Games, less than two years after undergoing surgery to receive a liver transplant. "I just realize how lucky I am to be out here doing what I love to do—traveling the world on my snowboard." Photo: Tom Zikas Photography

Living with PSC

Chris' ordeal began long before he received his liver transplant. He was diagnosed with PSC at age 21 during a routine physical. It wasn't a diagnosis anyone would wish for, but the fact that it was diagnosed early probably saved Chris' life. Legendary Chicago Bears football running back Walter Payton, on the other hand, was not so fortunate. Payton died because PSC wasn't discovered until it was too late to treat it effectively.

CHRIS KLUG

In PSC, the bile ducts that drain bile from the liver become inflamed, scarred, and eventually blocked. When the ducts are completely blocked, bile builds up in the liver and damages liver cells, leading to scarring of the liver, cirrhosis and ultimately liver failure. Researchers do not yet know what causes PSC. Among the theories under investigation are the role of bacteria and viruses, and problems in the immune system. PSC is often associated with ulcerative colitis, a type of inflammatory bowel disease.

Prior to his diagnosis, Chris had no warning signs that anything might be wrong. "I had a routine physical just before the 1992 World Cup competition season, and some strange numbers came back from my blood tests," says Chris. Even after he was diagnosed, Chris says he felt like "a million bucks," and that he often wondered if "they had the right person" with respect to his diagnosis. Yet this is typical for PSC. It usually begins between the ages of 20 and 50 and more often affects men than women. A person can have the disease for years before he or she feels bad in any way. The usual first symptoms are itching, fatigue, jaundice, and episodes of chills and fevers.

"After I was diagnosed, there was always this huge unknown," says Chris. "I never really knew if common cold symptoms were something I should pay attention to or if they simply indicated a common cold. I sometimes freaked over nothing." By Spring of 2000, however, his disease began to affect the way he felt and his athletic performance. The PSC caused anemia, a decrease in the number of red blood cells, which are responsible for delivering oxygen to the body. "I tried to maintain my workouts," says Chris, "but I just didn't have the energy or oxygen capacity." Eventually, he also began having pains in his side over the liver "as if someone had jabbed me with a dagger." After having an endoscopic retrograde cholangiopancreatography, or ERCP, a procedure which enables physicians to visualize an outline of the gall bladder and bile ducts in the liver, Chris was informed that his liver was severely scarred and approaching irreversible liver failure, known as end-stage liver disease. "I was told it was time to get serious about finding a new liver, meaning a transplant," says Chris.

Waiting for a New Liver

For Chris, and for many other transplant candidates, the hardest part is waiting for an organ to become available. Chris was on the waiting list for about a year-and-a-half. "I wore a pager every minute of the day and carried a cell phone as a backup in anticipation of receiving a call informing me that a liver was available that matched my blood type and age," says Chris. Once again, Chris was fortunate. "When I finally got the call, I was relieved that the wait was over, but scared to death of the prospect of possibly not surviving the surgery." Not only did Chris survive the surgery, but a month after his transplant he was back in the gym doing rehabilitation therapy, and three months after that was back on the World Cup snowboarding circuit.

"They tell me that 16 people die each day while on the transplant waiting list," says Chris. "I thought I might be one of them."

Chris credits his extraordinary recovery from surgery to lots of prayers, a great team of doctors and nurses, a donor family that said "yes," a perfect donor match, and his physical and mental preparation. Chris says, "In essence I trained for the transplant, both mentally and physically." Today, Chris remains on daily doses of medication to keep his immune system from attacking and rejecting his transplanted liver as "foreign" tissue, medication he will need to take for the rest of his life. Chris says, "except for colds that seem to last forever," he doesn't experience any serious side effects from the medication. "I just realize how lucky I am to be out here doing what I love to do—traveling the world on my snowboard," he adds.

CHRIS KLUG

Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL)

Over the last 20 years, liver transplantation has become the standard of care and the only cure for end-stage liver disease. Now more than 4,000 transplants are performed yearly. However, there are at least 17,000 patients like Chris on the transplantation list awaiting cadaveric liver donations. As the waiting list has expanded, waiting time also has grown, resulting in an increase in the numbers of patients who die while waiting.

Living donor liver transplantation is an alternative to cadaveric transplantation. By providing valuable information on the outcomes of living donor liver transplantation, NIDDK's A2ALL will assist physicians, patients, and potential donors in making life-saving transplant decisions. Use of living donors helps to avoid the lengthening waiting period for cadaveric transplant, as well as greatly reduce the ischemic period, or the time between removing the organ from the donor and transplanting it into the patient. It also allows more time for evaluation of the donor, and changes the operation from an emergency into a scheduled procedure.

By helping physicians, patients, and potential donors make life-saving transplant decisions, the NIDDK's Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) has the potential for changing the face of liver transplantation.

The major issue related to living donor liver transplants is that it is a difficult and potentially dangerous operation for the donor. More than half of the liver must be removed to provide enough liver for the transplant candidate. Even in the best hands, death of the donor can occur and its estimated rate is 1 in 250 donor operations. Living donor liver transplantation also provides the recipient with a smaller portion of liver than would have been received with cadaveric transplantation. The A2ALL study will provide a scientific, balanced, and unbiased evaluation of living donor liver transplantation, both its risks and its benefits, and help to insure optimal safety in this most challenging of all liver operations.

Chris' physician, Gregory Everson, M.D., is also a co-investigator for the NIDDK-A2ALL study. "The impact of the study on the current and future waiting list for liver transplantation will depend upon several factors, including living donor recipient outcomes, the donor's safety, and other factors, such as immunosuppression and recurrent hepatitis C infection, which may have specific issues in living donor liver transplant cases," says Dr. Everson. (Hepatitis C, a virus that targets liver cells, is a leading cause of liver failure and can reemerge in patients post-liver-transplant, attacking the healthy new liver tissue.) He adds that the current criteria established for living donor liver transplantation address the needs of only five to 15 percent of people on the organ waiting list, and may need to be expanded.

Even with these caveats, "This study has the potential to establish living donor liver transplantation as a viable alternative to standard cadaveric transplants for future potential recipients and, thereby, change the face of liver transplantation," says Dr. Everson.

Whether through living donor or cadaveric transplantation, the fact is that organ donations save lives. Just ask Chris Klug. "To receive the gift of life is a humbling experience, and I will be forever grateful for my second chance," says the extremely talented athlete who is extremely happy to be alive.