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 стратегический план-отчет/niddk-
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The liver's unique ability to regenerate is legendary, and was first noted in Greek mythology and the story of Prometheus. Scientists are still working to understand which cells are responsible for restoring the organ under normal conditions and after injury. As described in this chapter, one group of researchers has mapped the liver's growth and regenerative potential by examining three zones within the functional unit of the liver called the lobule. They used fluorescent markers in mice to tag cells in these zones and track their contributions to liver growth and regeneration after injury from toxins. These images are from one strain of mouse whose cells have been fluorescently tagged to trace them to certain zones (first three images left to right); the rightmost image shows a composite image of all the tagged cells together. Mouse strains like these allowed the researchers to study the regenerative potential of the different zones. Future studies could elucidate the role that cells in different zones might play in liver disease and provide the basis for therapies that boost liver regeneration.

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. NIDDK-supported scientists are pursuing research aimed at reducing the burden of digestive diseases. These efforts focus on better understanding how widespread these diseases are across the United States and in specific population groups, identifying their causes and how they progress, and testing new interventions for prevention and treatment, including drugs, surgery, and behavior modification.

Digestive diseases affect individuals across the lifespan, exacting a significant toll 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. 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 2018 national inpatient samples identified 4.0 million hospitalizations with a primary diagnosis of digestive diseases and 16.5 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 18.7 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling $107.6 billion in 2018.\(^3\)

Inflammatory bowel diseases (IBDs), which include Crohn's disease and ulcerative colitis, are marked by damaging intestinal inflammation 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 surgical removal of the affected portion 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, more personalized 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

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Annual estimates of the burden of digestive diseases list these diseases as the primary diagnosis in 66.4 million ambulatory care visits to physicians' offices and hospital emergency and outpatient departments.\(^1\)

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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](http://www.cdc.gov/nchs/ahcd/index.htm).
ulcer disease, which is typically caused by infection with the bacterium *Helicobacter pylori* or use of nonsteroidal anti-inflammatory drugs. Stomach and intestinal disorders also include functional gastrointestinal disorders, which can cause symptoms of abdominal pain and altered bowel habits. For example, irritable bowel syndrome (IBS) causes pain and constipation or diarrhea. IBS more frequently affects women, who may have 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 gastrointestinal 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. Gastroparesis, another type of functional gastrointestinal 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. Current therapies are directed toward helping people manage this chronic condition so they can be as comfortable and active as possible. Fecal incontinence, or impaired bowel control, is a 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 aim to examine barriers in addressing fecal incontinence and to develop improved treatment strategies. Scientists continue to strive for a deeper understanding of the causes of gastrointestinal disorders, which will lead to improvements in diagnosis and management.

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 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.

**Stomach and intestinal disorders include functional gastrointestinal disorders, such as irritable bowel syndrome and gastroparesis, which can cause symptoms of abdominal pain and altered bowel habits.**

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

**Microbes that inhabit the gastrointestinal tract are important factors in maintaining the balance between digestive health and diseases, such as inflammatory bowel diseases.**

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 performs many critical metabolic functions within the digestive system, including processing and distributing of nutrients such as fats. When the liver is functionally compromised by disease, serious adverse health effects can occur, which sometimes leads to complete liver failure, called 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 of nonalcoholic steatohepatitis. In recent years, however, NAFLD has been increasingly diagnosed in children in the United States as well, concurrent with rising overweight and obesity. 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. When liver disease reaches the end stage, the only treatment is a liver transplant. Because the number of livers available for transplant from deceased donors is limited, sometimes a healthy living person will donate part of his or her liver. 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 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 overweight and obesity.

The number of Americans with overweight or obesity 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 obesity, 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 to understand dietary needs in health and disease. NIDDK staff works collaboratively with representatives from across the NIH, including in the NIH’s Office of Nutrition Research, to advance nutrition research efforts.

The NIDDK works to advance nutrition research efforts, both within the Institute and collaboratively with others across the NIH, including the NIH’s Office of Nutrition Research.

GUT MICROBIOME AND NUTRITION

Designer Foods Target Microbiome To Boost Host Health: Researchers have developed foods designed to alter the gut microbiome, with an eye toward moving the needle on two immense public health challenges: malnutrition and obesity. These conditions represent opposite types of energy imbalance that co-exist in our modern world, sometimes within the same household. Decades of research has documented how the state of the community of microbes that inhabit the gut, or gut microbiome, reflects their human host's health. The gut microbiome also changes in response to dietary components that are metabolized by specific microbial species, such as fiber. Two recent studies explored the impacts of foods customized to shape the gut microbial landscape in children with malnutrition and adults with obesity.
One study represented the latest in an ongoing series of investigations supported by NIDDK, the Bill and Melinda Gates Foundation, and others of microbiome-based dietary interventions in malnourished children in Bangladesh. These children show signs of an immature gut microbiome for their age, which in turn impacts their response to therapeutic food interventions. Previously, this group of researchers from the United States and the International Centre for Diarrhoeal Disease Research, Dhaka, designed a "microbiota-directed complementary food," or "MDCF," containing flours and oils from nutrient-dense, locally available foods such as chickpeas, nuts, and bananas. In the most recent study, they compared the effects of their MDCF with the standard ready-to-use supplementary food given to malnourished children. Bangladeshi girls and boys ages 12 to 18 months with moderate malnutrition received either the standard supplementary food or MDCF twice daily for 3 months, and were monitored for changes in growth, levels of proteins linked to growth and neural development, and gut microbial species present. The results demonstrated that the MDCF dietary supplement not only supported a more age-appropriate gut microbiome, but also resulted in greater improvements in growth and markers of neural development in these children, compared to those given the standard ready-to-use supplementary food.

In another study, the scientists aimed to design snacks containing plant-based fiber to promote beneficial microbial responses in adults with overweight/obesity. Beginning with an animal model, male mice raised in a sterile environment free of microbes were colonized with gut microbes from women with obesity. The mice were then fed a fiber-deficient, high-fat diet supplemented sequentially with plant fiber from either peas, oranges, or barley. Over time, the abundance of microbial genetic material present in the stool increased dramatically for the enzymes needed to break down each unique fiber, and for microbial species that are associated with protecting against obesity such as *Bacteroides*. Pilot clinical trials tested whether this effect was translatable to people. Men and women with overweight/obesity were given prepared meals of a fiber-deficient, high-fat diet similar in nutritional composition to the one fed to the mice, supplemented with a snack composed of pea fiber, for several weeks. Similar to the results in mice, the study participants showed the same shift in microbial gene abundance toward a ramped up metabolic capacity for fiber. Follow-up studies testing snacks composed of multiple types of plant-based fibers, including those used in the mouse studies, demonstrated an even greater microbial shift towards fiber metabolism. Consumption of the extra fiber in snacks was also associated with altered protein profiles in participants' blood, indicating impacts on diverse physiological responses, such as metabolism and immune function. These findings provide compelling evidence of the strong connections among the gut microbiome, nutrition, and health impacts, and for the utility of mouse models of human response to food-based interventions that target the microbiome.


Two recent studies explored the impacts of different foods designed to change the community of microbes that inhabit the gut, or gut microbiome, in children with malnutrition and in adults with obesity. This research shows the promise of this approach for helping to address these disparate public health challenges.

**IDENTIFYING THERAPEUTIC TARGETS FOR INFLAMMATORY BOWEL DISEASE**

**New Potential Therapeutic Target Identified for Crohn's Disease:** New research has shed light on how known genetic risk factors can contribute to Crohn's disease and treatment response, opening the door to new treatment approaches. Crohn's disease is a form of inflammatory bowel disease in which the digestive tract is marked by lesions of damaging inflammation. It can start at any age, causing lifelong episodes of cramping, diarrhea, and malnutrition. Medications that block a major component of the inflammatory response called tumor necrosis factor (TNF) are effective for many people, but in some cases the disease does not respond to these drugs. Among the scores of genetic variations that have been linked to a higher risk for developing Crohn's disease, changes in a gene called NOD2 that impair its function have been found to be a major risk factor. Exactly how these NOD2 genetic variations could contribute to Crohn's disease has been unclear, however, which has been a major roadblock for developing new therapies.

Researchers set out to answer this question by analyzing
intestinal samples from a well-characterized group of male and female children with Crohn’s disease. They found that genetic variations inhibiting NOD2 function were linked to changes in fibroblasts (cells that make up connective tissue) and immune cells in Crohn’s disease lesions. Specifically, these cell types showed signs that they were “activated” and producing factors involved in inflammation. Importantly, activated immune cells and fibroblasts have also been found in lesions from people with refractory Crohn’s disease that is resistant to anti-TNF therapy, suggesting that these activated cells provide an additional route to inflammation that is independent of TNF-mediated inflammation. Using cultured cells and a zebrafish model that effectively mimics human Crohn’s disease, the researchers identified a protein known as gp130 that plays a critical role in activating these cells when NOD2 is impaired. Data from women and men with Crohn’s disease that did not respond well to anti-TNF therapy showed high levels of intestinal proteins in the cellular pathway used by gp130. Additionally, the researchers found that treating zebrafish or cultured cells with a gp130-blocking drug inhibits activation of inflammatory cells. More research is needed to determine if blocking gp130 will similarly reduce cellular activation in human intestinal lesions. However, this study suggests that drugs targeting gp130, when used in conjunction with anti-TNF therapy, might be effective treatments for people with Crohn’s disease resulting from NOD2 risk variants.


Researchers have discovered how variants in the NOD2 gene may contribute to intestinal inflammation, offering new possible therapeutic approaches to treat Crohn’s disease.

IDENTIFYING THERAPEUTIC TARGETS FOR INTESTINAL DISEASE IN CHILDREN

Potential Therapeutic Target Identified To Prevent Severe Diarrhea in Children: New findings suggest that rotavirus-induced severe diarrheal disease in children may be prevented by targeting a cell-to-cell signaling pathway in the gut. Rotavirus infections of the small intestine are the leading cause of severe diarrhea, vomiting, and dehydration in children worldwide; while an extremely effective vaccine for the most common form of the virus is now available, not every child has access, so improving therapeutic options remains a priority. A key question is how the virus causes severe disease even before damage to intestinal tissue is apparent. One theory has been that infected cells release a signal molecule that disperses and disrupts nearby uninfected cells, specifically by causing inappropriate increases in levels of calcium—a molecule critical to many cellular processes—within those cells. These increases in turn activate cellular pathways that lead to vomiting and diarrhea. Researchers studying rotavirus infections in both non-human primate epithelial cells and human intestinal epithelial cell models called “enteroids” have identified the molecule adenosine 5’ diphosphate, or ADP, as the candidate signal. They found that ADP released from infected cells activates a specific cell-surface receptor, called P2Y1, to cause increased calcium levels in neighboring uninfected cells—so-called “intercellular calcium waves” that they could both visualize and measure experimentally. Importantly, rotaviruses also require elevated calcium for their replication, and the team found that blocking ADP-P2Y1 signaling significantly reduced the amount of rotavirus produced by infected cells.

To help determine whether what they observed in laboratory-grown cells is relevant to actual disease, the researchers tested their findings in an animal model. They found that two different, orally administered drugs that block P2Y1 receptor function were each able to reduce severity of diarrheal disease in young male and female rodent pups infected with rotavirus.

Although not yet well studied, intercellular calcium waves induced by ADP may be a normal route of communication for intestinal cells. While rotaviruses employ other mechanisms to initiate calcium increases when infecting a cell, the study findings suggest that by exploiting a preexisting ADP signaling pathway in the gut, the virus can simultaneously boost calcium in “instigator” infected cells while also causing disruptions in neighboring uninfected cells that will facilitate viral spread to new hosts via diarrhea and vomiting. By identifying ADP-P2Y1 as the likely signaling pathway, researchers can now see whether a safe therapeutic intervention targeting this pathway can be developed that could easily be administered to infected children to prevent or reduce symptoms and also possibly prevent spread of rotaviral disease.

NEW INSIGHT INTO INTESTINAL BIOLOGY

Mucus Keeps Gut Bacteria at Bay To Prevent Inflammation: Research using a mouse model has provided a new understanding of how mucus coating the inner colon isolates bacteria from the gut wall, potentially offering new ways to diagnose and treat intestinal inflammation. A thriving community of bacteria (microbiome) lives in the human gut, helping with digestion and receiving nourishment from the food we eat. However, bacterial contact with the intestinal lining can trigger an inflammatory response (colitis), leading to chronic pain, bleeding, and diarrhea. One important way the body keeps inflammation in check is through a layer of mucus coating the inside of the colon, physically separating gut bacteria from the intestinal lining. A breakdown of this mucus layer has been implicated in several gastrointestinal diseases, but developing treatments to restore it has been challenging because of an unclear understanding of how it is produced.

To gain a better understanding of how the colon builds and maintains the mucus barrier, researchers conducted studies in male and female mice to develop a new way to visualize the mucus layer along the entire length of the colon. They found that the proximal area of the colon—where the colon joins with the small intestine—produces a thick layer of mucus that not only coats the intestinal lining, but also encapsulates fecal material and its associated bacteria. As the intestinal contents move further along the GI tract, they encounter a second, thinner, chemically distinct layer of mucus that is produced by the distal colon (the latter portion of the colon). The researchers generated mouse models with disrupted mucus production in either one or both areas of the colon and showed that both of the mucus layers were important for keeping bacteria sequestered in fecal pellets and separated from the intestinal lining. They also showed that both layers were critical for preventing spontaneous inflammation, with the most severe inflammation occurring when mucus production was turned off in both areas. The researchers also uncovered an intimate interaction between gut bacteria and the mucus layer: the presence of bacteria drove up mucus production in the proximal colon, while turning off mucus production changed the makeup of the bacterial community. This suggests that the proximal colon mucus provides an environment that favors growth of healthy bacteria, and a defective mucus layer could be a sign of an unhealthy microbiome.

These results in mice present a new model for intestinal mucus function, whereby the mucus layer dynamically insulates the intestinal lining from bacteria. Further research would be needed to confirm whether human colonic mucus functions in a similar way. If so, the fecal mucus coating could serve as a diagnostic tool to detect gastrointestinal disease, and, ultimately, as a target for new approaches to restore the gut to a healthy state.


LIVER MAINTENANCE AND REGENERATION

Location, Location, Location—Cell Position in Maintaining and Regenerating Liver: New research in mice has identified which cells of the liver contribute in large part toward maintaining the organ or regenerating it after injury. The liver is unique by virtue of its ability to regenerate and adjust its size in proportion to overall body size. At the microscopic level, the liver tissue is arranged in a honeycomb pattern with repeating hexagonal structures called lobules. These structures are made up of a central vein surrounded at each of the six outer points by a bundle consisting of a portal vein, hepatic artery, and bile duct. Lobule geography is mapped accordingly based on these landmarks into three areas, or “zones.” The same liver cell type can have unique capabilities depending on its zonal position, such as production of specific metabolic enzymes.

Scientists applied advanced genetic tools to answer a question that had conflicting results in the past: do cells in one zone contribute more to liver growth and regeneration than others? Using state-of-the-art gene editing technology, they generated 11 new strains of mice with modifications to switch on a fluorescent marker that selectively labels different groups of cells in the three zones of the liver lobule. In these mice and three other similar models, they tracked the abundance of new cells descended from the marked cells in these three zones. Under conditions of either normal day-to-day growth or regeneration after injury from...
two different toxins, cells in zone 2 showed the greatest increases in number to maintain or restore the liver. The researchers hypothesize that these cells may be more protected from insults coming from the circulation or bile ducts. Next, the researchers further probed how the zone 2 cells are better able to help the liver grow and regenerate by identifying which genes were ramped up or suppressed to support liver cell growth. They identified a cellular signaling pathway that is involved in the growth of these zone 2 cells, which could be important for the development of potential therapeutics.

This work provides compelling evidence for the importance of cellular positioning within the liver lobule, particularly in zone 2, in maintaining equilibrium within the organ and replenishing it after injury. Future studies could help to define the role of these cells in liver disease and inform therapeutic strategies to boost liver regeneration.


DEVELOPING NEW LIVER DISEASE THERAPIES

Lipid Nanoparticles Deliver Promise for Liver Disease Therapies

The success of messenger RNA (mRNA)-based vaccines, such as ones for COVID-19, depends on their delivery vehicle—a high-tech bubble of lipids (fats) called a lipid nanoparticle (LNP) encasing an inner package of fragile genetic material. This protective coating enables the mRNA to safely reach its destination inside target cells, where it produces viral proteins that train the immune system to resist infection. However, the potential medical applications of LNPs extend well beyond vaccines. Two groups of scientists have tested LNPs in mouse models to deliver treatments for multiple forms of liver disease, including liver fibrosis, nonalcoholic fatty liver disease, and drug-induced liver injury.

Targeted Hormone Treatment Transforms Liver Cells into Fibrosis-fighting Superheroes: New research in mice shows the potential for LNP-based therapies that incorporate a dynamic duo—the hormone relaxin and liver macrophage cells—on a mission to deactivate the liver’s fibrosis-promoting cells. Liver fibrosis (scarring associated with tissue injury), and its advanced stage of cirrhosis, are common health problems that develop over the course of diseases such as fatty liver disease. A cast of characters play a role in either activating or repairing liver fibrosis. Hepatic stellate cells are key players in liver fibrosis. When activated by liver injury, they participate in the wound healing response and contribute to scar tissue formation in the liver and subsequent fibrosis. Some other factors work to limit fibrosis, potentially by inactivating stellate cells, including the hormone relaxin, which is primarily known for its role in pregnancy-related changes in the female reproductive system. And finally, some cells act as a double agent, like the liver macrophage, a type of immune cell with the ability either to promote inflammation or to foster tissue repair.

Scientists used an animal model of liver fibrosis to unravel these interactions and unlock their therapeutic potential by employing the powerful LNP delivery technology. Male mice given a toxic chemical for several weeks developed liver injury and fibrosis. But this fibrosis could be reversed by 2 weeks of daily injection with LNPs delivering a gene-based therapy that boosted relaxin production in liver cells. However, when the researchers studied hepatic stellate cells in culture, they were surprised that the relaxin-treated cells remained active and fibrosis-promoting. This finding suggested that the cells in culture were missing essential cues from their environment to cause inactivation in response to relaxin. This prompted the scientists to identify relaxin receptors on the liver macrophages in mice and in samples taken from men with cirrhosis. Upon relaxin binding to its receptor, the macrophages transformed from fibrosis promoters to fibrosis-fighting cells that secrete small LNP-like packages of microRNAs (small pieces of genetic material that control the activity of other genes), which then targeted hepatic stellate cells and blocked their ability to induce fibrosis. The scientists engineered a different type of LNP to carry one of the microRNAs and delivered these along with the LNPs containing the relaxin gene. This combination treatment was even more powerful in reversing fibrosis, both in the liver fibrosis model and in a mouse model of nonalcoholic fatty liver disease.

These studies highlight the important role of macrophages in relaxin-mediated amelioration of liver fibrosis in diseases such as nonalcoholic fatty liver disease, through inactivating hepatic stellate cells. This work shows the potential for approaches combining gene therapy with LNP-based nanotechnology that directly target liver cell networks to provide new treatment options for liver fibrosis.

Potential Regeneration Therapy for Liver Injury Activates Timely Burst of Growth Factors: Scientists have showcased the ability of LNP-encapsulated mRNA to deliver controlled bursts of growth factors that boost regeneration as a potential therapy for acute and chronic liver injury. Effective therapies are lacking for common forms of liver disease, such as nonalcoholic fatty liver disease and cirrhosis. People with acute or chronic forms of liver injury can have a limited window of opportunity in which a therapy can curb damage and restore function of this vital organ. An ideal treatment would need to accomplish this feat of regenerating the liver during a narrow time frame and in a safe way.

Researchers designed LNP capsules containing mRNA that was modified to increase its stability to produce two growth factors, called hepatocyte growth factor and epidermal growth factor. When injected into female mice in these studies, the capsules were delivered to liver cells as their primary target, which manufactured the growth factors for approximately 3 days. In healthy mice, the short-term hepatic growth factor production boosted liver regeneration by ramping up liver cell production that typically maintains the organ. Furthermore, in mice fed a diet resulting in features of chronic liver injury similar to nonalcoholic fatty liver disease, treatment with LNPs containing mRNAs for both growth factors reversed fat deposits in the liver and enhanced liver function, more than in mice given a control LNP vehicle. In a mouse model of an acute liver injury due to overdose of the drug acetaminophen, treatment with both growth factors in the mRNA delivery vehicles accelerated liver regeneration and lowered liver enzymes to normal levels.

This research shows the usefulness of LNP-encapsulated mRNA for delivering discrete bursts of growth factors as a possible, safe therapy for promoting liver regeneration in animal models of acute and chronic liver injury. Future studies will explore whether this new treatment approach can be translated to the clinic to prevent liver disease progression and restore function.


Antiviral Drug Shows Promise Against Hepatitis C in Animal Models: Scientists in the NIDDK’s Intramural Research Program showed that a new antiviral drug, called fluoxazolevir, effectively fights infection by many types of hepatitis C virus, when given in combination with approved antiviral drugs in animal models. Hepatitis C is the most common chronic viral infection from a blood-borne pathogen in the United States. It can lead to damaging inflammation and liver disease, including cirrhosis, liver failure, and cancer. Current treatments with one or more drugs specifically targeting the virus are highly effective, with response rates of over 90 percent. Research efforts continue, however, to develop treatments for people infected with viral subtypes, or genotypes, that are less responsive to available drugs, and for viruses that develop drug resistance.

The researchers defined how fluoxazolevir blocks the hepatitis C virus from entering a human liver cell line in culture by blocking attachment with the outer membrane of the cell. The drug was effective in protecting the cells against infection with several viral genotypes. In male mice, rats, and dogs, the drug localized to the liver, an indication of potentially fewer side effects in other tissues. Additional testing in male mice transplanted with human liver cells showed that a 4-week treatment with the drug suppressed levels of multiple viral genotypes, without toxic side effects. When fluoxazolevir was given to the mice together with an antiviral drug already approved to treat hepatitis C, the combination treatment led to undetectable viral levels, indicating a sustained response to treatment that was not seen with the approved drug alone. This response was seen with infections by different viral genotypes, and no signs of viral drug resistance were observed. A longer 6-week treatment with fluoxazolevir in combination with two approved drugs for hepatitis C resulted in a sustained treatment response in mice infected with a drug-resistant strain of hepatitis C. Fluoxazolevir also showed promise at partially preventing hepatitis C, blunting viral levels when given prior to infection.

These studies demonstrate that the new drug fluoxazolevir, in combination with antiviral drugs already approved for hepatitis C, can achieve a sustained...
response against different genotypes of hepatitis C virus, with a shorter and potentially less costly treatment duration compared to current regimens and less chance of developing viral drug resistance. In combination with approved antiviral drugs, fluoxazolevir may represent a next generation treatment for hepatitis C.


**DIETARY SUPPLEMENTS AND METABOLIC HEALTH**

**A Treatment That May Improve Muscle Insulin Sensitivity in Postmenopausal Women:** A small, short-term clinical trial in postmenopausal women with overweight or obesity, who also had prediabetes, found that dietary supplementation with nicotinamide mononucleotide (NMN) can improve insulin sensitivity in muscle. NMN is an essential ingredient in the production of other biomolecules that are involved in numerous cellular processes, including those governing metabolism. NMN has therefore come under scrutiny in efforts to improve or boost metabolism. Previous research has shown that administering supplemental NMN to mice can partially overcome aging-related losses of insulin sensitivity, particularly in females. Based upon findings such as these, NMN has been marketed as a dietary supplement that can improve glycemic control, but no previous study with human participants has tested this assertion, and NMN has not been approved for this purpose by the U.S. Food and Drug Administration.

In new research, 25 postmenopausal women with overweight or obesity in addition to prediabetes were randomly assigned to receive either NMN supplementation or a placebo. The elevated blood glucose levels observed in people with prediabetes—detectable in a fasting blood test or through other measures—resulted largely from their impaired response to insulin in liver and muscle. After 10 weeks, study scientists found that the muscles of the women who had received NMN were more responsive to insulin than were those of the women who had received placebo. However, no difference was observed in the liver insulin response, and overall fasting glucose levels were not significantly different between the two groups. Further research will be needed to determine whether NMN has similar effects in younger women, in men, or in people with type 2 diabetes, whether its effects are safe and durable, and whether the supplement is therapeutically valuable for helping prevent or treat type 2 diabetes.

Understanding the Role of the Nervous System in Gastrointestinal Health

The movement (motility) of food through the gastrointestinal (GI) tract is required for proper absorption of nutrients, elimination of waste, and overall health. Chronic difficulties with regulating GI motility can contribute to functional GI disorders (FGIDs) which have GI symptoms with no obvious cause, such as irritable bowel syndrome, functional dyspepsia (indigestion), and many instances of gastroparesis (delayed stomach emptying). GI dysmotility also underlies conditions for which the underlying cause can usually be identified, such as gastroesophageal reflux disease (GERD, or acid reflux). A better understanding of how GI motility is controlled could lead to better treatments for these conditions.

One particular focus of GI motility research is the role of the enteric nervous system (ENS). The ENS is located entirely in the wall of the gut and uses peripheral nerves to send and receive information from other organs. Often called the “little brain” in the gut, the ENS is critical for the control of normal GI function. Understanding how the ENS regulates GI function could reveal new ways to treat not only GI disorders but also conditions where the peripheral nervous system is affecting the function of other organs.

NIDDK’s participation in the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program is one major aspect of NIDDK’s efforts to understand the ENS and treat GI motility disorders. A joint venture between NIH’s Common Fund and multiple NIH Institutes, SPARC is generating maps and tools to identify therapeutic targets within the neural circuitry of a wide range of organs and tissues. It is also funding high-risk, goal-driven research to accelerate development of therapeutic devices to control electrical activity in peripheral nerves. Such devices may ultimately facilitate treatments to improve the function of organs, including those in the GI tract. Current SPARC research projects include efforts to profile and map cells in the ENS to better understand how these cells control GI motility. SPARC is also testing medical devices that communicate with the nerve cells of the ENS as potential treatments and research tools for motility and other GI disorders.

Complementing the studies supported through SPARC, NIDDK is also interested in the “brain-gut axis,” the bidirectional communication between the “little brain” of the ENS and the “big brain” that is part of the central nervous system. NIDDK is also supporting research into how the ENS develops and into how defects in brain-gut communication could lead to motility disorders. Such research could better illuminate how the brain affects gut motility and vice versa. NIDDK is also supporting research into how pain is transmitted through sensory nerves. For example, researchers are examining how nerves that interact with the esophagus sense pain due to acid reflux and how they signal to the rest of the nervous system, information that may lead to better ways to treat the pain associated with GERD.

Another area of NIDDK-supported research involves a possible link between the ENS and brain disorders such as Parkinson’s disease. Growing evidence has suggested that the misfolding of a protein called α (alpha)-synuclein in the ENS could start a chain reaction that ultimately leads to changes in the brain seen in Parkinson’s disease. Several NIDDK-funded projects are studying α-synuclein’s role in Parkinson’s disease. Collectively, these efforts to understand how the ENS regulates GI functions such as motility will increase our understanding of how the peripheral nervous system regulates organ function, which could lead to new treatment options for diverse diseases and conditions.
NIH Meetings Explore Possible Role of Gut-brain Connections in Parkinson’s Disease

The NIDDK, together with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Environmental Health Sciences (NIEHS), co-sponsored two scientific meetings in 2021 focused on how connections between the gut and brain may drive Parkinson’s disease and other neurodegenerative disorders.

The most well-known symptoms of Parkinson’s disease are motor issues such as tremor (shaking), muscle stiffness, slowed movement, and impaired balance. But many people also experience gastrointestinal (GI) symptoms, such as constipation, nausea, and trouble swallowing, that can have significant impacts on quality of life. Intriguingly, these GI symptoms can precede diagnosis of Parkinson’s disease by decades and, therefore, may be some of its earliest indicators.

Competing theories exist as to the gut’s role in Parkinson’s disease development, or contributions from genetics, environmental chemicals, diet, gut microbes, or other factors. However, evidence has grown in recent years for the importance of bi-directional brain-gut communication in neurodegenerative diseases.

In March 2021, the three Institutes hosted a virtual symposium on “The Gut-Brain Axis as a Critical Element in the Development of Parkinson’s Disease,” designed as an introduction to current concepts of gut-brain communications in Parkinson’s disease. This was followed by a more comprehensive, virtual workshop in September-October 2021 on “Neurodegenerative Disorders and the Gut-Brain Axis: Parkinson’s Disease.” This workshop addressed research gaps and identified opportunities for research and collaboration among gut-brain investigators from the Parkinson’s disease, GI, and neuroscience fields, both in the wider research community and within NIH. It concluded with recommendations for future research opportunities. A summary of the workshop and its recommendations is planned for publication in the scientific literature.

A person with Parkinson’s disease had a key role in facilitating these meetings by serving on the organizing committee. Additional meeting participants represented the patient advocacy community and pharmaceutical industry. These activities reflect NIDDK’s commitment to stakeholder engagement in research, including people living with diseases in our mission and others who share an interest in improving health.

The main goal of these meetings was to build future collaborations for research to elucidate the role of the GI tract in Parkinson’s disease development, with an eye toward developing ways to potentially improve early diagnosis and prevention. Additionally, results from this research could have broader applicability to other forms of neurodegenerative disease with GI involvement. A related effort was the NIDDK’s release in 2021 of a notice of special interest in supporting research on causes, diagnosis, prevention, and treatment of GI dysfunction in people with neurodevelopmental disorders, which may also provide insights of relevance to neurodegenerative disorders.
The NIDDK-supported Research Community and the CCF’s IBD Plexus – A Fruitful Collaboration

The NIDDK seeks collaborative opportunities with professional societies and disease-oriented volunteer organizations to advance research and ultimately improve the health of people with diseases within the Institute’s mission.

One example of such an effort is in research on Crohn’s disease and ulcerative colitis (inflammatory bowel diseases, IBD), with a resource developed by The Crohn’s & Colitis Foundation (CCF). In 2015, the CCF launched the development of the IBD Plexus toward improving the quality of care of people with IBD. A cloud-based platform, IBD Plexus consolidates clinical, patient-reported, genetic, and other data from various IBD research cohorts, real-world clinical care settings, and the experiences of people living with IBD. The IBD Plexus includes pediatric and adult registries, a biobank, data and analytical platforms, high-performance computing, a centralized analytical lab, and a portal for researchers. Designed to support a variety of research activities, the platform provides data central to discovery (e.g., drug target discovery), clinical development (e.g., study feasibility), safety surveillance, and outcomes research (e.g., healthcare utilization). By optimizing and sharing data and samples across the research community, this resource could spur the development of new drug target treatments, biomarkers, and diagnostics. Access to IBD Plexus is available at no cost to qualified researchers.

NIDDK-supported investigators have made considerable use of the CCF-supported Pediatric RISK Stratification Study data available on the IBD Plexus to advance knowledge of diagnosis, progression, and treatment of IBD. This study, established in 2008, enrolled 1,800 participants from 28 clinics in the United States and Canada. Over 900 children newly diagnosed with Crohn’s disease generously provided collections of clinical, demographic, and biological samples every 6 months over the course of 36 months with continuing follow-up for 5 years.

This wealth of data and biosamples has led to many exciting discoveries. For example, two different studies of disease progression found that rare variants in the NOX1 gene predispose people to early onset IBD with progressive and severe disease, and these variants also convey resistance to conventional therapy. Other research showed that in older patients with Crohn’s disease, variants in other genes are associated with a more aggressive course of disease. Adding knowledge regarding Crohn’s disease complications, researchers identified a set of gene signatures in the small intestine that is associated with increased risk of stricture—a common complication in which there is a narrowing of the intestine that makes it difficult for stool to pass through and can lead to blockage. Toward predicting effective treatments for IBD, a recent study identified a combination of certain types of cells in people with Crohn’s disease whose symptoms did not improve with a treatment referred to as anti-TNF therapy; this finding could help health care providers predict which therapies would be most effective.

The generous contributions of research participants, the development of this valuable resource, and the ingenuity of NIDDK-supported researchers has brought exciting advances to the field, and opportunities for further research to improve the lives of people with IBD.


Advancing Treatments for Inflammatory Bowel Diseases in Children

Inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn’s disease (CD), are marked by chronic inflammation in the intestines that causes debilitating symptoms of abdominal pain and cramping, diarrhea, blood in the stool, nausea, and weight loss. The symptoms typically appear in affected individuals early in life, meaning that the impact is often felt for most of their lifetimes. Treatments aim to reduce inflammation and pain and, if needed, surgically remove damaged tissue, but treatment responses vary greatly from person to person. NIDDK-supported research has focused on advancing discoveries that will fuel greater understanding of IBD and improve its care, including uncovering the biological underpinnings of these variable treatment responses. (See inset for the story of a participant in an NIDDK-supported clinical research study of pediatric UC.)

ABOUT INFLAMMATORY BOWEL DISEASES

In both UC and CD, the chronic inflammation is caused by an autoimmune response where the immune system reacts inappropriately to a person’s own intestinal lining. The exact causes are unclear, but the inflammation is likely driven by genetic factors and triggered by an immune response to friendly gut bacteria or environmental factors. Both of these forms of IBD are typically diagnosed in childhood or early adulthood, a period when the compromised nutrition caused by intestinal inflammation can be especially detrimental to growth. However, other distinguishing characteristics set the two IBD types apart. In UC, the inflammation affects the inner lining of the colon (large intestine), while CD can affect any portion of the gastrointestinal (GI) tract, typically with patchy lesions that traverse several layers of the GI tract wall.

Treatments include drugs to reduce inflammation, such as corticosteroids, though these have side effects that could be serious if used for a long period of time. The nonsteroidal anti-inflammatory drug mesalamine (also known as mesalazine) is another available treatment. However, even with these treatments, the health of many people with IBD does not improve, and they will eventually need to be treated with more potent drugs that suppress the immune response that is causing inflammation (immunosuppressive drugs). More recently, multiple different therapies, such as monoclonal antibodies that target specific immune system components, have been shown to benefit some patients. In some cases, surgery is also needed to remove the damaged portion of the intestine. Determining the best treatment approach for children with IBD has proven difficult, not only due to varying individual responses, but also because most treatments are based upon results from adult studies.

PREDICTING TREATMENT RESPONSE IN CHILDREN

The variability from person to person in IBD symptoms and whether the disease responds to medications represents an opportunity to improve clinical care. Advance knowledge about which treatments will work for different children with IBD could enable them to be treated more effectively and undergo remission as quickly as possible.

The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study was conducted at 29 sites throughout North America and supported by the NIDDK, in collaboration with the Crohn’s and Colitis Foundation and their Pediatric Resource Organization for Kids with Inflammatory Intestinal Diseases (PRO-KIIDS) network. (For information on
PERSONAL PERSPECTIVE

additional IBD research collaborations between the NIDDK and the Crohn’s and Colitis Foundation, see the feature in this chapter.) From 2012 to 2017, this study evaluated whether a combination of clinical, genetic, and immunologic tests could be used to predict response to standard medical therapy for children newly diagnosed with UC. The two standard therapies tested were drugs to reduce inflammation: mesalamine, derived from the same chemical as aspirin, and prednisone, a type of corticosteroid. Based on pre-established criteria, if these anti-inflammatory drugs did not elicit responses, treatment was escalated to a therapy that modulated the immune system, such as thiopurines, or an antibody-based therapy that blocked an inflammatory protein called TNFα. The researchers mainly sought to determine whether 1 year of receiving the study therapy would lead to remission (i.e., decrease in or disappearance of symptoms) for the participants, without need for any additional steroid treatment.

Results from the PROTECT study found that higher amounts of an immunologic biomarker in the blood correlates with disease severity, suggesting that this biomarker, which also may be associated with resistance to standard therapy, potentially could be used as a diagnostic tool to help plan individualized treatments for children with the disease. More recent results from the study identified several other characteristics that can predict how well children with UC will respond to treatment, further enabling a more personalized approach to treating the disease. These characteristics—such as high hemoglobin levels, clinical remission after 4 weeks, and the makeup of the gut microbial community—were associated with achieving steroid-free remission, suggesting these characteristics can predict whether immunosuppressive drugs will be necessary.

The NIDDK recently initiated support of a planning grant for a study focusing on pediatric CD entitled ClinicAl, IMaging, and Endoscopic Outcomes of Children Newly Diagnosed with Crohn’s Disease (or CAMEO). The investigators will test whether study participants’ unique clinical, radiologic, genomic, and microbial features are associated with intestinal healing in response to treatment with a drug that inhibits the inflammatory protein TNFα. This study will build on the progress made by the PROTECT study toward achieving more personalized IBD therapy.

OTHER IBD RESEARCH EFFORTS

In addition to the PROTECT study, the NIDDK supports many other ongoing research efforts aimed at facilitating improved understanding and care for both forms of IBD. For example, the NIDDK-supported IBD Genetics Consortium works, in collaboration with the International IBD Genetics Consortium, to further knowledge of genetic contributors to IBD disease processes and inform better disease management.

NIDDK has sponsored research on microbial contributors to IBD, including a study as part of the larger NIH Integrative Human Microbiome Project that seeks to understand changes in gut microbes in adults and children with IBD. For example, NIDDK-supported studies in children and adults with IBD found changes in the gut microbes during disease flare-ups that could point to ways to predict these disease flares and treat them. Another NIDDK-supported study by an independent team of researchers showed that different treatments for CD have varying effects on the gut microbiome in children and teens.

The Intestinal Stem Cell Consortium, co-supported by the NIDDK and the National Institute of Allergy and Infectious Diseases, funds team-based science to develop novel therapies that target stem cells within the intestine and support intestinal regeneration after injury in diseases such as IBD. Recently, Consortium scientists developed “mini-intestines” using cells from people with UC that model many of the features of human disease and can enable greater insights into disease processes and interventions tailored to individuals.

In addition to these efforts, the NIDDK also supports many other studies initiated by investigators on advancing understanding, diagnosis, treatment, and prevention of IBD. The collective impact of these efforts to discover genetic, autoimmune, and microbial contributors to IBD, and to identify innovative ways to restore intestinal health, promises to facilitate new therapeutic approaches for young people with this disease.
PERSONAL PERSPECTIVE

BEN’S STORY

The picture of a healthy, busy 19-year-old, Ben engages in sports such as golf, waterskiing, and boating whenever he can, works summers as a farm technician picking and packing vegetables, and attends college full-time during the school year. Contrast that with his experience just 8 years earlier—of the debilitating stomach pain, nausea, diarrhea, weight loss, and other symptoms that accompanied his diagnosis of ulcerative colitis (UC). It has not been an easy journey, but Ben and his family have persevered and found meaning through participating in clinical research as part of the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study and also volunteering their time to help others with this condition.

Ben and his family—mother Jane, father Rex, and their family pet, a Westie dog named Gigi—are based in the Greater Cincinnati area. When Ben started feeling sick with stomach pain, nausea, and diarrhea at age 11, his mother immediately took him to see the pediatrician, who suspected a stomach bug. But after several days of no improvement in his symptoms, he was referred to the nearby campus of Cincinnati Children’s Hospital Medical Center (CCHMC), where he was treated for dehydration and nausea. Tests for intestinal parasites and bacterial infections came back negative, though gut tenderness signaled that inflammation was present. Ben was sent home with instructions to stay hydrated and continue taking medications to manage the nausea and pain. However, the next evening he experienced diarrhea with blood and mucus, as well as frequent vomiting. By the time they returned to their pediatrician’s office a few days later, Ben had lost 3 pounds over the course of 5 days, and the nausea and diarrhea still had not abated.

They were referred to Dr. Lee Denson, a gastroenterologist at CCHMC’s Inflammatory Bowel Disease (IBD) center, who suspected Ben might have UC and admitted him for diagnostic tests such as abdominal x-ray, colonoscopy, and endoscopy. Those tests showed that his stomach and intestines were irritated and inflamed. Ben was too young and ill at the time to remember all the details of his ordeal, but Jane recalls from her careful notes documenting the disease severity ratings that “he was one sick little boy.” He was diagnosed with severe UC and treated with intravenous corticosteroids.

“Although I was really young when I was diagnosed with UC and participated in the PROTECT study, I would recommend that others participate in research studies if they have the opportunity,” says Ben, who was a participant in the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study of ulcerative colitis (UC) treatment sponsored by the NIDDK.

At that time, the CCHMC staff informed Ben and his family about the opportunity to participate in the PROTECT study. Dr. Denson was the Principal Investigator of the CCHMC PROTECT study site—
1 of the 29 participating PROTECT sites throughout North America. Dr. Denson and his staff relayed to the family the details of the study process, how to take the mesalamine treatment used in the study, and how to track Ben’s daily medications. The family decided to enroll Ben as a study participant, and the next day he was able to return home, where he continued taking the mesalamine study medication, as well as the steroid, anti-nausea, and antacid drugs to manage his symptoms. Ben had a difficult time swallowing some of the pills, so early on the family would mix the medication in with applesauce or yogurt, until a medical psychologist at CCHMC helped him learn to more easily swallow the pills. At follow-up appointments, the doctors found that his UC responded well to the mesalamine treatment, with continued gut healing, to the point that he was able to wean off the steroid after only 12 weeks—a primary goal of the study.

The family credits the staff at CCHMC who helped Ben return to good health for serving as a trusted resource and positive influence throughout this challenging time. Jane describes the PROTECT study staff as “helpful and so easy to work with ... they were diligent and dedicated to the success of the study.” Ben also participated in several other clinical studies at CCHMC and would recommend the experience. “Although I was really young when I was diagnosed with UC and participated in the PROTECT study, I would recommend that others participate in research studies if they have the opportunity,” says Ben. “I feel that by participating, you are helping with research that could really benefit others in the future.” Jane echoes this sentiment: “I always felt that participating in a study that might benefit other patients and families was very important.... Our hope is that other kids and parents or caregivers will benefit from the research that is being done.”

“Our hope is that other kids and parents or caregivers will benefit from the research that is being done,” says Jane, whose son Ben participated in a clinical research study of pediatric ulcerative colitis.

In addition to participating in clinical research, Ben and his family have taken other actions that pay forward the support they received. Ben has volunteered as part of walks sponsored by the Crohn’s and Colitis Foundation—the same patient advocacy organization that collaborates with the NIDDK on the PROTECT study and also hosts a summer camp for kids with IBD that he attended as a child. Jane has served on the board of the Foundation’s southwest Ohio chapter and volunteered with its walks and fundraisers. Through these events, they are working to ensure better days ahead for those diagnosed with UC and other forms of IBD.

These days, Ben’s overall health continues to be good, and his UC is considered to be in remission. The last few years of his schooling have been affected by the COVID-19 pandemic, with many cancelled senior year activities and events, and taking classes from his dorm room during his first year at college. But he is currently in his sophomore year at college studying finance. He continues to take the mesalamine medication and vitamins, and sees his doctor for routine colonoscopies to monitor his condition. The latest showed only mild intestinal inflammation. “We are very pleased with these results,” says Jane.