This is a chapter from the NIDDK’s Annual Report. The full Report includes highlights of research on these and many other areas across the NIDDK’s mission and is available at:

www.niddk.nih.gov/about-niddk/strategic-plans-reports/niddk-recent-advances-emerging-opportunities
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The nervous system in the gut—such as the neurons (shown in red) and glia (shown in green) in the microscopy image above—relays signals between the brain and the immune system. As described in this chapter, scientists have demonstrated that stress exacerbated intestinal inflammation in different mouse models of inflammatory bowel disease (IBD) and found evidence for the specific molecular pathways responsible. The researchers found evidence that these pathways likely play the same role in IBD in people as well, a finding that sheds light on the underlying mechanisms linking stress to IBD flare-ups.

Image used courtesy of the lab of Dr. Christoph Thaiss, University of Pennsylvania. Image credit: Markus Schneider, Klaas Bahnsen, and Niklas Blank.
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. To reduce the burden of digestive diseases, NIDDK-supported scientists are pursuing research to better understand how widespread these diseases are across the United States and in specific population groups; identify their causes and how they progress; and test new interventions for prevention and treatment, including drugs, surgery, and behavior modification.

Digestive diseases can exact a significant toll on individuals across the lifespan, resulting in a lower quality of life, years lost due to premature death, and costs associated with hospitalization and pharmaceutical and surgical interventions. The burden of digestive diseases in the United States is substantial: based on recent data, it is estimated that digestive disease is the primary diagnosis in a total of 66.4 million ambulatory care visits to physicians’ offices and hospital emergency and outpatient departments in the United States each year.1 Similarly, analyses with 2020 national inpatient samples identified 3.5 million hospitalizations with a primary diagnosis of digestive diseases and 15.1 million hospitalizations with a primary or secondary diagnosis of digestive diseases.2 In addition, analyses focusing specifically on the clinical and economic burden of emergency department visits identified 15.5 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling $113 billion in 2020.3 (Note that the 2020 statistics are likely underestimates due to pandemic-related health care challenges.)

Inflamatory bowel disease (IBD), an umbrella term for chronic and painful intestinal diseases that include Crohn's disease and ulcerative colitis, is marked by damaging intestinal inflammation that can cause rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. IBD often strikes early in life, with a peak age of onset in adolescence or young adulthood. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to repair damaged intestinal tissue will help predict the best course of treatment and catalyze the design of novel, more personalized therapeutic strategies.

Scientists are investigating the complex interactions among the genetic, environmental, immune, microbial, and other factors that contribute to, or protect against, the development of inflammatory bowel disease.

Diseases of the stomach and intestines also include peptic ulcer disease, which is typically caused by infection with the bacterium Helicobacter pylori or use of nonsteroidal anti-inflammatory drugs. Other stomach and intestinal disorders include functional

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GI disorders, such as irritable bowel syndrome (IBS), which can cause abdominal pain and altered bowel habits. Gastroesophageal reflux disease, in which caustic stomach acids rise up into the esophagus, can lead to a heightened risk of esophageal cancer. Gastroparesis is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. Fecal incontinence, or impaired bowel control, is a very prevalent condition, and because it is difficult to talk about, many people suffer without seeking treatment. Scientists continue to strive for a deeper understanding of the causes of GI disorders, which will lead to improvements in diagnosis and management.

In individuals with celiac disease, the immune system reacts to ingestion of gluten—a protein component of wheat, barley, and rye—resulting 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. Research advances in the understanding of genes and environmental triggers that are involved in the development of celiac disease may contribute to improved diagnosis and treatment.

Research to advance understanding of genes and environmental triggers involved in the development of celiac disease may contribute to improved diagnosis and treatment.

The microbes that inhabit the GI tract—also known as the intestinal microbiome—are important in maintaining the balance between digestive health and disease. These bacteria, viruses, and other microorganisms can affect long-term health and nutritional status, depending on their interactions with each other, with intestinal cells, and with nutrients ingested by their human host. Disruptions in this microbial ecosystem are associated with diseases such as IBD or infections by the harmful bacterium \textit{Clostridium difficile}. Scientists are gaining insights into the ways these GI microbes influence the development and function of the digestive tract and other systems throughout the body, such as those with immune and metabolic functions, as well as how the composition of the GI microbial community changes with factors such as age, geography, diet, and antibiotic usage.

In acute and chronic pancreatitis, digestive enzymes attack the pancreas from within, causing inflammation, loss of function, and severe pain. Advanced pancreatitis can be debilitating and may lead to cancer or diabetes, and because pancreatitis is difficult to detect in its early stages, many cases are advanced by the time they are diagnosed. Research has elucidated genetic and other factors contributing to pancreatitis that may lead to ways to treat or prevent this disease.

Serious adverse health effects can occur when the liver is functionally compromised by disease, which sometimes leads to scarring. Severe scarring (cirrhosis) can result in complete liver failure (end-stage liver disease). Some liver diseases primarily affect children, such as biliary atresia (a progressive inflammatory liver disease), while others generally affect adults, such as nonalcoholic fatty liver disease (NAFLD) or its more severe form, nonalcoholic steatohepatitis. In recent years, however, NAFLD in the United States has been increasingly diagnosed in children as well, concurrent with rising rates of overweight and obesity. NAFLD is also associated with health disparities: while the disease occurs in people of all races and ethnicities, in the United States it is more likely to affect those of Hispanic ethnicity. Some forms of liver disease are caused by viral infection, as in most cases of hepatitis, or by genetic mutations such as alpha-1-antitrypsin deficiency; others arise from factors such as autoimmune reactions, drug toxicity, bile duct obstruction, and other triggers, some of which are unknown. Many liver diseases, such as chronic hepatitis B and C, place individuals at elevated risk for developing liver cancer. When liver disease reaches the end stage, the only effective treatment is a liver transplant. Research is critical to identify liver disease early, find methods to preserve liver function in people with liver disease, and develop and further study new treatment options, including experimental, cell-based approaches to liver regeneration.

In recent years, nonalcoholic fatty liver disease has been increasingly diagnosed in children and adults in the United States, concurrent with rising rates of overweight and obesity.

NIDDK also funds research on nutrition-related disorders that 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. Investigators also conduct basic, clinical, and translational research on the requirements, bioavailability, and metabolism of
nutrients and other dietary components to understand dietary needs in health and disease. NIDDK staff work collaboratively with representatives from across NIH, including in NIH’s Office of Nutrition Research, to advance nutrition research efforts.

**EXPLORING INTESTINAL FUNCTION IN HEALTH AND DISEASE**

**Signals Between Nervous System and Intestinal Cells Control Protective Mucus Layer Production in Gut:**

New research in mice has discovered connections between the nerve cells of the gastrointestinal tract and mucus production in the gut, pointing to a role for these nerves in protecting the intestinal lining from damage and inflammation. Inflammation in the gut (e.g., colitis) can cause abdominal pain, a hallmark of many gastrointestinal diseases and disorders. Pain-sensing nerve cells—called nociceptors—envelop the gut, however their interactions with the cells of the gut itself are not fully understood. By better understanding the “cross-talk” between these cells, researchers could find new ways to help resolve the inflammation or to protect the intestines from further damage. It could also help scientists understand and treat painful gastrointestinal conditions like inflammatory bowel disease.

Researchers working with a mouse model recently found that nociceptors come into close contact with goblet cells—cup-shaped cells in the intestinal lining that secrete mucus to coat the inside of the gut—suggesting that signals from nociceptors might control mucus production. The mucus layer provides nutrients and a habitat for bacteria that aid digestion. It also creates an important physical barrier to protect the gut from those bacteria, so mucus production is critical for both preventing intestinal damage and maintaining a healthy microbiome. The researchers found that male and female mice that were genetically engineered to lack nociceptors had thinner mucus layers on their intestinal linings compared to mice with an intact intestinal nervous system, demonstrating that nociceptors do indeed control mucus production. The researchers also found that capsaicin (the "spicy" chemical in peppers) or products from gut bacteria triggered the release of a chemical signal called calcitonin gene-related peptide (CGRP) from nociceptors, and the goblet cells responded to this signal by secreting mucus. This means that when the gut is exposed to potentially damaging agents—either from the diet or bacteria—nociceptors can bolster the gut’s defenses by stimulating more mucus production. Not surprisingly, the mice with thinner mucus layers also had disrupted microbiomes and were more susceptible to experimentally induced intestinal inflammation (colitis), but the mice were protected from inflammation when the researchers administered CGRP to compensate for the lack of nociceptors.

These results identify a pathway whereby nociceptors can sense insults to the gut and respond not only with pain but also with a signal to help protect the gut. More work is needed to confirm that a similar pathway exists in humans, but these insights could help researchers develop new ways to treat intestinal inflammation and abdominal pain while minimizing disruptions to the intestinal barrier.


**A Link Between Cellular Stress and Gut Inflammation:**

Scientists determined how a state of cellular stress in the inner lining of the gut promotes production of a type of immune cell linked to chronic inflammatory diseases. The inner lining of the gastrointestinal tract, called the intestinal epithelium, absorbs nutrients into the body and acts as a barrier restricting entry of harmful factors. Damage to the intestinal epithelium plays a role in chronic inflammation and development of inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis. Understanding how a healthy intestinal epithelium is maintained and what leads to damage is critical to broadening knowledge about inflammatory bowel diseases and developing prevention and treatment strategies.

In this study, scientists explored how the intestinal epithelium promotes production of Th17 cells—immune system cells that produce a protein called IL-17 and
contribute to both the protective barrier of the intestinal epithelium and to chronic inflammatory conditions. Th17 cell production is triggered by microbes adhering to the epithelium, but it is unclear how the epithelium orchestrates this response. Knowing that epithelial cells are susceptible to a cellular state known as endoplasmic reticulum (ER) stress, where the capacity of a cell to properly shape newly generated proteins becomes overwhelmed, they sought to determine if ER stress in the intestinal epithelium influenced production of Th17 cells. To do so, they utilized two mouse models of ER stress and found an increased number of Th17 cells in both models. Interestingly, this increase in Th17 cells occurred in the mouse model even in the absence of gut microbes. This suggests that ER stress is a key player in Th17 production, and that, in wild-type mice, microbes may boost Th17 cell production by invoking ER stress in the epithelium. Additional experiments revealed that this response required production of a family of molecules called purine metabolites, most notably the small molecule xanthine.

To explore whether ER stress was linked to Th17 cell production in humans, the researchers looked at genes with increased activity in biosamples from people with ulcerative colitis and people with Crohn’s disease. They noted that Th17-, ER stress-, and purine metabolism-associated genes were increased in the samples, suggesting that the response observed in mice is also associated with inflammatory bowel diseases in humans. These studies revealed how ER stress in the mouse intestinal epithelium leads to increased production of Th17 cells, generating new knowledge of intestinal epithelium biology. Additional research will be needed to elucidate what causes Th17 cells to promote chronic inflammation and lead to the development of inflammatory bowel diseases.

Duan J, Matute JD, Unger LW,...Blumberg RS. Endoplasmic reticulum stress in the intestinal epithelium initiates purine metabolite synthesis and promotes Th17 cell differentiation in the gut. Immunity 56: 1115-1131. e9, 2023.

The Complex Interplay of Diet and the Gut Microbiome Influences Human Health: In a controlled feeding study in people, researchers found that a diet designed to nourish the gut microbiome led to altered microbial composition, diversity, and function; changes in people's hormones; and improved energy balance (i.e., the relation of calorie intake to calories used or excreted). Gut microbes have long been associated with body weight and metabolism through their ability to harvest energy from food. However, prior studies in people have lacked the precision necessary for a comprehensive evaluation of the contributions of the gut microbiome to energy balance. Thus, in this randomized study, the researchers developed a diet intervention to address these critical knowledge gaps.

Employing a microbiome enhancer diet (MBD) designed to deliver more fiber and other dietary sustenance to the gut, the researchers gave 17 healthy, weight-stable men and women either the MBD or a standard, Western diet (WD) with less fiber and more processed foods for approximately 3 weeks. This was followed by the other diet for the same amount of time. Using specialized laboratory techniques in a metabolic ward, the researchers measured energy intake, energy expenditure, and energy output (fecal and urinary) in each participant on each diet and made "within-participant" comparisons. They found that, compared to the WD, the MBD led to an additional 116 calories lost in feces daily, meaning less energy available for the person to metabolize and improved energy balance. When they explored compositional and functional changes in the microbiome, they discovered that the MBD led to an altered diversity of microbes and to an increase in microbes with an ability to break down nutrients, such as fiber, more efficiently to produce beneficial molecules compared to the WD. In addition, the researchers uncovered a small, but measurable, decrease in body fat stores on the MBD. Lastly, the MBD was associated with a notable increase in circulating hormones that are known to promote a feeling of fullness.

Taken together, these results suggest that an intentional remodeling of the gut microbiome through provision of adequate dietary fiber and minimally processed foods can modulate human energy balance. Future research on the complex interplay of diet and the gut microbiome could lead to personalized nutrition approaches.


UNDERSTANDING INFLAMMATORY BOWEL DISEASE

Uncovering Biological Links Between Stress and Inflammatory Bowel Disease Flare-Ups: Researchers have identified biological pathways that link stress to worsening inflammatory bowel disease (IBD) symptoms,
suggested that strategies to reduce stress could be an important component of IBD treatment. IBD, such as Crohn’s disease and ulcerative colitis, is marked by chronic inflammation in the intestines that causes debilitating symptoms. Stress is known to significantly impact inflammatory processes in the body and has been associated with triggering IBD flare-ups. The biological processes that link stress to the severity of IBD flare-ups, however, are not well understood.

In new research, scientists found that stress exacerbated intestinal inflammation in different IBD mouse models. Comparing immune cells from colon tissue of stressed and control mice with IBD, the scientists found that stressed mice had higher levels of monocytes (a type of white blood cell) that promoted inflammation. The scientists next asked: how are stress signals transmitted from the brain to the gut to cause accumulation of monocytes? Surprisingly, they found that glucocorticoids—steroid hormones historically associated with reducing inflammation—were critical for triggering the observed stress-induced gut inflammation. They found that the glucocorticoids have two effects on the enteric nervous system (ENS, the gut’s nervous system). First, they activate inflammatory pathways in a subset of glial cells in the ENS. (Glia and neurons are the two main cell types in the ENS.) The glial cells in turn recruit monocytes to the gut, thereby exacerbating inflammation in the colon. Second, glucocorticoids result in more undifferentiated, or immature, neurons in the ENS. The larger proportion of undifferentiated neurons means there are less of the signals (neurotransmitters) that mature neurons release, resulting in abnormal intestinal motility (movement of content through the gut). Finally, by studying three different cohorts of people with IBD, the scientists found evidence that these pathways likely played a role in mediating the effect of stress on IBD flare-ups in people.

This study sheds light on underlying mechanisms that link stress to IBD flare-ups, identifying a key role for glucocorticoids interacting with glia in the ENS to increase the susceptibility of the gut to inflammatory triggers. It also suggests the importance of considering people’s mental health in the clinical management of IBD. Furthermore, the knowledge gained from this research may not only benefit people with IBD, but also those with other gut inflammatory diseases and other diseases that are worsened by stress.


Expanded Study Diversity Uncovers New Genetic Risk Factors for Inflammatory Bowel Disease: Researchers recently identified new genetic risk factors for inflammatory bowel disease (IBD) by analyzing the genomes of tens of thousands of people from countries in East Asia alongside the genomes of people with ancestry from European countries. The inclusion of people from East Asia significantly expands the diversity of IBD genetic studies and provides insights that will help to understand and predict the disease.

Finding effective treatments for IBD, an umbrella term for Crohn’s disease and ulcerative colitis, has been challenging because it arises from a complicated interaction between genetic and environmental factors, resulting in a disease that varies from person to person. Researchers in the International IBD Genetics Consortium, of which NIDDK’s IBD Genetics Consortium is a member, have been combing through the human genome to find genetic variations (variations in DNA) that increase risk of IBD. By 2022, genetic variations associated with IBD risk had been identified in close to 250 regions of the genome, providing insight into the biology of IBD and opening the door to the development of new treatments. Most of these studies, however, had been with participants from (or with ancestry primarily from) European countries, which limited genetic diversity and likely missed many genetic variations that could play important roles in IBD. (While everyone shares the same genes, and many genetic variations are also shared across ancestries, some genetic variations are more common in specific ancestries than others.)

Recently, researchers expanded the diversity of IBD genetics research by analyzing the genomes of close to 30,000 men and women from China, Japan, and Korea, including people with and without IBD, undertaking the largest IBD genetic analysis of participants from countries in East Asia to date. When the East Asian data were analyzed together with previous studies that included about 370,000 participants with ancestry from European countries, also including people with and without IBD, the researchers identified 81 new regions...
of the genome associated with the disease, raising the total number of IBD-associated regions to 320. The researchers found that, in general, the amount of IBD risk contributed by genetics was similar between the East Asian and European populations; however, the genetic risk for Crohn's disease was more influenced by ancestry than that for ulcerative colitis. They also tested whether the combined East Asian and European data would enable a more accurate prediction of IBD risk than the European data alone. Looking at IBD risk in Chinese individuals, the researchers found that the new data improved risk prediction significantly, underscoring the importance of including diverse study participants to improve ways of predicting the probability that any given individual might develop IBD.

By analyzing the genomes of tens of thousands of people from regions in East Asia, researchers identified new risk factors for inflammatory bowel disease (IBD), helping to understand and predict the disease.

In addition to improving risk prediction, increasing the diversity of participants in IBD genetic studies also deepened the understanding of IBD by enabling identification of specific genetic variations that could drive the disease in all people. NIDDK’s IBD Genetics Consortium is currently expanding the diversity of its cohorts further; additional studies could determine exactly how genetic variations may affect IBD development across individuals and whether they could potentially serve as targets for new IBD therapies.


IMPACTS OF PANCREATITIS PAIN

Pain Linked to Lower Physical and Mental Health in People With Chronic Pancreatitis: Researchers have shown that people who experience severe or constant abdominal pain due to chronic pancreatitis also have significant loss of physical and mental health, suggesting that they may benefit from ways to detect and manage pain-related conditions.

While researchers continue to search for effective ways to treat—and ultimately cure—chronic pancreatitis, other important efforts have focused on ways to manage the most commonly reported symptom: pain, which can be debilitating. In other chronic diseases, pain has been shown to affect several aspects of health, causing anxiety and depression, for example. Knowing the effects of pain on the quality of life for people with chronic pancreatitis is important because it could guide treatment approaches that would help manage the disease.

To determine how pain might shape the lives of people with chronic pancreatitis, researchers gathered information from men and women (488 with pancreatitis and 254 without) participating in the Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED). PROCEED is one of many clinical studies being conducted by the NIDDK- and NCI-sponsored Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, and is the first study in the United States to track chronic pancreatitis symptoms and progression in people over time. The researchers used a state-of-the-art assessment system for self-reported health called PROMIS (Patient-Reported Outcomes Measurement Information Systems), which was developed previously with NIH support. This assessment consists of questionnaires that provide highly reliable, precise measures of self-reported pain, along with measures of physical, mental, and social well-being. Applying PROMIS, the researchers found that the pain from chronic pancreatitis varies from person to person, ranging from no pain to severe pain, and from intermittent to constant pain. Most study participants, however, reported pain that was severe or constant, resulting in lower scores for overall physical and mental health. Severe or constant pain was also linked to declines in several specific health-related quality of life areas, including higher anxiety, depression, fatigue, and sleep disturbance. Participants with these categories of pain also had lower physical function, such as the inability to do everyday chores, and compromised ability to fulfill social roles.

This study provides strong evidence that, in addition to the life-threatening organ and tissue damage caused by chronic pancreatitis, the associated pain can have profound effects upon an individual’s mental and physical well-being. This suggests that people with chronic pancreatitis may benefit from additional screening and treatment to manage pain and pain-related conditions.

**PREVENTING AND TREATING LIVER DISEASE**

**Limits on Acetaminophen in Acetaminophen-Opioid Combination Medications Affected Causes of Acute Liver Failure:** Researchers found that a U.S. Food and Drug Administration (FDA) mandate limiting the amount of acetaminophen in combination opioid-acetaminophen pain relievers was associated with lower rates of acetaminophen and opioid-induced liver failure, although rates of liver failure from acetaminophen alone increased. The harms stemming from the opioid addiction crisis in the United States are well recognized, but pain relievers used in combination with (or instead of) opioids can also present safety hazards. Acetaminophen (or paracetamol) is a pain reliever and fever reducer commonly available over the counter and in prescription formulations combined with opioids. However, too much acetaminophen can cause liver injury or failure, and consumers can unintentionally ingest a dangerously high dose, especially if taking multiple acetaminophen-containing medications together. Combination acetaminophen-opioid medications can provide pain relief with lower doses of the two drugs, but previous research found that these combination medications might contribute disproportionately to acetaminophen overdoses. In January 2011, the FDA mandated that by March 2014 prescription combination acetaminophen-opioid products could only contain up to 325 mg of acetaminophen, reduced from the previous maximum of 750 mg. Manufacturers were also required to add a warning about the risk of liver injury to these medications’ labels. (This mandate did not affect over-the-counter acetaminophen products.)

To study the potential effects of this change, researchers used two large independent data sources, one on hospitalizations in the United States and the other on men and women with acute liver failure. By comparing hospitalization and acute liver failure rates, scientists concluded that after the FDA mandate went into effect, there was a significant reduction in the rate of hospitalizations associated with a combination of both acetaminophen and opioids, and in the rate of acute liver failure associated with this combination of medications. However, the rate of acute liver failure attributed to acetaminophen alone increased in the same time frame. Thus, the FDA rule on limiting the acetaminophen dose in combination acetaminophen and opioid preparations correlated with a decrease in the rate of acute liver failure and hospitalization associated with these medications. More research will be required to determine if this specific reduction in acetaminophen dosages caused these changes or if they were due to other factors, such as changes in labeling, prescribing patterns, or usage of either opioids or acetaminophen alone. Overall, these results illustrate the complexities of how acetaminophen is used and of balancing pain management and drug safety in real-world situations.


**Disrupting “Talk” Amongst Liver Cells Yields Therapeutic Targets for Nonalcoholic Fatty Liver Disease:** Researchers “listening in” on how liver cells chemically “talk” amongst themselves have uncovered a host of new targets for therapies against a common and advanced stage of nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease and its more severe form of nonalcoholic steatohepatitis (NASH) are common in both adults and children in the United States and around the world. No approved therapy exists for NASH, which is among the leading causes of liver transplantation and liver cancer. NASH is marked not only by excess fat accumulation in the liver, but also by liver inflammation and fibrosis, or scar tissue formation, mostly driven by overactivity of a type of liver cell called a hepatic stellate cell (HSC). Mechanisms driving this activation, or how to halt or even reverse it, are not fully understood.

One potential way HSCs can become activated is by talking amongst themselves and with other cells nearby. As part of this “conversation,” the activated HSCs also send their own signals, creating self-perpetuating feedback loops or circuits. Scientists wondered if, by zeroing in on these signaling circuits, they could interrupt them, breaking the cycle that keeps the liver cells activated and causes disease. They used a new technology capable of analyzing genetic products of single cells—simultaneously for millions of cells—to provide a unique signature for each cell based on its signaling components. Examining liver samples from women and men with NASH and from male and female mice with diet- and chemical-induced NASH, they identified some common circuits, composed of 68 unique proteins and their receptors, that emerge in the activated liver cells only during the late stage of NASH. The researchers then visualized these circuits using technologies that map contacts among neighboring cells. In this way, they showed the liver cells physically reaching out and becoming increasingly well-connected.
to each other over the disease course, enabling exchange of short-range signals to sustain their collective activation and drive disease progression. To explore the therapeutic applications of this finding, the team blocked one of the protein-receptor signaling circuits in cultured human liver cells and in the animal model and found that blocking this circuit led to inactivation of disease-causing liver cells.

In this study, the research team applied cutting-edge technologies in single-cell sequencing and imaging to uncover new insights into how to interrupt the “vicious cycle” of cellular signals underlying fibrosis in late-stage nonalcoholic fatty liver disease. This work offers a basis for developing what could be the first dedicated therapy for this common and severe form of liver disease.


Optimizing Treatment Regimens for Adults With Chronic Hepatitis B: In adults with chronic hepatitis B participating in NIDDK-funded Hepatitis B Research Network (HBRN) studies across North America, investigators tested whether a combination treatment regimen could increase long-term clearance of the virus. Chronic hepatitis B, a form of viral hepatitis, is a global problem that disproportionately affects people living in or originating from certain geographic areas, such as Asia and sub-Saharan Africa. If not appropriately treated, the disease can lead to cirrhosis, liver failure, and liver cancer. Effective treatments for chronic hepatitis B include interferon-based therapy, which targets immune cell function, and a class of drugs called nucleoside analogues that inhibit viral enzyme activity. However, these drugs’ effectiveness varies across individuals, in terms of reliably clearing the virus and ultimately preventing development of severe liver disease. In addition, these drugs often must be taken lifelong to prevent recurrence of disease; therefore, better treatments that clear the virus long-term are needed.

The NIDDK-funded HBRN conducted clinical trials of treatment approaches for chronic hepatitis B in a study population that was primarily men, women, and children of Asian descent. Though the Network studies concluded in 2022, data analysis and publication of results have continued, with study samples available for additional research through the NIDDK Central Repository. One HBRN clinical trial in adults, results of which were recently published, assessed the safety and efficacy of combining two treatments—a long-lasting form of interferon called peginterferon and the nucleoside analogue tenofovir—to increase the currently low or variable rates of viral clearance. Two hundred people with hepatitis B were treated, all of whom had active disease with high levels of viral DNA and elevations in serum liver enzymes, which indicate liver inflammation or disease. Half of the study participants’ samples contained the hepatitis B e antigen (HBeAg), a protein produced by the hepatitis B virus that signals an active infection. All study participants were treated with tenofovir for approximately 4 years; half also received peginterferon, but only for the first 6 months. After 4 years, those individuals who had received combination therapy had a higher rate of clearing the viral proteins and viral DNA, though nearly all study participants had an excellent clinical and biochemical response. An overall complete response with clearance of all hepatitis B proteins, however, was uncommon. Furthermore, almost all responses occurred in people with HBeAg and a single type of hepatitis B virus called genotype A2, found mostly in White and Black populations and rarely among those of Asian ancestry. At the 4-year point, study participants were eligible to continue or to stop tenofovir therapy, based on withdrawal of therapy being one approach to increasing the rate of complete viral clearance. One year after withdrawal of tenofovir therapy, slightly more of the participants who stopped treatment had complete clearance than those who continued therapy. Furthermore, a proportion of the study participants who elected to withdraw from further tenofovir therapy had a severe flare of hepatitis and had to be restarted on treatment.

These results indicate that the addition of peginterferon to tenofovir therapy for hepatitis B leads to an increased rate of response, but only in people with the viral protein HBeAg. Withdrawal of therapy after 4 years did not seem to increase the rate of complete response and could be followed by worsening of the hepatitis, requiring restarting of therapy. Future studies will continue to build on these findings to develop more effective, individualized approaches to treating people with hepatitis B.

CONNECTING THE MICROBIOME AND LIVER DISEASES

Complex Interplay Among Gut, Liver, and Microbes Underlies Metabolic Changes in Chronic Hepatitis C: A team including researchers from NIDDK’s Intramural Research Program uncovered how complex metabolic changes in the gut, its microbes, and the liver mirror the state of diseases such as chronic hepatitis C, which could lead to the development of new treatments for liver disease. The gut, the microbes it houses, and the liver all play central roles in the body’s metabolism of nutrients and their by-products. Nutrients and microbial products absorbed in the gut travel directly to the liver through the portal vein before they are further metabolized and distributed throughout the body. Liver disease, such as that resulting from chronic infection with the hepatitis C virus, not only damages the liver through inflammation and fibrosis (scar tissue formation), termed cirrhosis in severe cases, but also disrupts metabolic processing by human cells and microbes.

Scientists selected chronic hepatitis C as a disease model in which to study how these complex metabolic and microbial changes correlate with the degree of liver disease. They recruited 23 men and women with chronic hepatitis C, either with or without cirrhosis present, to participate in a study at the NIH Clinical Center. Assessments included measures of human- and microbe-produced metabolites in blood samples from the portal vein and arm, liver biopsies, and fecal samples, taken initially and then 6 months after treatment with antiviral drugs to eliminate the viral infection. Over time, they found an anticipated uptick in immune activity and inflammation in these individuals, but also dampened gut-liver metabolism, particularly in utilizing fat for energy. Within the liver, these metabolic changes were localized to cellular structures called peroxisomes and mitochondria that handle inflammation-fighting antioxidants and energy production, and the changes persisted in cases of severe liver fibrosis even after the viral infection was cleared. Gut microbial activity was also altered with worsening liver disease, as microbes boosted fat production, reduced methane metabolism, and degraded the protective mucus lining the intestine, changing the mix of metabolites feeding into the liver and leaving both organs more vulnerable to inflammation.

These findings illustrate how the fates of gut and liver are intimately linked, and that multiple disruptions in cellular and microbial metabolism in these organs are associated with inflammation and disease severity in the setting of chronic liver disease, in this case due to hepatitis C infection. They offer clues for future exploration into disease processes and therapeutic remedies to counter these metabolic changes and slow disease progression.


The Yin and Yang of Microbial Influences on the Liver Disease Primary Sclerosing Cholangitis: Studies in an animal model of primary sclerosing cholangitis (PSC), and in samples from adults with the disease, reveal gut microbes’ vital role in both countering and fueling this form of chronic liver disease. PSC results from autoimmune-driven inflammation and fibrosis (scarring) that block the ducts that carry bile out of the liver. These blockages cause bile to accumulate, leading to further damage and possibly liver failure. Males are more likely to develop PSC, which often occurs together with other autoimmune conditions. Factors influencing disease development and progression are unclear, and available treatments are limited to surgeries to re-open the bile ducts. Past research in people with PSC suggested that gut microbes might play a role, though exactly which species were protective or detrimental was unknown.

To probe this important question, scientists studied an animal model of PSC: male and female mice that were genetically altered to develop features of the disease. They raised some of the mice under germ-free conditions and inoculated other mice with specific microbes, then tracked their overall survival, weight, liver enzymes and fibrosis, gut microbes, and genetic and metabolic products. Overall, the presence of gut microbes was beneficial—mice that had been raised in sterile conditions gained lower than normal amounts of weight as they grew and had elevated liver enzymes and bile, bile duct damage resembling PSC, and shortened lifespans, compared to similar mice with gut microbes. The fates of each group could be switched by changing their microbes—either by giving germ-free mice a fecal

Researchers studying adults with chronic hepatitis C have uncovered how complex metabolic changes in the gut, its microbes, and the liver mirror disease state, offering clues to counteracting disease progression.
microbial transplant from the other group, or by giving antibiotics to the mice with microbes. By studying these mice and the effects of different antibiotics, the researchers were able to identify bacteria that exerted protective or pathogenic effects. Bacteria in the Lachnospiraceae family protected against liver damage while those in the Escherichia genus promoted it. Relevance to human PSC was tested through analyses of the bacteria in stool samples from Norwegian and German studies of men and women with PSC.

Studies on the chronic liver disease primary sclerosing cholangitis revealed how the balance of different gut microbes can both counter and fuel disease, knowledge that could lead to more individualized therapies.

These human PSC samples supported the mouse findings, with the presence of Lachnospiraceae bacteria correlating with better disease outcomes and some Escherichia bacteria correlating with more severe disease. Antibiotic use in people with PSC also appeared to shift the balance of these bacteria toward species associated with worse disease.

Results from this study of PSC help form the knowledge base needed to enable more individualized predictions of disease progression based on the balance of beneficial and harmful microbes present. These results may also inform the development of personalized, microbe-based approaches to therapy for this liver disease.

Research Aims to “Triumph” Against Childhood Liver Disease

The impacts of liver disease can be devastating for children and their families. NIDDK and its partners support a wide range of research on liver diseases that affect children, with studies focusing on the early identification of disease resulting from multiple causes, preservation of liver function, and development of new treatment options. Much of this work is initiated by individual investigators supported by NIDDK, but the Institute also funds large networks of researchers focusing on specific types of liver disease in children.

In addition, NIDDK has supported pediatric research on the relatively common disease of nonalcoholic fatty liver disease (NAFLD) and its more severe form of nonalcoholic steatohepatitis (NASH). For example, the Nonalcoholic Steatohepatitis Clinical Research Network conducts clinical studies of nonalcoholic fatty liver disease in children. Recent studies by the Network have linked genetic risk factors to outcomes in children with NAFLD that can inform clinical care, and the Network has partnered with pharmaceutical companies to develop new treatments for these conditions.

Porphyrias are rare, often inherited diseases that can affect the liver and other organs from a young age. NIDDK has provided support for studies on porphyrias through the Porphyrias Consortium, part of NIH’s Rare Diseases Clinical Research Network. The Consortium is supported by NIDDK and NIH’s National Center for Advancing Translational Sciences. The Consortium’s studies aim to understand disease mechanisms and progression of multiple forms of porphyria and develop new approaches to diagnosis, treatment, and prevention, with children currently participating in some of these studies.

RARE LIVER AND BILIARY DISEASES

Since 2008, NIDDK has sponsored studies through its Childhood Liver Disease Research Network (ChiLDReN). The Network’s goals are to facilitate the understanding of many rare biliary diseases in which the liver is damaged due to impaired bile flow in children, to discover new diagnostic and treatment options, and to help train the next generation of investigators specializing in pediatric liver diseases. ChiLDReN consists of sites across the United States and Canada, with additional support provided through partnerships with the Cystic Fibrosis Foundation and the Alpha-1 Foundation. The Network conducts studies on a variety of liver diseases affecting children, including Alagille syndrome, alpha-1-antitrypsin deficiency, biliary atresia, cystic fibrosis liver disease, progressive familial intrahepatic cholestasis, and others. Several important advances have come from the Network’s research, such as important insights into the genetics, pathogenesis, and treatment of biliary atresia and Alagille syndrome. For example, one Network study helped to provide the data necessary for the U.S. Food and Drug Administration to approve the first dedicated treatment for severe itching associated with Alagille syndrome in children.

NONALCOHOLIC FATTY LIVER DISEASE

In addition, NIDDK has supported pediatric research on the relatively common disease of nonalcoholic fatty liver disease (NAFLD) and its more severe form of nonalcoholic steatohepatitis (NASH). For example, the Nonalcoholic Steatohepatitis Clinical Research Network conducts clinical studies of nonalcoholic fatty liver disease in children. Recent studies by the Network have linked genetic risk factors to outcomes in children with NAFLD that can inform clinical care, and the Network has partnered with pharmaceutical companies to develop new treatments for these conditions.
companies and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development on clinical trials testing the safety and efficacy of new treatments for pediatric NAFLD.

**ACUTE LIVER FAILURE**

Acute liver failure in children can result from damage due to viruses, metabolic disorders, drugs and toxins, or other causes. It is one of the most common reasons for children to need a liver transplant. The Institute has sponsored studies in children on severe liver injury caused by drugs, herbs, and dietary supplements through its Drug-Induced Liver Injury Network, which aims to develop better tools for diagnosis and prevention, and to enhance knowledge of disease processes. Recently, Network investigators found that antimicrobial and anti-epileptic drugs are leading causes of this form of liver injury in children, which can lead to acute liver failure requiring a liver transplant.

The newest of NIDDK’s pediatric liver disease research initiatives is also geared toward aiding children with acute liver failure. Launched in 2021, the Treatment for Immune Mediated Pathophysiology, or TRIUMPH study, is testing immunosuppressive therapy for children with acute liver failure of unknown cause. NIDDK has supported past studies on this topic through the Pediatric Acute Liver Failure Study Group, which paved the way for efforts such as TRIUMPH. The goal of the current study, which is currently enrolling participants at 20 sites across the country, is to test the safety and efficacy of two different treatments for improving survival of children with the rare and potentially life-threatening condition of acute liver failure for which no cause can be identified. Recent research supports the theory that many of these patients have liver injury related to heightened inflammation caused by an immune response to everyday infections or environmental exposures. Treatments to reduce inflammation may improve recovery in children with acute liver failure linked to immune disorders, increasing their chance of surviving and avoiding a liver transplant.

**LIVER TRANSPLANT**

Related to this work, NIDDK supports the Improving Medication Adherence in Adolescents who Had a Liver Transplant Network (iMALT) study, which is testing an intervention in young people who have had a liver transplant due to multiple causes, including liver diseases and acute liver failure. The study involves monitoring of blood medication levels and remote communications from study staff, in order to boost adherence to taking the immunosuppressive medications needed to prevent rejection of the transplanted organ.

Through the collective efforts of these multi-center networks and investigator-initiated studies, NIDDK aims to help children and their families "triumph" over liver disease.

*For additional information on the ChiLDReN and TRIUMPH studies see: childrennetwork.org/Clinical-Studies and www.pedsalf.com.*
Nonalcoholic fatty liver disease, or NAFLD, is one of the most common and growing types of chronic liver disease in adults and children, marked by excess fat storage in the liver. An estimated quarter of people in the United States have NAFLD, and up to 70 percent of people with type 2 diabetes also have NAFLD, though it often goes undetected. The disease often accompanies obesity and type 2 diabetes as part of a cluster of conditions called metabolic syndrome, though NAFLD can occur even in people who are lean and do not have diabetes, including those who carry some genetic factors and/or whose ancestors are from regions of the world with higher risk. Its more severe form of nonalcoholic steatohepatitis, or NASH, includes additional features of inflammation and scarring (fibrosis) that can lead, over many years, to compromised liver function; permanent damage, termed cirrhosis; liver cancer; and liver failure requiring transplantation. There are currently no dedicated therapies approved by the U.S. Food and Drug Administration (FDA) for NAFLD and NASH. The current standard of care is weight loss through diet and exercise, which is challenging to achieve. Additionally, diagnosing these diseases is difficult because it relies on an invasive liver biopsy. New approaches are needed to prevent and treat NAFLD and NASH and to develop noninvasive means to identify people who could benefit from therapies as they become available.

NIDDK supports a long-standing, multifaceted, and highly collaborative research program to improve understanding of NAFLD/NASH disease processes and identify new treatment approaches. The progress achieved through these efforts is made possible through the collective efforts of research teams and study participants at institutions across the country, at NIH, and internationally.

EARLY STUDIES OF DISEASE DEVELOPMENT

NIDDK sponsored early research on NAFLD and NASH to identify the biologic processes involved and chart the course of disease development and progression. In the 1990s, studies of liver biopsies from patients with obesity (with or without diabetes) identified some of the key morphologic changes that take place in NASH. They also tracked disease progression in these patients, some of whom developed fibrosis, which can progress to cirrhosis. Furthermore, these studies pointed to a link between NASH and insulin resistance, a condition that is also associated with type 2 diabetes. Additional studies in the early 2000s confirmed the link between NASH and insulin resistance, as well as other metabolic abnormalities, such as increased fatty acid breakdown and oxidative stress in the liver. NIDDK also sponsored population-level studies in the United States documenting the prevalence and risk factors for these diseases in people of different ages, genders, and ancestry. For example, disease risk at the time was found to be higher in people with ancestry from Hispanic and South Asian countries than in people with ancestry from African or European countries.

CONNECTING RESEARCHERS TO ACCELERATE NEW APPROACHES

In 2002, NIDDK dramatically ramped up these efforts by establishing the NASH Clinical Research Network (NASH CRN), which supports a collaborative group of clinical researchers at centers across the country focusing on adult and pediatric forms of NAFLD.
and NASH. Currently made up of teams and study participants at 17 participating clinical centers and a data coordinating center, the Network aims to advance understanding of disease causes and processes, and to also develop new approaches to diagnosing, treating, and managing these diseases. During the Network’s history, NIDDK has partnered with the National Cancer Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development at NIH, and with the pharmaceutical industry, on clinical trials testing the safety and efficacy of new treatments for NAFLD/NASH.

Over the past two decades, the Network has made many important contributions to the field, including developing a scoring system for diagnosing the disease and its progression, assessing genetic and other risk factors, and testing multiple candidate therapies. To date, the Network has enrolled thousands of adults and children who have participated in its many observational studies and clinical trials. These include trials showing that a daily dose of the natural form of vitamin E improved NASH in adult study participants and in some children. Network trials tested other possible therapeutic approaches, including the diabetes drug pioglitazone in non-diabetic adults with NASH and the kidney disease drug cysteamine bitartrate in children with NAFLD, both of which improved some features, but did not reduce overall disease. In 2015, Network investigators released results of a trial finding that a small molecule drug called obeticholic acid improved liver health in people with NASH, though the drug was associated with some increases in itching and total cholesterol. These findings helped fuel an explosion of industry-sponsored NASH clinical trials of this drug and others. The NASH CRN collaborates with and complements industry partners by testing existing, low-cost agents that industry is unlikely to pursue, as well as conducting early phase studies of agents with novel mechanisms of action.

Recent findings flowing from Network studies have shown a direct link between disease stage and outcomes in adults, with severe, later-stage disease associated not only with a higher risk of liver-related complications and death, but also with complications in other organ systems. And Network studies have uncovered new knowledge about the underlying biology of this disease, such as new genetic factors associated with responsiveness to vitamin E treatment in adults with NASH. Network research on genetic factors in children with NAFLD showed that some gene variants increase risk of the disease, particularly its more severe form. Because the majority of study participants were children with ancestry from Hispanic countries, these findings are particularly valuable for this at-risk population. These findings add to the evidence base for determining prognosis and informing clinical care for both adults and children with NAFLD.

The goal of the Network’s current phase is to continue database-driven studies of disease processes and to conduct new trials of NASH therapies for children and adults, with a constant emphasis on low-cost agents that could be implemented across the population. In recent years, a Network study found that the anti-hypertension drug losartan did not reduce signs of liver disease in children with NAFLD. Another study is determining the minimum effective dose of vitamin E in adults with NAFLD needed to improve liver enzyme levels. And the Network’s impacts are further amplified through availability of its databases and vast repository of samples for additional studies by other scientists. For example, a current ancillary study is characterizing and testing treatments for the disease in people living with HIV, a population in which NAFLD is projected to become the leading cause of liver disease.

The Network also continues to develop and validate less invasive ways to diagnose NASH, such as by identifying biological markers of the disease and using imaging technologies. A recent ancillary study builds upon the NASH CRN to identify biomarkers in the blood that could be used in noninvasive tests related to NASH and NAFLD. Using data and samples from participants in four Network studies, the researchers provided evidence that these biomarkers could be used for noninvasive diagnosis of people at risk for NASH and for assessing the degree of fibrosis severity. This study was conducted through a collaborative...
A project called Noninvasive Biomarkers of Metabolic Liver Disease, or NIMBLE, overseen by the Foundation for the NIH with participation from the FDA, academia, and industry partners, with partial funding provided by NIDDK and NIH’s National Center for Advancing Translational Sciences. If approved by the FDA, these markers could be used instead of biopsies to more easily screen and diagnose people with NAFLD and NASH as early as possible in their disease course—an important milestone in clinical care.

INVESTIGATOR-GENERATED RESEARCH ADVANCES

In addition to the highly productive NASH CRN, a wealth of investigator-initiated research efforts supported by NIDDK have made important, complementary contributions to advancing knowledge in this area.

For example, NIDDK-sponsored investigators have performed clinical studies to identify genetic factors that could predispose some individuals to developing NAFLD. A 2008 study scanned the genomes of participants in a large population-based study to show that a variant in a gene called PNPLA3 was strongly associated with NAFLD and was more common among study participants of Hispanic ancestry with higher liver fat and inflammation. This was followed by a 2010 study conducted by NIDDK scientists working at the NIH Clinical Center to further analyze genomic data from participants in the NASH CRN, as well as from people with NASH who participated in non-Network studies at the Clinical Center. This study found that the PNPLA3 variant was associated with earlier disease development in children. Other studies, including international ones, are identifying additional regions of the genome associated with NAFLD and are determining their functional significance as prospective treatment targets across diverse populations.

Basic research in animal and cell models conducted by NIDDK-supported scientists has revealed new insights into disease development and possible treatment approaches. For example, a team of researchers supported by NIDDK and other NIH Institutes used mice and human liver cells to investigate how high amounts of fructose, a common ingredient in processed foods in the American diet, may promote NAFLD. They reported in 2020 that fructose can damage the intestinal barrier, which leads to inflammation and effects on the liver. Two teams of NIDDK-supported scientists tested lipid nanoparticles—used to deliver messenger RNA-based vaccines such as those developed against COVID-19—in mouse models to improve delivery of treatments for liver fibrosis and NAFLD. Researchers “eavesdropping” on how liver cells chemically talk amongst themselves in animal and cell models uncovered a host of new potential therapeutic targets for advanced-stage NAFLD. NIDDK is supporting ongoing research to develop innovative models for fostering new discoveries, such as stem cells, genetically altered cells in culture, and three-dimensional organoids (“mini-livers” grown in the lab) derived from people with NAFLD/NASH to develop personalized diagnostic biomarkers and treatments.

IMAGINING THE FUTURE OF NAFLD/ NASH TREATMENT: PAST PROGRESS FUELING NEW STRATEGIES

Recent years have witnessed the most rapid expansion yet of new treatment options under development for NAFLD and NASH. Many studies have focused on a new class of hormone-based drugs approved by the FDA for treating type 2 diabetes and obesity, such as semaglutide. These drugs work through a protein called the glucagon-like peptide 1 (GLP-1) receptor, and the development of these drugs stemmed from NIDDK-supported foundational research on GLP-1 and related factors. This class of drugs causes delayed stomach emptying, reduced appetite, increased satiety, and enhanced insulin release and lower blood glucose levels, in addition to significant weight loss. In 2021, an industry-sponsored clinical trial featuring participation by NIDDK-supported scientists found
that daily semaglutide treatment over a year and a half did improve disease resolution, based on the absence of inflammation or worsened liver fibrosis, but did not improve fibrosis stage in people with NASH but no cirrhosis. A 2023 study partially supported by NIDDK reported no improvement in disease, including resolution, in people with NASH and early cirrhosis who were treated weekly for a year with semaglutide, though the treatment did appear to be safe and have positive impacts on liver enzymes and liver fat. Researchers are conducting trials to determine whether longer-term treatment is required in people with cirrhosis resulting from NASH. NIDDK-supported researchers are currently conducting a clinical trial of semaglutide at the NIH Clinical Center in people with NAFLD/NASH to understand the mechanisms by which it may prove beneficial in treating the disease and identify predictors of clinical response. Additionally, NIDDK is supporting a new study testing another GLP-1 drug called liraglutide in young people with obesity, prediabetes or new onset type 2 diabetes, and NAFLD. And industry-sponsored trials are showing promising results in adults with obesity, type 2 diabetes, and fatty liver disease treated with similar drugs such as tirzepatide and testing other agents that target more than one receptor related to proteins like GLP-1.

Other novel treatment approaches are being investigated in parallel, including a study supported by NIDDK examining the impacts of intermittent fasting and aerobic exercise on NAFLD, which in combination were found to reduce liver fat more than either intervention alone. Another clinical trial is currently testing a low dose of the diabetes drug pioglitazone for improving signs of liver disease in people with both type 2 diabetes and NASH. NIDDK also supports many research projects overseen by industry scientists through the Small Business Innovation Research program that are testing new approaches to NAFLD/NASH therapy.

**ONGOING “NETWORKING” TO FACILITATE TREATMENTS**

NIDDK continues to seek new opportunities to connect scientists studying NAFLD and catalyze research progress in this area, in addition to the ongoing NASH Clinical Research Network. In 2021, the Institute established the Liver Cirrhosis Network to conduct clinical and translational research toward expanding treatment options and transforming clinical care for cirrhosis caused by NAFLD and other forms of chronic liver disease. Network scientists are working in collaboration with a diverse population of adult study participants, some of whom have been underrepresented in past studies despite carrying a higher disease risk and burden. The Network is conducting an observational study, including on risk factors across racial and ethnic groups, to determine what drives cirrhosis progression and point to possible treatments. Current Network studies are also testing whether statins, which are drugs commonly taken for high cholesterol, can protect against cirrhosis progression. The goal of the Network's studies is to usher in a new era of cirrhosis management, with a wider array of effective treatment options beyond liver transplantation, for NAFLD and other causes of severe liver disease.

For more information on NIDDK-sponsored research on NAFLD/NASH, such as the NASH Clinical Research Network, please see: [www.niddk.nih.gov/health-information/liver-disease/nafld-nash/clinical-trials](http://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/clinical-trials).

For more information on the NIDDK's Liver Cirrhosis Network, please see: [www.lcnstudy.org](http://www.lcnstudy.org).
People who have pancreatitis experience extreme, radiating pain caused by inflammation in the pancreas, a flat and oblong gland located behind the stomach. Aside from making hormones such as insulin needed to control blood sugar (glucose), the pancreas also performs another vital function: producing powerful enzymes for secretion into the small intestine, where they become activated and help break down food. But if these digestive enzymes are activated before leaving the pancreas—due to a blockage that prevents their flow into the intestine, for example—they can irritate or damage the pancreas, leading to painful inflammation that is often accompanied by other symptoms like nausea, vomiting, and fever.

**THE VALUE OF RESEARCH**

Pancreatitis is typically classified as acute (coming on suddenly and typically resolving over several days), or chronic (long-lasting), although there appears to be no clear boundary between these two types. Brief, acute episodes of pancreatitis can progress to the chronic form. It is possible, for example, to experience multiple unpredictable acute episodes (a condition called "recurrent acute pancreatitis"), stretching out the disease over years. Currently, there is no certain way to predict whether someone will progress from acute to chronic pancreatitis, which, if unchecked, can lead to serious life-threatening complications like kidney failure, breathing difficulty, and malnutrition. Additionally, the long-term inflammation and damage to the pancreas can impair insulin production, leading to diabetes. It also significantly raises the risk for pancreatic cancer.

There is no specific treatment for pancreatitis. The causes and course of the disease vary from person to person, making it difficult to find suitable targets for therapy. Several different factors can cause pancreatitis in different people; for example, some people have genetic variants that cause or contribute to the disease, though for many people with the disease, the cause remains unknown. (More information about pancreatitis is available on NIDDK’s website.) The search for treatments has also been hampered by the lack of large, long-term studies to understand the host of factors that influence how the disease develops and progresses. In addition, researchers have yet to identify early disease biomarkers—proteins or other chemicals in the body that could signal whether someone may eventually develop chronic pancreatitis. To address these needs, NIDDK, along with the National Cancer Institute (NCI), launched the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer in 2015. The Consortium’s goal is to design and conduct clinical studies to understand pancreatitis and its complications, including diabetes and pancreatic cancer. (See inset for the story of a participant in one of the Consortium’s studies.)

**GAINING A BETTER UNDERSTANDING OF PANCREATITIS**

Since its inception, the Consortium has overseen several major clinical studies. PROCEED (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) has thus far enrolled close to 2,000 adult volunteers to understand disease progression, test potential biomarkers, and pave the way for clinical trials to test new therapies. Study participants are categorized into one of three groups: people with no pancreatic disease, people with suspected chronic pancreatitis (including those who have had one or more episodes of acute pancreatitis), and people with definite chronic pancreatitis.
PERSONAL PERSPECTIVE

By collecting data and biological samples over time from all three groups, researchers can identify biomarkers and gain a better understanding of how pancreatitis progresses. For example, researchers in PROCEED recently found molecular markers in the immune system that are different between people with acute pancreatitis and people with the chronic form, suggesting these markers could serve as indicators for different stages of the disease. The researchers also identified inflammation signals that gradually increased as the disease progressed. These results provide a potential way to distinguish between someone experiencing pancreatitis or someone having unrelated abdominal pain. And, importantly, the study identified components of the immune system that could represent targets for new treatments.

Consortium researchers are also investigating complications that result from pancreatitis. Both chronic pancreatitis and pancreatic cancer could cause a form of diabetes called type 3c diabetes, which can be challenging to distinguish in the clinic from the more widespread type 2 diabetes. This is important because people with type 3c diabetes would likely require different treatment approaches from those with type 2 diabetes—they typically require insulin treatments earlier, for example. Recent results from the DETECT study (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis) have found that, compared to people with type 2 diabetes, people with type 3c diabetes have lower levels of a substance called pancreatic polypeptide in their blood after consuming a test meal. This means measurement of pancreatic polypeptide levels could be used to differentiate type 3c from type 2 diabetes. Also, because type 3c diabetes often precedes other signs of pancreatic cancer, measurements such as this could potentially serve as tools to help detect pancreatic cancer in its early stages when treatment is more likely to be successful.

While both PROCEED and DETECT are studying pancreatitis in adults, the Consortium’s INSPIRE 2 study (International Study Group of Pediatric Pancreatitis: In Search for a Cure) is characterizing acute recurrent and chronic forms of pancreatitis in over 800 children and adolescents. (INSPIRE 2 is an expansion of INSPIRE, an earlier pediatric pancreatitis study that predates the Consortium.) Similar to PROCEED, INSPIRE 2 is gathering information from children with pancreatitis to help researchers determine the prevalence, causes, and progression of the disease. INSPIRE 2 researchers have shown that the risk factors and course of the disease are different in children than in adults, a finding that could help researchers and clinicians develop better approaches to diagnose and treat children with pancreatitis.

Along with these large clinical studies, the Consortium is continuing to engage in other research that focuses on the diagnosis and treatment of pancreatitis, including new ways to treat pain, with the goal of improving the lives of people living with the disease. The Consortium’s researchers—with the invaluable collaboration of the thousands of people participating in studies—are making great strides in understanding pancreatic disease, paving the way toward new treatments and bringing hope to those with pancreatitis.

For additional information on the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, please visit its website at: www.dmscro.org/cpdpc.
Dianna’s Story

On a winter night in Western Pennsylvania 20 years ago, Dianna was at a friend’s house when her stomach suddenly began to hurt. Only a minute later, she was vomiting uncontrollably in the bathroom and experiencing the most excruciating abdominal pain she had ever felt in her life. Her friend’s mother drove her to a local emergency room, where she was told she had the flu.

Looking back, Dianna, now a working mother of two in her mid-forties, knows the symptoms she had been experiencing were her first encounter with recurrent acute pancreatitis, which would continue to barrage her pancreas with repeated bouts of painful inflammation. But she had little reason to suspect she had the disease at the time—no one in her family had it, and she had no risk factors that she had been aware of. So, a week and a half after that emergency room visit and with the vomiting under control, she started her new job. She would still feel sore for weeks. “I just pushed through it,” she says with a casual grin and a shrug.

“I get zero warning,” Dianna says of her pancreatitis attacks. “I could be talking to someone, and by the end of our conversation I could be on the way to the emergency room because the pain comes sharp, and I just start vomiting... and off we go.”

Dianna speaks with an entertaining, witty, and wry sense of humor. She has always been good at math and problem solving, talents she uses to design simulators—life-sized replicas of control stations that provide hands-on training for students. They have all the switches, gauges, and warning lights that the real equipment has. “You want [the students] to be trained so they know what to do when a component fails, and how to rectify it,” she says.

But pancreatitis episodes do not come with warning lights, and there is no way to prepare for the debilitating pain. If untreated, pancreatitis could lead to organ failure and death. “I get zero warning,” she says. “I could be talking to someone, and by the end of our conversation I could be on the way to the emergency room, because the pain comes sharp, and I just start vomiting... and off we go.”

CLOSE CALLS

In August of that same year when Dianna had her first episode, she was visiting her parents when, out of the blue, she began vomiting every hour.
on the hour, like clockwork. Still unaware of her pancreatitis—and suspecting something less serious like the stomach flu—she decided to wait until the next day to see a doctor. The doctor immediately sent her to a hospital where she waited for 12 hours in a backed-up emergency room. She was severely dehydrated by the time she was admitted, and her kidneys were starting to fail. “They had no idea what was wrong,” she says. “They pulled my mother outside and told her I was dying.”

Eventually the medical staff were able to stabilize her. She was diagnosed with pancreatitis and stayed in the hospital for 11 days while the doctors searched for a cause. An important clue had come in her bloodwork: it was normal except for her triglycerides, which were “sky-high,” she says. A healthy triglyceride level is under 150 milligrams per deciliter (mg/dL); Dianna’s would regularly be well over 1,000 mg/dL—and at times much higher.

Like so many aspects of the disease, the role triglycerides play in pancreatitis is not completely understood. One possibility is that high levels of triglycerides could cause the pancreas to over-produce digestive enzymes. The resulting buildup of these powerful enzymes in the pancreas could lead to permanent damage and other life-threatening complications—including a higher risk for pancreatic cancer—all the while causing painful inflammation in the abdomen.

Dianna’s pancreatitis, she later learned, is caused by three genetic variations in her DNA: one that raises the overall risk of the disease and two that cause high triglycerides. Keeping her triglycerides lower has been a challenge. She tries to limit her diet to low-fat and low-carb foods, and some triglyceride-lowering medicines she’s taken had very serious side effects, including severe depression.

Dianna describes the pain caused by pancreatitis as like a very bad friction burn, but on the inside of the body, and it can last for weeks. “It becomes so severe that you just want to double over, and nothing you do makes it feel any better,” she says. Given the choice, she would prefer the pain from natural childbirth—which she experienced when each of her two sons were born—over the pain from pancreatitis.

The August trip to the hospital was the first time Dianna came close to dying. The second came several years later. This time the hospital was full, and she was directed to a smaller hospital that struggled to get her symptoms under control. While she slipped into unconsciousness, “they worked feverishly to keep me alive,” she says. “As soon I was conscious again, they told my husband and me to say a last word to each other because they weren’t sure if they were going to pull me through.”

She remembers her husband refusing to say goodbye: “He said, ‘I’m not saying it, because you’re making it through this. Because we’re not done. This is not the end.’” With those words, she says, “he really gave me strength.”

The small hospital airlifted Dianna by helicopter to the University of Pittsburgh Medical Center (UPMC), where, luckily, she was able to recover.

**PROCEEDING THROUGH LIFE WITH PANCREATITIS**

At UPMC, Dianna met Dr. Dhiraj Yadav, a gastroenterologist and investigator in NIDDK’s Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, who took her on as a patient. He also encouraged her to participate in one of the Consortium’s major research efforts, Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED), which has thus far collected data on close to 2,000 volunteers to better understand pancreatitis. The study’s ultimate goals are to develop new therapeutic options and create tools to predict how the disease might progress in any individual, which would also help to guide treatment approaches.
Dianna says her participation in PROCEED is simple: it involves completing an annual questionnaire and giving blood and stool samples. “I found it easy,” she says. “And I feel like it’s a two-way thing. If something can be learned from me, maybe it'll turn around and benefit me as well.” And, she says, one of her worst fears is that her sons may have inherited the disease. “So, even if it takes 10 years to figure out, maybe it'll help my kids.”

Dianna’s harrowing experiences with pancreatitis attacks—she’s had 16 of them over the years—have given her a new perspective in life. Her motto has become “laugh, don’t cry,” partly because she always looks for the silver lining in bad situations, and partly because she spent a lot of time in the hospital connected to a feeding tube that went through her nose, which she says can be especially uncomfortable with stuffy sinuses from crying. (She likes to make hospital staff laugh by referring to the medical tubes clinging to her neck as “her jewelry.”) “There are times when crying is very much needed,” she says. “But if you can find something to laugh about first, no matter how small, then you can tap into that feeling of ‘Yes, I can do this!’”

Her friends share her sense of humor. Once, wishing they could give her a new, disease-free pancreas, they presented her with a stuffed plush version instead. “It’s those kinds of things that help,” Dianna says. “Laughter is the better medicine.”

Still, she draws much of her resiliency from within. “Even though it can get depressing, and I’m spending a week or two in the hospital at a time, I bounce back,” she says. “I keep going.”

“There are times when crying is very much needed,” Dianna says of her many hospital stays due to pancreatitis. “But if you can find something to laugh about first, no matter how small, then you can tap into that moment of ‘Yes, I can do this!’”