The gut has long been known to communicate with the brain. The stomach and intestines can send information about hunger or feeling full, or even about the presence of microorganisms. However, scientists thought that this exchange of information occurred through a slow diffusion of hormones released by intestinal epithelial cells into the bloodstream. Given that circulating hormones take several minutes after food is consumed to reach their target and a person already has a sense of satiety, it seemed possible that a faster mechanism existed. Research described in this chapter using a mouse model shows that the gut has a dedicated sensory circuitry, like that of taste in the tongue. It is a direct neural connection between the gut and the brain that can exchange information in fractions of a second. Using a technique to detect cellular connections, the investigators were able to trace the signal of a fluorescently tagged novel subtype of intestinal cell, named neuropod by the investigators, all the way to cells, called neurons, in the brainstem. In the top left image, the specialized neuropod cells are shown connecting with neurons, both in green, set among other cells in the small intestine, shown in blue. This neural circuit was recreated in the laboratory in a cell culture system. In the bottom left image, a green label shows neurons from the brainstem connecting directly to red-labeled neuropod cells. The illustration on the right depicts the pathway of this circuit in a mouse after nutrient consumption. Further studies could provide insight into whether this direct gut-brain circuit can transmit more specific information such as caloric content of food.

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. The latest concerted effort to address the burden of all digestive diseases combining multiple 2016 national data sources 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 2016 national inpatient samples identified 4.1 million hospitalizations with a primary diagnosis of digestive diseases and 15.9 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 19.2 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling $94.9 billion in 2016.3

Some digestive diseases are common and others quite rare. Yet collectively, they strike individuals across the lifespan, exacting 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. NIDDK-supported scientists are vigorously pursuing research with the ultimate goal of reducing the public health burden associated with digestive diseases. Such efforts aim to better understand how widespread these diseases are across the United States and in specific population groups, to identify their causes and how they progress, and to test new interventions for prevention and treatment, including drugs, surgery, and behavior modification.

Inflammatory bowel diseases (IBD), which include Crohn’s disease and ulcerative colitis, are marked by damaging 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 frequently requires prolonged use of multiple drugs and may require surgery, including removal of the affected region of the intestine. Scientists are investigating the complex interactions among the genetic, environmental, immune, microbial, and other factors that contribute to, or protect against, the development of IBD. The continued discovery of predisposing genetic variations, potential autoimmune and microbial influences, and new methods to repair damaged intestinal tissue 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)...

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1. National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), U.S. Centers for Disease Control and Prevention; available at: www.cdc.gov/nchs/ahcd/index.htm.
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 turn into an intestinal type of cell, is associated with a heightened risk of esophageal cancer—one of the cancer types still on the rise in the United States. Scientists are working to understand the causes of functional bowel disorders, which will lead to improvements in diagnosis and management for patients with these conditions. Fecal incontinence, or impaired bowel control, is a bowel disorder that poses a major public health burden. Although fecal incontinence is more common in older adults, it can affect people of any age. Because it is difficult to talk about, many people suffer without seeking professional treatment for this surprisingly prevalent condition. Researchers thus aim both to examine barriers in addressing fecal incontinence and to develop improved treatment strategies.

Gastroparesis, another type of functional bowel disorder, is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. Most cases of gastroparesis are of unknown origin, which makes it difficult to treat. Most current therapies are directed toward helping people manage this chronic condition so they can be as comfortable and active as possible.

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 ingestion of gluten—a protein component of wheat, barley, and rye—and damages 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. Recent and continued 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 new ways to treat this condition in the future.

The microbes that inhabit the GI tract are important factors in maintaining or tipping the balance between digestive health and disease. These bacteria, viruses, and other microorganisms can affect long-term health and nutritional status in some surprising ways, 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 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.

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 include gallstones, heavy alcohol use, inherited genetic factors, and some medicines. In all forms of 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, but 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 disorder.

The liver is an organ within the digestive system that performs many critical metabolic functions, including processing and distribution of nutrients such as fats. When the liver is functionally compromised by disease, serious adverse effects on health can occur, which sometimes leads 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 nonalcoholic steatohepatitis (NASH), a form of nonalcoholic fatty liver disease (NAFLD). In recent years, however, NAFLD has been increasingly diagnosed in children in the United States as well, concurrent with rising overweight and obesity. 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 diverse 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. 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, sometimes a healthy living person will donate part of his or her liver, most often to a family member who is recommended for a liver transplant. The living donor’s liver eventually regenerates and grows back to normal size, as does the part of the liver that is donated. Research is critical to identify liver disease early, find methods to preserve liver function in people with liver disease, and develop new treatment options, including experimental, cell-based approaches to liver regeneration. Additionally, a unique web-based health information program on drug-induced liver disease called LiverTox, jointly sponsored by the NIDDK and the National Library of Medicine, provides concise, up-to-date information on more than a thousand medications and supplements and their potential to harm the liver (available at http://livertox.nih.gov).

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, microbial, behavioral, 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 that may arise from research, existing bariatric surgical techniques are being evaluated for their long-term impacts on weight loss, obesity-associated disease, 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. Investigators also conduct basic, clinical, and translational research on the requirements, bioavailability, and metabolism of nutrients and other dietary components in order to understand dietary needs in health and disease. The NIDDK and its Office of Nutrition Research plays a leading role in the NIH Nutrition Research Task Force, chaired by the NIDDK Director and co-chaired by Directors of the National Heart, Lung, and Blood Institute, the National Cancer Institute, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force was established to coordinate and accelerate progress in nutrition research across the NIH and has been involved in the development of the first NIH-wide strategic plan for nutrition research.

**GUT MICROBIOME AND NUTRITION**

**Feeding the Microbiome To Help Malnourished Children:** Recent findings from an ongoing series of studies of malnourished children demonstrate that complementary foods (i.e., foods given in addition to those consumed in the diet) that are designed to boost maturation of their gut microbiome can improve markers of normal growth, neural development, and immune function in these children. Research has shown that adequate recovery from severe childhood malnutrition requires more than access to healthy food (or breast milk in the case of the youngest children). Even when supplemented with life-saving, so-called “complementary” or “therapeutic” foods high in calories and protein, severely malnourished children do not recover completely and remain moderately malnourished in a way that can still cause stunting and other effects on health. Studies in resource-limited populations living in Bangladesh and Malawi have shown that malnutrition leaves a lasting impression on a child’s developing gut microbiome—the collection of microbes and their genetic material—resulting in an underdeveloped, “immature” microbiome less capable of supporting human metabolism and growth. Building upon their past findings, scientists set out to identify a combination of food ingredients that would support maturation of the microbiome to encourage healthy growth and development of malnourished children. They measured health and metabolic indicators, as well as microbes present, in severely malnourished young girls and boys, ages 6 to 36 months, living in Bangladesh over the course of treatment with one of three types of “conventional” formulations of therapeutic foods, consisting of either rice
and lentils, chickpeas, or a commercially available peanut-based food. This initial study provided a baseline of information on how the gut microbiome typically changes during treatment with conventional complementary foods, as children made a partial recovery from severe to moderate malnutrition with continued immaturity in their microbiomes. In parallel, to identify potential complementary foods that could be more effective in improving the gut microbiome during malnutrition, they transplanted gut microbes from severely malnourished children into male mice raised in sterile conditions, to test microbial levels in response to 12 food ingredients found in the Bangladeshi diet. Based on these findings, they identified combinations of these 12 complementary food ingredients that, given together with a representative diet consumed by malnourished children, most improved the microbiome and growth markers in these mice and also in piglets similarly given microbes from the children. Coming full circle back to humans, the investigators then conducted a randomized controlled feeding study in children ages 12 to 18 months with moderate malnourishment. This study compared three complementary food combinations with the best results on the gut microbiome in the animal models. When the complementary foods were given in addition to the children’s regular diet, one combination in particular—containing chickpea, soy, peanut, and banana—led to improved markers of growth, neural development, and immune function that more closely resembled those seen in healthy children. Through developing and testing complementary foods that are custom-designed to reverse microbiome immaturity caused by malnutrition, scientists hope to provide the means to more fully restore health to these children.


Gut Feeling: A Direct Pathway for Gut-brain Communication: Researchers have identified for the first time a direct line of communication between the gut and the brain that allows for rapid signaling of sensory information about food intake. It has long been known that the stomach and intestines communicate with the brain. However, scientists thought that this exchange of information occurred through a slow diffusion of hormones released by specialized intestinal cells termed “enteroendocrine cells” into the bloodstream upon ingesting nutrients. Recently, a team of investigators wondered if a faster conduit through the nervous system might exist, given that circulating hormones reach their peak several minutes after food is consumed and a person has already had a sense of feeling full.

To determine if a direct neural pathway exists, the researchers used a technique to detect cellular connections in mice with a modified, fluorescently tagged rabies virus, as rabies spreads through the body via connections between nerve cells (neurons) until it reaches the brain. They introduced this virus into the colons of the mice, and, remarkably, they were able to trace the fluorescent signal as the virus traveled from a novel subtype of intestinal enteroendocrine cell (named neuropod by the investigators) all the way to cells in the brainstem, called vagal neurons, indicating the presence of a direct circuit. To recreate the gut-brain connection in the lab, the researchers next grew these gut cells from mice in the same dish as vagal neurons. They saw the neurons’ extensions crawl along the bottom of the dish to connect to the gut cells and begin communicating. Using a technique to measure the speed of the signal, they found that adding a sugar solution to the dish triggered a message to travel between gut and brain cells. The speed of communication was extremely fast—measured in milliseconds, much faster than the blink of an eye. When sugar was added to vagal neurons in the absence of gut cells, there was no measurable signal, suggesting that the message was being sent from the gut cells only in the presence of a food source. Because such rapid communication between the brain and other organs involving the five senses—smell, taste, touch, vision, and hearing—often occurs via a chemical messenger called glutamate, the researchers next investigated if glutamate was also responsible for delivering these fast signals from the gut to the brain. When they blocked the release of glutamate with a chemical agent in a dish containing vagal neurons and gut cells, the messages were silenced, suggesting that glutamate is the chemical messenger responsible for this communication; when they washed away the blocking agent, the signal was recovered. Thus, the researchers had discovered that certain gut cells connect with and speak the language of brain cells in rapid communication.

Taken together, these results lend new meaning to a “gut feeling” as a “sixth sense,” in terms of sensing and rapidly communicating information about the food we eat. Future research could
provide insight into whether this gut-brain system relays specific information about nutrients and caloric intake of food.


MICROBIAL FACTORS IN INFLAMMATORY BOWEL DISEASE

Close Ties Between the Microbiome and Inflammatory Bowel Disease: Two recent studies have identified changes caused by the community of microbes living in the gut that could contribute to inflammatory bowel disease (IBD), including microbial metabolic byproducts (substances produced by microbes) and the human immune system's response. One of the drivers of IBD (which includes Crohn's disease and ulcerative colitis) is thought to be an improper immune response to the gut microbiome, the trillions of microbes living in the gastrointestinal tract. Studies have implicated the microbiome as a key player in IBD, but the many and complex ways in which the microbiome affects the disease are not well understood. One complicating factor is that the disease is not active all the time—people typically experience periodic "flare-ups" of symptoms interspersed with latent periods—and the microbiome during an inactive period may be different from during a flare-up.

To better understand the interactions between the microbiome and its human host during IBD, the NIDDK supported studies through the NIH's Integrative Human Microbiome Project, which includes a multi-center study to understand how the gut microbiome changes over time in adults and children with IBD. Researchers recruited 132 adult and pediatric volunteers, both female and male, either with IBD (Crohn's disease or ulcerative colitis) or without. Changes in the participants' guts and their microbiomes were tracked and catalogued through analysis of stool and other samples over 1 year, including microbiome composition, microbial metabolites, microbial and human gene activities, and immune response. The researchers found that, in the people with IBD, the composition of the microbiome changed significantly during a disease flare-up and then returned to an individual's initial, "baseline" composition when the flare subsided. There were corresponding changes in microbial metabolites during a flare-up, such as lower levels of short-chain fatty acids, which play important roles in digestive health and have been shown to protect against digestive diseases. Also, blood samples from patients experiencing flare-ups showed higher levels of antibodies produced in response to microbial infections and inflammation, implicating the immune response as another key player in active IBD. These changes provide clues to the causes of IBD and could point to therapeutic targets or diagnostic markers to help predict flare-ups, which could be treated aggressively before symptoms become severe.

Another NIDDK-supported study delved further into the changes in the microbiome and the microbial metabolites in people with IBD. Researchers analyzed stool samples from 155 men and women with IBD (Crohn's disease or ulcerative colitis), or with no IBD, to identify differences in their microbiomes. They found that the microbial communities in people with IBD were less diverse than those in healthy people, confirming results from previous studies. Looking at over 8,000 different microbial metabolites, the researchers found higher levels of some metabolites in people with IBD, although a majority were depleted in the disease, reflecting the lower microbial diversity. By comparing these differences in metabolites with the differences in the microbiomes, the researchers were able to link specific metabolites to the types of gut bacteria that produce them, revealing new markers to help with diagnosis of IBD, and importantly, new targets for therapy.

The relationship between IBD and the gut microbiome is complex, but gaining a better understanding of it would present potential new targets for therapy. These studies and others represent pioneering work to more comprehensively characterize the metabolic and immune impacts of host-microbial interactions that contribute to disease development.


PREDICTING EFFECTIVE TREATMENTS FOR INFLAMMATORY BOWEL DISEASE

Predicting the Most Effective Treatment Approach for Pediatric Ulcerative Colitis: Recent results from a multi-center clinical study identified several patient characteristics that can predict how well children with ulcerative colitis (UC) will respond to treatment, pointing toward a more personalized approach to...
treating the disease. UC, a type of inflammatory bowel disease, is caused by a complex combination of genetic, microbial, and environmental factors that provoke chronic and painful inflammation in the lower gastrointestinal tract, resulting in diarrhea, cramping, and malnutrition. People with UC are typically treated with the non-steroidal anti-inflammatory drug mesalazine or corticosteroids, but many do not improve and eventually need to be treated with more potent drugs that suppress the immune response that causes inflammation (immunosuppressive drugs). Advance knowledge of which children with UC only respond to immunosuppressive treatments could enable them to be effectively treated and undergo remission as quickly as possible. However, predicting treatment responses to UC has been difficult due to the disease’s variability from person to person. Determining the best treatment approach has been especially difficult for children with UC because most of the treatments are based upon results from adult studies.

To streamline treatment approaches for UC, particularly in children, the NIDDK supported the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study, which recruited several hundred boys and girls from 29 centers in the United States and Canada who were recently diagnosed with UC. The participants were initially given mesalazine or corticosteroids. After a year, only 38 percent of the participants were able to achieve corticosteroid-free remission—that is, they needed only mesalazine or no treatment at all. A majority of the participants required more intensive treatments, including immunosuppressive drugs, and several required surgeries to remove the colon. Importantly, several patient characteristics—such as high hemoglobin levels, clinical remission after 4 weeks, and the makeup of the gut microbial community—were associated with achieving corticosteroid-free remission, suggesting these characteristics can predict whether immunosuppressive drugs will be necessary. PROTECT researchers also identified certain genes that were more active in the participants who were responsive to corticosteroids, which opens the possibility of genetic screening to help determine which patients would be most likely to benefit from this treatment. Additionally, the researchers found that mitochondria—the tiny battery-like cellular components that supply energy—were less active in the colons of UC patients, such that boosting energy production in colonic cells might be another effective therapeutic approach.

The results from the PROTECT study suggest that the best treatment approaches for UC are those that are tailored to individuals with the disease based upon their clinical, genetic, and microbial profiles. The study also presents a framework for additional clinical studies that will further move UC therapy toward more personalized, and ultimately more effective, approaches.


INTESTINAL REGENERATION

**Immune Cells Influence Balance of Intestinal Stem Cell Renewal and Maturation:** Scientists have discovered that intestinal stem cells interact with nearby immune cells in a bi-directional manner that affects both the renewal of this stem cell source and remodeling of the intestinal lining during infection. The intestinal lining is constantly regenerating (in humans about once a week) with its regenerative capacity depending upon resident stem cells. Within the intestine, stem cells must be able to mature into specific cell types to replace old or damaged cells, and they also must divide and maintain their numbers as a source of future cell lineages. The replenishment of mature intestinal cells is especially important during gut infections, when the intestinal lining may be severely damaged by the pathogen and the resulting inflammatory response. The scientific community has focused on discovering how the stem cells’ environment of neighboring cell types and signals supports them in their important work maintaining the gut.

A team of investigators focused on investigating the role of immune cells residing in the intestine, including the chemical signals they release, called cytokines. They showed that intestinal stem cells from male and female mice produce a class of molecules, called “MHC II” molecules, typically only found on cells that signal to immune cells when detecting an infectious or “foreign” protein. Next, they mixed mouse intestinal stem cells in a dish with immune cells (from female mice) and a test protein that the immune cells could recognize. The stem cells used their MHC II molecules to present this protein to the immune cells, which became activated and secreted cytokines. To explore these interactions in a model more closely resembling the intestine, they turned to mouse intestinal organoids—miniature tubes of cells in culture that recapitulate some of the features of the intestine. Adding different types of the
immune cells, or the cytokines they produce, modified the balance between the number of stem cells present and how many of them matured into specific intestinal cell types within the organoids. To study the stem cells during infection, the researchers moved to a whole-organism model. They gave female and male mice either Salmonella bacteria or a parasitic worm, and found that interactions between intestinal stem cells and immune cells were important for stem cell maturation into distinct cell types that reconstitute the intestinal lining during infection.

These studies performed in a wide range of experimental models—from single cells to organoids to whole animals—demonstrate the importance of crosstalk between intestinal stem cells and neighboring immune cells for maintaining the stem cell pool and healthy intestinal lining in both healthy and infected states. More research is needed to understand how these interactions affect the balance between renewal of the stem cell pool and maturation into cell types that may be needed at a given time to perform distinct functions within the intestine.

**MODELING FATTY LIVER DISEASE**

**Organoids Model Human Fatty Liver Disease:** Scientists have developed a remarkable model of human fatty liver disease using human cells to generate spherical “organoids”—miniature livers in a dish with complex cellular and structural features. Fatty liver disease, or steatosis, can in some people progress to steatohepatitis, a form of fatty liver disease marked by inflammation and damage, as well as fat accumulation. One form of this disease—nonalcoholic steatohepatitis—is becoming increasingly common in both adults and children in the United States and other countries along with the rise in obesity. However, not all individuals with obesity develop the disease, and nonalcoholic steatohepatitis can sometimes occur in people who do not have obesity. Despite many animal model studies of the disease, no approved drugs have been developed to treat steatohepatitis, and treatment guidelines consist of advising individuals who have overweight or obesity to lose weight. In these experiments, scientists used several stem cell lines capable of forming multiple cell types from healthy men and women and from women and girls with liver disease, to create human liver organoids with multiple liver cell types, similar to the natural organ. With all these cell types, the organoids were functionally similar to human liver tissue in terms of their activation of genes, including those involved in fat metabolism. When treated with fatty acids to replicate high circulating levels of fats in the body due to excess fat tissue and/or a high-fat diet, the organoids showed many of the sequential features of human fatty liver disease. These features included fat accumulation, inflammation, and scar tissue formation, the last of which could be detected by measuring the stiffness of the organoids, simulating stiffness measurements of liver scarring in humans. Finally, organoids created from the cells of children with a genetic form of severe steatohepatitis, called Wolman disease, showed many features of the disease found in humans, and responded favorably to a protein called fibroblast growth factor 19, which is known to be produced by intestinal cells in response to a drug being tested as a fatty liver disease treatment. This research provides a new path forward to study human fatty liver disease in a more personalized way, using cells from individuals to create organoids, and may enable future discovery of effective treatments for this disease.

**PEDIATRIC LIVER DISEASE RESEARCH**

**Study Identifies Gene Variants Associated with Biliary Atresia Splenic Malformation Syndrome in Children:** Researchers have identified gene variants present in infants with biliary atresia splenic malformation syndrome that may increase susceptibility to this severe and potentially deadly childhood liver disease. Biliary atresia is a serious liver disease that occurs during the first few months of life in which bile ducts that drain from the liver, delivering bile acids to the intestine, become inflamed and scarred, leading to a back-up of bile into the liver. This back-up can result in liver damage and, if not treated with surgery or liver transplantation, can lead to liver failure and death. Although a rare disease, biliary atresia remains the most common form of severe liver disease in children and the leading cause for pediatric liver transplantation. Some infants with biliary atresia have additional complications caused by improper positioning of some internal organs, such as the spleen, within the body; this condition is referred to as biliary atresia splenic malformation (BASM) syndrome. The causes of biliary atresia and the rarer BASM syndrome are not fully understood.
With support from the NIDDK, the National Center for Advancing Translational Sciences, and other sources, researchers set forth to identify genetic factors that might play a role in the development of BASM syndrome by studying infants enrolled in the NIDDK’s Childhood Liver Disease Research Network (ChiLDReN) and their parents. They sequenced portions of the genomes of the families and looked for genetic variants that likely disrupt biological functions previously implicated in biliary development and in organ positioning. In particular, they examined variants that might be associated with blockage of bile flow or dysfunction in the cilia (hair-like projections) that line the bile ducts and play a role in cell signaling. The investigators found variants of one gene in particular, called PKD1L1, in about 12 percent of the children studied with BASM. The protein produced by this gene is important for both ciliary signaling and proper positioning of internal organs during embryonic development, underscoring its possible role in BASM syndrome. Also, the researchers tested a tissue sample from one of the children with PKD1L1 variants and found reduced activity of this gene within the bile ducts, meaning the functionality of the gene may be affected.

This study identifies PKD1L1 as a new candidate gene in the development of BASM syndrome—and possibly some cases of biliary atresia without BASM syndrome, given the important role of this gene product in biliary function—in young children. Future studies in both humans and cell or animal models could explore the functions of this gene and the possible mechanisms by which these genetic variants might contribute to these rare diseases.


**HEPATITIS B RESEARCH**

**Trials Test Combination Treatment for Chronic Hepatitis B in Adults and Children:** Two clinical trials of a combination drug therapy—one in adults and another in children—found it was of limited benefit in treating chronic hepatitis B. Hepatitis B is a major health problem around the world and in the United States, particularly in people of Asian or African origin who emigrate from countries without the long-term universal vaccination and screening programs in this country. The chronic form of the disease can progress to cirrhosis and liver cancer, if not successfully treated. Infection with the hepatitis B virus (HBV) often occurs at birth or in childhood. Unlike hepatitis C, no relatively short course of a drug or combination of drugs has been found to elicit a long-term response in people with chronic hepatitis B, for which the most effective drugs available need to be taken for years, decades, or even life-long.

The NIDDK’s Hepatitis B Research Network is a multi-center study of both children and adults with hepatitis B at 28 sites throughout the United States and Canada, with a goal to better understand the natural history of hepatitis B and disease processes, and to test therapy approaches. The aim of these two Network trials, in adults and children, was to determine the safety and benefit of therapy with a limited course of a combination of drugs in the early phase of chronic HBV infection. In this phase, infected persons have no symptoms or abnormal liver tests, despite high levels of HBV in the bloodstream (called “immune tolerant” chronic hepatitis B). In both the adult and pediatric trials, 90 percent or more of participants were of Asian ancestry. The adult cohort had equal numbers of men and women, while 75 percent of the pediatric participants were girls. The treatment regimen was entecavir—a once-a-day, oral direct-acting antiviral drug—to which was added peginterferon, an immune-stimulating protein given weekly by injection. Entecavir was given alone for 8 weeks and then combined with peginterferon for the following 40 weeks. Researchers conducting the trials measured success by how well the combination therapy decreased levels of HBV DNA and proteins (called “HBeAg” and “HBsAg”) in the blood, and whether the 48 weeks of treatment led to a permanent loss of the viral proteins and DNA, as measured 48 weeks after stopping treatment. With treatment, levels of HBeAg, HBSAg, and HBV DNA decreased in all patients. However, none of the 27 adult trial participants and only three of the 60 children (5 percent) experienced complete resolution of hepatitis B, losing both viral proteins and DNA and developing antibodies during the 48 weeks following treatment.

Thus, this particular combination treatment was found to be of limited benefit in adults and children at the early, mild stage of chronic hepatitis B infection. Yet, this study offers promising evidence that a complete response to therapy could be achievable in people with chronic hepatitis B. In particular, the dramatic and complete response seen in a small proportion of children suggests that combination therapy—using these drugs, together with another agent(s)—is likely to achieve a beneficial response in a high proportion of people with chronic hepatitis B.
Genetic Variant Linked to Drug-induced Liver Injury: In the largest, international drug-induced liver injury (DILI) genetic study to date, researchers found that persons with a genetic variant implicated in autoimmune diseases are at increased risk of liver injury triggered by drugs. DILI is one of the most common causes of acute liver failure in the United States and is one of the most frequent obstacles in the development and approval of new drugs. Yet DILI is difficult to prevent, predict, or treat because of its rarity, the lack of specific diagnostics, and the unidentified disease-causing characteristics unique to each individual. In the past 20 years, several human leukocyte antigen (HLA) genes, which are responsible for regulating the immune system, have been associated with DILI, which means that at least some cases may result from an improper immune response to the drug or its metabolites (breakdown products). But previous studies have included too few people with DILI to determine if there was a link to other types of genes.

In this study, a collaboration of NIDDK’s Drug-Induced Liver Injury Network (DILIN) with the International DILI Consortium (iDILIC), researchers compared the genomes of over 2,000 individuals with DILI and 12,000 people who did not have DILI. The large DILI cohort included men and women, children and adults, individuals of European, African-American, and Hispanic descent, and persons with liver injury from a wide variety of drugs, nutritional supplements, and herbal products. Through this analysis, the researchers found that a variant of a gene outside the HLA region called PTPN22 was found to be more common in people with DILI than in the healthy controls. This genetic variant of PTPN22 is also known to increase the risk for several autoimmune diseases such as psoriasis and rheumatoid arthritis—further implicating a role for the immune system in DILI. Importantly, this genetic variant was linked to liver damage caused by many drugs, unlike the genetic variants of HLA genes, which were usually linked to one specific drug. In addition, the PTPN22 risk variant added to the risk of having liver injury from specific drugs in people with the known HLA risk variants. For example, the PTPN22 variant almost doubled the risk of DILI in persons with liver injury caused by the antibiotic amoxicillin-clavulanate—the most common cause of DILI after acetaminophen in the United States.

These findings suggest that DILI is caused by an improper immune reaction to certain drugs or its metabolites that is ordinarily suppressed by PTPN22. Importantly, this study opens the possibility of developing therapies for DILI that focus on improving the activity of PTPN22 and the related cellular pathways that curb immune responses.
Workshop Explores Ways To Improve Diagnosis and Treatment of Pancreatic Disease Through Precision Medicine

On July 24, 2019, the NIDDK, in collaboration with the National Pancreas Foundation, sponsored a workshop to understand the current status of precision medicine—the use of specific information about disease mechanisms and features to guide more targeted and effective medical care—in the diagnosis and management of pancreatic disease. An additional goal was to identify ways to apply precision medicine to tailor treatments for people with pancreatic disease. The workshop took place in conjunction with an annual meeting of pancreatitis researchers called PancreasFest in Pittsburgh, Pennsylvania.

Pancreatic diseases such as pancreatitis and pancreatic cancer are not easy to detect in their early stages, and by the time they are diagnosed they tend to be advanced and difficult to treat. These diseases also have complicated origins with contributing factors that vary from person to person, making it difficult to identify universal markers that could be used to make early diagnoses. Precision medicine approaches, which take into account genetic, environmental, and lifestyle factors, would be helpful for early diagnosis and treatment. For example, identifying genetic variations that are associated with pancreatitis could enable screening individuals to identify those at higher risk while also pinpointing potential targets for therapy. Precision medicine would also allow doctors and researchers to predict more accurately which treatment and prevention strategies will work in which groups of people.

The workshop included an introductory lecture on precision medicine in cancer treatment as an example of how it has been successful in that field and what aspects need to be further developed. The rest of the workshop was divided into four sessions: (1) general considerations for analyzing large sets of data, including using artificial intelligence; (2) analyses of genes, proteins, and metabolic products to identify risk factors and markers for pancreatic disease; (3) advances in imaging techniques to assess the severity of disease; and (4) gaps, barriers, and needs that prevent applying precision medicine to tailor treatments for patients with pancreatic disease. Key areas identified for future efforts were: collaboration among institutions to generate and share large data sets; new ways to collect, interpret, and measure data to help understand disease mechanisms; new clinical trial designs to test and improve therapies; and a framework for measuring and assessing the value of precision medicine approaches to the health care system.

The workshop brought together people from the NIH and researchers throughout the nation. In general, the participants felt that precision medicine approaches can identify patients early in the course of their pancreatic disease and prevent progression to chronic or fatal illness.

The meeting organizers have developed a manuscript for publication in the scientific literature describing the workshop proceedings.1 Recommendations from the workshop will help inform future NIDDK efforts to advance research, as a foundation for accelerating the development of new approaches to managing pancreatic disease.

Pancreatitis in Children

A painful, chronic disease is hard enough for an adult to manage, but when a child faces such a disease, it proves even more difficult. Pancreatitis is one of these conditions, placing a significant burden on children and their families—physically, emotionally, and financially, as well as in terms of overall quality of life. For a child with pancreatitis, every aspect of their life is affected, including the ability to eat, be active, and go to school. Treatments are currently limited to supportive therapy for pain management and surgical procedures. Although relatively rare, pancreatitis in children is more common than was previously thought, and it can progress in a surprisingly short timeframe.

Over the years, NIDDK-supported research has made important strides toward better understanding pancreatitis in children and contributing to efforts to improve its diagnosis, treatment, and, ultimately, prevention.

HOW PANCREATITIS AFFECTS CHILDREN

Pancreatitis is an inflammation of the pancreas, an organ located behind the stomach. The pancreas performs many important functions, including the secretion of insulin and other key hormones, as well as production of a fluid containing precursor forms of enzymes and bicarbonate that flows through ducts into the intestine, where the enzymes become activated and aid digestion of food. In pancreatitis, the digestive enzymes become activated too early—while still inside the pancreas. This causes inflammation and damage to the organ, leading to the symptoms of pancreatitis—the main one being abdominal pain that is often severe, as well as nausea and vomiting.

The disease can occur in three forms: acute, acute recurrent (two or more acute episodes), and chronic. Acute pancreatitis can progress to the chronic form, which carries with it an increased risk of pancreatic cancer. Once considered an uncommon disease in children, the incidence of pediatric acute pancreatitis has increased over the last 10 to 20 years and currently affects approximately 1 in 10,000 children. Chronic pediatric pancreatitis, in which children have diagnostic or functional evidence of irreversible pancreatic damage, is estimated to have an incidence of approximately 2 per 100,000 children per year. Both acute recurrent and chronic forms of pediatric pancreatitis place a significant burden on children and their caregivers.

Risk factors for pancreatitis differ for children compared to adults. In children, the main risk factors are inherited genetic variants, followed next by obstructed ducts caused by congenital abnormalities or gallstones. In adults, risk factors include genetics and gallstones, but environmental factors such as alcohol and tobacco use are the most predominant. Although diabetes is another risk factor for pancreatitis, it is not as common in children as adults. An insufficient production of pancreatic enzymes is found in both children and adults with pancreatitis. Emergency room visits and hospitalizations are common in children and adults with the disease, as are missed days of school or work. Pain, whether it comes in discrete episodes or is constant, is frequently difficult to treat, leading to lost school time for children and increased utilization of health care and high medical costs.

There are currently no drugs that effectively halt progression of this potentially debilitating disease or that reverse the disease process. Treatment options to manage the severe, often unremitting pain typically accompanying chronic pancreatitis include opioids, which carry the risk of addiction. If traditional pain management fails, a child with pancreatitis may need a surgical procedure called a total pancreatectomy-islet autotransplantation (TP-IAT), in which the pancreas is surgically removed and its insulin-producing islet cells, which regulate blood glucose (sugar), are

collected and infused into the liver, where the cells implant and function. (See the chapter on Diabetes, Endocrinology, and Metabolic Diseases for a profile on an individual who underwent TP-IAT for pancreatitis.)

This current state of knowledge of and care for children with pancreatitis is based, in part, on groundbreaking advances from studies conducted over the past several years with NIDDK support, including the following examples.

EARLY CLUES TO PANCREATITIS DEVELOPMENT

A hereditary form of chronic pancreatitis, which affected multiple family members over generations, was first recognized in 1952, only a few years after the NIDDK was established. However, the discovery of the first genetic mutation associated with this disease would occur more than 40 years later. In 1996, NIDDK-supported scientists reported that a mutation in a gene called PRSS1 was associated with hereditary pancreatitis; this gene codes for the protein trypsinogen, an inactive precursor of the digestive enzyme trypsin. This study and others identified a number of genetic variants associated with pancreatitis in the trypsinogen gene, in more genes that affect trypsinogen/trypsin, and in genes with additional functions. These discoveries were made possible by the availability of information on human gene sequences through such efforts as the NIH’s Human Genome Project.

Around the same time of these discoveries by individual investigators, in 1996 the NIDDK funded the beginnings of the first large clinical cohort study of pancreatic disease in the United States, called the North American Pancreatic Study (NAPS) Group. Additionally, the NIDDK provided some support for a later study in European families on clinical and genetic characteristics of hereditary pancreatitis that associated different PRSS1 mutations with age of symptom onset and disease progression, and showed a median age of 10 years for the onset of first symptoms of the disease in families with one of the mutations. These studies, together with a subsequent larger cohort study in adults called the North American Pancreatitis Study 2, or "NAPS2," advanced knowledge of the numerous genetic and environmental factors playing a role in pancreatitis, including the first genome-wide association study of pancreatitis in 2012, which identified new genetic regions associated with the disease.

INSPPIRE-D TO ADVANCE KNOWLEDGE OF PEDIATRIC PANCREATITIS

In 2009, a group of international investigators came together to form the first multi-center group dedicated to studying pancreatitis in children, which would come to be called the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) Consortium, established with support from the NIDDK. The Consortium’s focus was the characterization of acute recurrent and chronic forms of pediatric pancreatitis, in terms of their global distribution, causes, disease processes, and outcomes at 14 sites throughout the United States, Canada, Israel, and Australia. This multi-center approach, assembling the largest cohort of children with pancreatitis to date, was necessary to have sufficient numbers of participants for studying the relatively rare disease of pediatric pancreatitis.

The work of the INSPPIRE investigators, together with study participants, proved extremely productive, yielding multiple research advances and publications. For example, one study presented a fuller picture of the significant burden placed on children with chronic pancreatitis by quantifying their experiences of severe, often constant pain, resulting in hospitalizations and missed school days. Another study revealed the steep economic cost of acute recurrent and chronic pancreatitis in children, due to repeated hospitalizations, tests, procedures, and medications. Other findings focused on better characterizing the genetic risk factors often at work in these forms of pediatric pancreatitis and how they influence disease onset and progression.

Following the success of the original INSPPIRE study group, and based on recommendations stemming from NIH workshops on pancreatitis...
Research held in 2012 and 2013, the NIDDK and the National Cancer Institute co-sponsored the formation of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer in 2015. The INSPPIRE group became part of this larger Consortium as "INSPPIRE 2," featuring an even larger and more diverse population of study participants.

Within the last few years, INSPPIRE 2 and the broader Consortium have made major contributions relevant to pediatric pancreatitis. Consortium studies of adult pancreatitis established standards for imaging procedures used to diagnose and assess disease severity as part of pancreatitis care. One analysis performed by the INSPPIRE 2 investigators better characterized risk factors and disease progression in children with pancreatitis, showing both commonalities and differences with adult patients. Other INSPPIRE 2 findings included the observation of the surprisingly short timeframe for children with acute recurrent pancreatitis to develop chronic pancreatitis, occurring over 2 to 4 years, with more rapid progression in those who were diagnosed later in childhood and who carried PRSS1 genetic variants associated with the disease. Another study conducted by an NIDDK grantee associated with the INSPPIRE program found that several genetic risk variants are likely to play a significant role in progression to acute recurrent chronic disease after the first attack of pancreatitis in children. NIDDK-supported researchers also found that carriers of these pancreatitis-associated risk variants are at higher risk for developing pancreatic cancer later in life. These studies, reported in 2018 and 2019, could help researchers and clinicians develop better approaches to diagnose and treat children with pancreatitis.

**FUTURE DIRECTIONS IN PEDIATRIC PANCREATITIS RESEARCH**

The NIDDK has been continuing its support for the "inspiring" work of the INSPPIRE 2 investigators and study participants, as well as others studying pancreatitis in children. In the future, INSPPIRE 2 researchers will continue the long-term cohort study to probe deeper into remaining questions, such as better understanding risk factors involved in pancreatic disease progression, determining how chronic pancreatitis first develops, defining pancreatic enzyme insufficiency (a lack of digestive enzymes that hinders proper digestion of food), and improving treatment options. For example, one study is testing the first drug-free approach for pediatric pancreatitis—a web-based cognitive behavioral therapy intervention to manage pain without opioid exposure and improve quality of life in adolescents with chronic pancreatitis. Other ongoing INSPPIRE 2 investigator studies of pediatric pancreatitis are monitoring rates across sites, identifying the earliest diagnostic imaging evidence of disease, defining metabolic and skeletal complications, understanding why chronic pancreatitis more commonly affects girls, and understanding the contribution of drug-induced pancreatic diseases. The NIDDK also continues to support investigator-initiated research in this area, such as the recent development of the first pre-clinical mouse model to faithfully mimic human chronic pancreatitis—made possible through genetic alterations in the trypsinogen gene of mice—that can be used to inform the development of new treatments.

While providing ongoing support for research on pediatric pancreatitis, the NIDDK regularly sponsors scientific workshops that bring together leaders in the research community to discuss how to advance pancreatitis research. Past workshops have focused on research opportunities relating to such themes as research challenges in chronic pancreatitis, biomarkers of pancreatic disease, and optimizing use of the TP-IAT procedure. In 2018, the NIDDK, with additional support from the National Pancreas Foundation, sponsored a workshop focused on ways to accelerate the development of new treatments for pancreatitis. The workshop's recommendations were shared widely with the scientific community through multiple publications in the scientific literature. Most recently, in 2019, the NIDDK sponsored a workshop on how precision medicine-related methods and technologies can be applied to new and more personalized ways to diagnose and manage pancreatitis and other forms of pancreatic disease. These workshop recommendations and additional sources of external stakeholder input will continue to inform the NIDDK’s efforts to reduce the burden of pediatric pancreatitis through research.
PATIENT PROFILE

Jeff: The Endurance To Overcome Drug-induced Liver Injury

Jeff is an executive at a successful furniture company, is active in his church, and volunteers with youth. In his spare time, he skis and is a competitive mountain biker—a successful one, too, with a history of winning races in his age category. Not surprisingly, he tries to take good care of his body. Aside from a couple of treatable medical conditions, he is a healthy 60-year-old. He is also accustomed to training hard for races, but there was no way he could have prepared for his encounter with drug-induced liver injury.

In 2016, eager to rid himself of a lingering and headache-inducing sinus infection, Jeff started taking a 6-week antibiotic course prescribed by his allergist. Four weeks later, he was experiencing nausea, headaches, and a low-grade fever. At that time, he was due to meet up with some friends for a 2-hour motorcycle ride from his hometown in Michigan to spend a few vacation days in a cottage at a ski resort. Despite feeling miserable, he made the trip with his wife riding on the seat behind him. At the cottage he became overwhelmed by cramps and vomiting, even briefly losing consciousness. He spent most of his remaining vacation confined to a bed. At that point, Jeff decided to stop taking the antibiotic. He wasn't fully aware of it at the time, but his liver was experiencing a severe reaction to the drug, and only after a harrowing trip to the emergency room and months of recovery would he begin to feel somewhat normal again. During that time, he would directly experience the agony and alarm that coincide with drug-induced liver injury. He would also join the NIDDK’s Drug-Induced Liver Injury Network (DILIN), becoming part of a concerted, multi-site study to understand, manage, and prevent this potentially deadly disease.

SIGNS OF A ROUGH ROAD AHEAD

Drug-induced liver injury occurs when a prescription drug, an over-the-counter drug, or a dietary or herbal supplement damages the liver. Some types of drug-induced liver injury, such as those caused by acetaminophen overdoses, are relatively easy to foresee and avoid because the type of injury tends to be similar among people and directly dependent on the amount of drug ingested. Others, such as Jeff’s case, are called “idiosyncratic.” They are relatively uncommon, with effects that are harder to predict and largely determined by a combination of factors unique to an individual, such as genetics and the condition being treated. This makes it difficult to know who will respond
adversely to a given drug—even at dosages that are safe for most people.

Unsure of what was happening but knowing he needed medical treatment, Jeff decided to return home. When he and his wife got back, it was Father’s Day, and his daughter and son-in-law came by for a visit. His son-in-law noticed that the whites of Jeff’s eyes were tinged with yellow and his skin was darkened with a yellow-orange appearance. Jeff’s daughter began to worry that there was something seriously wrong with his liver and urged him to seek treatment. He went to his family doctor, who ordered blood tests to detect markers for liver health, like bilirubin and the liver enzymes alanine aminotransferase (ALT) and alkaline phosphatase.

A high level of bilirubin, along with elevated levels of liver enzymes in the blood, are signs of liver damage, and Jeff’s bilirubin level was almost six times the normal amount. Over the next few days, it continued to slowly rise, and there was seemingly nothing he could do to stop it. Jeff was starting to worry that something terrible was on the horizon. “As that was happening,” he recalls, “I’m starting to wonder, how bad was this going to get?”

Jeff’s doctor was beginning to suspect that drug-induced liver injury, triggered by the antibiotic, was the cause of Jeff’s deteriorating health. The antibiotic that Jeff took was actually a combination of two drugs—amoxicillin and clavulanate—commonly called Augmentin®. Prescribed to treat mild-to-moderate bacterial infections, it is designed to be a double knock-out punch for bacteria: amoxicillin is an antibiotic derived from penicillin, and clavulanate targets bacteria that can degrade the amoxicillin before it can do its job. The combination is usually effective and safe and is one of the most frequently prescribed antibiotics. In a small percentage of people (about one in 2,500 people treated), it triggers an allergic response when it is broken down by the liver. The body appears to misread the breakdown products as unwelcome foreign invaders and sends powerful immune cells streaming into the liver. The resulting immune reaction wreaks havoc on the vital organ, causing jaundice and, in severe cases, acute liver failure.

Jeff’s doctor thought he should see a digestive disease specialist to keep a closer eye on his liver, so Jeff went to a gastroenterologist. In the meantime, his bilirubin level continued to climb.

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A RACE TO THE EMERGENCY ROOM

Jeff felt extremely weak and tired, but he pushed himself to continue working over the next several weeks. Then, shortly before the Fourth of July weekend, he got a call in the middle of a meeting: his test results were so alarming that his gastroenterologist urged Jeff to go to the emergency room right away. He remembers calling his wife, stopping by the house to grab some clothes, and then driving to the hospital, his mind racing. “All of a sudden, reality strikes me,” he recalls. “What’s going to happen here? Do I get a liver transplant? Do people die from this?”

Jeff’s anxieties were not unfounded. Although most cases of idiosyncratic drug-induced liver injury resolve after the patient stops taking the drug or dietary supplement that triggered the disease, recovery is dependent upon a timely diagnosis, proper identification of the offending agent, and other factors such as genetics and the overall health of the liver. One complicating factor is that the injury from amoxicillin and clavulanate (and some other antibiotics) typically arises weeks after exposure to the drug, so symptoms may not manifest until 1-3 weeks after a short antibiotic course is completed. With rare exceptions, there are no current treatments that are effective in reversing this type of liver injury. The first and most important
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Step in management is to stop taking the drug—and to not ever take it again (even if there are doses remaining in the prescribed course of antibiotics). This includes throwing away any leftover amounts of the drug and clearing it from the medicine cabinet as extra insurance that it is not used again. People who have experienced this type of liver injury should also make note of the drug so they can tell their doctors if they are ever prescribed it again. The liver has an amazing ability to heal itself and recover from damage, but if the damage is too great, liver failure occurs, and only a liver transplant will guarantee recovery. Drug-induced liver injury, although rare, is the major cause of death from acute liver failure in the United States and other developed countries of the world.

At the hospital, Jeff underwent hourly blood tests to monitor his liver. His bilirubin had soared to over 20 times the normal level—a surefire sign that his liver was under severe distress. “It was definitely a surreal feeling, realizing that I could die,” he remembers. His wife was sending out alerts and prayer requests to his friends and members of his family; his son and daughter-in-law, who live in Seattle, were trying to sort out whether to catch the next flight to Michigan.

“I just remember realizing what was important in life at that point,” says Jeff when remembering his visit to the emergency room for a liver injury. “Your faith, your family, and your friends ... everything else didn’t matter.”

Jeff and his family spent that night in the emergency room praying and waiting anxiously for each test result. “I just remember realizing what was important in life at that point,” he recalls. “Your faith, your family, and your friends ... everything else didn’t matter.”

On the second day, to everyone’s relief, Jeff’s bilirubin level finally began to ease downward. He spent a few more days at the hospital, weakened to the point of barely being able to walk. After getting discharged, he sat at home on his deck, thankful, enjoying the Michigan summer weather and thinking, “I’m just happy to be here.”

THE SLOW, UPHILL PATH TO RECOVERY

Soon after Jeff left the hospital, Dr. Robert Fontana, a liver specialist and principal investigator in the NIDDK’s multi-center DILIN program, contacted Jeff from the University of Michigan to see if he would be interested in joining the study. Jeff willingly agreed, even though he was still extremely fatigued from his episode in the emergency room. “I could hardly walk a hundred feet without becoming exhausted,” he recalls. “That’s pretty unusual for me, since I’m used to doing significant bike and ski races.”

He understood that joining the study would not only contribute to advancing medical knowledge but would also provide an opportunity for his recovery to progress more quickly and smoothly because it would be closely monitored with regular checkups. “It was an opportunity to have really good care and to be monitored on a regular basis,” he says. “I think that was the biggest thing, that they would be watching over me, trying to understand this better, and trying to help in the future.”

The NIDDK established DILIN in 2003 to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal and dietary supplements. Since that time, DILIN has collected data and specimens from more than 2,000 cases of liver toxicities due to these agents and made major contributions to understanding why certain medications and dietary supplements are more likely to damage the liver, why only some people are affected, and how the liver can heal itself after the injury. Answering these questions about the disease will continue to help researchers prevent and treat it. Genetic information from the Network’s participants, for example, is providing clues into how genetics could
determine whether people react negatively to a drug or dietary supplement, even opening the possibility of screening patients before prescribing certain drugs to minimize the possibility of liver damage.

Jeff's participation in the DILIN study initially began with visiting the University of Michigan every 6 months for blood tests. At each visit he also underwent a specialized ultrasound procedure that detects the amount of scarring in the liver—a painless, noninvasive way to measure how well the liver is healing. His bilirubin level settled back into the normal range within 3 months after the trip to the emergency room, but other blood markers for liver health remained elevated, so he underwent a liver biopsy, which confirmed his liver was healing well. It was about a year after the initial injury when his liver markers came back close to the normal range—and that is where they remain 3 years after the injury, "not completely normal, but they're close to normal," Jeff says.

Jeff maintains a spreadsheet to keep track of his test results, and, with some trepidation, he still looks forward to getting his blood tested, which happens yearly now. "I want to know if I'm getting better," he says. "But at the same time, I'm very anxious about it and concerned that it's going to be moving backwards, so there's definitely still some feelings that linger, like, 'can this get worse?'"

In spite of his worries, 5 months after his liver injury Jeff was again racing in mountain bike competitions. Within a year, he was back to winning statewide races in his age group. "So, I was kind of back into full swing," he admits modestly.

SPOTTING THE FINISH LINE: OVERCOMING DRUG-INDUCED LIVER INJURY

DILIN continues to build upon its successes. The NIDDK renewed the Network for a new project period beginning in 2018 and included provisions for pilot studies that would lay the groundwork for future clinical trials to treat severe drug-induced liver injury. The NIDDK also partners with the NIH's National Library of Medicine on an online resource called "LiverTox" (http://livertox.nih.gov), which features sample cases of people with drug-induced liver injury based on the Network's data, as well as a database summarizing liver injuries caused by drugs, including amoxicillin-clavulanate, and various herbal and dietary supplements. Meanwhile, Jeff continues to participate in the DILIN study and has adopted a new outlook. He admits that, like most people, he knew next to nothing about drug-induced liver injury before he was affected by it; now, after gaining firsthand knowledge, he wants to raise public awareness about it. He is thankful for everyone who supported him through his illness: his family and friends, his church, his gastroenterologist, and Dr. Fontana, who once jokingly called him "the healthiest sick person I know."

"It was an opportunity to have really good care and to be monitored on a regular basis," Jeff says about joining the Drug-Induced Liver Injury Network study. "I think that was the biggest thing, that they would be watching over me, trying to understand this better, and trying to help in the future."

His experience has left an indelible impression on Jeff's life, particularly with regards to his health. While there is no approved therapy for this type of liver injury, there are ways to manage it that focus on health maintenance and avoiding further injury, including stopping all medications except the most necessary, stopping alcohol consumption, paying careful attention to nutrition, and getting adequate rest. Once the injury resolves, it is possible to resume other medications and modest alcohol intake. "[The injury] is at the back of your mind," he says. "For example, I always liked a glass of wine or beer now and then, but [shortly after the injury]..."
“I’m living my life to the fullest, because you don’t know what’s going to happen,” says Jeff of his outlook after recovering from a potentially life-threatening liver injury.

there was no alcohol. I didn’t have any of that for at least a year. When things returned to normal, I would have just a little bit. So those kinds of things are always on your mind.”

He also has a renewed desire to get the most out of life. “After the injury, I was looking at things differently,” he remembers. The next winter, when he and his family went on their annual skiing trip to the Canadian Rockies, he tried something new: heli-skiing. He and his son rode in a helicopter to a remote area at the top of a mountain, where they were deposited in fresh snow to ski down the untouched slope. “I said, ‘OK, I’m just going to do this,’ and it was great,” he recalls, adding that this is an example of how liver injury affected the way he looks at things. “I’m living life to the fullest, because you don’t know what’s going to happen,” he says. “Now I want to live life even more.”