The gut is home to trillions of bacteria that play many roles in human health and disease. One goal of digestive disease research is to devise ways to "reprogram" this diverse microbial community by incorporating more bacterial species that are beneficial to their human hosts. Research described in this chapter has identified several factors, including the availability of nutrients, that determine how successfully an introduced bacterial species can displace native bacteria in the gut. The above pictures show a microscopic view of a strain of the "friendly" gut bacterial species *Bacteroides thetaiotaomicron* (green) that was engineered by scientists to metabolize porphyran, a nutrient derived from a type of seaweed. The engineered strain was introduced into the gastrointestinal tract (blue and white) of mice that already harbored a normal strain of *Bacteroides thetaiotaomicron* (red) that could not metabolize porphyran. The engineered strain failed to colonize the intestine when the mice were fed a diet that lacked porphyran (left panels, higher magnification on bottom). However, when porphyran was added to the mice's diet, the engineered strain displaced the normal strain from the intestine (right panels), suggesting that nutrient availability—along with the ability to utilize that nutrient—can determine the success of bacterial colonization. These results point to ways to selectively colonize the gut with specific, beneficial bacterial species, which could help guide the design of new, tailored probiotic therapies.

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 big data sources, estimated that digestive disease is the primary diagnosis in a total of 72 million ambulatory care visits to physicians’ offices and hospital emergency and outpatient departments in the United States each year.¹ In addition, 4.6 million hospitalizations with a primary diagnosis of digestive diseases and 13.5 million hospitalizations with a primary or secondary diagnosis of digestive diseases were reported.¹ More recently, a study focusing specifically on the clinical and economic burden of emergency department visits reported 15.1 million emergency department visits with a primary diagnosis of digestive diseases and costs totaling $27.9 billion in 2007.²

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) 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. The NIDDK’s Gastroparesis Clinical Research Consortium is fueling research on the causes and progression of gastroparesis and exploring new approaches to treat the disorder.

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 and viruses 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 drugs. 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, and because pancreatitis is difficult to detect in its early stages, many cases are advanced by the time they are diagnosed. Research has elucidated genetic and other factors contributing to pancreatitis that may lead to ways to treat or prevent this 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 a form of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). 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 and further study new treatment options, including experimental, cell-based approaches to liver regeneration.

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’s Office of Nutrition Research spearheaded a process to develop the first NIH-wide strategic plan for nutrition research by the NIH Nutrition Research Task Force that is chaired by the NIDDK Director and co-chaired by Directors of the NHLBI, NCI, and NICHD. Staff from these Institutes and a number of other NIH components have participated in the Task Force’s plan development.

**GUT MICROBIOME IN HEALTH AND DISEASE**

**Finding a New Home—How Good (and Bad) Bacteria Colonize the Gut:** Three studies have revealed details of what happens when a community of bacteria inhabiting the gut is disrupted and then rebuilt by a change in diet or by adding bacteria from a healthy donor, providing valuable insights that could help with the design of microbe-based therapies for the treatment of gastrointestinal infections and other digestive diseases. The digestive tract provides a home to the gut microbiome (also called gut microbiota), which includes trillions of bacteria that aid digestion and help to prevent disease by acting as a competitive barrier to pathogenic microbes. For example, a healthy microbiome can effectively prevent infections by *Clostridium difficile* (*C. difficile*), an opportunistic bacterial species that can thrive in the gut when the microbiome is disrupted, such as after antibiotic-based treatments. *C. difficile* bacteria produce a toxin that causes inflammation in the intestinal wall, creating an even more welcoming home for themselves but severe diarrhea and pain for their human host. One treatment option in use for this infection is fecal microbiota transplantation (FMT), whereby a sample containing gut bacteria from a healthy donor is introduced to help re-establish a functional gut microbiome. Although there is accumulating evidence for the effectiveness of this therapy in people with recurrent *C. difficile* infections, significant roadblocks remain, such as how to predict which bacteria will settle the gut and what factors influence their colonization.

In the first study, researchers sought to develop a method to predict which bacteria will colonize the gut following FMT. To do so, they monitored the
microbiomes of 19 people with recurrent *C. difficile* infections after they underwent FMT from one of four healthy donors. Stool samples were collected from the donors and the *C. difficile* patients before the procedure and from the patients in follow-up visits afterward to track which types of bacteria from the donors colonized and persisted in the patients’ guts. While previous studies were limited to cataloging gut bacteria at the species level, the researchers developed a more precise method, called "Strain Finder," to deduce specific strains within the species. Applying Strain Finder to the data garnered from the samples, the researchers found that the degree of colonization was determined by the species of bacteria, along with how much of that species was in the donor’s sample. They also found that only a fraction of bacterial species colonized the gut, and the strains within those species colonized in an all-or-nothing fashion—generally, either all strains from a species colonized the gut, or none did. Based on these results, the researchers were able to create a mathematical formula that they could use to predict which species and strains of bacteria from an FMT donor will successfully colonize a recipient’s gut. To test their formula, the researchers applied it to analyze studies of groups of people who were treated with FMT for *C. difficile* infections or, in research at an earlier stage of exploration, people who were given FMT to see whether it might affect metabolic syndrome (a condition characterized by a set of risk factors for cardiovascular disease and diabetes).

The model’s further evaluation for patients with a condition besides *C. difficile* infection was particularly important because the *C. difficile* patients received antibiotics to attempt to treat the infection prior to FMT—potentially affecting colonization of incoming bacteria—while other patients did not. Overall, the results of this study will help to optimize FMT and to develop the composition of specific and effective microbiome-targeted treatments. However, even though these results can be used to predict which bacterial strains will colonize the gut after FMT, they raise the question of why these strains will colonize while others will not.

In the second study, another group of researchers attempted to answer this question by using a mouse model to test whether access to specific nutrients would affect the ability of bacterial strains to settle in the gut. They engineered a strain of gut-friendly *Bacteroides* bacteria to enable it to metabolize porphyran, a complex carbohydrate found in a species of seaweed. They added porphyran to the diet of both male and female mice, which harbored either a conventional mouse microbiome or a microbiome from a human fecal sample, to determine whether the porphyran would allow the engineered bacteria to colonize the mice’s guts. The researchers found that not only did the engineered strain readily colonize the mice that were fed porphyran, but it also displaced native *Bacteroides* strains that were unable to metabolize this nutrient. In fact, the researchers were able to calibrate the number of engineered bacteria that settled in the guts by varying the amount of porphyran in the mice’s diets. These results show that nutrient availability can be an important factor in determining whether a bacterial strain will successfully colonize the gut and that the gut’s environment can potentially be manipulated to favor colonization by a select bacterial strain. This knowledge could help in the design of microbiome-based therapies to enable the introduction of specific desirable bacterial strains into the gut.

The third study examined how changes in diet could bolster the microbiome’s ability to keep *C. difficile* infections at bay. The researchers focused on microbiota-accessible carbohydrates (MACs)—carbohydrates in fiber from plant-based foods that are resistant to digestion and therefore available for metabolism by beneficial bacteria in the lower intestine. They had previously shown that a diet low in MACs could stoke inflammation in the gut, so they decided to test whether such a diet could also exacerbate *C. difficile* infections, presumably by disrupting the microbiome. The researchers infected female and male mice harboring human gut microbiota with *C. difficile* and fed the mice diets that were either deficient or rich in MACs. While the MAC-deficient mice maintained persistent *C. difficile* infections, the mice fed the MAC-rich diets were able to clear the infection. These mice also had more diverse communities of bacteria in their microbiomes, but that seemed unrelated to the ability to clear *C. difficile* infections because mice fed only a specific kind of MAC called inulin also cleared the infections even though inulin did not increase microbiota diversity. Rather, the effects of the MAC-rich diet appeared to be caused by an increase in some products of bacterial metabolism, called short-chain fatty acids, that suppress *C. difficile* growth. The researchers also found that the amount of *C. difficile* toxin in the infected mice initially increased under a MAC-rich diet, even as the number of *C. difficile* bacteria decreased, suggesting that the
bacteria respond to a MAC-rich diet by ramping up toxin production in an effort to maintain an inflammatory environment. The overall level of toxin declined after a few days, however, as the C. difficile population decreased. These results point to diet-induced changes in the microbiome as a valuable means of overcoming gastrointestinal infections. Although it remains to be seen whether the results of these studies in mice can be translated into humans, they offer significant progress in the understanding of the relationships among diet, the intestinal environment, the microbiome, and bacterial infections, including interactions among specific types of bacteria. More importantly, they also provide insight into how future therapies could be designed to treat or prevent disease by shaping the gut microbiome.


How the Body Brings About Tolerance to a Gut Microbe: A recent study in mice suggests that the body’s ability to “tolerate” the presence of a specific gut microbe is mediated by the interplay of two different types of immune system cells, and that defects in this interaction can contribute to intestinal disease. Humans host trillions of microbes in the gut, including bacteria and viruses and other microorganisms, referred to collectively as the "gut microbiota" or "gut microbiome." These diverse intestinal inhabitants process dietary components and contribute to nutrient absorption and metabolism, interact with the immune system, and produce molecular signals that affect not just the intestines but also other organs throughout the body. However, while normally tolerating the microbiome as a whole, the immune system can react inappropriately to components of the microbiome, launching a long-lasting attack that damages the intestinal lining and results in diseases such as inflammatory bowel disease.

In the new report, scientists describe how the immune system can establish a condition of tolerance in the gut. In a mouse model, a type of bacteria called Helicobacter hepaticus (H. hepaticus) was used to investigate the response of the host immune system. H. hepaticus is known to play a role in gut inflammation and cancer in immunocompromised mouse strains, yet can coexist without harm in other, “healthy” strains. Colonization of H. hepaticus in the large intestine of both female and male healthy mice resulted in an increase in immune system white blood cells called T\textsubscript{H}17 cells, specifically a subset called T\textsubscript{H}17 cells. T\textsubscript{H}17 cells have been previously shown to be key players in host defense as they produce interleukin 17 (IL-17), a protein that recruits other immune cells to fight an invading microbe. Additional experiments showed that, following H. hepaticus colonization, the immune system also produces a second type of immune system cell, called iTReg cells, to selectively restrain the activity of T\textsubscript{H}17 cells—thereby inducing tolerance to this bacterial species. Using genetically modified mice, the researchers then found that iTReg cells were dependent on a protein called c-MAF for their ability to induce tolerance. Specifically, in the presence of H. hepaticus, iTReg cells lacking c-MAF resulted in the accumulation of T\textsubscript{H}17 cells and intestinal inflammation.

The results of these experiments in mouse model systems suggest that when iTReg cells are missing or defective (e.g., lacking c-MAF), certain bacteria may circumvent tolerance and contribute to the development of immune system-mediated disease, such as inflammatory bowel disease. These results point to potential therapeutic approaches that bolster the iTReg cell population to help prevent the immune system from launching improper attacks on the gut microbiome.


Gut Microbe Helps Program Immune Cells via Dietary Metabolites: Scientists have identified an important role for a gut bacterial species and its metabolites in the maturation of a key immune

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Many cells of the immune system rely on the presence of specific gut bacteria to be programmed into mature, functioning immune cells. In fact, these immune programming processes are absent in animals lacking gut bacteria, such as mice raised in germ-free conditions.

Researchers endeavored to find the gut bacteria responsible for promoting maturation of a recently discovered gut immune cell called the double-positive intraepithelial lymphocyte (DP IEL). DP IELs are formed in the intestine from another immune cell type—the CD4+ T cell—upon activation of a specific molecular program known to be influenced by the presence of gut microbes. The DP IEL performs a wide range of important functions, including ensuring the immune system’s tolerance of substances in the gastrointestinal (GI) tract, such as food components and microbes, that might otherwise provoke a negative reaction and inflammation. Their first clue to identifying the gut microbe(s) important for DP IEL formation came from the observation of a wide variation in levels of these immune cells between mice of the same genetic strain obtained from two different companies. When the mice from different sources were co-housed, those animals initially lacking the immune cells went on to develop them, indicating that some transmissible factor—such as a microbe—was at work. The researchers were able to identify the gut bacteria present in the mice by sequencing genetic material from the animals’ intestines. Homing in on a bacterial species called Lactobacillus reuteri (L. reuteri) present in the mice with high DP IELs, the scientists tested two L. reuteri strains and found they were able to induce DP IEL formation when given to mice lacking these immune cells. Next, scientists wanted to uncover the mechanism by which L. reuteri bacteria accomplish this feat. Some bacteria exert powerful effects on human cells through metabolism of dietary components to create bioactive metabolites, such as short-chain fatty acids. Likewise, L. reuteri bacteria grown in culture in the presence of tryptophan—an amino acid present in high-protein foods—were found to produce a class of metabolites called indole derivatives. When added to CD4+ T cells in culture, these metabolites set off a cascade of molecular signals to transform the cells into the DP IEL cell type. Additionally, mice harboring L. reuteri and other bacteria in their guts had elevated DP IELs when given a high-tryptophan diet compared to animals eating a standard chow or low-tryptophan diet. Yet, L. reuteri bacteria do not appear to act alone—female germ-free mice colonized solely with one L. reuteri bacterial strain and given a high-tryptophan diet did not form DP IELs at all. Additionally, as observed in one of the earlier experiments, germ-free mice colonized only with the other L. reuteri bacterial strain and fed a regular diet experienced only a slight increase in DP IELs. In other words, the larger microbial context also plays a role in this immune cell programming process.

Future studies will be needed to explore potential applications for these findings that L. reuteri prompts formation of this key intestinal immune cell, and whether this is also the case in humans. One possible use for the bacteria could be as a probiotic, along with tryptophan-rich foods, for digestive diseases in which the immune system is overly active, such as inflammatory bowel disease.


**MICROBIAL FACTORS IN INFLAMMATORY BOWEL DISEASE**

**Antibiotic-altered Gut Microbial Communities May Increase Risk of Inflammatory Bowel Disease Across Generations:** Antibiotics can adversely alter gut microbial communities, and scientists recently discovered that these alterations can pass from pregnant mice to their offspring and increase the offspring’s risk for intestinal inflammation similar to human inflammatory bowel disease (IBD). Microbes in the gut (also called the gut microbiota), as well as their collective genetic material (microbiome) are passed down from mothers to their offspring at birth and play an essential role in the development of a healthy immune system, which can protect against diseases such as IBD. Antibiotics can be life-saving for mother and child when prescribed appropriately, and they are routinely prescribed during pregnancy and for young children. However, they are sometimes overprescribed when not warranted, and they can disrupt the gut microbiome and are a known risk factor for increasing susceptibility to IBD. Further research is needed to inform health care decisions weighing the benefits and risks of antibiotic use in these populations.
Researchers were curious to find out the impact of antibiotic exposure during pregnancy on offspring’s risk for later developing IBD. They also aimed to tease apart the effects of the antibiotic-altered set of microbes themselves from any other effects of antibiotic treatment. They designed their study so that pregnant mice raised under sterile conditions free of microbes were colonized a week before giving birth with microbial samples taken from other female mice given a course of low-dose antibiotics, or nothing, in their drinking water. Some of the pregnant mice that received microbes from antibiotic-treated or untreated donors lacked a key immune molecule called IL-10 as a result of a genetic variant; this deficiency increases IBD susceptibility. Fecal samples taken from mothers and their male and female pups revealed that the microbes were passed down effectively between generations, with some pups “inheriting” a normal microbiota and others inheriting an antibiotic-altered microbiota. These differences in the offspring’s gut microbes persisted even at 5 months of age, which is nearing adulthood for mice. Pups who inherited the antibiotic-exposed microbes had gut microbial communities that were less diverse and more unstable than animals whose mothers passed on the untreated gut microbes. Furthermore, the pups that lacked IL-10 and also inherited antibiotic-exposed microbes had a dramatically higher risk of developing a severe form of IBD than the pups who inherited an untreated gut microbial community. By sequencing bacterial genetic material from fecal samples in the experimental groups, researchers were able to sketch a rough outline of the key microbial species altered in the mice with elevated IBD due to the presence of both antibiotic-exposed microbes and IL-10 deficiency.

These findings show how antibiotic exposure alters not only gut microbiota, but also the IBD susceptibility of future generations. Further research will be required to identify which specific microbial species increase risk for IBD and which may protect against this disease, and whether transplanting a healthy mix of gut microbes into mice with the antibiotic-altered microbiota and genetic risk can save these mice from developing severe IBD. It also remains to be seen whether similar results are observed in humans. Nevertheless, this research raises new questions as to how much of the inherited IBD risk, previously thought to have only a genetic basis, might be due to the gut microbiota passed down from mothers to offspring.


Becoming Unglued: How a Genetic Variant May Affect the Gut Barrier and Contribute to Inflammatory Bowel Disease: Researchers have found that a genetic variant may impart risk for inflammatory bowel disease (IBD) by disrupting the cellular “glue” that keeps the gut’s lining intact. People with IBD suffer from chronic inflammation in the gut, resulting in symptoms such as diarrhea, cramping, and weight loss. Scientists have been sorting through the complicated mix of factors that contribute to IBD, including numerous possible genetic components that are important for maintaining effective physical and immunological barriers to the multitude of bacteria that inhabit the gut. The International IBD Genetics Consortium, of which the NIDDK-supported IBD Genetics Consortium is a member, has identified over 200 regions of the human genome that are associated with IBD. Scientists are now combing through these regions to identify genes—and variants of those genes—that are involved in the disease.

One of the genetic variations that consortium scientists had identified as a risk factor for IBD was in a gene called C1orf106; however, until recently it was not clear exactly how variants of this gene might lead to disease. Researchers attempting to uncover the function of “normal” C1orf106 found that laboratory-grown gut cells produced high amounts of the C1orf106-encoded protein when they were in close contact with each other. This suggested that C1orf106 may contribute to cellular junctions—the “glue” that cobbles gut cells together to create a continuous, sheet-like barrier. Another hint was uncovered when the researchers found that the C1orf106 protein interacts with cytohesin-1, a protein that disrupts cellular junctions by activating a molecular switch called ARF6. Functional C1orf106 in cells caused degradation of cytohesin-1 and lower ARF6 activity, stabilizing cellular junctions. These signs pointed to a role for C1orf106 in maintaining the intestinal barrier by keeping cytohesin-1 levels in intestinal cells relatively low.
Likewise, male and female mice engineered to lack C1orf106 had higher levels of cytohesin-1 than mice whose genes were unaltered. These mice also showed greater intestinal damage after they were infected by a bacterial pathogen, supporting the idea that C1orf106 is important for maintaining a barricade against gut pathogens. However, some variants of the C1orf106 gene may not be as effective as others. In fact, when the scientists replaced C1orf106 in cells with the specific variant of the gene that is associated with human IBD, the cells were unable to make enough of the C1orf106 protein to form proper junctions. These studies strongly imply that defects in C1orf106 contribute to IBD by failing to maintain an adequate intestinal barrier. This information could help to guide the development of improved therapy for people with this genetic variant, although more work is needed to determine if the observations from the mouse model hold true in humans.


**Bacterial Enzyme Implicated in Inflammatory Bowel Disease:** Using human samples and animal models, researchers have found that an enzyme produced by certain bacteria could disrupt the gut microbiome, potentially playing a significant role in the development of inflammatory bowel disease. People with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis suffer from symptoms, including diarrhea, cramping, and unintended weight loss. Among other factors, inflammatory bowel disease is associated with changes in the makeup of the microbiome, including the trillions of bacteria living in the gut. Like other organisms, these bacteria thrive by breaking down nutrients to produce components that are critical for growth and survival. However, it is not clear how these bacterial products, or "metabolites," affect the microbiome and disease development.

In a recent study, researchers attempted to determine whether specific bacterial metabolites could be altering the gut microbiome in people with Crohn's disease. They analyzed fecal samples from 90 individuals younger than 22 years old with Crohn's disease and compared them to samples from healthy persons of similar age to identify metabolites associated with disease. Most of the metabolites that were found at higher levels in the samples from people with Crohn's disease were amino acids, which are the building blocks of proteins. Knowing that many types of bacteria will produce amino acids by breaking down a nitrogen-rich compound called urea, the scientists focused on an enzyme—urease—that is critical for this process. The researchers first sought to establish mouse models that harbored bacteria with high urease levels to determine if bacterial urease might be important for the development of Crohn's disease. To do this, they treated mice with antibiotics and a gut-purging agent to deplete their microbiomes, clearing the way for the establishment of new microbiomes in the guts of these mice. They next inoculated the mice with either bacteria lacking urease (Ure- bacteria) or bacteria engineered to produce urease (Ure+ bacteria) and allowed the mice to naturally re-establish their microbiomes over the next month. The scientists found that the two groups of mice developed significantly different microbiomes: the mice initially inoculated with the Ure+ bacteria were more likely to develop microbiomes that contained relatively greater numbers of bacteria that are associated with poor health. In fact, when this experiment was repeated in mice that were engineered to develop a form of inflammatory bowel disease, the mice that were inoculated with Ure+ bacteria showed a more aggressive form of the disease. These results suggest that urease may play a role in exacerbating inflammation in the gut by disrupting the microbiome. This research also points to urease as a possible target for therapy, either by direct inhibition or by manipulating the microbiome's bacterial components to decrease the amount of urease in the gut. The findings also indicate that a therapeutic strategy to rehabilitate the gut microbiome may require first removing some of the existing bacteria before administering a probiotic with a more healthy bacterial mix. However, more research is needed to determine whether these results seen in mice translate to humans.


**INTESTINAL REGENERATION**

A "Support System" for Intestinal Stem Cells Renewing the Gut Lining: Researchers have uncovered a key role for a unique cell type, called a telocyte, in supporting proliferation and maturation of the nearby intestinal stem cells that perpetually
replenish the inner lining of the gut. The telocytes accomplish this feat by regulating important growth signals sent to the stem cells.

The intestinal lining is continually turning over and replacing cells, regenerating itself in humans about once every week. This high turnover is needed to make up for cells lost in the course of performing the intestinal lining's many functions, including nutrient absorption, waste elimination, and protection against potential pathogens. The intestinal stem cells are highly concentrated in deep pits called crypts located at the bottom of hair-like projections called villi that line the inside of the intestine, effectively increasing its surface area and absorptive power. Scientists have been interested in finding out how the local "neighborhood" of cell types and signals surrounding the intestinal stem cells might contribute to this regenerative process.

A group of researchers focused on an important growth signal called FOXL1, emanating from a layer containing the relatively rare telocytes located just beneath the intestinal lining. For the experiments, they genetically engineered male mice so that their intestinal telocytes would emit a fluorescent green light upon producing Foxl1, the mouse version of the protein. They mapped telocytes using the glowing green marker, showing how the cells formed a network in close proximity to cells lining the intestine, including stem cells. They found these telocytes also produced a potent mix of factors that regulate intestinal stem cells, including a class of essential proteins for stem cell proliferation called Wnts. Surprisingly, in addition to Wnts themselves, the telocytes also produced factors to both stimulate and inhibit Wnt activity. Exploring this further, the scientists discovered that the telocytes finely calibrated production of Wnts, Wnt activators, and Wnt inhibitors depending on their location, with cells closest to the stem cell-rich crypts producing more pro-growth signals. Additional evidence confirming the telocytes' critical role in intestinal stem cell growth came from experiments in male mice genetically altered to inhibit Wnt production from telocytes when given a particular drug. The mice lacking telocyte-derived Wnts showed dramatically reduced populations of stem cells in their small and large intestines and reduced capacity to renew the intestinal lining.

This research illustrates the importance of telocytes in supporting continual replenishment of the intestinal stem cells, the source of the regenerative capacity in the intestinal lining that performs so many vital functions. Future studies can build on this work to further explorations into the nature of these telocytes and their role in the intestine.


IRRITABLE BOWEL SYNDROME RESEARCH

**Primarily Home-based Cognitive Behavior Therapy as Effective as Standard Therapy for Treatment of Irritable Bowel Syndrome**: New research has shown that a mainly home-based behavior therapy regimen to treat irritable bowel syndrome (IBS) is just as effective as a similar, more expensive, strictly clinic-based therapy, and is more effective than an education-only approach. IBS is marked by a group of symptoms that occur together, including recurring pain in the abdomen and bowel movement issues, such as diarrhea, constipation, or both. Although the cause of IBS is not clear, its symptoms are often triggered by stress, so a significant portion of IBS research has focused on the gut’s intimate connection with the brain. This has led to interest in the use of a type of evidence-based, structured psychological treatment called cognitive behavior therapy (CBT), which typically consists of regular counseling sessions with a licensed psychotherapist. Although CBT has been shown to be an effective treatment for IBS, several barriers have prevented it from being widely adopted, including cost, time, therapist availability, and stigmas associated with IBS and psychosocial therapies.

To make CBT more accessible and less costly, a group of researchers recently developed a modified form of CBT for IBS that is primarily home-based, consisting of only four clinic visits over 10 weeks and relying more on home-study materials to strengthen skills that had been introduced in the clinical sessions. To test the new therapy’s effectiveness, 436 people with IBS underwent standard, clinic-based CBT (10 weekly counseling sessions),
primarily home-based CBT (four weekly counseling sessions with home-study materials), or four education-only sessions that provided information on the roles of diet, stress, and exercise in IBS. In both the mainly home-based and standard CBT groups, counseling sessions involved education on the relationship between stress and IBS, along with coaching on relaxation exercises, methods for relieving stress and pain associated with the syndrome, and certain problem-solving strategies. About 80 percent of the participants were women, reflecting the fact that women are more likely than men to develop IBS. By the end of the treatments, 61 percent of the people who participated in the mainly home-based CBT reported moderate to substantial improvements in their symptoms, compared to about 55 percent for clinic-based CBT participants, suggesting that home-based CBT is at least as effective as standard CBT. In participants who received only educational sessions, about 44 percent reported symptom improvements. Assessment of participants by gastroenterologists after completion of study therapies supported these findings, and the general differences in symptom improvement scores among the three treatments persisted for at least 6 months. These results suggest that the primarily home-based CBT, with more limited therapist contact than standard CBT, is an effective method to treat IBS, providing a more low-cost, time-efficient, and accessible alternative to the standard clinic-based therapy.


PEDIATRIC LIVER DISEASE RESEARCH

New Biomarker To Diagnose Life-threatening Liver Disease in Children: Researchers have identified a protein present at high levels in blood from infants with biliary atresia that may enable early and accurate detection of this potentially deadly disease. Biliary atresia is a serious liver disease that occurs during the first few months of life. In this disease, 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, as evidenced by jaundice, or the yellowing of the skin and eyes. If not treated with surgery or liver transplantation, biliary atresia can lead to liver failure and is ultimately fatal in these infants. 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. While its causes are not fully understood, both inherited and environmental factors appear to play a role in disease development. Early diagnosis and treatment are critically important for ensuring the best outcomes for infants with biliary atresia, but often diagnosis is delayed because jaundice in infants is fairly common, resulting from a number of conditions that affect bile flow.

Researchers set forth to identify a clinically useful biomarker for diagnosing biliary atresia by analyzing proteins present in samples from infants enrolled in the NIDDK-supported Childhood Liver Disease Research Network (ChiLDReN). By comparing blood samples from infants with biliary atresia to those from infants with other forms of impaired bile flow, they found that a number of proteins were elevated in infants with biliary atresia. One of these proteins in particular, called matrix metalloproteinase-7 (MMP-7), was able to best distinguish the biliary atresia samples from the others, especially when combined with another marker of impaired bile flow called γ-glutamyltranspeptidase. Exploring MMP-7’s potential role in biliary atresia development, they found it is produced by the cells lining the bile ducts outside the liver. While MMP-7 levels were not associated with the degree of liver damage in infants with biliary atresia, tests in a mouse model of biliary atresia showed that the protein was released into the blood upon bile duct injury. The investigators also found that MMP-7 inhibitors protected against bile duct obstruction and liver damage in the mouse biliary atresia model.

These findings suggest that MMP-7 is not only a promising candidate as a much-needed biomarker for improving early diagnosis of biliary atresia, but also likely plays a role in disease development and may be a therapeutic target. Future studies will be required to confirm MMP-7’s utility as a diagnostic tool, to test its usefulness for monitoring disease progression long-term—after interventions in infancy—and to pave the way for possible treatment trials of MMP-7 inhibitors in humans.

Genetic Risk Factors for Obesity and Insulin Resistance Identified in Hispanic Boys with Nonalcoholic Fatty Liver Disease: Researchers have identified novel genetic variants that are associated with obesity and insulin resistance in Hispanic boys with nonalcoholic fatty liver disease (NAFLD). A form of chronic liver disease marked by excess fat stored in the liver, NAFLD has affected an increasing number of people in the United States and around the world in recent years, including children, in whom it is now the most common form of liver disease. Its more severe form, called nonalcoholic steatohepatitis (NASH), can lead to cirrhosis, liver failure, and liver cancer. NAFLD is often associated with obesity and insulin resistance, as well as with a cluster of conditions known as “metabolic syndrome” that is linked to increased risk of heart disease, stroke, and diabetes. People of some racial/ethnic backgrounds, such as individuals of Hispanic descent, are also at increased risk of developing NAFLD. Although peoples’ genetic backgrounds appear to affect risk of the disease, little is known about the genes that drive NAFLD susceptibility in children.

As part of the NASH Clinical Research Network, scientists conducted a genetic study at 12 clinical centers located throughout the United States, which recruited 234 Hispanic boys who had been diagnosed with NAFLD or NASH based on liver biopsy. The study participants were also obese or overweight with signs of insulin resistance. Investigators analyzed DNA from the participants' blood samples, leading to the identification of 10 genetic variants associated with overweight/obesity and nine associated with insulin resistance. The variants associated with elevated fat mass implicate specific elements of the metabolic machinery, such as a protein involved in glucose formation in the liver.

These findings highlight some potential genetic factors in Hispanic boys with NAFLD that influence development of obesity and insulin resistance in this population. This analysis can help improve understanding of the underlying mechanisms driving NAFLD and some of its associated metabolic conditions. Further studies will be required to test if these genetic associations are relevant to other populations, such as Hispanic girls with NAFLD or young people of other racial/ethnic groups.

New Strategic Plan for NIH Nutrition Research

Recently, the NIH developed its first agency-wide strategic plan for nutrition research. The Strategic Plan for NIH Nutrition Research emphasizes cross-cutting, innovative opportunities for advancing NIH-supported nutrition research across a wide range of areas—including basic, translational, and clinical research, as well as research training activities—over the next decade. The Strategic Plan also highlights ways to enhance new and ongoing research efforts across NIH to improve health and prevent or combat diseases and conditions affected by nutrition.

The Strategic Plan was developed by the NIH Nutrition Research Task Force with crucial and extensive input from researchers and others external to NIH. The Task Force was established in 2016 by the NIH Director, Dr. Francis Collins, and chaired by Dr. Griffin Rodgers, NIDDK Director, with Co-chairs Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute; Dr. Norman Sharpless, Director of the National Cancer Institute; and Dr. Diana Bianchi, Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The NIDDK Office of Nutrition Research, which coordinates nutrition research across NIDDK and the NIH, spearheaded the NIH-wide nutrition research strategic planning process, with the Office’s Director, Dr. Christopher Lynch, serving as Executive Secretary of the Task Force. The Task Force was also assisted in this effort by representatives from across the NIH’s many Institutes, Centers, and Offices participating in its Working Group and Senior Leadership Group, as well as external experts serving on its Thought Leaders Panel and others.

Throughout its development, the Strategic Plan was informed by broad stakeholder input. The Task Force started by collecting information on the landscape of existing nutrition research plans and recommendations from the research community, including professional societies, academic researchers, nonprofit organizations, and federal agencies. In spring of 2017, the Task Force set up a “crowdsourcing” website to solicit ideas for the nutrition research planning effort from a broad swath of researchers and members of the public. The Task Force then convened a Thought Leaders Panel of federal and external nutrition experts for a 2-day series of meetings in June 2017 to provide their recommendations on research priorities. The diverse input received from these sources informed the Task Force’s Working Group and Senior Leadership Group in their work developing a draft of the Strategic Plan in spring of 2018, which was circulated for comment within NIH and then posted for public comment on the NIH website, prior to its revision and finalization. Throughout the planning process, the Task Force convened regularly to discuss priorities and progress.

The Strategic Plan identifies a number of cross-cutting research areas—such as addressing minority health/health disparities, women’s health, and other critical areas—that will underpin successful future activities across the field of nutrition research. The Strategic Plan is structured around major scientific themes, each of which is linked to a list of associated research priorities and examples of potential future research activities.

In the years ahead, the Task Force plans to implement the recommendations made in the Strategic Plan to advance NIH-sponsored nutrition research in a way that is responsive to emerging opportunities and the changing scientific landscape.

For additional information on the Strategic Plan for NIH Nutrition Research, please visit the NIH Nutrition Research Task Force website at: www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/nih-nutrition-research-task-force
Workshop Explores Ways To Accelerate Pancreatitis Treatment Development

On July 25, 2018, the NIDDK, with support from the National Pancreas Foundation, sponsored a workshop to identify research gaps and opportunities in the development of new drugs and clinical testing approaches to managing acute and chronic forms of pancreatitis. The workshop was organized and led by staff from the NIDDK's Division of Digestive Diseases and Nutrition and took place in conjunction with an annual meeting of pancreatitis researchers called PancreasFest in Pittsburgh, Pennsylvania.

In addition to producing the hormone insulin and other hormones, the pancreas produces a fluid containing both enzymes and bicarbonate that is released into ducts leading to the intestine, where the enzymes are activated to digest food. Pancreatitis is a condition caused by the activation of these digestive enzymes while they are still inside the pancreas, resulting in damage and inflammation. Acute and chronic pancreatitis are leading causes of emergency room visits and hospitalizations from gastrointestinal conditions. In individuals with acute pancreatitis, some experience recurring episodes—termed acute recurrent pancreatitis; acute forms of pancreatitis can develop into chronic pancreatitis, which carries an increased risk of pancreatic cancer.

Currently, there are no effective drugs specifically for pancreatitis that halt progression of this potentially debilitating disease or reverse the disease process. Available treatments are limited to supportive therapy for pain and also surgical procedures. Although there are potential treatments in the pre-clinical stage of the drug pipeline, challenges exist in moving these compounds into clinical trials. For example, there are no guidelines available from the U.S. Food and Drug Administration (FDA) for researchers to use in designing trials to test new therapies targeting pancreatitis.

The workshop objectives included: 1) identifying requirements, obstacles and opportunities to enhance the development and clinical testing of agents for the treatment of acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis; 2) identifying research gaps that currently inhibit drug development and clinical testing; and 3) engaging representatives from the FDA to assist with the development of guidance documents that will help investigators in studies of the treatment of these diseases.

The workshop brought together presenters and participants from the NIH, FDA, researchers throughout the Nation and from other countries, health care organizations, pharmaceutical industry representatives, and patient advocacy groups with a goal of sparking research to enhance development of new treatments and testing methods for pancreatitis. During the workshop, working groups focused on challenges specific to drug trials for acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis.

Presentation topics included past successes in drug development for other diseases, as well as research on children and adults with pancreatitis conducted through the Consortium for the Study of Pancreatitis, Diabetes, and Pancreatic Cancer, which is supported by the NIDDK and the National Cancer Institute.

The meeting organizers and members of its three working groups have developed multiple manuscripts describing the workshop proceedings. Recommendations from the workshop will inform future NIDDK efforts—in partnership with FDA, patients, researchers, and others—to advance research accelerating the development of new pancreatitis therapies.

The NIDDK hosted a workshop on September 26–27, 2018, to explore approaches to dietary biomarkers research.

Our health is influenced by what we eat. While the primary goal of nutrition research is to optimize health through diet, this requires establishing firm associations between nutrient intake and disease outcomes. For example, it would be extremely valuable to know which foods might increase risks for certain cancers—and which foods might help to prevent them. However, accurate measurement of dietary intake is a major challenge in nutrition research. Collecting data on what people eat usually relies on self-reporting, which is limited by their memories of what and how much food they ate. Precise measurement of the effects of diet on health will require an independent, unbiased approach to detecting dietary components in the body following a meal.

One potential approach would be to use dietary biomarkers, which are detectable molecules in the body (such as in the blood) that serve as indicators for which nutrients had been absorbed from food. Biomarkers would be extremely helpful to track nutrient intake in studies that are probing links between diet and disease. Several dietary biomarkers are already in use by clinicians, who frequently measure protein intake by analyzing the amount of nitrogen in urine, for example. However, there is a critical need to identify more biomarkers that are specific for certain foods and that could be utilized to improve assessments of dietary intake.

The NIDDK’s workshop explored approaches for identifying and using such biomarkers. Among the topics discussed were tools to assist in the discovery and validation of new biomarkers, optimal strategies for designing biomarker studies, and what statistical approaches should be used to accurately analyze data. A particular focus was placed on identifying new biomarkers using “omics” methods to examine diet-related changes in the body, such as proteomics (analyzing changes in bodily proteins) and metabolomics (analyzing molecular products of human metabolism), and how different types of these omics approaches might be integrated to enhance biomarker discovery. The workshop culminated in discussions of topics such as challenges to biomarker discovery, new tools for biomarker identification and validation, platforms for sharing data, and new opportunities to use biomarkers in nutrition research.

Recommendations from the workshop will be made available to the scientific community through a publication in a scientific journal. These recommendations will help improve nutrition research by highlighting new ways to examine the link between dietary components and health outcomes.
After leaving the stomach, ingested food travels through approximately 25 feet of small and large intestines. The innermost part of the intestinal lining that comes in direct contact with food—called the intestinal epithelium—is composed of a diverse mix of cells that perform critical roles for digestion, including absorption of nutrients and secretion of substances that aid in the sensing and movement of intestinal contents. Surrounding the epithelium is a conglomeration of blood vessels, nerves, and muscle cells. Also within the intestinal lining are immune cells that act as sentinels ready to defend the body against gastrointestinal pathogens. These immune cells are overly active in people with inflammatory bowel disease (IBD), leading to painful inflammation that can devastate the intricate intestinal lining. The accompanying symptoms can be crippling. For example, diarrhea results if inflammation shuts down absorption in the intestine. In severe cases, lesions develop, accompanied by intestinal bleeding. IBD can also lead to malnutrition when nutrients from food cannot be absorbed, a condition that is especially harmful to children because it can stunt growth.

The development of effective IBD treatments has been inhibited by a lack of understanding of the causes of the underlying inflammatory process. But in recent years, researchers have discovered ways in which the bacteria and other microbes that reside in the gut—the gut microbial community or microbiome—can affect risk of IBD, and efforts such as the NIDDK’s IBD Genetics Consortium are shedding new light on the genetic foundations of the disease. With its Intestinal Stem Cell Consortium and clinical research efforts, the NIDDK is already leveraging those insights to test new approaches to therapy for IBD. The story of IBD is one of increasing complexity, but also the discovery of new immunologic, genetic, and microbial links to the disease, and the potential for novel, more effective therapies.

AN EARLY PICTURE OF IBD: CROHN’S DISEASE AND ULCERATIVE COLITIS

Inflammation is normally a part of the immune system’s response to fighting infection, but in the latter half of the nineteenth century clinicians described cases of intestinal inflammation that did not seem to have an infectious origin. By the 1930s, it had become apparent that most of these cases could be segregated into two separate diseases: ulcerative colitis and Crohn’s disease. These two diseases would eventually be grouped under the umbrella term “IBD.”

There are fundamental differences between Crohn’s disease and ulcerative colitis. In ulcerative colitis, the inflammation encompasses only the colon (large intestine) and is generally limited to the innermost layers that make up the intestinal wall. In Crohn’s disease, which is not as common as ulcerative colitis, the inflammation may involve any part of the gastrointestinal tract (although it usually manifests
in the small intestine and the beginning of the colon) and is not continuous, resulting in patchy lesions. These lesions also tend to be deeper than in ulcerative colitis, producing strictures (places where the intestines narrow) and fistulas (abnormal passageways between areas of the intestine).

Early treatments for IBD were limited to surgical removal of the affected area—a strategy that is still in practice today for people who have severe inflammation that does not respond to other therapies. For people with ulcerative colitis, this usually means removal of the entire colon. For Crohn’s disease, surgery is limited to smaller affected areas. However, removal of a lesion does not cure Crohn’s disease, and it is possible that additional lesions will appear elsewhere.

The recognition that IBD encompasses two distinct but related entities was a major step toward understanding these diseases, but researchers sought to understand the excessive inflammation underlying both forms. They would eventually discover that the intestinal inflammation results from multiple interplaying factors, including the immune system, genetics, and the environment.

SUPPRESSING THE IMMUNE RESPONSE

The knowledge that inflammation was the driving force behind the symptoms of IBD led naturally to the first useful, non-surgical therapeutic approach: reducing inflammation. Since the 1950s, for example, clinicians have prescribed anti-inflammatory drugs such as corticosteroids, which are fast-acting and powerful enough to suppress flareups (the sudden worsening of symptoms) but cannot be used as a long-term treatment because of potentially serious side-effects. Aminosalicylates, such as mesalamine-based drugs, are another class of anti-inflammatory medications. While they are generally well-tolerated, they may not be effective for people with severe IBD symptoms, so their use is generally limited to people with mild to moderate cases.

Other medications reduce the inflammatory response by hampering the immune processes that drive it. These therapies, called immunomodulators, have been used to treat people with IBD since the 1960s. Although they can be an effective treatment for those who do not respond to (or cannot tolerate) corticosteroids or aminosalicylates, immunomodulator-based treatments are not without risks. They could produce potentially severe side-effects, including an increased risk of infections because the drugs reduce the activity of the body’s immune system.

Despite the long history of using immunomodulators to treat IBD, the risk-benefit profile of one such medication has only recently been thoroughly ascertained: methotrexate, an inexpensive yet potentially toxic immunomodulator that is prescribed for adult Crohn’s disease patients in whom established therapies have failed. The NIDDK funded the Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) study to determine its risk-benefit profile in the more common form of IBD. Recent results from this study showed that methotrexate did not improve ulcerative colitis symptoms compared to a placebo, suggesting that this drug, which could lead to chronic liver disease and liver fibrosis, is not beneficial for colitis patients.

Other means of modulating the inflammatory response in IBD have been suggested by advances in basic research on the immune system. For example, immunologists have identified several key molecular signals that trigger inflammation. Among these are molecules called cytokines, which are secreted by immune cells and play important roles in driving the inflammation in the gut. The pro-inflammatory cytokines found to be involved in IBD include tumor necrosis factor alpha (TNFα) and interleukin-12/interleukin-23 (IL-12/IL-23), which play major roles in other inflammatory diseases such as arthritis and psoriasis. Researchers found that blocking the activity of these cytokines can suppress inflammation in the gut. There are numerous drugs that have been developed to target TNFα and IL-12/IL-23, or the cellular signals...
that are elicited by these cytokines. Other drugs have been developed to block molecules, called integrins, that immune cells use to stick to the walls of blood vessels as they move out of the blood and into the tissue where they contribute to inflammation. Not every person with IBD responds to these anti-cytokine and anti-integrin treatments, however, and these drugs too can cause serious side-effects, including a heightened risk of infections. Also, most of these drugs are proteins and would be digested and broken down before they reach the site of inflammation if taken orally. Therefore, they must be administered through regular injections.

DIGGING THROUGH THE GENETICS OF IBD

By the end of the twentieth century, with evidence mounting that IBD varies significantly from person to person, it was apparent that developing safer, more effective therapies would likely depend on determining the factors that contribute to the inflammation in ulcerative colitis and Crohn's disease. IBD tends to run in families, so scientists strongly suspected that genetic factors were important. Identifying the genes involved in the disease could reveal new targets for therapy. A better understanding of IBD genetics might also enable clinicians to screen for people at risk for IBD—and early detection might make it possible to prevent the inflammation before it starts and becomes difficult to restrain. Genetic studies might even lead to personalized therapy by predicting which individuals would respond best to different types of IBD treatment.

Therefore, through grants to researchers at academic medical research institutions across the United States, the NIDDK established the IBD Genetics Consortium (IBDGC) in 2002 to identify genes that are involved in IBD susceptibility. In collaboration with the International IBD Genetics Consortium, of which it is a member, the IBDGC has enrolled thousands of IBD patients and identified about 200 regions of the human genome that are associated with risk of IBD. This work has yielded important new insights into the complex and individual nature of the disease. In one IBDGC study, for example, researchers analyzed data from over 29,000 men and women with IBD and found that, in Crohn's disease, inflammation in the ileum of the small intestine (near the junction with the colon) has distinct genetic causes from forms of Crohn's in which inflammation occurs in the colon. In other words, there are actually at least three distinct types of IBD—ulcerative colitis and two forms of Crohn's disease—which could help guide targeted treatments in the future. Other advances from the IBDGC have identified genetic variants that affect the microbiome (the diverse community of bacteria and viruses living in the gut), the immune system, or the integrity of the intestinal epithelium—all of which play important roles in IBD. Despite these advances, many of the specific genes involved in IBD, along with their respective genetic variants that contribute to IBD susceptibility, have yet to be precisely identified. A goal of the current phase of the IBDGC, which was renewed in 2017, is not only to continue identifying regions of the genome associated with genetic risk for IBD, but also to identify the specific genes and genetic variants within these regions that influence IBD susceptibility. Consortium members are also exploring the role of epigenetics—how genes are turned on and off independently of their DNA sequences—and how genetic factors influence the development of IBD by investigating the functions of candidate genes.

Exploring the genetics of IBD has provided insight into its origins, along with an abundance of possible molecular targets for screening or therapy. It also has cemented the understanding of IBD as a disease that could vary greatly from person to person, depending on genetic backgrounds, highlighting the need for more personalized approaches to treatment and prevention.
THE ROLE OF THE MICROBIOME

IBD was rarely diagnosed before the twentieth century, and today it is more common in industrialized regions of the world. Although this may stem in part from greater awareness of the disease, it also suggests that while genetics are an important contributor to IBD susceptibility, environmental factors—including the microbiome or factors that affect the microbiome—also likely play a role. Scientists thinking along these lines considered the possibility that an abnormal immune reaction to components of the microbiome might provide the long-sought explanation for the inflammation that leads to IBD. In fact, numerous studies have shown correlations between IBD and changes either in the microbiome or in how the body reacts to it.

Early support for this idea came from a study in a rat model that found a link between the composition of gut microbes and colitis. Scientists also showed that feeding a diet high in saturated fats from milk to mice with a genetic susceptibility to intestinal inflammation altered their intestinal microbial communities and the composition of their bile acids, induced changes in their immune function, and increased intestinal inflammation. More recently, a study in children and teens showed that different treatments for Crohn’s disease, such as immunosuppressive medication or a defined formula diet, have varying effects on the gut microbiome—a finding with implications for approaches to monitoring treatment response and for potentially developing microbiome-targeted therapies.

Important insights are also coming from the NIH’s Human Microbiome Project (HMP), which was launched in 2007 to characterize the community of microbes present in humans. As part of the HMP, the NIDDK co-funded and managed a study designed to understand how the gut microbiome is altered in IBD. This study integrated many different types of measurements of gut microbes as they change within IBD patients, including both children and adults, over time. The researchers found that the microbiomes of people with IBD were more volatile and fluctuated to a greater extent than those of healthy people, providing still more evidence that changes in the microbiome are closely linked to the disease.

Future research will seek to elucidate the specific ways in which components of the microbiome may promote IBD—or protect from the disease. Microbiome analyses in individuals with IBD may one day even help personalize treatment of their disease.

THE FUTURE OF IBD THERAPY: PERSONALIZED MEDICINE

Armed with what they have learned about the many factors affecting susceptibility to IBD, researchers are now seeking to develop personalized therapeutic approaches that consider the complex interactions among the immune system, genetics, and the environment driving development of the disease in any given individual.

It is now becoming possible to correlate specific genetic variants and other clinical test results with disease severity and responsiveness to therapies. For example, the NIDDK-sponsored Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study has been evaluating whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. Recent results from the PROTECT study found that higher amounts of an immunologic biomarker called pANCA in the blood correlates with disease severity, suggesting that this biomarker, which also may be associated with resistance to standardized therapy, could potentially be used as a diagnostic tool to help plan individualized treatments for children with the disease.

Another personalized approach that holds promise is the manipulation of the microbiome to maintain it in a healthy state. This could be accomplished by restoring a health-promoting profile of bacteria in the gut of a person with IBD using tailored probiotics to reintroduce underabundant bacterial species, or by fecal microbiota transplant whereby
the gut bacteria from a healthy donor would be introduced into a person with IBD.

An additional therapeutic approach would be to use cellular models of the gut to develop new personalized treatments in the laboratory and to possibly replace the damaged tissue in a person with IBD. Toward this goal, members of the NIDDK-supported Intestinal Stem Cell Consortium (ISCC) are developing methods to generate small conglomerations of cells that look and behave like a miniature portion of a human intestine. The ISCC has demonstrated that these “mini-intestines” can be generated using adult cells as starting material, suggesting that a patient’s own cells could be used to screen for drugs that would be effective for that individual’s disease. Personalized mini-intestines could also be potentially invaluable research models to study the genetic roots of IBD and how the intestine heals itself when injured. Additionally, mini-intestines may one day be implanted to repair or replace areas of the gut that have been damaged by inflammation, and because they could be derived from a patient’s own cells, they would less likely be rejected by the immune system. ISCC scientists have already used these mini-intestines to generate a functional enteric nervous system—the mesh-like arrangement of nerves that governs the function of the gastrointestinal tract—demonstrating their potential as models for bona fide intestines. They also generated mini-intestines that resemble different parts of the intestine, such as the ileum (the lower end of the small intestine) and duodenum (the section of the small intestine closest to the stomach). This is important from a replacement therapy standpoint because distinct regions of the intestine have different functional roles in digestion. Although research into regenerative medicine-based approaches is still in its early stages, these advances hint that the coming years may eventually see intestinal stem cell-based therapies for IBD.

IBD is indeed a complicated disease with many players. But for every cytokine, gene, or bacterial species linked to IBD, a new path opens for the development of a method to detect, prevent, or treat the disease. With more research into how combinations of factors drive the disease, and how they vary from person to person, we come closer to a future of far better health outcomes for people with IBD.
Dr. Shivdasani began his presentation by remarking that the intestine is an ideal model for regenerative medicine research, partly because the intestine is the most rapidly regenerating organ in the body. In fact, the intestinal lining completely renews itself once every five days. Research into how this feat is accomplished has provided valuable insight into how the intestine repairs itself. And, as Dr. Shivdasani hinted, it has forced scientists to rethink their assumptions about organ regeneration in general.

Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function that was lost because of age, disease, damage, or congenital defects. This field holds the promise of fixing damaged body parts by stimulating previously irreparable organs to heal themselves. Regenerative medicine also empowers scientists to grow tissues and organs in the laboratory and safely implant them when the body cannot heal itself. Thus, importantly, regenerative medicine has the potential to solve the problem of organ shortage—that is, the relatively small number of organs that are currently available for a large number of people who need a life-saving organ transplantation. But before scientists can optimally generate organs for use in people, they first must understand how organs grow, develop, maintain a healthy state, and repair themselves when damaged.

THE INTESTINE AS A MODEL FOR REGENERATIVE MEDICINE

Dr. Shivdasani described the intestine as being carpeted with millions of fingerlike projections called villi. These millimeter-long protrusions add to the surface area of the intestine, effectively increasing its absorptive power. Coating the villi are the most common cells in the intestinal lining—the enterocytes—whose primary role is to absorb water and nutrients. Interspersed among the enterocytes is a diverse mix of other cell types that secrete mucus, produce hormones, and regulate immune responses.
In the 1960s, scientists began to suspect that all the different cell types in the intestine descend from a small population of cells—stem cells—that are nestled at or near the bottom of “crypts,” which are pit-like structures that are contiguous with villi. With the hope of finding the key to intestinal regeneration, scientists began searching for these stem cells.

THE SEARCH FOR INTESTINAL STEM CELLS

Dr. Shivdasani explained what scientists started looking for in their search for intestinal stem cells: cells that could reproduce to form more stem cells, or differentiate—turn into cells with specialized intestinal functions. They made three assumptions based on what was currently known about the stem cells in the bone marrow that give rise to all red and white blood cells in the body. The first assumption was that all stem cells would divide slowly. This would be important for preserving the stem cell population because cells that divide slowly are less susceptible to genetic damage, such as from radiation or chemicals. The second assumption was that all stem cells would divide into two cells asymmetrically—that is, they would make one copy of themselves along with another cell that would take on a more specialized role. This starts some cells on the path to specialization while maintaining the valuable stem cell population. The third assumption was that all populations of stem cells would be rare, which would make them difficult to find.

Researchers began looking for cells in the intestinal crypts that fit these descriptions, but they were hampered by technological limitations. Eventually they narrowed their search to a population of slender cells wedged in the bottom of the crypts. Labelling these so-called “crypt-based columnar cells” (CBCs) in mice, so that scientists could track them and their progeny, revealed that CBCs were the source of several different intestinal cell types, implicating them as stem cells. But Dr. Shivdasani noted that CBCs were found to be constantly dividing and exclusively producing exact copies of themselves (i.e., dividing symmetrically), which did not fit the traditional assumptions of what stem cells should do. They were also not a rare population—it is not uncommon to find a dozen of these cells within each of the millions of crypts.

Advances in technology eventually made it possible to define cells in the crypts by scanning them for molecular markers, which are proteins that can be used to identify cells. The CBC cells were found to produce a protein called LGR5, so these cells are also referred to as "LGR5-positive cells." The use of molecular markers also allowed scientists to find another population of possible stem cells that were located several cells up from the bottom of the crypts, at the so-called +4 position. These +4 cells were rarer than LGR5-positive cells and, unlike LGR5-positive cells, they were slow to replicate—characteristics that fit the assumptions of what stem cells should be. This led to a model of intestinal regeneration that uses two populations of stem cells—the LGR5-positive population that lies near the base of the crypts, and the +4 cells, which were rarer, more dormant, and act as a backup in case the LGR5-positive cells become damaged.

This model provided a novel and intricate view of organ regeneration. However, the biology of intestinal crypts—and the stem cells they harbor—was about to get even more complicated.

REDEFINING STEM CELLS

Dr. Shivdasani explained another important discovery that introduced a twist to the intestinal stem cell model. Experiments in an animal model showed that both the LGR5-positive and +4 cell populations could be eliminated, and the intestine could still recover. In fact, the lost stem cells would eventually be replenished. This led to the discovery that other, more differentiated cells—the cells that had arisen from the stem cells—could return to a stem cell state, and this appeared to be regulated by signals produced in different areas of the crypt.
Dr. Shivdasani went into further detail, explaining how cells in the crypt transition back and forth between a stem cell state and a more specialized state. The dividing LGR5-positive cells at the bottom of the crypt exert force on adjacent cells, providing the “motor” for an escalator-like mechanism that pushes all the cells above towards the top of the crypt and into the villi. As the cells are pushed upwards, they lose contact with signals at the bottom of the crypt and are exposed to new signals that originate closer to the top. This change in environment coaxes the cells to take on more specialized characteristics, eventually becoming enterocytes or secretory cells. However, if the cells at the bottom of the crypt are damaged or lost, cells from higher up can relocate to the bottom and become re-exposed to factors that revert them to a stem cell state. Thus, the transition between intestinal stem cells and specialized cells is a two-way street.

Scientists are still sorting through all the signals that drive the transitions to and from the stem cell state, but the Wnt family of proteins appears to have a major role. Wnt protein levels are highest near the bottom of the crypt, where they stimulate the cell division that pushes all other cells upwards. In fact, interfering with Wnt signaling disrupts the entire architecture of the intestinal lining and reduces the fingerlike villi to a flat sheet of cells. But Wnt proteins do not act alone—other proteins called R-spondins are important for amplifying the effects of Wnt signaling, and additional factors (such as Notch and bone morphogenic protein) trigger signals in the cells to steer them towards specialization.

Dr. Shivdasani noted that this model of intestinal cell production offers an important lesson about regenerative medicine. The assumptions that were made about intestinal stem cells were based on what was known about hematopoietic (blood) stem cells, but the intestinal lining takes a different route to regenerate itself. For example, intestinal stem cells divide symmetrically, which, from blood cell research, would be counterintuitive. However, the intestinal crypt itself is asymmetric, so the population of dividing stem cells at the base of the crypt is preserved while its progeny become more specialized as they move upwards. Thus, almost all the attributes that had been thought to be necessary characteristics of stem cells are simply the success story of the hematopoietic system, which happens to use a rare population of stem cells that replicate infrequently and divide asymmetrically. But another organ may use a different process to regenerate itself. And studies of the intestine have convinced scientists to revisit their assumptions of stem cell properties, allowing for a broader definition.

From a gut regenerative medicine standpoint, the important idea is that almost any intestinal cell that has started down the road of becoming a specialized cell retains the potential to move back to a stem cell state if necessary. This is a “game changer,” Dr. Shivdasani explained, because it may no longer be crucial to specifically target and isolate the intestinal stem cells as a source for regenerative tissue. Instead, nature has provided a way to work with several populations of cells that are readily convertible.

**PUTTING KNOWLEDGE TO USE: MAKING MINI-INTESTINES AND DEVELOPING THERAPIES**

Scientists are applying what they have learned to demonstrate the potential for using intestinal stem cells to generate laboratory models of disease, and for building tissue for the therapeutic purpose of replacing damaged intestinal lining. For example, scientists in NIDDK’s Intestinal Stem Cell Consortium have successfully grown intestinal organoids—miniature versions of intestines—by culturing intestinal stem cells or crypts in collagen-based scaffolds along with a cocktail of growth factors. Another avenue is to start with induced pluripotent cells, adult cells that have been “reprogrammed” to assume a primitive state with the ability to give rise to cell types as diverse as nerve, blood, and pancreas cells. Consortium members recently developed methods to generate intestinal organoids from such pluripotent cells and also to generate tissue layers underneath the crypt, such as the system of nerve cells in the gut.
One eventual goal of building mini-intestines in the lab would be to replace damaged intestinal tissues in people with inflammatory bowel disease and reduce the odds of transplant rejection by using the patients' own cells as starting material. There are still several obstacles to overcome before scientists are ready to test transplants in humans, however. In mouse models, the efficiency of successful implantation is low, and the process of generating organoids requires culturing the cells in an expensive form of collagen scaffolding, although other substrates are being explored. Also, to be effective, the implant would need to cover vast areas in the gut and be connected to the vascular system.

Nevertheless, there are plenty of examples of how using a regenerative medicine approach could treat gastrointestinal diseases and disorders. One would be Crohn's disease, which involves inflammation and ulceration of the intestinal tract and is often treated by removing portions of the gut. Regenerating the intestinal tissue for individuals with this condition would help to avoid short bowel syndrome, a disorder that causes chronic diarrhea. Another disease that could potentially be treated with regenerative medicine is necrotizing enterocolitis, a devastating and poorly understood condition of some premature infants wherein a portion of the intestine is destroyed by infection and inflammation. Restoration of the damaged tissue could be a reasonable treatment component for this potentially fatal disease.

Dr. Shivdasani finished by discussing how the discovery and characterization of intestinal stem cells could play an important role in designing future therapies for diseases beyond the gut. It is worth considering, he noted, that just as bone marrow transplantation and hematopoietic stem cells have been enormously valuable models for understanding the nature of certain stem cells, the intestine offers a parallel model. It is possible that the lessons learned from the intestine could be applied to repair other organs. The urgency of developing such regenerative medicine-based therapies is underscored by the problems currently faced by many people waiting for the availability of replacement organs. But because of scientists' innovative research advancing the field of intestinal stem cell biology, the future of regenerative medicine in the gut—and beyond—looks promising.
PATIENT PROFILE

Raeann and Shirley: Giving Back to Other Families Affected by Celiac Disease

In the Winter of 2003, Shirley noticed that her younger daughter, Raeann, then just shy of 2 years old, would tire easily when chasing her older daughter around the house. Not long after, when Raeann started throwing up frequently at meals, the family knew something was wrong. They would eventually learn that Raeann had celiac disease. As Shirley later read through the information available about celiac disease and its treatment on the internet, she sensed the challenge that lay before them. It was just the beginning of her family’s journey learning about life with celiac disease, empowering themselves and others along the way with the knowledge needed not only to survive with the disease, but to thrive.

WHAT IS CELIAC DISEASE?

Celiac disease damages the digestive tract and results from an autoimmune reaction triggered by consuming gluten, a protein found mainly in foods containing wheat, barley, and rye. Gluten can also be found in other foods, as well as some supplements and other products. This autoimmune reaction—where the body damages its own cells—occurs in the small intestine, limiting nutrient absorption and potentially resulting in gas and bloating, diarrhea or constipation, and abdominal pain, as well as nausea and vomiting. However, a wide range of symptoms may occur outside the gastrointestinal tract as well. In children, celiac disease can have severe consequences, such as delayed growth and development, while in adults it may manifest as anemia, bone loss, rashes, fatigue, or other complications. Celiac disease affects an estimated 1 in 141 Americans.1 The disease is more common in Caucasians, females, and those with a family history of celiac disease or with other specific diseases, including other autoimmune conditions such as type 1 diabetes. Diagnosis of celiac disease can be difficult and is often delayed; it is based on a series of physical exams, blood and genetic tests, and, lastly, an intestinal biopsy if other tests suggest the disease is present. Celiac disease usually resolves quickly with strict adherence to a gluten-free diet and avoidance of any other products containing gluten—but it can take longer for healing of any intestinal damage that may have already occurred, and the necessary dietary and other changes require constant, lifelong vigilance.

PATIENT PROFILE

TUMMY TROUBLES

Initially, it took some sleuthing and persistence to get to the bottom of Raeann’s vomiting and lethargy. Though her vomiting was frequent, it was not at every meal. Their pediatrician ruled out a viral infection but was not able to pinpoint the cause. Shirley kept a journal noting when the vomiting occurred and what foods Raeann had eaten. “It was to the point that I took out strawberries and I took out chocolate and different things out of her diet, but nothing really seemed to fit,” says Shirley. After some scary incidents where Raeann gagged while eating in her high chair, they returned to the pediatrician’s office, who referred them to a gastroenterologist. There, they had some tests done that finally gave them an answer. “They did blood work, and they called and said ‘I think she has celiac disease,’” remembers Shirley. “My first question was ‘what is that?’,” recalls Shirley. The doctor then explained what celiac disease is and how it is treated. “He said ‘you go on a gluten-free diet,’” says Shirley. “I thought ‘what is gluten?’ I had no idea.”

No one else in their family had ever been diagnosed with celiac disease or any other autoimmune disease. The doctor informed Shirley that they would need to take a biopsy from Raeann’s intestine to confirm the diagnosis. Reluctant to put their young child under general anesthesia for the biopsy procedure, Shirley sought a second opinion from the head of the Celiac Disease Program at Children’s National Health System, a children’s hospital in Washington, D.C. They called day after day, hoping for an appointment to open up, and when one did, they drove there through the snow. After seeing Raeann, the doctor strongly supported the diagnosis. “He kind of pointed out these things we hadn’t noticed much, like … a distended belly,” says Shirley. “Then he said ‘she has really skinny arms, her hair’s kind of thin, you’re telling me that she’s kind of tired a lot, and looking at the blood work I’m 98 percent sure she has celiac, but you want to be 100 percent sure before you change her diet, so you need to do the endoscopy.’” They went ahead with the procedure that took a biopsy of Raeann’s intestine, showing a flattening of the villi—tiny hair-like projections on the inside of the intestine that absorb nutrients—a sign that the intestinal lining was being eroded by her overactive immune system. The doctor confirmed the diagnosis of celiac disease and advised that Raeann immediately start eating a gluten-free diet.

A RADICAL DIETARY CHANGE

Thankfully, Raeann’s celiac disease was caught early, before long-term gluten exposure could cause more lasting damage. After six weeks of eating 100 percent gluten-free, when they brought Raeann back to the gastroenterologist’s office, she was well on her way to recovery. “She was like a changed child,” remembers Shirley. “She was starting to run and jump and laugh, and, over the next year, she talked.” In retrospect, the family realized that not only had Raeann experienced a delay in her language and other development, but her growth had also been slower. Once on the gluten-free diet, she caught up and gained 10 pounds over the next year. “It was really kind of a miracle—no medication, no surgery, just a very radical diet change,” says Shirley.

But, as easy as the prescription of a gluten-free diet sounded, it required Raeann and her family to approach food in a whole new way. They went online and studied the lists of foods that Raeann could and could not eat. "We got rid of every bit of gluten. We went through all of our pantries and looked at everything," says Shirley. Shirley put together a notebook with information on gluten-free foods and recipes. As there were few stores where gluten-free items, such as baked goods like breads and cookies, were available, they ordered many items online. “I would order a
dozen loaves of bread from a company, and they would deliver it packed in dry ice on my doorstep," recalls Shirley. Over time, they identified gluten-free baked goods and mixes that Raeann liked. Shirley and her husband helped Raeann come to terms with the diagnosis by reading her a children's book about a little girl diagnosed with celiac disease. "It was this whole thing about 'she's not different, she's just special,'" recalls Shirley. “It was nice to have a story she could relate to and feel like 'oh yeah, that’s just like me.'"

"It was really kind of a miracle—no medication, no surgery, just a very radical diet change," remembers Shirley of the period after daughter Raeann went on a gluten-free diet for her celiac disease.

LEARNING TO THRIVE WITH CELIAC

Despite learning as much as they could about celiac disease, the family experienced its share of challenges and setbacks along the way. But they took these in stride as learning experiences that helped them achieve the minor victories necessary for Raeann to thrive throughout childhood and now, as a healthy and active teenager. On the rare occasions when Raeann accidentally consumed even small amounts of gluten, she would become violently ill 2 to 3 hours later. Raeann's family ingrained in her that she had to ask what was in any food she consumed and empowered her with the knowledge of what to avoid. Over the years, the family evolved strategies for managing Raeann's celiac disease. They slowly re-introduced gluten into the house for other family members to consume, along with a set of strict rules that the family and any visitors must follow to keep Raeann safe: no double-dipping in foods like peanut butter, a separate toaster for gluten-free bread, repeatedly wiping down the counters, and a place reserved for Raeann at the family table. "Everyone in our family is very good with it, and I have my own cabinet with all gluten-free stuff," says Raeann. The family also juggles her brother’s tree nut allergy. Every Halloween, Raeann and her brother would trade candy based on their different food restrictions.

As Raeann grew, she served as her own advocate, making sure as much as possible not to consume any gluten even when her family was not around to protect her. When Raeann was in first grade, Shirley would include a note reassuring her daughter that her packed lunch was gluten-free. “There was one day,” says Raeann, "where she wrote a note that said 'your sandwich is gluten-free,' and then I looked at the sandwich and it wasn’t the same bread that I usually had." She asked her teacher, who thought it was OK to eat, but called Shirley to check. When Shirley arrived at the school, she realized that she had accidentally switched Raeann's sandwich with her sister’s, which did contain gluten. Although Shirley and Raeann’s teacher felt terrible about the mix-up, they were glad that Raeann had spoken up and taken care of herself. Another time, when she had a friend sleep over, Raeann became ill after dinner. Her friend had to leave, and the family were left wondering whether the cause was cross-contamination from her friend's pizza to Raeann's gluten-free one or another source. "When something like that happens, we always wonder, 'what could it have been?' ... there's no way to really know," says Shirley. Due to the severity of her symptoms when she accidentally consumes gluten, Raeann must avoid foods that well-meaning friends and neighbors try to make gluten-free for her, in case their preparation or handling introduced any gluten contamination.

Eating out presents its own unique challenges for someone with celiac disease. Raeann is always careful and plans ahead when eating in a restaurant, sometimes bringing her own food or eating at home before or afterwards, but even foods that are advertised as gluten-free can be problematic. Recently, while eating out with friends for her junior year homecoming dance, she pre-ordered a gluten-free meal. "When the waitress served me
my meal, she said this was the allergy meal, and I said ‘it’s gluten-free, right?’ and she seemed kind of confused,” recalls Raeann. “Everyone was eating their meals, so I said ‘oh, I’ll just eat it.’” She went home sick that night, missing out on time with friends and tarnishing her memories of the dance.

When Raeann was growing up, Shirley would always make gluten-free birthday cakes for everyone in the family, so Raeann could enjoy them. Raeann would always bring her own gluten-free cupcake that her mom had made to any birthday party she attended. But in recent years, a growing awareness of celiac disease and the wider availability of new foods and dining options for those following a gluten-free diet has made life easier in some ways. For Raeann’s sixteenth birthday, her friends and family went to one of her favorite restaurants featuring a gluten-free menu, culminating with a delicious, gluten-free cake. “It was a big cookie cake,” Raeann recalls fondly. “All my friends ate it too and it was the best cake I’d had.”

A CIRCLE OF GIVING

In the early years after Raeann’s diagnosis, Shirley and Raeann went to events hosted by the local chapter of a support group for families with children with celiac disease, where they found a welcoming community. There, Raeann participated in activities such as making gluten-free holiday cookies while Shirley learned from other parents of children with the disease. Eager to learn all they could about their daughter’s condition, Shirley and her husband also attended a celiac disease group event at a local library, featuring a presentation by a researcher in the field.

Starting when Raeann was in middle school, the family began sharing with others what they had learned in their years managing her celiac disease. At that time, two other parents contacted Shirley about meeting up and sharing experiences. “They were really interested in talking to me because I had had so many years [dealing with a child’s celiac disease], and their children had been more recently diagnosed,” says Shirley. They learned from her experience, but Shirley also learned from them, including finding out about an app for her phone with information on sources of gluten-free food in the area or when traveling. “That sharing is so important,” remarks Shirley.

In describing why she and mother Shirley reach out to share their experiences managing her celiac disease, Raeann says, “People get so scared about it … so it’s good to talk to people.”

When Raeann and her sister went through their bat mitzvah ceremonies—Jewish coming of age rituals—they chose as their community project to raise money for celiac disease research through a 5K race called “Making Tracks for Celiacs” in Baltimore, Maryland. In addition to collecting donations for the cause, they also participated in the walk/run with Shirley. Afterwards, they enjoyed the rows of gluten-free vendors and raffles. “There were people doing raffles for all different things, and the money goes to celiac research,” says Raeann. They also enjoyed the camaraderie of being around other families managing celiac disease.

In the past year, the family has reached out to area elementary and middle schools, on their neighborhood Facebook page, and through email groups, such as one for parents at the NIH, where Shirley works in a communications office, to share what they have learned. “We said ‘I have celiac, if you or anyone you know has celiac, we’d be happy to help,’” says Raeann. “It had been several years, and we feel like we have our arms around the problem,” adds Shirley. Both Raeann and Shirley responded to people who contacted them, sharing information on their experiences and resources, such as how Raeann approaches life with celiac disease and her favorite area restaurants. “We want to give back a little bit because people helped us and it was useful,” says Shirley. “People get so scared about it … so it’s good to talk to people,” says Raeann. Shirley also stays current on the latest advances in celiac disease.
research by subscribing to an email newsletter from the NIDDK. (See further information below related to celiac disease available through the NIDDK.)

"It's one of the interesting things about myself," says Raeann about her celiac disease, adding that "it comes up right away when I make friends ... it's kind of like part of me."

In June 2018, Raeann and Shirley attended the Washington, D.C. Gluten-Free Expo and Education Day, where Raeann participated as a speaker on a teen panel. The session was part of a day-long series of meetings on challenges confronting those on a gluten-free diet, with this particular session exclusively by and for teens. "I thought it was just going to be us talking," recalls Raeann. Instead, "they were all sharing their experiences and asking questions, so it was actually a lot of fun," she says. Raeann and Shirley also volunteered with the vendors, handing out gluten-free samples. There, they marveled at the wealth of gluten-free foods available and watched some cooking demonstrations, a stark contrast from the scarcity of gluten-free options and more limited awareness of celiac disease when Raeann was first diagnosed.

These days, Raeann stays in excellent health as she juggles her academic work, including honor societies and tutoring responsibilities, sports such as lacrosse and cross-country, and planning for college. Like the message of the children's book her parents used to read her, Raeann views her formative experiences growing up with celiac disease in a positive light, writing about them in school essays and openly sharing her story with people she meets. "It's one of the interesting things about myself," she says, adding that "it comes up right away when I make friends ... it's kind of like part of me." While she and her family all wish she didn't have celiac disease, their advice to others affected by the disease is that it is manageable. "It may seem hard to change your whole diet, but it's not as bad as you think," says Raeann. "This is something that affects my food and my eating, but that's not a big barrier ... I can still do so many things," she notes. "Anything really," adds Shirley.

NIDDK CELIAC DISEASE RESEARCH AND EDUCATION

The NIDDK engages in multiple activities to advance research on celiac disease, including supporting studies conducted by scientists at institutions across the country to gain insight into the underpinnings of the disease and enable the development of improved diagnostics and treatments. Researchers have identified some of the molecular, dietary, and immune mechanisms underlying celiac disease development; revealed the prevalence of celiac disease, including a growing number of undiagnosed cases; and identified subclinical symptoms and tested new diagnostics in children with the disease. For example, The Environmental Determinants of Diabetes in the Young (TEDDY) is a long-term study supported by the NIDDK to understand environmental factors causing type 1 diabetes and celiac disease in children with high genetic risk living in the United States and European countries. In another celiac disease research effort, the Institute provided support for the National Health and Nutrition Examination Survey (NHANES), a program led by the Centers for Disease Control and Prevention (CDC), to gather data that are being used for ongoing analyses on the disease risk factors and dietary intake over time nationwide. The NIDDK also provides online fact sheets for the public and health care professionals with information on celiac disease symptoms, diagnosis, and a gluten-free diet, as well as updates on research. Information is available through the NIDDK website at www.niddk.nih.gov