



Researchers have found that cellular changes take place in the stomachs of patients with gastroparesis—a gastrointestinal disorder in which food is delayed in leaving the stomach. This digestive disorder is thought to result from damage to nerves that control the muscular contractions needed for moving food through the stomach. Gastroparesis can be linked to diabetes or be of undetermined cause. These images, taken as part of a study described in this chapter, use transmission electron microscopy to visualize changes that occur in some of the cell types found in the stomach, such as interstitial cells of Cajal (ICCs), which act as “pacemakers” controlling smooth muscle cell contraction in the stomach. In a sample of cells from a person with diabetic gastroparesis, the ICC has some unusual features (left image), including large empty holes or “vacuoles” inside, as well as a thickened outer membrane with some gaps (asterisks). Also, the ICC from the person with gastroparesis does not make contact with the neighboring smooth muscle cell (SMC; left), as it does in a tissue sample from an individual without this disorder (right, see arrow). Identifying these cellular changes helps scientists to better understand how diabetic and other forms of gastroparesis develop and can lead to new therapeutic targets.

*Images provided by Dr. Pankaj J. Pasricha, Dr. Gianrico Farrugia, and Mr. Peter R. Streve, and reprinted from *Gastroenterology*, 140, Grover M, Farrugia G, Lurken MS, Bernard CE, Faussone-Pellegrini MS, Smyrk TC, Parkman HP, Abell TL, Snape WJ, Hasler WL, Ünalp-Arida A, Nguyen L, Koch KL, Calles J, Lee L, Tonascia J, Hamilton FA, Pasricha PJ, Cellular changes in diabetic and idiopathic gastroparesis, 1575-1585, copyright 2011, with permission from Elsevier.*

Digestive Diseases and Nutrition

Digestive diseases are among the leading causes of doctor visits, hospitalizations, and disability in the United States each year. These conditions span a wide spectrum of disorders that affect the gastrointestinal (GI) tract, liver, gallbladder, and pancreas, as well as obesity and other nutrition-related disorders. In 2004, more than 35 percent of all emergency and outpatient hospital visits—some 100 million—were associated with a diagnosis of a digestive disease.¹ While some digestive diseases are common and others quite rare, collectively, they exact a significant toll on public health in terms of their effects on quality of life, years lost due to premature death, and costs associated with hospitalization and pharmaceutical and surgical interventions. To reduce the public health burden associated with digestive diseases, NIDDK-supported scientists are vigorously pursuing research to better understand how widespread these diseases are across the United States and in specific population groups, to identify the causes of these diseases and how they progress, and to test new interventions for prevention and treatment of these costly diseases, including drugs, surgery, and behavior modification.

Inflammatory bowel diseases (IBD), which include 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. These diseases often strike early in life, with a peak age of onset in adolescence or young adulthood. Treatment may require surgery, including removal of the affected region of the intestine. Scientists are investigating the complex interactions among the genetic, environmental, and cellular factors that contribute to the development of IBD. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to grow intestinal tissue in cell culture will help catalyze the design of novel therapeutic strategies. Research on controlling intestinal inflammation has potential benefits not only for patients with IBD, but also for those at risk of developing colorectal cancer.

Diseases of the stomach and intestines include some of the most common digestive diseases, such as peptic ulcer disease, which is typically caused by an infection with the bacterium *Helicobacter pylori* or use of non-steroidal anti-inflammatory drugs. Stomach and intestinal disorders also include functional bowel disorders, which result in symptoms of abdominal pain and altered bowel habits. For example, irritable bowel syndrome (IBS) causes pain and constipation

or diarrhea. IBS more frequently affects women, who may display a different range of symptoms and respond differently from men to pharmacologic treatments for the disease. While diet and stress contribute to this disorder, its underlying causes are unknown. Gastroesophageal reflux disease, in which stomach acids rise up into the esophagus, is a common functional bowel disorder that can lead to a condition known as Barrett's esophagus. This condition, in which cells lining the esophagus transform into an intestinal type of cell, is associated with a heightened risk of esophageal cancer, the most rapidly rising cancer in the United States. Gastroparesis is another functional bowel disorder, which is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. A common cause of gastroparesis is diabetes, which is thought to damage nerves leading to the stomach and controlling movement of food. Fecal incontinence, or impaired bowel control, is another bowel disorder that poses a major public health burden, particularly in the elderly.

¹ Everhart JE, editor. *The burden of digestive diseases in the United States*. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office, 2008; NIH Publication No. 09-6443.

Some digestive diseases can be triggered by the body's reaction to certain foods. For example, in individuals with celiac disease, the immune system reacts to the protein gluten—a component of wheat, barley, and rye—and results in damage to the small intestine. This damage interferes with the ability of the intestine to absorb nutrients from foods and can result in chronic diarrhea, bloating, anemia, and, in children, slower growth and short stature. The only current treatment for celiac disease is maintenance of a strict gluten-free diet, which is difficult for many people. The greater challenge now facing patients and their health care providers is to improve methods capable of diagnosing celiac disease early, before damage occurs or other conditions develop. Recent and continued advances in the understanding of genes that predispose individuals to develop celiac disease may contribute to improved diagnosis in the future through genetic-based screening.

The microorganisms that inhabit the GI tract are important factors in maintaining or tipping the balance between digestive health and disease. These microbes can affect intestinal health in some surprising ways, depending on their interactions with each other, with intestinal cells, and with nutrients ingested by their human host. Scientists are gaining insights into the ways these GI microorganisms influence the development and function of the digestive tract, as well as other systems throughout the body, such as those with immune and metabolic functions.

The exocrine pancreas, which secretes enzymes required for digestion, is vulnerable to disorders such as acute and chronic pancreatitis, and their complications. Common causes of pancreatitis may include gallstones, heavy alcohol use, and inherited genetic factors. In both forms of pancreatitis, digestive enzymes attack the pancreas from within, causing inflammation and severe pain. Research has elucidated genetic factors contributing to pancreatitis that may lead to ways to treat or prevent this disorder.

The liver is an organ within the digestive system that performs many critical metabolic functions, as well as distribution of nutrients such as fats. When the liver is functionally compromised by disease, this can have serious adverse effects on health and can sometimes lead to complete liver failure. Some liver diseases primarily affect children, such as biliary

atresia (a progressive inflammatory liver disease), while others generally affect adults, such as a form of nonalcoholic fatty liver disease (NAFLD) known as nonalcoholic steatohepatitis. In recent years, however, NAFLD has been increasingly diagnosed in children in the United States as well, concurrent with rising overweight and obesity. While some forms of liver disease are caused by viral infection such as hepatitis B and C, or by genetic mutations such as alpha-1-antitrypsin deficiency, others arise from diverse factors such as autoimmune reactions, drug toxicity, and other triggers, some of which are unknown. Many liver diseases, such as chronic hepatitis C, place individuals at elevated risk for developing liver cancer. A healthy liver is necessary for life, and the only treatment for end-stage liver disease is a liver transplant. Because the number of livers available from deceased donors is limited, research is of critical importance to identify liver disease early, preserve liver function in people with liver disease, and develop new treatment options, including transplants performed with liver tissue from living donors.

The number of Americans who are overweight or obese has risen dramatically in recent decades and is now at epidemic levels. Obesity is associated with numerous diseases, including type 2 diabetes, heart disease, and cancer. Multiple factors contribute to obesity. As scientists elucidate the molecular, genetic, and environmental factors that influence appetite, metabolism, and energy storage, they are identifying potential avenues for the development of new intervention strategies to promote safe, long-term weight loss. In addition to new pharmacologic interventions for obesity, existing bariatric surgical techniques are being evaluated for their long-term impacts on weight loss and well-being. Investigators are also continuing research to help people achieve healthy lifestyles that include physical activity and improved diet. (Additional information on NIDDK-supported research endeavors focusing on obesity is provided in the Obesity chapter.)

Other nutrition-related disorders under investigation involve specific, inherited alterations in nutrient metabolism. NIDDK-supported research has enhanced knowledge of how these nutritional disorders develop, and how they can best be treated.

NEW DISCOVERIES ABOUT BACTERIA IN THE GUT

“Microbial Signatures” Identified for Irritable Bowel Syndrome in Children: Researchers have found that certain mixes of intestinal bacteria are associated with pediatric irritable bowel syndrome (IBS). IBS symptoms, which include abdominal pain, constipation, gas, and bloating, can make this a difficult and debilitating syndrome for children. At this time, the cause of IBS is unknown, IBS is less defined in children than adults, and there are no satisfactory treatments for either adults or children. Researchers have now looked to children’s intestinal bacteria for clues to the cause and possible cure of this syndrome.

For this study, the researchers compared the intestinal bacteria populations of 22 children with IBS to those of 22 healthy children. All of the children were between the ages of 7 and 12 years. Over a 2-week period, the children collected stool samples for the study and entered a description of each stool and any pain associated with the stool in diaries. From the stool samples, the researchers isolated and sequenced the DNA of all the bacteria present, which is known as the “microbiome.” Analyses of the bacterial DNA sequences in each sample provided the researchers with information on the number of total bacteria, identified the bacterial species that were represented, and determined the relative size of each type of bacterial population. Comparisons of the microbiomes showed that the children with IBS and the healthy children had similar total numbers of intestinal bacteria; however, the relative abundance of bacterial types differed. For example, the microbiomes of children with IBS were characterized by significantly greater percentages of the class gamma-proteobacteria and much smaller percentages of several *Bacteroides* species than the microbiomes of healthy children. In addition, the researchers were able to distinguish between two pediatric IBS subtypes—IBS with constipation and IBS unsubtyped—by analyzing the composition of the bacteria in samples from children with IBS and the pain that they described in their diaries. Based on differences in microbial composition and recurrent abdominal pain associated with pediatric IBS, the researchers developed “microbial signatures” associated with IBS in children and its unique subtypes.

This pioneering study presents important insights into the relationship of pediatric IBS, a painful condition with no known cause, and intestinal bacteria. The scientific community can now use these microbial signatures of pediatric IBS as clues to uncovering the mysteries of this syndrome.

Saulnier DM, Riehle K, Mistretta T-A, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology 141: 1782-1791, 2011.

Gut Immune Cells Need a Little Help from Their Bacterial “Friends”: Scientists have found that a “friendly” bacterium, one of the many that lives in the human intestine, actively engages with gut immune cells through molecular communication processes to maintain the “tolerance” response required for a symbiotic (mutually beneficial) relationship. The immune system senses both harmful and friendly bacteria in the gut and normally mounts an immune reaction only to harmful bacteria, while remaining tolerant of friendly bacteria that perform beneficial functions for their human host. One of the main mechanisms the immune system uses to accomplish this task is mediated through Toll-like receptors (TLRs) on host immune cells that recognize patterns of molecules on the surface of both harmful and beneficial bacteria. However, if the TLRs recognize both “good” and “bad” bacteria, how do immune cells distinguish the “good” ones and react appropriately by peacefully co-existing with them?

Scientists aimed to solve this mystery by studying how the immune system interacts with a prominent member of the community of helpful gut bacteria called *Bacteroides fragilis*. *B. fragilis* is known to use a molecule on its surface called polysaccharide A (PSA) to shape the host immune response. Using a number of animal and *in vitro* models, the researchers selectively manipulated elements of the host immune cells and the gut bacterial community, including *B. fragilis* and its production of PSA, to reveal how *B. fragilis* bacteria let intestinal cells know that they are helpful, not harmful. They found that some *B. fragilis* live very close to cells lining the colon. There, in close proximity to the cells of the intestinal immune system, the bacteria communicate through PSA binding directly to a TLR on the surface of a host immune cell, causing molecular signals to be transmitted within and between immune

cells that ultimately suppress an inflammatory immune response. PSA is unique in its ability to activate the TLR in such a way that an immune response is suppressed; by contrast, molecules on harmful bacteria have been shown to activate immune responses.

These findings provide fresh insights into how the intestinal immune system has apparently co-evolved with gut bacteria to exchange molecular signals that distinguish helpful from harmful microbes. The results of this study show that friendly microbes contribute directly to establishing immune tolerance in the host gut cells, which is needed for a symbiotic relationship. This research suggests that in humans, intestinal immune cells may need help from the bacteria themselves in reacting appropriately to these microbes as “friend” rather than “foe,” a finding with important implications for diseases in which these interactions are abnormal, such as inflammatory bowel diseases.

Round JL, Lee SM, Li J, et al. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 332: 974-977, 2011.

Communication and Protein “Fences” Make Good Neighbors of Gut and Bacteria: Scientists have shown how a microbe-fighting protein helps create a protective buffer zone between the inner walls of the small intestine and the bacteria contained within. Scientists have also found that communication between cells lining the intestinal wall (epithelial cells) and immune cells is necessary to sense potentially harmful bacteria nearby and release this antimicrobial protein. These findings may explain how, in a healthy state, helpful bacteria can survive in the digestive tract without triggering an immune attack, while harmful bacteria are appropriately targeted and neutralized.

Researchers have long known that about 100 trillion bacteria reside in the intestines of the human body. Many of these microbes help us digest food and absorb important nutrients, while others can have ill effects. In the colon, a dense layer of mucus creates a physical barrier between the gut’s walls and microbes. The mucus helps to prevent bacterial infection and immune attack. However, in the small intestine, the mucus layer is thin and permeable to allow absorption of nutrients. Scientists have puzzled over how the mutually beneficial relationship between bacteria and host is maintained.

This research group suspected that certain immune mechanisms might work in partnership with the mucus layer in the small intestine to keep bacteria at bay. They first assessed in mice how microbes are naturally positioned relative to the intestinal lining. Using a technique that makes bacteria glow green and intestinal walls blue, the scientists found a zone of separation between the bacteria and the lining. The researchers then studied mice lacking the protein MyD88, which activates a branch of the immune system that recognizes certain molecular patterns in disease-causing microbes. With this portion of the immune system impaired, bacteria invaded the protective zone and came into direct contact with the intestinal lining. MyD88 also controls the production of several antimicrobial proteins in specialized cells in the intestine’s lining. Following this clue, the researchers identified a protein called RegIII γ as responsible for the bacteria-free zone. Mice lacking RegIII γ lacked the buffer zone between bacteria and the intestinal wall. The intestinal lining had increased numbers of bacteria adhering to it—a feature sometimes seen with digestive disorders such as inflammatory bowel diseases. These findings highlight the protective zone between the intestine and bacteria and its importance for maintaining intestinal health, with the antimicrobial protein RegIII γ playing a critical role in maintaining this zone.

In a related study, the research group focused on the role of intestinal immune cells called $\gamma\delta$ intraepithelial lymphocytes (IELs) in selectively defending the intestine against potentially harmful bacteria. IELs are found in large numbers between epithelial cells in the intestinal mucosa and are an important part of the mucosal immune response to intestinal bacteria. Researchers purified $\gamma\delta$ IELs from the small intestines of mice lacking intestinal microbes (raised under sterile conditions) or mice with intestinal microbes (raised under standard conditions), and compared the genes turned on in these cells using microarray technology. They found that the IELs turned on antimicrobial proteins such as RegIII γ , but only when intestinal microbes were present, specifically harmful bacteria that invade epithelial cells such as *Escherichia coli* and *Salmonella typhimurium*. To investigate how the IELs might receive the signal to defend against these harmful bacteria, the scientists next investigated communications with neighboring epithelial cells equipped with bacteria-sensing receptors. Using mice that had been genetically altered so that some of their epithelial

cells lacked the protein MyD88, which helps the cells sense bacteria, the researchers showed that this protein is needed for the epithelial cells to alert neighboring IELs to the presence of harmful bacteria, prompting their antimicrobial protein production. They also showed that these IELs act early in the course of bacterial exposure to limit epithelial invasion of harmful bacteria, using mice genetically altered to lack $\gamma\delta$ IELs compared to wild-type mice. This research has shown how the immune cell $\gamma\delta$ IEL plays an essential role, in collaboration with nearby epithelial cells, in maintaining “homeostasis,” or balance between the intestinal immune system and the intestinal bacterial community, by acting quickly and discriminately to limit invasion by harmful bacteria.

These findings offer insights into unique aspects of the intestine’s built-in defense system against pathogens, which is set up to “screen” microbes and react to harmful bacteria, but peacefully co-exist with beneficial species. This system involves good communication among intestinal cell types to coordinate responses and also a physical barrier or “demilitarized zone” between the intestine and bacteria. The key elements of this system identified in these studies, including antimicrobial proteins such as RegIII γ and the bacteria-sensing protein MyD88, as well as IEL immune cells, offer clues to how some “system failures” may come about in certain digestive disorders and represent potential new targets for treating or preventing these disorders.

Vaishnava S, Yamamoto M, Severson KM, et al. The antibacterial lectin RegIII γ promotes the spatial segregation of microbiota and host in the intestine. Science 334: 255-258, 2011. Information on this reference adapted from NIH Research Matters; original article by Ms. Vicki Contie, published on October 24, 2011.

Ismail AS, Severson KM, Vaishnava S, et al. $\gamma\delta$ intraepithelial lymphocytes are essential mediators of host-microbial homeostasis at the intestinal mucosal surface. Proc Natl Acad Sci USA 108: 8743-8748, 2011.

GENETICS OF INFLAMMATORY BOWEL DISEASES

Study Doubles Number of Genetic Variants Associated with Crohn’s Disease: An international group of researchers, including those from the

NIDDK’s IBD Genetics Consortium, have combined data from six genome-wide association studies to uncover additional genetic variants associated with Crohn’s disease, effectively doubling the number of known genetic associations in this disease. Crohn’s disease is a form of inflammatory bowel disease that can occur in the small intestine and colon. It is thought to result from a complex interplay between genetic factors, which set up the host immune system to respond inappropriately, and the environmental factors they sometimes respond to, such as benign microbes living in the intestine. Research groups from around the world, including the NIDDK IBD Genetics Consortium, have been extremely successful in identifying 32 genetic regions associated with Crohn’s disease that have led to new insights into disease processes. Still, they estimated that these factors accounted for only about 20 percent of the genetic contribution to this disease.

To improve their chances of finding the additional genetic variants that play a role in the development of Crohn’s disease, a research team called the International IBD Genetics Consortium, which includes the NIDDK IBD Genetics Consortium, utilized data from six genome-wide association studies of samples from patients with Crohn’s disease compared to people without this disease. They conducted a “meta-analysis” of genetic data from all of these studies, combining their findings to analyze a larger number of people together, which could enable them to bring to light the effects of additional genetic variants. With this approach, the team identified 30 new genetic regions associated with Crohn’s disease and replicated results with additional genetic variants that had been identified previously, bringing the total up to 71. Some of the genes located in these genetic regions are associated with other types of chronic inflammatory disorders and perform functions that would explain some of the underlying disease mechanisms. However, identifying the specific roles of these genes in Crohn’s disease, their therapeutic potential, and the vast remainder of genetic factors contributing to the disease will require further research.

Franke A, McGovern DPB, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn’s disease susceptibility loci. Nat Genet 42: 1118-1125, 2010.

Study Greatly Increases Number of Genetic Variants Associated with Ulcerative Colitis:

Research scientists have taken a significant step toward understanding the genetic basis of ulcerative colitis (UC) with the identification of 29 new genetic variants that increase the risk for UC, more than doubling the number of previously known variants. UC and Crohn's disease are related complex genetic diseases that are both major forms of IBD. Risk for these diseases is caused by many genetic variants with contributions ranging from strong to subtle impacts. However, genetic risk factors identified in past studies explain only 11 percent of the inherited component of UC. Genetic studies have shown that risk variants for IBD can be common to both UC and Crohn's disease or unique to either disease. The current study identifies additional variants that are unique to UC and some that are shared by both diseases, pointing the way to understanding biological processes underlying IBD.

The first phase of this study began with an analysis of data from six genome-wide association studies, conducted by the NIDDK IBD Genetics Consortium and five other international research groups, which had previously identified a combined total of 18 genetic variants associated with UC. This "meta-analysis" of data collected from multiple studies had the statistical advantage of a much larger number of study participants, enabling the scientists to identify an additional 29 variants, bringing the total number of genetic risk factors for UC to 47. Next, the researchers turned their attention from the identification of these new risk associations in unique chromosomal locations, or loci, to identification of genes within the loci that confer disease risk. Most of the loci identified in the meta-analysis contain multiple genes, and the scientists used various analytical tools to determine which of the genes were likely to confer disease risk and to identify key biological pathways involving these genes. One new analytical tool that was employed is a statistical method known as "GRAIL" (Gene Relationships Among Implicated Loci), which mines the scientific literature to assess genes from various loci for whether they have related biological functions and may thus be involved as a group in a disease pathway. Another of the research methods identified risk variants that changed the structure of the protein coded for by the candidate gene. With these analyses, the scientists identified several candidate genes with roles in intestinal barrier integrity, immune

response, autophagy (a cellular mechanism causing cell death, previously implicated in Crohn's disease), and other biological pathways.

The researchers compared the UC risk loci from this study to a set of Crohn's disease risk loci that were identified in a previous study (also described in this chapter). Several loci were found that were common to both UC and Crohn's disease. Based on this analysis, the total number of identified IBD risk loci has increased to 99, with 28 genetic variants in common between UC and Crohn's disease. These studies identified biological mechanisms and pathways that may be associated with UC. However, further research is required to confirm which of the genes within these loci are causing the effects. Although these results represent only a small percentage of predicted UC genes and associated pathways, they are part of a critical foundation on which important advances in UC research and treatments can be built.

Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet 43: 246-252, 2011.

INSIGHT INTO CELIAC DISEASE DEVELOPMENT

A Surprising Role for Vitamin A in Model of Celiac Disease Development: In research on the mechanisms underlying the development of celiac disease, scientists have uncovered an unexpected role for a form of vitamin A called retinoic acid, while simultaneously filling in details of the larger immunological and cellular machinery at work and creating a new animal model of the disease. The human intestine contains a resident immune system tasked with distinguishing between helpful substances, such as nutrients and health-promoting microbes, and harmful ones, such as unhealthy bacteria. In celiac disease, this system goes awry, with immune cells inappropriately reacting to the dietary protein gluten, which is found in grains such as wheat. The precise mechanisms by which this loss of immune "tolerance" of a dietary antigen occurs have remained mysterious, beyond the knowledge that some individuals have a genetic susceptibility to celiac disease.

Researchers set out to fill in some of the details behind celiac disease development by identifying some of the key molecules and cells involved in this process. They focused their attention on intestinal immune cells and the molecules they produce, called cytokines, as well as a form of vitamin A called retinoic acid. Retinoic acid plays a role in the development (differentiation) of a type of immune cell called the regulatory T cell, which typically suppresses the development of inflammation-promoting immune cells and helps to maintain tolerance of ingested nutrients. The scientists created mice with a genetic mutation boosting levels in their intestinal immune tissues of the cytokine IL-15, which is known to be elevated in the intestines of patients with celiac disease. In these mice and in cultures of cells taken from them, high IL-15 levels suppressed differentiation of the regulatory T cells—the first clue as to how this cytokine takes the brakes off of the intestine’s natural tolerance of dietary substances. When they added retinoic acid to the mix in mice with high intestinal IL-15, they found a surprising result—rather than countering IL-15’s effects on suppressing regulatory T cell differentiation, retinoic acid enhanced it. These synergistic effects of IL-15 and retinoic acid led to a cascade of events associated with an inappropriate immune response, including turning on signaling pathways, increasing release of other cytokines, and activating inflammation-promoting immune cells. Next, the researchers created a new animal model of early-stage celiac disease. They engineered mice to have high intestinal IL-15 levels and also to have on their cells certain proteins that are associated with human celiac disease, called HLA-DQ8, which interact particularly well with gluten. They then fed the mice gliadin, a component of gluten. In these animals, an inappropriate intestinal immune reaction was mounted towards the ingested gliadin, which was further promoted by also feeding them retinoic acid.

This study has improved understanding of how celiac disease develops, including the immune mediators involved, and also yielded a new animal model of early-stage celiac disease to enable future research. It also highlights a surprising role for retinoic acid, which, in the context of underlying inflammation and elevated IL-15, further enhances inappropriate immune responses, rather than protecting against them as it does in other immunological settings. These findings warn against using vitamin A or retinoic acid as a treatment

for patients with celiac disease, and potentially other diseases with inappropriate immune responses marked by high IL-15 levels. Lastly, this research identifies molecules such as IL-15 as potential targets for new drug development to treat those with celiac disease who are not completely responsive to a gluten-free diet.

DePaolo RW, Abadie V, Tang F, et al. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. Nature 471: 220-224, 2011.

VISUALIZING THE UNDERLYING DISEASE PROCESS OF GASTROPARESIS

Changes in Stomach Cells Associated with Two Forms of Gastroparesis: Researchers have found evidence of changes at the cellular level in the stomachs of individuals with gastroparesis, yielding new insights into this digestive disorder. Gastroparesis is a chronic condition characterized by impaired “motility”—the muscular contractions that move food along the gastrointestinal tract. This limited motility results in delayed food emptying from the stomach into the intestines, as well as many symptoms that compromise quality of life, including nausea, vomiting, bloating, weight loss, and abdominal pain. Gastroparesis is most commonly associated with diabetes, which is thought to damage nerves connecting to the stomach that control muscular contractions. However, often the cause of the disorder is unknown or “idiopathic.” Clinical studies on this disorder have been limited.

Scientists in the NIDDK’s Gastroparesis Clinical Research Consortium are now conducting research at sites across the nation to improve understanding of disease processes and develop effective treatments for this disorder. For this study, they collected stomach tissue samples from individuals with diabetic and idiopathic forms of gastroparesis, as well as control samples from patients undergoing gastric bypass surgery who did not have gastroparesis, in order to compare their cellular structures. To identify the cells under a microscope, including cells of the nervous system, interstitial cells of Cajal (ICCs), smooth muscle cells, and immune cells, the scientists used visible molecular tags in combination with antibodies that react to unique proteins on the surface of these different cell types. A stain was also used to estimate the amount

of scarring in the tissue—a sign of cellular damage. Researchers noticed cellular abnormalities in the majority of samples from patients with either diabetic or idiopathic gastroparesis. The most frequent type of abnormality seen in stomach tissue from gastroparesis patients was a reduction in the number of ICCs, which play an important role as “pacemakers,” controlling muscular contractions in the stomach. Another common alteration was seen in the shape and increased number of immune cells present in the muscle layer. Some alterations in the gut nervous system were also observed.

Using transmission electron microscopy, the researchers were able to peer further inside these cell layers. They again saw reduced ICCs and some altered nerve structures, as well as an abnormal connective tissue layer with some scarring. Many of the ICCs present in both forms of gastroparesis looked unusual, with large holes called vacuoles, swollen mitochondria (energy-generating structures within the cell), and no visible contact with neighboring nerves, muscle cells, or other ICCs. Some unique cellular features were also noted between diabetic and idiopathic gastroparesis—in diabetic gastroparesis, ICCs also featured a thickened but broken outer membrane, and some scarring was noted around muscle cells, while idiopathic gastroparesis showed scarring in connective tissue around nerve structures.

This Consortium study represents the most comprehensive, clinical study of diabetic and idiopathic gastroparesis to date. The finding of cellular abnormalities in the stomachs of most individuals with this disorder—including changes in the structure and number of ICCs, nerve cells, and immune cells—sheds light on the underlying disease processes at work in both forms of gastroparesis, and paves the way for future therapeutic development. Future research by the Consortium members will continue to explore these abnormalities, such as how loss of contact amongst these cells might translate into the limited gastrointestinal motility seen in patients with gastroparesis.

Grover M, Farrugia G, Lurken MS, et al. Cellular changes in diabetic and idiopathic gastroparesis. Gastroenterology 140: 1575-1585, 2011.

BIOENGINEERED APPROACHES TO TREATING FECAL INCONTINENCE

Functioning Bioengineered Anal Sphincter Implants in Mice: Building on research that may have implications for future treatment for fecal incontinence, scientists have successfully implanted a physiologically functional bioengineered internal anal sphincter (IAS) in mice. The IAS is a ring-like muscle located just inside the rectum; along with the external anal sphincter, these two muscles keep the anus closed and maintain fecal continence. Loss of IAS muscle tone is a primary cause for the uncontrolled release of stool that occurs in people with fecal incontinence, a condition that places devastating emotional, social, physical, and economic burdens on people who are affected by it.

Scientists used smooth muscle cells obtained from human IAS to bioengineer three-dimensional IAS rings. The researchers grew the cells using special plates that contained a mold around which the cells could create the appropriate three-dimensional ring structure. The plates were first coated with mouse nerve cells that were then overlaid with the human IAS cells. Once the IAS ring had formed, it was surgically implanted into a small pocket under the skin of a mouse. After allowing the bioengineered sphincters to develop for nearly 1 month, the researchers removed and examined them. They found that the IAS rings had developed an ample blood supply and nerve connections. They exhibited appropriate muscle tone, and relaxed and contracted in response to various chemical stimuli. All of these observations suggest that the bioengineered IAS is physiologically functional.

Previous studies demonstrated that it was possible to grow bioengineered IAS from isolated human IAS circular smooth muscle and to successfully implant physiologically functional bioengineered mouse IAS constructs in mice. The current study is the first to demonstrate implantation of a bioengineered human IAS in a mouse where both the muscular and nerve components are viable and responsive to stimuli. This study may be translated into bioengineered IAS for people suffering from fecal incontinence. This would be of enormous benefit, greatly improving the daily lives of these individuals and alleviating the social and financial burdens associated with this disorder.

Raghavan S, Gilmont RR, Miyasaka EA, et al. Successful implantation of bioengineered, intrinsically innervated, human internal anal sphincter. *Gastroenterology* 141: 310-319, 2011.

RESEARCH ON NONALCOHOLIC FATTY LIVER DISEASE

Vitamin E Helps Diminish a Type of Fatty Liver Disease in Children: In a recent clinical trial, the Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC), a form of vitamin E improved the most severe type of fatty liver disease in some children. Nonalcoholic fatty liver disease is the most common chronic liver disease among U.S. children. It ranges in severity from steatosis, defined as fat in the liver without injury, to nonalcoholic steatohepatitis or NASH, which is characterized by fat, inflammation, and liver damage. Fatty liver increases a child's risk of developing heart disease and liver cirrhosis. Most children with fatty liver disease are overweight and have insulin resistance, a hallmark of both prediabetes and type 2 diabetes. Boys are more likely affected by fatty liver disease than girls, as are Hispanic children compared to African Americans and whites. Weight loss may reverse the disease in some children, but other than advice about diet and exercise, there are no specific treatments. Excess fat in the liver is believed to cause injury by increasing levels of oxidants, compounds that can damage cells.

In the clinical trial, conducted by the NIDDK-supported NASH Clinical Research Network, researchers studied whether fatty liver disease in children could be improved by either vitamin E, which is an antioxidant, or the diabetes drug metformin. A total of 173 children ages 8 to 17 participated in the trial. The majority of participants were white and Hispanic boys. The children were divided into three groups and given vitamin E, metformin, or placebo daily. The researchers then analyzed blood samples from the participants to determine whether there was a sustained reduction in levels of the liver enzyme alanine aminotransferase (ALT) to be closer to normal. They also looked for improvements in the liver as shown by biopsy, a more rigorous test. Although a sustained reduction in ALT was not achieved, after treatment for almost 2 years, researchers found that 58 percent of the children on

vitamin E no longer had NASH, compared to 41 percent of the children on metformin, and 28 percent on placebo, as assessed with liver biopsies. Vitamin E was better than placebo because it significantly reduced enlargement and death of liver cells. The results of this study in children are similar to a previous study, also conducted by the NASH Clinical Research Network, that had shown vitamin E to be effective in some adults with the disease. However in the TONIC trial, neither vitamin E nor metformin was significantly better than placebo in improving the children's ALT levels. From other observations, the researchers concluded that the children benefited from the frequent diet and exercise advice provided throughout the study. While the vitamin E results based on liver biopsy are encouraging, patients should be under a doctor's care if vitamin E is used. Researchers now hope to build on these results by looking for other therapies for fatty liver disease and reliable, non-invasive ways to monitor the disease and response to therapy.

Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 305: 1659-1668, 2011.

Possible New Therapeutic Target for Treating Fatty Liver Disease Associated with Diabetes:

Researchers have discovered that a protein thought to be involved in protecting liver cells from damage may actually be involved in regulating glucose and lipid (fat) metabolism in the liver. Scientists were looking for genes in mice that are turned on by a protein called FXR, which is one of a group of proteins called nuclear receptors that are involved in varied aspects of metabolism. They focused on one gene identified as being turned on by FXR in mice, called *AKR1B7*. Previous research suggested that the *AKR1B7* protein, an enzyme capable of catalyzing biochemical reactions in cells, may protect against the by-products of a process called lipid peroxidation, which can result in cellular damage. To investigate this possibility, the researchers experimentally introduced high levels of *AKR1B7* protein into the livers of mice. Surprisingly, the protein did not have an effect on lipid peroxidation in the liver. Rather, it caused the animals' blood glucose levels to drop, in association with reduced glucose production by the liver. The scientists did the

same experiment in a diabetic mouse model and again observed a decrease in the animals' blood glucose levels; the treated diabetic mice also had lower levels of fat in their livers. These findings identify a novel role for AKR1B7 in regulating liver and glucose metabolism. The scientists note that a human protein (AKR1B10) may be structurally similar to mouse AKR1B7. If future research shows that the human protein has similar functions, it may be a potential therapeutic target for treating fatty liver disease associated with diabetes.

Ge X, Yin L, Ma H, Li T, Chiang JYL, and Zhang Y. Aldo-keto reductase 1B7 is a target gene of FXR and regulates lipid and glucose homeostasis. JLipid Res 52: 1561-1568, 2011.

TREATING CHRONIC HEPATITIS C

Combination Antiviral Therapy More Effective for Pediatric Chronic Hepatitis C: A clinical trial conducted at 11 sites throughout the United States has shown that combination therapy with peginterferon and ribavirin is more effective than therapy with peginterferon and placebo in treating chronic hepatitis C in children. Children can contract the hepatitis C virus at birth from mothers who are infected or through transfusion with infected blood, though the U.S. blood supply is screened to prevent this. Although chronic hepatitis C in children is less common and generally less damaging than in adults, it can lead to cirrhosis requiring liver transplantation, or liver cancer, later in life. Treatment of this disease in children with a combination therapy using the antiviral drugs peginterferon and ribavirin has been based on extensive adult studies, but only a single, uncontrolled clinical trial in children, who may respond differently to the drugs. For example, children show a higher response to peginterferon than adults, and ribavirin has been shown to be potentially harmful to young animals. Therefore, a well-controlled clinical trial was needed to test the true safety and efficacy of combination antiviral therapy compared to peginterferon treatment alone for maximizing care of children with chronic hepatitis C.

Researchers in the Peds-C Clinical Research Network conducted a prospective, randomized controlled clinical trial at 11 U.S. medical centers in which they treated people ages 5 to 18 years who have chronic hepatitis C.

The Network was funded by the NIDDK with other Federal and non-Federal support. The children and adolescents in this trial were given either a combination of peginterferon and ribavirin, the standard combination therapy used in adults, or a combination of peginterferon and placebo for 1 year, and then followed for 1 to 2 years after going off the treatment. During this time, they were monitored for whether they had hepatitis C virus in their blood (as measured by the viral genetic material, or RNA). Sustained response to treatment was defined as undetectable hepatitis C viral RNA in the blood 6 months after treatment. The group receiving the combination therapy with both antiviral drugs had a 53 percent sustained response rate compared to 21 percent in those receiving only the antiviral peginterferon and placebo. Notably, some participants who did not respond early to the treatment nevertheless went on to have a sustained response. Additionally, those who responded to treatment in either group still had undetectable viral levels 2 years after stopping treatment. Some adverse effects were observed in both treatment groups, including flu-like symptoms, headache, GI symptoms, and low levels of certain immune system cells (neutrophils) in the blood, requiring a reduction in the treatment dose in some cases.

The addition of ribavirin to peginterferon as part of combination therapy greatly increased response rate in children and adolescents with chronic hepatitis C with minimal change in side effects, providing much-needed evidence for designing optimal therapy for this group. This study also shows the benefits of giving the full course of combination therapy to young people who do not show early signs of responding, as well as the importance of monitoring for common side effects such as low neutrophils.

Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology 140: 450-458, 2011.

Dietary Supplement Improves Response to Antiviral Therapy for Hepatitis C: Scientists have shown that a dietary supplement, S-adenosyl methionine (SAME), safely and effectively boosts response to standard antiviral therapy in people infected with a type of hepatitis C virus that typically does not respond well to such therapy. The current standard of therapy

for hepatitis C—a combination of the antiviral drugs pegylated interferon and ribavirin—is effective in less than half of those with this disease. Interferon is also produced naturally by the body in the early phase of viral infection to mobilize the immune response and clear the virus. A type of hepatitis C virus called genotype 1, which is the most prevalent type of virus infecting people in the United States, is particularly unresponsive to antiviral treatment. Therefore, scientists have been seeking ways to improve response to therapy.

In this study, the research team tested SAME, which is a naturally occurring compound found in living cells. The clinical portion of the research included people with chronic hepatitis C who were infected with the genotype 1 virus and, thus, did not respond well when treated in the past with standard antiviral therapy. In the study, they were given standard antiviral therapy for a few weeks to establish a baseline response and serve as their own controls in the trial, then taken off antiviral drugs and given SAME for a few weeks prior to treatment with the combination of antivirals and SAME for 1 year. After each course of antiviral therapy, with or without SAME, the researchers measured viral response (the amount of virus still detectable in the blood) and also the genes activated in response to interferon in the patients' blood cells that help the body fight off viral infection. Both viral response and molecular indicators of response to interferon improved when the antiviral therapy was given together with SAME, compared to when the same patients were previously given antiviral drugs alone. In cultured liver cells infected with hepatitis C virus, a similar boost in response to interferon treatment was observed when the cells were pretreated with SAME. Additional cell culture studies showed that SAME likely works through countering viral inhibition of a molecule that transmits the response to interferon.

The dietary supplement SAME improved response to antiviral therapy in people with hepatitis C who had not responded to therapy in the past, both in terms of viral response and host immune response. Thus, SAME could be a helpful addition to antiviral therapy in such people with hepatitis C, particularly those infected with the genotype 1 virus. Future research will also determine whether people with hepatitis C who have never received antiviral treatment can benefit from SAME taken during therapy.

Feld JJ, Modi AA, El-Diwany R, et al. S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. Gastroenterology 140: 830-839, 2011.

LIVER TRANSPLANTATION RESEARCH

Living Donor Liver Transplantation Improves Survival Compared to Other Options:

Adult-to-adult living donor liver transplantation—removal of part of a living adult's healthy liver for transplantation into another adult whose organ has been damaged—has been performed in the United States since the late 1990s. Recipients of living donor livers include people with end-stage liver disease due to causes such as chronic hepatitis C, or in those with liver cancer or acute liver failure. However, as with other organs, the demand for livers for transplant far exceeds the supply of available living donor or deceased donor organs. Moreover, the living donor procedure carries some risks for the donor.

The need to distribute available organs in a way that is fair and also maximizes survival benefits led to the development of a numerical scale, based on laboratory tests, that is used to determine how urgently a patient needs a liver transplant. It is called the Model for End-stage Liver Disease (MELD). Yet, even with this system in place, information is lacking to assist the decision-making process of candidates for deceased or living donor liver transplantation, their health care providers, people who might consider being living donors, and those who manage organ allocation.

The Adult-to-Adult Living Donor Liver Transplantation (A2ALL) Study, conducted from 2002 to 2009 and currently supporting ongoing ancillary studies, investigates outcomes for candidates for living donor liver transplantation, as well as donors, compared to outcomes for those who receive organs from deceased donors. As part of the A2ALL study, researchers collected data at nine liver transplant centers around the country on 4.5-year outcomes for candidates for liver transplantation who received a living donor transplant, compared to a group of those who remained on the waiting list or received a transplant from a deceased donor. By tracking mortality data on these groups, the researchers found that those who received living donor liver transplants had significantly higher survival rates

compared to the other group. Interestingly, this benefit was seen across MELD “scores” in patients with liver disease of varying severity.

Previous studies had suggested that there was little or no benefit to performing transplants in patients with lower MELD scores who were less ill. In contrast, this study demonstrates that there is a greater chance of survival for patients who receive a living donor liver transplant, although this benefit was not seen in individuals with liver cancer, likely due to the priority they are given to receive deceased donor transplants relatively quickly,

so that they spend less time on the organ waitlist.

Although potential risks to liver donors must continue to be weighed, living donor liver transplantation shows clear benefits for transplant recipients. This information will be useful for patients, their caregivers, and physicians who are advising transplant candidates about the benefits of living donor liver transplantation.

Berg CL, Merion RM, Shearon TH, et al. Liver transplant recipient survival benefit with living donation in the model for endstage liver disease allocation era. Hepatology 54: 1313-1321, 2011.

Dining In with a Few Trillion Fascinating Friends— How Gut Bacteria Affect Health and Disease

What we eat, or do not eat, affects our health in surprising ways—by sustaining not only us, but also the trillions of bacteria that reside in our gut. Over the past decade, a researcher supported by the NIDDK, Dr. Jeffrey Gordon has illuminated the extraordinary and diverse roles our gut microbes play in health and disease.

Dr. Gordon has described the complex interactions between us and our gut microbes as “dining in with a few trillion fascinating friends.” Building on knowledge that bacteria are able to digest some dietary components that our own intestinal cells cannot, Dr. Gordon speculated that some bacteria may be better at this than others—and thus might contribute to obesity in their human or animal “host.” His research team found that, in fact, the relative abundances of different types of gut bacteria differ between lean and obese mice and people, and the bacteria more prevalent in obesity are better able to extract nutrients, and associated calories, from food. These microbes also influence whether their hosts burn calories or store them as body fat. Dr. Gordon and his colleagues have discovered that these microbes play other surprising roles in the health of their hosts: they help direct normal development of blood vessels in the digestive tract, and may even modulate risk for type 1 diabetes. Additionally, humans’ indigenous bacteria communicate with their surrounding host cells in ways that maintain a peaceful and productive relationship; at the same time, they fortify the intestines against unwanted invaders by inducing host cells to produce anti-bacterial proteins. Other researchers have implicated aberrant immune reactions to our resident gut microbes as contributing to inflammatory bowel diseases, and have found differences in gut bacteria associated with irritable bowel syndrome.

Dr. Gordon has suggested that a strategy for preventing or treating disease may be to alter the types of bacteria in our gut—through probiotics or other means. Such an approach would require deeper understanding of what the different types of bacteria have to offer—that is, what functions may be encoded by their collective genomes,

referred to as the gut “microbiome.” And, scientists would need to know how to shape these communities of microbes effectively.

Because the local cuisine may attract different types of bacteria, in the past year Dr. Gordon and his team have investigated whether the kinds of foods we eat may affect the mix of microbes in our gut. In an innovative study, published this past year, Dr. Gordon and his team explored whether very different diets are associated with distinct collections of gut bacteria.¹ With cutting-edge technology and computational methods, the scientists canvassed the gut bacterial communities from a wide range of animals, sequencing and analyzing the bacterial genomes. They found that the sets of bacterial species within each of the animals differed depending on whether the animals were meat eaters, plant eaters, or ate both forms of food. Regardless of diet, however, the microbial communities within the guts of all of the animals shared in common a core set of bacterial genes, perhaps required for living in an intestinal neighborhood. Yet, other aspects of the bacterial genomes did vary according to diet. For example, the meat-eaters’ bacteria harbored more genes for breaking down proteins, while the plant-eaters’ bacteria were enriched for genes involved in synthesizing the building blocks of proteins. In subsequent analyses of gut microbiomes from people who kept strict records of the types of foods they ate, the researchers found that different diets correlated with different bacterial species and different sets of bacterial genes within humans.

In another study, also published this past year, Dr. Gordon and other scientists in his laboratory tested the effects of different foods on the relative abundance of the different bacterial species with experiments in mice.² To focus on the types of microbes that live in our gut, the researchers first raised mice under sterile (germ-free) conditions, and then gave them intestinal bacteria taken from humans. With an initial set of microbial residents in place, the researchers then fed the mice a series of defined diets with simple ingredients: pure sugar, cornstarch, corn oil, and

casein (protein). Based on changes in the gut microbial communities, the scientists developed a mathematical model to predict how the relative abundance of different bacterial species would vary in response to different dietary components. To test their model, they served the mice meals more similar to what people eat, in the form of various combinations of pureed baby foods: apples, peaches, peas, sweet potatoes, beef, chicken, oats, and rice. Largely as predicted, they observed that the community of gut bacterial species fluctuated in response to changes in diet.

By further defining the genomes and food preferences of humans' intestinal dining companions, these new studies from Dr. Gordon's laboratory may help guide dietary, probiotic, or other strategies to modify the composition of our gut bacteria. More broadly, the NIDDK and other NIH Institutes currently support research by Dr. Gordon and a

number of other investigators on the multitude of microbes that inhabit not only our gut, but also niches elsewhere in the body, through the NIH Human Microbiome Project (<https://commonfund.nih.gov/hmp/>) and other studies. With a better understanding of our bacterial partners, scientists may be able to develop novel interventions to enhance nutrition, prevent or treat disease, and improve public health.

¹ Muegge BD, Kuczynski J, Knights D, et al. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* 332: 970-974, 2011.

² Faith JJ, McNulty NP, Rey FE, and Gordon JI. Predicting a human gut microbiota's response to diet in gnotobiotic mice. *Science* 333: 101-104, 2011.

Launching the New NIDDK Bowel Control Awareness Campaign

On June 2, 2011, the NIDDK launched the Bowel Control Awareness Campaign, “Let’s Talk About Bowel Control.” Fecal incontinence, commonly known as bowel control problems, is the inability to hold a bowel movement until reaching a bathroom. Fecal incontinence also refers to the accidental leakage of solid or liquid stool. Many feel upset or embarrassed by incontinence, but it can be caused by various medical conditions, and treatments are available. Thus, talking about fecal incontinence with a health care provider can help patients get successful treatment.

In December 2007, the NIH held the “State-of-the-Science Conference: Prevention of Fecal and Urinary Incontinence in Adults,” sponsored by the NIDDK and the Office of Medical Applications of Research, to review current knowledge and develop recommendations for addressing fecal incontinence. A Conference Statement prepared by the State-of-the-Science Panel recommended that efforts be made to raise public awareness of incontinence and the benefits of prevention and management. The new Awareness Campaign was developed in response to this recommendation.

“Our findings indicate that fecal incontinence is a significant public health burden in the United States—affecting close to 10 percent of the adult population over 40 years old. The Bowel Control Awareness Campaign’s main objective is raising public awareness of fecal incontinence to aid in prevention of incontinence and to improve the lives of

men and women living with the condition,” said Dr. Griffin Rodgers, NIDDK Director.

Developed by the NIDDK, along with professional and patient-advocacy organizations that focus on fecal incontinence, the Bowel Control Awareness Campaign, “Let’s Talk about Bowel Control,” is located at www.bowelcontrol.nih.gov. The web-site features:

- A fact sheet on fecal incontinence
- An easy-to-read booklet on bowel control
- NIH bowel control research information
- Links to professional and patient-advocacy organizations
- A link to the National Digestive Diseases Information Clearinghouse

“The lack of communication between health care professionals and patients appears to be one of the main challenges with bowel control problems. Being able to talk about the problem is the first step in both prevention and treatment,” said Dr. Stephen P. James, Director of the NIDDK’s Division of Digestive Diseases and Nutrition. “People experiencing bowel control problems need to know that they are not alone and that the condition can be managed. The Bowel Control Awareness Campaign will inform health care professionals and the public that bowel incontinence is a common condition and that effective treatments are available.”

STORY OF DISCOVERY

Celiac Disease

Although celiac disease had been described and named by the Greek physician Aretaeus of Cappadocia in the Second Century A.D., nearly 2 millennia passed before the cause of this disease was identified and a reliable treatment was discovered. Celiac disease is now known to be driven by an aberrant inflammatory immune response to foods that contain gluten, a component of wheat, rye, and barley. People with this disease may have symptoms such as vomiting, diarrhea, weight loss, and, for children, failure to grow and thrive. However, great individual variation in the intensity and spectrum of symptoms makes celiac disease difficult to diagnose. The critical identification of gluten as the trigger of celiac disease took place in Europe in the mid-20th century. Since then, the NIDDK has also been a major supporter of scientific advances that are now revealing the mysteries of this complex disease.

During what was known in the Netherlands as the “Winter of Starvation” during World War II, the Dutch pediatrician, Willem-Karel Dicke, substantiated his belief that cereals were responsible for the symptoms of celiac disease. Although the pressures of the war had brought unprecedented food shortages, Dr. Dicke, Medical Director of the Juliana Children’s Hospital in The Hague, witnessed improvement in his young celiac patients who had been suffering from abdominal pain and diarrhea before basic foods such as cereal became scarce, only to relapse when bread was dropped into the Netherlands by Allied planes. Watching this scenario unfold convinced Dr. Dicke that grain was the cause of his young patients’ illnesses and he began a series of experiments that would validate his theory. Dr. Dicke published two articles in 1953, the first showing that wheat flour (not wheat starch) caused celiac disease, and the second demonstrating that the gluten component of wheat flour was the primary cause of the disease. Within 4 years, two additional medical breakthroughs significantly changed the methods for diagnosis of celiac disease. One was

the description of a deterioration of the intestine’s fingerlike projections, called “villi,” that resulted in a characteristic flattening of the surface of the intestinal lining in celiac patients. The other was the development of a procedure to perform biopsies of the small intestine to detect and monitor this villi atrophy. The biopsy was soon improved with the introduction of a more flexible device called the “Crosby Capsule.” In 1969, the “Interlaken criteria” was developed as the gold standard for diagnosing celiac disease. In 1990, the Interlaken criteria was modified to take advantage of a research study published the previous year that determined accurate diagnosis could be accomplished by screening with celiac-specific antibodies that had been identified, followed by a single biopsy.

Celiac disease at one time was thought to be primarily a European disease. However, a study in 2003 showed the prevalence of celiac disease in the United States was approximately 1 percent of the population—100 times greater than previously thought. In another NIDDK-supported study, researchers sought to determine the incidence of celiac disease and how it may be affected by genetic variation within *HLA* genes, a set of immune system genes. They screened over 22,000 newborns for a particular *HLA* gene known to be associated with celiac disease and followed a subset of the infants for 5 years. Comparisons of celiac disease onset in children having zero, one, or two copies of the celiac disease-associated *HLA* gene found that, overall, about 1 percent of the children at age five were estimated to have celiac disease. Children with one or two copies of the celiac-associated *HLA* gene were shown to be at increased risk of celiac disease compared to children without the gene.

The *HLA* genes *DQ2* and *DQ8* are the strongest genetic contributors to celiac disease. Coincidentally, *HLA-DQ2* and *-DQ8* are also type 1 diabetes susceptibility genes, and having one of these diseases is associated with

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increased risk for the other disease. In celiac disease, the HLA proteins (encoded by the *HLA* genes) present gluten fragments to immune T cells via “receptors” on the surface of the cells, and this interaction initiates an aberrant immune response against the gluten protein. To better understand how HLA-DQ8, in particular, interacts with gluten, NIDDK-supported researchers examined the molecular properties of the DQ8 protein. The researchers found that the DQ8 variant contains an unusual positive electrical charge that enables it to interact not only with a negatively charged, modified gluten fragment but also with the unmodified native gluten fragment to elicit an immune response. However, gluten fragments with different electrical charges interact with different sets of T cell receptors. Negatively charged fragments interact with a large repertoire of receptors. In contrast, the unmodified gluten fragments interact with a very limited set of receptors. The ability of DQ8 to elicit immune responses to both forms of gluten fragments may lead to the excessive immune reactivity to gluten in celiac disease.

Although HLA-DQ8 is linked to celiac disease, not everyone who has this form of HLA develops the disease. Researchers thus sought to gain additional insights into the immune response to gluten by generating a new mouse model of the disease. These mice not only had the *HLA-DQ8* gene, but they also produced high levels of another immune molecule, IL-15, similar to humans with celiac disease. IL-15 can alter a pathway that normally allows tolerance to food; this pathway also involves retinoic acid, a vitamin A metabolite. The researchers fed a component of gluten to these and other mice. They found that mice that harbored HLA-DQ8 but not elevated IL-15 were tolerant of the gluten protein. By contrast, in the mice with both HLA-DQ8 and elevated IL-15, the retinoic pathway was altered by the presence of excessive IL-15, triggering an inflammatory response to gluten characteristic of celiac disease.

Through genome-wide association studies, researchers supported by the NIDDK have successfully identified

additional celiac disease susceptibility genes and are gaining insight into their disease consequences. One study identified two gene variants that are required for celiac disease and 12 chromosome regions associated with celiac disease risk. A subsequent study looked for variants that could have smaller, yet critical, effects on disease risk. This study included DNA samples from a larger number of celiac disease patients and healthy volunteers that were analyzed using a denser concentration of probes. This approach was successful in uncovering 13 new chromosome regions associated with celiac disease and 13 additional chromosome regions with suggestive celiac disease associations. Many of the regions were found to contain genes with functions related to the immune system. In addition, analysis of the genetic variants led to the identification of four specific immunological pathways that are relevant to the pathogenesis of celiac disease.

Research on the effects of undiagnosed celiac disease has had mixed results. One study compared undiagnosed celiac disease in three groups of men by screening samples of their blood for celiac disease-specific antibodies, which would indicate presence of the disease. Samples from U.S. Air Force personnel that were taken and stored frozen 45 years earlier were compared to current samples from men the same age as the Air Force personnel, and younger men, the age the Air Force personnel were when their blood samples were taken. Death rates from all causes were found to be nearly 4-fold higher for men with undiagnosed celiac disease than for those without the disease. Analyses comparing the older and younger men found that the prevalence of undiagnosed celiac disease increased more than 4-fold over 50 years. Another study screened almost 17,000 American men and women 50 years of age and older, and found that over a 10-year period, undiagnosed celiac disease did not increase their risk of death, although other health consequences were observed. Those who had undiagnosed celiac disease had increased risk of osteoporosis and hypothyroidism, but they also had lower BMIs (body mass index) and cholesterol levels.

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Because these two studies differ in epidemiological criteria, such as the participants' ages and periods of observation, direct comparisons cannot be made between them. New studies will be needed to better understand the effects of undiagnosed celiac disease.

Research has also led to a new strategy for detection of celiac disease. A study compared tests for two different types of antibodies made by the immune system of celiac patients: antibodies to a small modified gluten protein called DGP, and those to a protein called transglutaminase (TGAA). The scientists followed 50 children, 6 months to 17 years of age, who were participants in the NIDDK-sponsored Celiac Disease Autoimmunity Research (CEDAR) study. The children were at high risk for developing celiac disease because of their genetic predisposition to celiac disease and/or type 1 diabetes. Antibody levels to DGP and TGAA were tracked over time, beginning prior to their disease diagnosis until they were detected. The study found that detection by the newly developed DGP antibody test was earlier in certain individuals and provided a more sensitive tool for evaluating the success of a gluten-free diet intervention.

Through NIDDK-supported studies of the cells lining the intestine, scientists have made additional discoveries about what goes awry in celiac disease. These intestinal cells possess fingerlike villi that protrude into the intestine, creating a large surface area through which small nutrient molecules are absorbed. Aligned closely together, these cells are joined by "tight junctions" that normally form a barrier to large molecules such as gluten. In people with celiac disease, the intestinal cells secrete a protein called zonulin which causes the tight junctions to loosen, allowing gluten to breach the intestinal barrier. Once gluten breaches this barrier, it precipitates an inflammatory response. Of note, small intestinal exposures to bacteria and gluten have been identified as two of the more powerful stimuli of zonulin secretion. The knowledge that gluten-triggered zonulin

release led to the hypothesis that inhibiting zonulin might prevent gluten from entering and damaging intestinal tissue. Early clinical studies with a zonulin inhibitor have shown promise, but additional studies are needed to determine if this approach will be a successful treatment.

Although research studies had shown that the prevalence of celiac disease in the United States was approximately 1 percent, it was considered by many to be a rare disease and, therefore, at risk of being undiagnosed. In 2004, the NIDDK and the NIH Office of Medical Applications of Research sponsored the Consensus Development Conference on celiac disease, focusing on awareness, diagnosis, and management of celiac disease. In the Consensus Statement following the meeting, a Conference panel concluded that heightening awareness of celiac disease was imperative and recommended that the NIDDK lead an educational campaign for physicians, dietitians, nurses, and the public, informing them about celiac disease. In response to this recommendation, the NIDDK's National Digestive Diseases Information Clearinghouse launched the Celiac Disease Awareness Campaign. The Campaign remains a vital resource for the celiac disease community, offering fact sheets, booklets, practice tools for health professionals, NIH research information, and resources from professional and voluntary organizations that focus on celiac disease. These science-based Campaign materials can be accessed at www.celiac.nih.gov/

The NIDDK and the many celiac disease research scientists it supports continue the quest to gain insight into the complex underpinnings of celiac disease in pursuit of improved diagnostics, treatments, and a cure. Until the time this is accomplished, a gluten-free diet provides a treatment that relieves the symptoms of most celiac disease patients, and the Awareness Campaign continues its mission as an important resource for the celiac disease community.

New Clues to Liver Cell Death by “Toxic Fat”

Dr. Gregory J. Gores

Dr. Gregory J. Gores is the Reuben R. Eisenberg Endowed Professor in Gastroenterology and Hepatology, Professor of Medicine, and Chair of the Division of Gastroenterology and Hepatology at the Mayo Clinic in Rochester, Minnesota. Dr. Gores earned his M.D. from the University of North Dakota and completed his residency in internal medicine and fellowship training in gastroenterology and hepatology at the Mayo Clinic, followed by a post-doctoral fellowship in the Department of Cell Biology at the University of North Carolina at Chapel Hill. His research is focused on the mechanisms of liver cell death in models of relevance to human disease. Dr. Gores has received support from the NIDDK since 1989, and he has received a MERIT award from the Institute for his high research productivity. He has published over 400 original articles, book chapters, reviews, and editorials. Dr. Gores presented research findings from work conducted in his laboratory at the February 2011 meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council. The following are highlights from his presentation.

Dr. Gores set the stage by describing the problem of nonalcoholic fatty liver disease, a condition in which excess fat is stored in the liver. Usually associated with other metabolic conditions, such as obesity and type 2 diabetes, this condition and its more severe form, called nonalcoholic steatohepatitis (NASH), have increased in prevalence in American adults and children in concert with the obesity epidemic. In those who develop NASH, their livers not only store excess fat, but also show signs of cell injury, inflammation, scarring (fibrosis), and cell death that are similar to changes found in the livers of individuals with alcoholic liver disease. But, the case of exactly how liver injury and cell death develop as nonalcoholic fatty liver disease progresses is far from closed, as researchers

track down the cellular pathways and molecular partners responsible. If scientists could crack the case of how nonalcoholic liver disease and NASH develop, they would then be able to design better prevention and treatment strategies. Dr. Gores shared some of his lab's progress in solving the mystery of how fat in the liver turns “lipotoxic” (literally, toxic fat), injuring cells and contributing to the development of nonalcoholic fatty liver disease and NASH.

Exhibit A: Death by Apoptosis

Upon close inspection under a microscope, liver samples taken from people with NASH display a sobering scene, with many of the liver cells, called hepatocytes because they represent the major type of “hepatic” or liver-related cell, undergoing a type of cell death called apoptosis. When cells die by apoptosis, their DNA and other cellular components break down into small “apoptotic bodies.” Because Dr. Gores and his team of experienced investigators had seen this before in other types of liver disease, they asked whether hepatocyte apoptosis was a truly unique hallmark of NASH compared to other conditions involving fatty liver, such as simple steatosis (fat in the liver without noticeable signs of injury) and alcoholic hepatitis. Using an assay that counts the number of cells undergoing apoptosis, they compared liver samples taken from people with these conditions. They found that hepatocyte apoptosis was indeed more dramatically elevated in the livers of people with NASH. Additional assays showed that the number of hepatocytes dying by apoptosis correlated with the level of inflammation and scarring present. From this evidence, they deduced that liver cell death by apoptosis plays an important part in NASH. These researchers went on to find that fragments of major structural liver cell proteins, broken down during apoptosis, ended up in the blood of people with

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NASH, but not in those with only fat in the liver or no liver condition, offering a possible diagnostic alternative to liver biopsy.

Dr. Gores next turned to his group's investigations into the fate of the many apoptotic bodies that are formed in the livers of patients with NASH when hepatocytes undergo apoptosis. They knew that another cell type in the liver—the stellate cell—contributed to fibrosis (scar tissue formation) following liver injury in many forms of chronic liver disease. Could the liver's stellate cells be engulfing these apoptotic bodies and then developing “indigestion,” promoting the development of scar tissue formation? To test their theory, they treated hepatocytes grown in the laboratory (in cell culture) with UV light to prompt damage and the formation of apoptotic bodies, which were then added to a culture of human hepatic stellate cells. Because the researchers also marked the apoptotic bodies and the cells with different fluorescent dyes, they could clearly see the stellate cells swallowing up the apoptotic bodies. Soon after engulfing the apoptotic bodies, the stellate cells increased their production of collagen, a material that accumulates during scar formation. These findings implicated stellate cells in the development of liver scarring.

Prime Suspects at the Molecular Level

Dr. Gores and the members of his lab knew that the stellate cells were not acting alone to cause nonalcoholic fatty liver disease. Other prime suspects in causing liver injury in this disease were “free fatty acids,” which are released into the blood in large amounts by the body's fat tissue in individuals who are obese, insulin resistant, and/or have nonalcoholic fatty liver disease. These fatty acids were suspected of traveling to the liver, where they might behave like Dr. Jekyll or Mr. Hyde—either quietly storing energy as a form of fat called triglycerides, which are thought to be relatively harmless to the liver, or having a more sinister effect by causing hepatocytes to die by apoptosis. But, the researchers had to catch the fatty acids in the act.

They set up cell cultures with rodent hepatocytes and then added either of two types of free fatty acids: a saturated fatty acid called stearic acid, found in animal tissues and foods such as meat and dairy products, or a monounsaturated fatty acid called oleic acid found in olive oil. Then they watched as a large number of the cells cultured with stearic acid died by apoptosis—the saturated fatty acid had been caught red-handed. When they treated mouse and human liver cells in culture with another saturated fatty acid, palmitic acid, they observed the means by which these fatty acids can cause liver cell death. Palmitic acid stimulated liver cell production of a protein known to increase apoptosis called PUMA. Elevated PUMA levels were also detected in liver tissue samples taken from patients with NASH. The researchers inferred that saturated fatty acids acted through PUMA to cause liver cell apoptosis in NASH.

For further proof of PUMA's role in mediating the toxic effects of saturated fatty acid on liver cells, the researchers removed PUMA from the equation by genetically altering mice to be deficient in this protein. Without PUMA, hepatocytes were resistant to apoptosis caused by the saturated fatty acid palmitic acid, implicating PUMA as a go-between in carrying out the fatty acid's lipotoxic effects. Upon additional sleuthing, they identified another accomplice in the form of a signaling protein called JNK1. In mouse hepatocytes treated with palmitic acid, PUMA levels rose in mice with normal JNK1, but not in mice lacking this protein. A picture was beginning to emerge of this complex chain of events: in nonalcoholic fatty liver disease, saturated fatty acids released by the fat tissue traveled to the liver and activated the signaling molecule JNK1, which elevated PUMA levels, leading to liver cell death by apoptosis, followed by stellate cell activation and scar formation.

Tiny RNAs to the Rescue?

Now that the researchers had their line-up of molecular suspects involved in liver cell death and scarring due to toxic fat, they turned their attention

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to looking for ways to limit this group's activities in the future and prevent nonalcoholic fatty liver disease progression. MicroRNAs were a natural choice as a possible disease-fighter because others had noticed that levels of these tiny molecules were altered in human NASH. MicroRNAs are capable of blocking protein production. In liver samples from people with NASH compared to obese people without NASH, levels of a particular type of microRNA known as miR-296 were reduced and accompanied by higher PUMA levels. By boosting levels of miR-296 in hepatocytes in culture, they were able to keep PUMA levels in check, suggesting new therapeutic possibilities for limiting hepatocyte apoptosis in human NASH. For example, by developing drugs or therapeutic microRNAs that target PUMA or other components of the cell death pathway, scientists may one day find a means to reduce liver damage in patients with NASH.

Conclusions

In presenting his lab's ongoing research, Dr. Gores made the case that free fatty acids, especially the saturated kind, are a major culprit underlying liver cell death by apoptosis in nonalcoholic fatty liver disease, and he showed that stellate cells play a key role in subsequent scar formation. These investigations also shed light on the cellular partners and pathways used by the free fatty acids to carry out this deed, as well as possible molecular targets for limiting disease. This research is improving understanding of the molecular pathways responsible for the liver injury that occurs in forms of nonalcoholic fatty liver disease such as NASH. Beyond getting to the bottom of this hepatic whodunit, these investigations could also lead to the development of new diagnostic and therapeutic approaches to nonalcoholic fatty liver disease in the future.

Durga Dingari

One Woman's Journey Living with Chronic Pancreatitis



Durga Dingari

When 42-year-old Durga Dingari says she has her “good days and bad,” for most of us that would be a gross understatement.

A native of India, now living in the United States, Durga experienced her first pancreatic attack in her home country in 1994, at the age of 26. “I didn’t know what was happening to me. The pain was unbearable,” she says. “I started vomiting.” At first she thought it was acid reflux.

Shortly after the attack, Durga underwent a procedure called an endoscopic retrograde cholangiopancreatography, or ERCP, which enables physicians to diagnose problems in the liver, gallbladder, bile ducts, and pancreas. But the test revealed nothing.

The following year, Durga, her husband, and their then 4-year-old son immigrated to the United States for her husband’s job as a software engineer. “At the time I arrived in the United States, I was 70 pounds,” says

Durga. However, within months she says she started feeling better, regained the weight she had lost, and had completely forgotten about her pancreatic attack. Everything seemed to be going fine.

Then, in 1998, while attending her mother-in-law’s funeral in India, Durga suffered another major pancreatic attack. Again, she recovered. A CT scan showed some calcification (hardening due to calcium deposits) of her pancreas, but her gynecologist told the Dingaris that it would be safe to go ahead with their plans for having a second child.

“It was a hard pregnancy,” Durga says. She suffered from the pancreatic attacks, as well as gestational (pregnancy-related) diabetes, and in the final stages of her pregnancy ended up on bed rest. Despite these difficulties, her daughter was born in January 2000, which “was the happiest day of our lives,” after such a tense pregnancy. The Dingaris named their daughter Spoothi, which means “inspiration.”

Ever since then, Durga has needed all the inspiration she can muster to battle her pancreatic condition and the pain it brings.

“I didn’t know what was happening to me. The pain was unbearable,” says Durga of the first pancreatic attack that began her journey living with chronic pancreatitis.

Within 2 weeks of giving birth to her daughter, Durga again suffered severe pain that began a cycle of hospital admissions and a seemingly endless series of medical procedures, including the removal of calcified

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stones from her pancreas. Her attacks continued, and Durga next underwent a pancreatic operation called a Puestow procedure. In this operation, used to treat pain associated with chronic pancreatitis, the pancreatic duct is connected to the small intestine so that pancreatic secretions can drain directly into the intestine. During the operation, Durga's surgeons realized that her gallbladder was also damaged and they removed it. Durga spent the next month in the hospital recovering from her surgeries.

Once again, she was fine for a few months before the pancreatic attacks started to recur. "Eating caused pain and lots of attacks. It's hard to describe what my family and I were going through," says Durga.

Her health continued to deteriorate. "But I was given new hope from another chronic pancreatitis patient who told me that she had gotten her life back" through a surgical intervention called a Whipple procedure.

During this surgery, the head of the pancreas, a portion of the bile duct, the gallbladder, and part of the small intestine are removed. Occasionally, a portion of the stomach may also be removed. After these structures are removed, the remaining pancreas, bile duct, and intestine are sutured back together to direct gastrointestinal secretions back into the gut.

But before physicians could do the procedure, Durga first had to regain her weight and nutritional status. It was now 2001, and Durga's weight had dropped back down to 70 pounds. So surgeons implanted a type of feeding tube called a jejunostomy tube, or "J-tube" in the upper section of her small intestine, just below the stomach. The purpose of the J-tube is to provide elemental nutrients—including salts, glucose, amino acids, lipids, and added vitamins—to the patient while bypassing the usual process of eating and digestion.

Once Durga's weight and nutritional status were satisfactory, she underwent the Whipple procedure. Unfortunately, in a relatively short period of time, her

pain returned. "I was totally devastated," says Durga. She was told then that she had a form of pancreatitis called "idiopathic" chronic pancreatitis.

About Chronic Pancreatitis

The pancreas is a small gland nestled near the small intestine. It is responsible for producing enzymes that, mixed with bile from the gallbladder, aid in the digestion of food. In a healthy pancreas, these enzymes are released in an inactive form, to become activated only when they reach the intestine. However, when the pancreas is inflamed, as in pancreatitis, these enzymes become activated while still within the pancreas, where they degrade the very tissue that produced them, causing episodes of pain that can range from mild to severe. Pancreatitis can be acute, with inflammation resolving within a few days, or chronic, involving long-term inflammation and tissue damage.

A variety of factors may contribute to chronic pancreatitis, including genetic and other factors, but the form of the disease that Durga has, "idiopathic" chronic pancreatitis, is the result of unknown causes. People who have a history of diabetes in their family also are at greater risk for contracting the disease, usually between the ages of 30 and 40. In Durga's case, many of her relatives have either type 1 or type 2 diabetes.

Over time, chronic pancreatitis leads to permanent damage to the pancreas. In addition, patients who, over a long period of time, suffer with the disease are at increased risk for pancreatic cancer, which is one of the most devastating of all malignancies.

Pancreatitis also can be excruciatingly painful. On a good day, medications keep Durga's pain bearable. "On a bad day I feel like the pain is going to kill me," says Durga. In the past, these painful episodes have often necessitated a trip to the nearest hospital emergency room.

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Currently, there are no cures or preventive therapies for chronic pancreatitis. Even when their appetite and eating habits are normal, people with chronic pancreatitis often lose weight. The weight loss occurs because the body does not secrete enough pancreatic enzymes to digest food, so nutrients are not absorbed normally. Patients' symptoms and complications from the disease are treated through a combination of rehydration and pain management therapy, nutritional support and pancreatic enzyme supplementation, and eating a nutritious, low-fat diet while also avoiding smoking and alcohol consumption.

Living with Chronic Pancreatitis

Over the years, Durga has undergone two pancreatic surgeries and numerous other procedures related to her condition. She often takes up to 10 painkillers a day. Even before the onset of her chronic pancreatitis, Durga was a small woman weighing approximately 100 pounds. Today, she takes pancreatic enzyme supplements when she eats to make up for her limited pancreatic function and aid her digestion. However, Durga says she struggles to maintain her weight at 94 or 95 pounds.

"My diet consists mainly of toast with honey, coconut water, and yogurt," she says, but adds that even these mild foods often don't agree with her. Currently, Durga is getting much of her nutrition from a combination of the J-tube and a treatment called total parenteral nutrition, or "TPN," a nutritional support intervention in which a nutrition-laden solution runs through a line connected to one of her veins, and like the J-tube, bypasses the usual process of eating and digestion.

In the meantime, Durga courageously struggles on a daily basis with her pain, and strives to lead as productive and normal a life as she can with her family, including her now 21-year-old son and 11-year-old daughter.

"I try to keep myself as busy as possible so I don't think about my condition," says Durga, and adds with

great emotion, "I don't want my kids to worry about me too much. They are good, smart kids and I want them to have a good and normal life."

Despite her pain, Durga hosts her own Internet radio show in her mother tongue, Telugu, in which she selects Indian songs and comments on their style and lyrics, "especially if they relate to my life and family. I share everything with my listeners—things regarding my health, my children, my family, everything." She also authors her own blog, and of late has taken an interest in beadwork, which she does to pass the time when she's taking in nutrients through her J-tube. "I give most of my beadwork away as gifts," she says with a sense of joy and satisfaction, which helps to make the bad days a little brighter.

"I try to keep myself as busy as possible so I don't think about my condition," says Durga, a wife and mother-of-two who does beadwork, authors a blog, and even hosts her own Internet radio show. "I share everything with my listeners—things regarding my health, my children, my family, everything," she says.

Hope Through Research

The NIDDK actively supports research on many forms of pancreatitis to help people like Durga, who suffer from this disease. NIDDK-sponsored research has led to such advances as the discovery of genetic factors associated with hereditary and chronic forms of pancreatitis, as well as understanding the mechanisms by which pancreatic enzymes are formed and lead to damage in acute pancreatitis. The NIDDK also supports an initiative to encourage clinical and epidemiological research studies to facilitate the translation of promising new developments into the clinical setting for diseases such as pancreatitis.

With NIDDK support, scientists are currently conducting research to identify biomarkers to

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facilitate diagnosis, additional genetic triggers to improve understanding of risk factors and disease processes, mechanisms underlying debilitating pancreatitis symptoms such as pain, and nutritional support and novel treatments. For example, the North American Pancreatic Study 2 is a multi-center clinical study building on past research to try to uncover additional genetic markers that may help to identify individuals susceptible to pancreatitis. Researchers hope to discover new approaches to prevent and/or treat pancreatitis and its disease progression. The study is also investigating whether there are any racial or ethnic differences that put some groups at higher

risk than others for developing pancreatitis in response to genetic and environmental factors. An ongoing clinical trial, the Study of Nutrition in Acute Pancreatitis (SNAP), is designed to test the effectiveness of different “enteral” feeding methods—which deliver nutrients through a tube placed either through the nose to the stomach or in the small intestine—in providing nutrition to patients with severe acute pancreatitis who cannot eat by mouth.

For more information:

<http://digestive.niddk.nih.gov/ddiseases/pubs/pancreatitis/index.aspx>