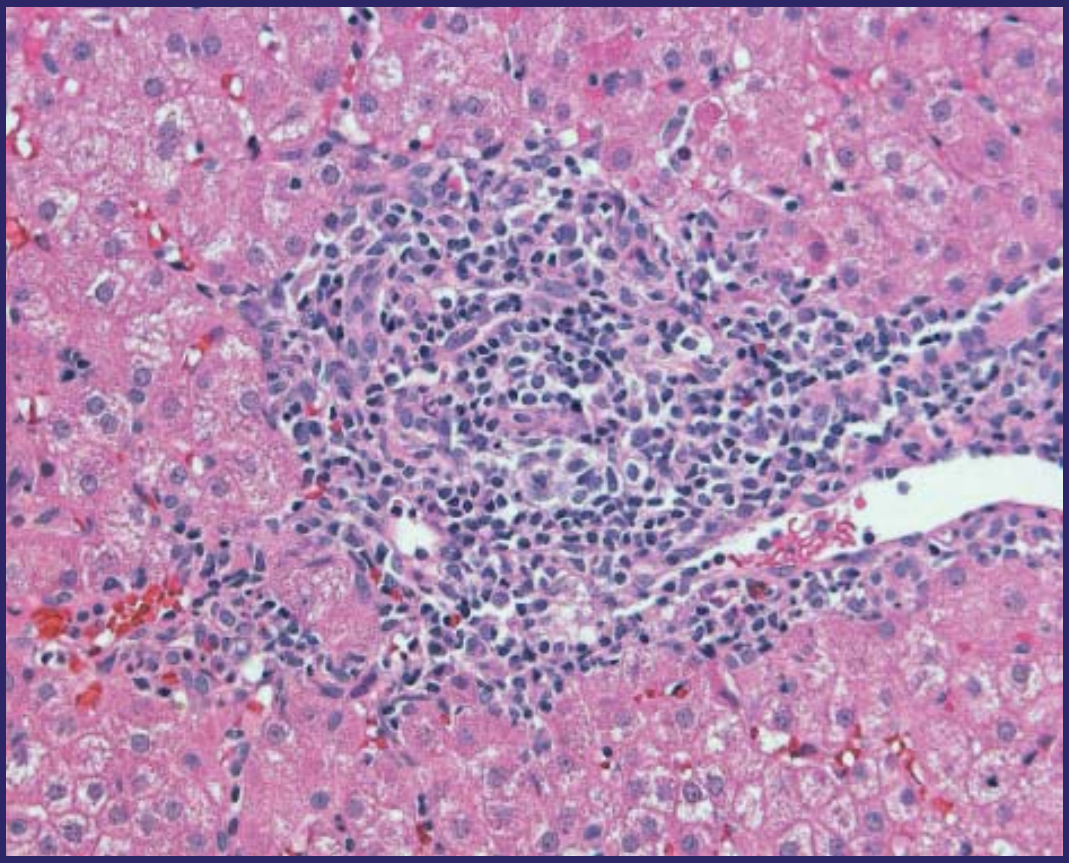


In a patient with active hepatitis C infection, inflammatory cells of the immune system (stained dark blue) congregate in infected liver tissue (stained pink) in reaction to presence of the hepatitis C virus. Hepatitis C infection is a leading cause of liver disease and liver transplantation. The NIDDK supports basic and clinical research aimed at improving treatments for this disease and preventing its occurrence. Photo: Dr. David Kleiner, National Cancer Institute, National Institutes of Health.

Digestive Diseases and Nutrition

Digestive diseases are among the leading causes of hospitalization, surgery, and disability in the U.S. They include disorders of the gastrointestinal tract, liver, gallbladder, and pancreas, as well as obesity and other nutrition-related disorders. NIDDK-supported scientists are vigorously pursuing research to understand how common these diseases are across the U.S. population, to identify the causes of these diseases and how they progress, and to test pharmacological, surgical, and behavioral interventions for treatment and prevention.

A functional liver is essential for life. Several types of liver disease have serious adverse impacts on health, and some can lead to complete liver failure and the need for a liver transplant for survival. Scientists are intensifying research on a variety of liver diseases, from those primarily affecting children, such as biliary atresia, to those commonly affecting adults, such as non-alcoholic steatohepatitis. Some, such as hepatitis C, are caused by infection, while others result from such diverse factors as autoimmune reactions, genetic mutations, drug toxicity, and as-yet-unknown triggers. With livers from deceased donors in short supply, and the death rate among patients on the waiting list for a liver transplantation having risen by a factor greater than 10 during the past decade, identifying ways to facilitate safe and effective transplantations from living donors is critical. Efforts are under way to coordinate and bolster each of these areas of liver disease research within the NIDDK, across the NIH, and with other organizations to respond to this health problem.

The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels. Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, and cancer. While multiple factors contribute to obesity, dietary intake clearly plays a key role in weight gain. As scientists elucidate the molecular factors that control appetite, metabolism, and energy storage, they are identifying potential targets for the development of new pharmacologic agents to promote safe, long-term weight loss. Investigators are also continuing behavioral research to help people achieve healthy lifestyles that include increased physical activity and improved diet. (Additional information on research endeavors focusing on obesity supported by the NIDDK is provided in the next chapter.)

Intestinal disorders include functional bowel disorders, which result in symptoms of abdominal pain and altered bowel habits. One such disorder is irritable bowel syndrome (IBS), which causes pain and constipation or diarrhea. IBS more frequently affects women, who, in comparison to men, display a different range of symptoms and respond differently to pharmacologic treatments for the disease. While diet and stress contribute to this disorder, its underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. Scientists are accelerating research to better understand these intestinal disorders.

Another serious intestinal disorder is inflammatory bowel disease (IBD). IBD, which encompasses Crohn's disease and ulcerative colitis, is marked by destructive inflammation in the intestinal tract leading to rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. Surgical treatment is often required. Scientists are dissecting the complex interactions among the genetic, environmental, and cellular factors that contribute to

the development of IBD. The continued identification of predisposing genetic variations and their interactions, as well as other factors, such as potential autoimmune and microbial influences, will help spur the design of novel therapeutic strategies.

Small but powerful players in tipping the balance towards digestive health or disease are the microorganisms that inhabit the gastrointestinal tract. These microbes can affect intestinal health in some surprising ways, depending on whether they work with, or against, the cells of their host. Scientists are gaining insights into how these microorganisms that normally reside in the gut influence the development and function of the digestive tract.

Among other diseases of the digestive tract are those of the pancreas, including various forms of pancreatitis. An inflammation of the pancreas, pancreatitis, results in abdominal pain, weight loss, poor digestion, and, in more serious cases, tissue damage and infection. Chronic pancreatitis, serious in and of itself, increases susceptibility to pancreatic cancer, one of the deadliest malignancies. Scientists are identifying both genetic and environmental factors associated with pancreatic disease and pancreatic cancer.

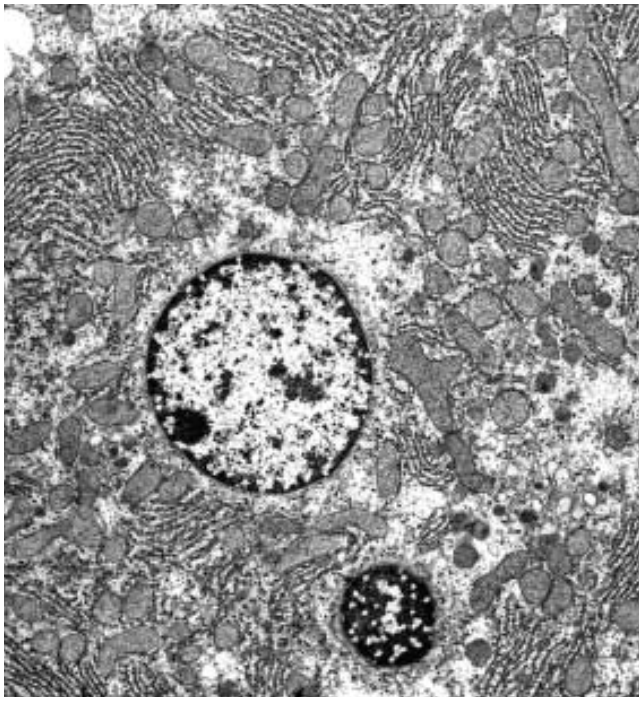
Finally, digestive disease can also be triggered by foods. In individuals with celiac disease, the immune system reacts to a protein called gluten, which is a component of wheat, barley, and rye. This reaction leads to damage to the small intestine, consequently interfering with its ability to absorb nutrients from foods and resulting in chronic diarrhea, bloating, anemia, and, in children, growth failure. Celiac disease is also associated with other serious conditions, such as osteoporosis, and, rarely, increased risk of certain cancers. Following a gluten-free diet is difficult, but is the only effective treatment. The greater challenge now facing patients and their healthcare providers is to improve methods capable of diagnosing celiac disease early, before damage occurs or other conditions develop. Recent and continued advances in the understanding of genes that predispose individuals to develop celiac disease may contribute to improved diagnosis through genetic-based screening in the future.

STRENGTHENING EFFORTS IN LIVER DISEASE

The liver, the largest organ in the body, is essential for keeping the body functioning properly. It removes or neutralizes poisons from the blood, processes drugs, produces immune agents to control infection, and removes germs and bacteria from the blood. The liver also makes proteins that regulate blood clotting, produces bile to help absorb fats and fat-soluble vitamins, and stores nutrients used for energy. Liver diseases that interfere with these essential functions can therefore severely threaten health. Unlike degenerative diseases, which typically manifest in old age, liver diseases in the United States frequently strike individuals in some of the most productive years of life, between the ages of 40 and 60 years. Even some of the very young are, in rare cases, afflicted with neonatal liver diseases, such as biliary atresia. Liver disease in the U.S. also disproportionately affects minorities and the economically disadvantaged. For those whose condition reaches "end stage," or liver failure, liver transplantation offers hope for survival, but demand for donor organs far exceeds supply. New planning and research activities within the NIDDK are currently strengthening efforts in liver disease research to advance knowledge in this area, with the ultimate goal of reducing the burden on patients suffering from liver disease.

Liver Disease Research Branch: In June 2003, the NIDDK Director established the Liver Disease Research Branch within the Institute's Division of Digestive Diseases and Nutrition. This Branch brings together experts in liver disease research to accelerate progress and coordinate liver-related research activities across the NIH and with other federal agencies. Among the Branch's long-term responsibilities are the planning and management of research and training. However, one of its first and most important tasks is to coordinate the

preparation of an Action Plan for Liver Disease Research, with a targeted release date of Spring 2004. Already, the Branch has assembled representatives from across NIH as part of the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee. This Subcommittee will oversee and guide the development of the Research Action Plan, which will draw on the insights of these NIH representatives, as well as those of experts from other federal agencies and from the external liver disease research and advocacy communities. This Research Action Plan will provide an overview of current research funding in liver disease; challenges to advancing liver disease research; opportunities for future research; and a tactical plan for addressing these challenges and opportunities. The Research Action Plan will strengthen the collaborations necessary to advance NIH-wide planning for liver disease research to achieve optimal scientific and clinical benefits.



Transmission electron micrograph of a rat liver cell (hepatocyte), showing the nucleus (center) surrounded by a high density of cellular organelles important for carrying out the many functions of these highly active cells–including protein synthesis and energy production and storage. Photo: Prof. M.V. Parthasarathy, Cornell Integrated Microscopy Center, Cornell University, Ithaca, NY. © CIMC.

Adult Liver Transplantation–New Hope from Living Donors: For patients with end stage liver disease, liver transplantation represents the only available cure. Yet, more than 17,000 Americans are currently awaiting transplantation due to the shortage of livers available for transplant from deceased donors. The practice of transplanting portions of livers from living donors began over a decade ago with transplants from adult donors to children, due to the shortage of livers from deceased donors. Because of the liver's amazing ability to regenerate, the donor's liver eventually regrows to its previous size, and the portion transplanted also grows in the recipient.

Adult-to-adult living donor liver transplantation, first accomplished in the late 1990s and introduced into the U.S. in 1997, is a promising procedure that enables adult patients as well to receive part of a liver from a living adult donor, rather than from a deceased donor. Since its introduction, the number of adult-to-adult living donor transplants performed has grown considerably, now accounting for approximately 5 percent of all liver transplants in the U.S. However, liver transplantation between two adults is a more extensive and life-threatening operation for the donor than the adult-to-child operation, because it requires more of the donor's liver to be removed in order for the tissue to function successfully in the adult recipient. Indeed, between 1998 and 2003, there were two widely known deaths of healthy, adult donors after adult-to-adult living donor liver transplantations. The potentially serious, but as yet ill-defined, health risks posed to living donors, coupled with the enormous potential benefit for the vast number of patients on transplant waiting lists, make adult-to-adult living donor liver transplantation an important and timely area of study.

In order to understand both how this increasingly popular procedure is being performed on a national scale and the complications that can result from it, NIDDK-supported researchers recently collaborated on a survey of all liver-transplantation programs in the U.S. Reviewing data from 69 percent of the programs, they found that the number of liver transplants from living donors rose rapidly in just a few

years, increasing from one transplant in 1997, when this procedure began, to 266 transplants in 2000. Importantly, they found that overall mortality among donors is low, approximately 0.2 percent. However, serious complications occur in approximately 14 percent of donors. This study highlighted the critical importance of continuing research on the effects of the procedure on both the donors and recipients in order to improve strategies to combat adverse effects.

Given that adult-to-adult living donor liver transplantation procedure in the U.S. is expected to become even more widespread in years to come, it is important to comprehensively assess and monitor the risks to potential donors and to develop uniform criteria for matching donors with recipients. An ongoing effort to address these issues is the Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL). This study is supported by the NIDDK in collaboration with the Federal Health Resources and Service Administration (HRSA) and the American Society of Transplant Surgeons. The initiative was launched in 2001 to carefully evaluate the risks and outcomes for donors and patients. This multi-center clinical cohort study currently consists of nine liver transplant centers experienced in performing the procedure, and a data coordinating center responsible for maintaining a clinical database of patients. The study will follow both donors and recipients before and after the operation to assess their clinical outcomes and quality-of-life. The primary goal of the study is to provide valuable information on the outcomes of living donor liver transplantation that can be used to aid decisions made by patients, potential donors, and physicians in considering this potentially life-saving procedure.

Facilitating Research on Pediatric Liver Disease–The Biliary Atresia Research Consortium: The need for liver transplantation is not limited to adult patients with liver disease. The neonatal liver disease known as biliary atresia is the single most common reason for liver transplantation in children, and is a major challenge for early detection, diagnosis, and management. Biliary atresia is characterized by a progressive inflammatory process in the liver beginning soon after birth. The inflammation causes obstruction of the ducts that drain bile from the liver, damage to the liver cells, and scarring of liver tissue, leading to jaundice and weight loss. The cause(s) of the disease, however, remains elusive and its optimal management is still unsettled. Because biliary atresia and other forms of neonatal liver disease are relatively rare, no single referral center in North America treats a sufficient number of new patients each year to permit an intensive analysis of etiology and risk factors, or to assess critically novel means of diagnosis or treatment.

In 2002, the NIDDK created the Biliary Atresia Research Consortium to facilitate and perform clinical, epidemiological, and therapeutic research in children with biliary atresia and other neonatal liver diseases. At present, the Consortium consists of nine pediatric liver disease Clinical Centers and a Data Coordinating Center. The Consortium has recently developed a clinical trial to optimize the success of the Kasai procedure. This surgical procedure removes the biliary ducts outside the liver and attaches the small intestine to the liver, at the site where bile is formed. If this procedure is successful, it can reverse the effects of biliary atresia on the liver, removing the need for liver transplantation. It is also hoped that the establishment of this Consortium and the serum and tissue bank will stimulate other scientists to develop an interest in investigating the etiology and pathogenesis of neonatal liver diseases.

In addition to these initiatives, many new and ongoing clinical efforts in liver disease research are being supported by the NIDDK. These include two sets of multi-center clinical trials of treatments for hepatitis C, known as the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial and the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C). Also, the Acute Liver Failure Study Group combines a prospective database with a study of acute liver failure to test a treatment for cases of the disease that result from

factors other than damage due to acetaminophen. With respect to one of the most common causes of liver disease in the U.S., nonalcoholic fatty liver disease, the NIDDK supports an effort on one form of the disease, the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network. This network includes a database of patients and provides additional resources and support for clinical studies of new therapies. Finally, to address the problem of liver injury due to medications, which is one of the most common causes of acute liver disease, the NIDDK has established a Hepatotoxicity Clinical Research Network. This multi-center network will characterize drug-induced liver injury and provide samples to collaborating researchers. Collectively, these clinical research efforts should spur research advances in various types of liver disease.

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COMPREHENDING THE COMPLEXITY OF INFLAMMATORY BOWEL DISEASE

Within the human gastrointestional tract exists an ecosystem teeming with life. Microbes coexist alongside nutrients, molecules, ions, and debris. Cells forming the wall of the gastrointestinal tract serve as a permeable barrier that permits beneficial molecules to pass through, while preventing entry of harmful microbes and molecules. Under healthy conditions, the ecosystem is beneficial to the host. Pathogens are kept at bay, commensal bacteria reside peacefully, and probiotic bacteria break down molecules so that they can be absorbed through the intestinal wall as nutrients for the host. Under certain disease conditions, however, the ecosystem is perturbed when the host's immune system spins out of control and attacks friendly as well as pathogenic bacteria, which causes inflammation and eventual breakdown of the intestinal wall.

One million Americans suffer from inflammatory bowel disease (IBD), the general name for diseases causing inflammation in the small and/or large intestine. The two primary IBDs are Crohn's disease and ulcerative colitis (UC). While the cause(s) of IBD is not entirely known, it appears that IBD arises from a complex interplay of factors involving the environment, heredity, and the immune system. IBD is characterized by a breakdown in the regulation of immune responses to microbes residing in the gastrointestinal tract. The mechanisms underlying these aberrant responses are very complex and the target of intense research investigation. Another important aspect of IBD research is the genetics of this complex disease. The intricacy of mechanisms of this disease is reflected in the diverse research being conducted, as illustrated by the following recent advances.

"Trading Spaces"–Modulating Gut Bacteria to Reduce Inflammation: Researchers are finding that the composition of gut microbes is one factor influencing IBD and intestinal irritation. In a rat model of colitis (inflammation of the large intestine), called SPF B27 TG, administration of antibiotics that kill gut bacteria can prevent or treat this condition. Symptoms recur when treatment is stopped, however. In a recent study, researchers demonstrated for the first time in this model that administering both antibiotic drugs and a "probiotic" commensal bacterium synergistically confers partial protection against the relapse of colitis. When the probiotic bacterium, called *LGG*, was introduced to SPF B27 TG rats with established colitis following antibiotic treatment, the rats were less likely to have a relapse. Other species of the bacteria were tested to see if they conferred partial protection against relapse, but when the rats were treated with other related bacteria, they were not protected. Thus, the partial protection demonstrated with *LGG* bacteria is species-specific. These results are particularly significant because regimens combining probiotic bacteria with antibiotics have shown promise as

treatments for intestinal maladies in humans–including as a therapy to prevent post-operative recurrence of Crohn's disease. Interestingly, at the end of the experiments, the total amount of colon bacteria was the same between rats which did or did not receive the *LGG* bacteria, but the treated rats had 10-fold more of this type of bacteria in their colons. While further investigation is necessary to confirm these results and to elucidate the mechanisms involved, this work in an animal model suggests that specific modulation of the bacterial species present in the intestine, through a combination antibiotic/probiotic approach, may help reduce the inflammation in diseases such as IBD.

Insights Into Inflammatory Mechanisms: Amazingly, despite constant exposure to up to 1,000 species of commensal bacteria and their pro-inflammatory molecules, the gut maintains a state of controlled inflammation. In this state, immune system cells capable of attacking "good" bacteria are present, but their activity, and hence their potential to do harm, is being held in check. It is thought that intestinal inflammation in diseases such as IBD may be due in part to faulty control mechanisms. Scientists recently examined the contribution of certain immune system cells, called $CD4^+$ T cells, to the delicate balance of immune tolerance and sensitivity observed in the intestine. Previously, using a mouse strain that spontaneously develops colitis, the researchers had identified a subset of CD4+ T cells that react to bacteria that are normally tolerated in the colon, leading to inflammation. The mice recover from their colitis; however, the pathogenic $CD4^+$T cells can still be found in these mice. Moreover, if transferred to another mouse strain, these cells can still cause colitis. In the new study, the researchers have found evidence for why this is so. They were able to isolate and culture a specific set of regulatory T cells from the special mouse model that can communicate with the pathogenic $CD4^+$ T cells to rein in their growth and killing activity *in vitro*. These regulatory cells were also able to prevent colitis when transferred with the pathogenic cells into new mice. Importantly, when the researchers examined intestinal tissue from normal mice, they found evidence for the same regulatory activity in the $CD4^+$T cells in that tissue. These experiments provide further evidence of regulatory mechanisms that may contribute to the inflammatory process in colitis.

Researchers are also uncovering the contribution of other body components to inflammation that may be highly relevant to IBD. Platelets are particles that circulate in the blood where they are available to stop bleeding by forming blood clots, or scabs. Platelets normally circulate in an inactive state until injury occurs. At that time, they are activated through a series of molecular events initiated by the injury. Recently, scientists found that activated platelets express a protein, CD40 ligand (CD40L), on their surface. This discovery meant that platelets are capable of interacting with cognate CD40-positive cells lining the intestine and of initiating a cascade of events leading to intestinal inflammation. Scientists have also discovered that the platelets of IBD patients circulate in an activated state. Based on this new knowledge, researchers wanted to determine if platelets from IBD patients also express enhanced levels of CD40L. They found that, indeed, the platelets of IBD patients express increased amounts of CD40L compared to healthy controls, and that the activated platelets are located in the inflamed intestine, as well as in the circulation. Through additional experiments, they determined that the binding of platelet CD40L to human intestinal microvasculature cells *in vitro* results in increased expression of soluble and cell adhesion molecules that attract and retain inflammatory cells in the vasculature. The platelets from IBD patients also produce higher amounts of a molecule called RANTES, which may contribute to the chronic nature of IBD. This knowledge of the properties of the highly activated platelets presents a potential target for therapeutic intervention.

The IBD5 Gene Confers Susceptibility to Inflammatory Bowel Disease: Major progress is being made in understanding the genetic underpinnings of both forms of IBD–Crohn's disease and ulcerative colitis. In 2001, scientists made a landmark achievement when they demonstrated that the *NOD2* gene (also called *CARD15*) confers susceptibility to Crohn's disease. In a recent NIH-supported controlled study of Canadian Crohn's disease patients, scientists subsequently identified *IBD5*, located in part of chromosome 5 (specifically, the chromosomal region 5q31), as a Crohn's disease susceptibility region that contains a number of candidate susceptibility genes. Now, these scientists have replicated the findings of that study in a German population of Crohn's disease patients. In addition, *IBD5* was found to contain one or more likely susceptibility genes for ulcerative colitis. Further analysis revealed that *IBD5* and *CARD15* act independently to confer either risk for (*IBD5*) or clinical manifestations of (*CARD15*) Crohn's disease. The data also suggest that *IBD5* and *CARD15* may act synergistically to promote the development of ulcerative colitis. These findings provide the basis of a model for IBD diseases in which *IBD5* is a general risk factor for IBD, and genes such as *NOD2/CARD15* determine the clinical expression of the disease. Molecular classification of patients with IBD, combined with clinical data, may lead to the identification of patient subgroups and to greater precision in tailoring treatments for IBD patients.

IBD research has experienced tremendous progress in the face of enormous challenges, but much remains to be understood about this set of diseases. The NIDDK is continuing to advance IBD research through its strong support and scientific leadership. The recently established, NIDDK-supported IBD Genetics Consortium is attempting to identify additional susceptibility genes for IBD. To that end, the Consortium is creating a repository of patient data, immortalized cells lines, and DNA samples, and will ultimately be forming an extensive database for analysis. Other recent efforts include an initiative to study in great detail non-endocrine progenitor cells of the digestive tract, including the intestine, which will provide investigators with tools and knowledge to better understand both normal and diseased cells more fully. Furthermore, NIDDK-supported Digestive Diseases Centers with a focus on IBD continue to enhance interdisciplinary research efforts.

Finally, the NIDDK is actively engaged in strategic efforts to enhance IBD research. The statutory Digestive Diseases Interagency Coordinating Committee, which is led by the NIDDK, meets four times yearly to discuss current issues and to coordinate research activities among agencies within the Department of Health and Human Services and extramural organizations. In its April 2003 meeting, the DDICC focused on research advances and needs in IBD. The group discussed the latest advances in research on the intestinal epithelium, the microbiota, and the immune system, and their interactions in disease, as well as predisposing genetic factors and IBD epidemiology. The NIDDK also partners with the Crohn's and Colitis Foundation of America (CCFA) to enhance research in IBD. The Institute will work in partnership with the CCFA to attempt to address the scientific opportunities and hurdles outlined in the CCFA Strategic Plan entitled, "Challenges in IBD Research." These steps toward building a comprehensive understanding of the mechanisms underlying disease pathology, as well as the normal intestinal ecosystem (see "'Good' Bacteria–How Do They Help?"), will provide the springboard for more effective prevention and treatment strategies for IBD.

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"GOOD" BACTERIA—HOW DO THEY HELP?

Many strains of bacteria cause illness. They are unwanted invaders that the immune system must eliminate. However, not all bacteria are unwanted; "good" bacteria live throughout the body with benefit to both host and microbe. Recent studies have shed light on how the "good" bacteria found in the gut are beneficial.

A type of cell found in the gut, the "Paneth" cell, appears to have a significant role in fighting disease. Researchers showed that the Paneth cells in mice produced a molecule, called Ang4, which is important in preferentially attacking harmful, invading microbes. Interestingly, the resident "good" bacteria in the gut were responsible for directing the Paneth cells to make Ang4. Another research team showed that the "good" bacteria, again working through Paneth cells, had an important role in developing the capillary networks found in the small intestine. In the absence of bacteria, these networks–which are important for absorption of nutrients–do not form properly.

In addition to providing insights into intestinal infections, this research is paving the way toward improved understanding of how bacteria and cells interact to guide the formation of new blood vessels–knowledge that could provide the basis for future experimental therapies for intestinal injury and cancer. The significance of appropriate interactions between intestinal cells and bacteria in creating a healthy intestinal immunity was also demonstrated by this research. With this knowledge, researchers have a better perspective on what goes awry in some intestinal diseases.

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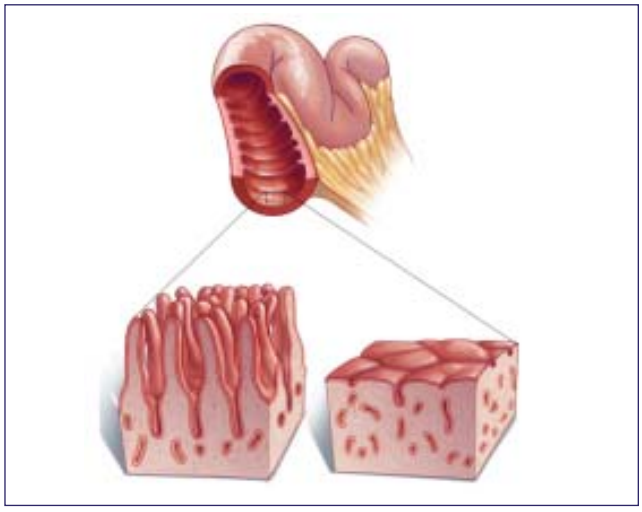
A DIFFERENT KIND OF FOOD FIGHT—MAKING PROGRESS IN CELIAC DISEASE

Celiac disease is an autoimmune, gastrointestinal disorder characterized by intolerance to a protein found in many foods–gluten. Children with the disease have symptoms that can include chronic diarrhea, bloating, anemia, and failure to grow at a normal rate. Early intervention is key to preventing damaging complications of this disease, especially in childhood cases. There is a genetic predisposition to developing celiac disease, and a large majority of patients have at least one copy of a gene, called HLA-DR3. (See also the "Patient Profile," "Celiac Disease: A Family Affair.")

In order to estimate incidence of the disease in the general population, researchers conducted a large, genetic screen of over 22,000 newborns in Denver, Colorado. A subset of the infants were followed for five years to compare disease development in those having zero, one, or two copies of the susceptibility gene. Overall, roughly one percent of all children at age 5 were estimated to have the disease. The children who had either one or two copies of the



This diagram illustrates how the structure of the tissue in the small intestine (top) is altered in celiac disease. Normal tissue from the surface of the small intestine (bottom left) has finger-like protrusions called villi, which are crucial for nutrient absorption. In patients with celiac disease, the villi become smoothed out and no longer function properly (bottom right)–leading to malnourishment and consequent complications. Illustration: Stephen Graepel. Copyrighted by and used with permission from the Mayo Foundation.

susceptibility gene were at an increased risk compared to children without the gene. In addition, the researchers found that females had a higher risk for disease development than males.

These results show that celiac disease is common in a population representative of the general population, and new screening strategies based on the study may help identify children at increased risk. Interestingly, other new studies have been revealing that onset or clinical symptoms of celiac disease is not restricted to children. New knowledge about prevalence of celiac disease in all ages and other pressing scientific and diagnostic issues will be the subject of a scientific conference at the NIH in June 2004.

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TREATING FUNCTIONAL BOWEL DISORDERS

Functional bowel disorders, also called motility disorders, result from poor nerve and muscle function. Symptoms such as gas, pain, constipation, and diarrhea come back again and again, but–unlike intestinal diseases such as IBD, which can have similar symptoms–there are no signs of disease or damage in intestinal tissues. However, the symptoms themselves can be quite debilitating, and limiting to normal life activities. Irritable bowel syndrome (IBS), which specifically affects the colon, is a commonly encountered functional bowel disorder. The cause of IBS is unknown, but diet, emotions, and stress contribute to IBS symptoms. It affects an estimated one in five Americans, but is more common in women. New hope for understanding and treating IBS and other functional bowel disorders is arising from recent research advances.

Comparing Psychological Treatment Strategies for Women with Bowel Disorders: Patients with functional bowel disorders (FBD) have symptoms, such as abdominal pain and altered bowel habits, that can vary from person to person. Patients with moderate to severe symptoms often suffer from greater depression and psychological distress than those with less severe symptoms. A randomized, multi-center clinical trial of 431 women compared the value and utility of different approaches for treating psychological disabilities associated with FBD. In one comparative study, researchers compared two different types of sessions with trained psychologists. One group of women received educational training on their disorder, while the other group underwent cognitive-behavioral therapy (CBT). The latter is a type of therapy that emphasizes the role of using conscious thoughts to develop more effective coping strategies. In a second comparative study, separate groups of patients were treated with either an antidepressant or a placebo. Researchers found that CBT was far more beneficial than education therapy. Antidepressant therapy was equally effective as CBT, but the drug had side effects that prevented some

patients from staying on the medication. The researchers compared subpopulations of patients, such as those with differing severity of illness or depression. Subgroup analysis demonstrated that both treatments were more effective in patients with moderate symptoms than in those with severe symptoms. However, FBD symptoms of patients who also had depression were not improved with CBT or antidepressant therapy. This study suggests that patients with FBD can benefit from certain types of treatment strategies which can, in turn, improve their quality-of-life.

Sex Differences in Neurological Responses to Bowel Distention in IBS Patients: Women are more likely than men to develop IBS, to experience certain IBS symptoms, and to respond differently to pharmacological treatments for the disease. Though the reasons for these sex/gender-related differences are unknown, previous research has suggested that differences may exist between men and women in the brain's response to pain and stress experienced with IBS. Previous knowledge of which areas of the brain process such signals as pain emanating from the pelvic area (where the large intestine is located) or emotions of fear or stress, provided researchers with a number of places to look for differences in brain region activity of female *versus* male IBS patients.

To test for gender differences in the activity of brain areas associated with IBS symptoms, researchers measured blood flow to specific parts of the brain, as a reflection of activity level. Men and women were tested under three conditions: at rest, during inflation of a balloon inserted into the colon to mimic painful bowel distention during IBS, and while anticipating the balloon inflation. They found that, though there were some similarities, clear differences were seen in the activity of certain brain regions during colon distention or even anticipation of distention between women and men with IBS. In response to both distention and expectation of distention, women showed greater activation of emotion-processing areas, while men showed more activity in brain areas involved in pelvic pain.

This study's findings improve our understanding of the unique neurological mechanisms underlying IBS symptoms in female *versus* male patients. Because the cause of IBS is unknown and better treatments are needed, a more sophisticated understanding of the neurological basis of IBS symptoms will help spur the development of more effective treatments for these patients. These findings will be particularly useful as a basis for designing gender-specific therapies that relieve symptoms by targeting specific neural pathways at work in female and male patients.

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STORY OF DISCOVERY

The Art of Liver Transplantation

It was the 2002 Winter Olympic Games at Park City, Utah and the world looked on in awe as 29-year-old American snow boarder Chris Klug competed in the giant slalom race wearing a broken boot held together with duct tape. The crowd cheered as he crossed the finish line. Chris had won the bronze medal with tape securing his boot, but even more amazing, 18 months earlier he had undergone a liver transplant. Chris had spent years training for this event, encountering hurdles, large and small, and now he had medaled. Chris continues in his pursuit for excellence and in the 2006 Winter Olympic Games, he will be aiming for the gold.

Success in clinical research is similar to striving for the gold. It does not come with one major victory, but instead it requires persistent small but steady progress, punctuated with major achievements along the way. One scientist has shown the courage and commitment to perfect liver transplantation therapy in just this manner. Dr. Thomas Starzl, with continued NIDDK support, performed the first human liver transplant in 1963 and has spent the last 40 years perfecting this procedure. The achievements of Dr. Starzl and many other dedicated scientists save the lives of thousands of patients annually who have end-stage liver disease (ESLD).

Liver transplantation in humans was preceded by careful animal studies that enabled researchers to develop and test surgical procedures, and the result is that the procedure is safer and more successful. For example, NIDDK investigators developed a venous-venous bypass technique that reduces excessive blood loss and renal failure that sometimes seriously compromised the health of previous liver transplant recipients.

Preserving donor organs to be used as transplants was another research hurdle. In 1984, an NIDDK grantee developed a preservation solution-called the "UW solution"– that effectively doubled the time a donor liver remains usable, to an average of 12 hours. Donor livers could then be procured from much greater distances and still arrive in a viable state for transplant.

In the late 1950s, animal research provided the foundation for determining that the drug combination of azathioprine and prednisone was the most effective immunosuppressive therapy at that time. Immunosuppressive therapy was greatly enhanced in the early 1980s with the introduction of cyclosporine, first as a single agent and then in combination with steroids. Largely as a result of cyclosporine's arrival, the frequency and success of liver transplant therapy began to grow. Indeed, a 1983 National Institutes of Health Consensus Development Conference concluded that liver transplantation was a therapeutic modality for ESLD.

Now, tacrolimus is the drug of choice. Discovered in 1984, it is effective and has fewer side effects than cyclosporine. Drugs like tacrolimus prevent graft rejection by inhibiting the immune system, but this does not come without a price. An inhibited immune system leaves the body susceptible to opportunistic infections and puts patients at higher risk for cancer. Thus, the drugs that prevent graft rejection can cause serious illnesses themselves.

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Dr. Starzl and his colleagues are now taking a new approach to the concept of graft rejection. Rather than striving to suppress the immune response that threatens graft survival, they are seeking to minimize the patient's dependence on anti-rejection drugs following transplant surgery. Patients are pretreated with a broadly reacting drug before their transplants, and then are treated by tacrolimus monotherapy beginning the day after transplantation. This regimen diminishes, but does not destroy, the immune system's ability to attack the new organ. It also enables the immune cells from the host and the "passenger" immune cells that are transplanted with the donor organ to interact with each other. Eventually, a type of peaceful co-existence develops, imparting a degree of host tolerance to the engrafted organ. At that point, medication is gradually reduced. Weaning from tacrolimus is continued until the patient is receiving a very low dose. Mild graft rejection is allowed; however, if serious symptoms begin to develop, the patient's medication is increased to a higher dose until he or she is ready to begin the weaning process again. This new regimen has been highly successful for patients who have received the treatment. Most are able to reduce their medication, and some take as little as one dose of tacrolimus a week. The timing and dosage of this regimen is based on principles of organ engraftment and acquired tolerance and, therefore, is effective for the transplantation of other organs, as well as the liver.

Although great strides have been made in facilitating liver transplantation, a chronic problem remains. There are far fewer livers available than are needed, and many lives are being lost because of the lack of available donor livers. Therefore, novel approaches to transplantation are being developed to fill this void. In December 2000, the NIDDK held a workshop on Living Donor Liver Transplantion. With this protocol, a donor gives part of his or her liver to an individual with ESLD. Ideally, the partial livers regenerate quickly into complete livers. However, this protocol presents a serious potential risk to the donor. The NIDDK is supporting research to improve the safety and outcomes of living donor transplantation therapy. Another therapeutic approach is the transplantation of liver cells (hepatocytes). This avenue of treatment is particularly suitable for patients with metabolic disorders. With this regimen, liver cells from a donor are infused into to the portal vein of a recipient, take up residence in the patient's liver, and become fully functional. In 1998, a child with Crigler-Najjar syndrome, which causes a build up of serum bilirubin levels, received a hepatocyte transplant. The engraftment improved her condition and lasted 11 months until she was able to receive a liver transplant. Recently, an infant received a hepatocyte transplant for a urea cycle disorder, a condition that results from a missing enzyme normally produced by liver cells. Her condition was also improved temporarily as a result of the transplanted cells.

Dr. Starzl and his colleagues are also exploring genetically-altered pigs as potential organ donors. Pigs normally express the antigen 1,3-galactose (1,3-Gal) on their cells surface. Because this protein is not synthesized in humans, it is the major cause for rejection of pig-to-human liver grafts. Starzl's group developed genetically engineered pigs that no longer make the 1,3-Gal protein by "knocking out" both copies of the pig's 1,3-Gal gene. Without this antigen on their cells surface, the pig organs are much safer to use as donors for human transplants.

Improved surgical procedures, preservation solutions, immunosuppressive drugs, and protocols designed to use the body's natural mechanisms for tolerance are major successes that were achieved because of smaller research accomplishments along the way. These advances, as well as the novel approaches to liver transplantation that are in various stages of development today, are being pursued by dedicated scientists "aiming for the gold," a cure for liver disease.

PATIENT PROFILE

The Traffs

Celiac Disease–A Family Affair

Elizabeth and R.J. Traff say that when Emily was 4 years old they felt they were watching their daughter starve to death in front of their very eyes. "Emily had stick arms and a bloated belly," says Mrs. Traff, "and other than her having had a bad case of the flu, we couldn't figure out what was wrong." A procedure called endoscopy, whereby a thin, flexible optical fiber is inserted down the esophagus, the interior of which can be viewed through or seen on a TV monitor, finally revealed that Emily has celiac disease. Celiac disease is a digestive disease that damages the small intestine and interferes with absorption of nutrients from food. At the time of Emily's diagnosis, the Traffs had never heard of celiac disease or that people who have it cannot tolerate a protein contained in many foods, called gluten. What they also didn't know is that the disease runs in families and, unlike Emily, some people may not have symptoms–yet, they are still at risk for the complications of the disease. These complications range from cancers, such as lymphoma and adenocarcinoma, to osteoporosis, to short stature and seizures. It wasn't until nine years after Emily's diagnosis, and completely by chance, that the Traffs learned that several other members of their immediate family either have the disease or are at risk of contracting it.

Research supported by the NIDDK is discovering that celiac disease may be far more prevalent in the U.S. than previously believed. Once thought to be a pediatric, or children's, disease, epidemiological studies are finding that celiac disease can actually develop in adulthood or remain undiagnosed well into adulthood. People at greater risk of developing celiac disease include those with type 1 diabetes, and researchers continue to uncover other risk factors.

The Traff family. Clockwise from the top: R.J., Elizabeth, Joseph, David, Laura, and Emily Traff.

Facts About Celiac Disease

- People with celiac disease cannot tolerate gluten, a protein in wheat, rye, or barley.
- The disease damages the small intestine and interferes with nutrient absorption.
- Treatment is important because people with celiac disease could develop complications, such as anemia, nutritional deficiencies, short stature (in children) or, rarely, cancer.
- A person with celiac disease may or may not have symptoms.
- Methods of diagnosis include blood tests and biopsy of tissue from the small intestine.

- Because celiac disease is hereditary, family members of a person with celiac disease may need to be tested.
- Celiac disease is treated by eliminating all gluten from the diet. The gluten-free diet is a lifetime requirement.

About Celiac Disease

Because the body's immune system causes the damage in celiac disease, celiac is considered an autoimmune disorder. When a person with celiac disease eats foods that contain gluten, which many foods do, his or her immune system responds by damaging the small intestine. Specifically, tiny fingerlike protrusions, called villi, on the lining of the small intestine become smoothed out and no longer function properly. Nutrients from food are absorbed into the bloodstream through these villi. Without protruding villi to absorb nutrients, a person becomes malnourished, regardless of the quantity of food eaten. This explains why Emily looked emaciated before her diagnosis.

"Knowing what we know now, if someone in a family is diagnosed with celiac disease, it makes good sense to test everyone else in the family for the disease," says Mrs. Traff.

Celiac disease also is a genetic disease, meaning it runs in families. About 10 percent of an affected person's first-degree relatives (i.e., parents, siblings, or children) will have the disease. Unfortunately for the Traffs, their percentage turned out to be much higher. About 9 years after Emily was diagnosed, the family voluntarily decided to take part in an NIDDK-funded study on the familial incidence of celiac disease–and it was fortunate that they did. It was during the course of the study that the family learned that Mr. Traff, as well as then 10-year-old daughter, Laura, both totally symptom-free, actually have the disease, and that the Traffs' younger son, David, has the genetic marker but currently shows no disease.

The Traff's older son, Joseph, is the only one in the family aside from Mrs. Traff who shows no genetic marker. In Laura's case, the blood tests used to detect celiac disease showed particularly troublesome values. At the same time, her villi were in the process of being severely damaged, despite the fact she manifested no symptoms. "Knowing what we know now, if someone in a family is diagnosed with celiac disease, it makes good sense to test everyone else in the family for the disease," says Mrs. Traff.

"The disease appears to be on my side of the family," says Mr. Traff. "My mother has had stomach problems all her life, but she was never diagnosed as having celiac," he adds. "She's now had a blood test and an endoscopy and is waiting for the results of a biopsy for a firm diagnosis. My brother is in the same situation."

Living with Celiac Disease

Emily, now 15, would be the first to tell you that living with celiac disease isn't exactly fun, but after 10 years she's gotten used to her gluten-free diet. "There are lots of foods I can eat, like hamburgers without the bun and French fries," she says. "It's really not that bad. There are a lot worse things than not eating anything with gluten in it." Mrs. Traff offers a slightly different perspective, however. "Emily plays by the rules," says Mrs. Traff, "but try finding something gluten-free to eat!"

After Emily was diagnosed, Mrs. Traff devoted a lot of her time to researching the disease and the impact of gluten, and quickly learned that many of the foods we eat contain the protein. Obvious sources are foods containing wheat, rye, and barley, including most breads, pastas, cereals and processed foods. But there are hidden sources as well, including food additives, preservatives and stabilizers not always clearly marked on processed-food labels. Some medicines and mouthwashes also contain gluten. Mrs. Traff's rule of thumb is "When in doubt, don't eat it."

She also strongly recommends connecting with a celiac support group, especially when the diagnosis is new. "Dealing with all the details of diet can become overwhelming," she says. "To be connected with people who have 'been there, done that' can be a great source of information and comfort."

Mrs. Traff was heartened recently when she picked up a processed-food product in her grocery store that said "gluten-free" on the packaging. She also said that some national restaurant chains now have menus that give information about whether their offerings are gluten-free. "It's good seeing nationally known companies taking these kinds of steps," she says, but adds that much more still needs to be done. Consequently, the local celiac disease support group Mrs. Traff belongs to has gone to several restaurants in her area to educate them about the disease. Mrs. Traff also has visited the cooks in the school cafeteria where her daughters eat to explain what her children can and cannot eat, "and they have cooperated beautifully," she says.

Cost is yet another issue. "It can be expensive to eat gluten-free," says Mrs. Traff. In her experience, a pound of gluten-free pasta, for example, can cost as much as $6.65. But considering the long-range health implications to her family if they do not eat gluten-free foods, she feels it is well worth it.

Recent Findings

Joseph Murray, MD, is an NIDDK-supported researcher at the Mayo Clinic in Rochester, Minnesota, who is conducting a study on the epidemiology and familial incidence of celiac disease. It was through Dr. Murray's study that the Traff family learned that several of their members, previously undiagnosed, have celiac disease. Dr. Murray says that many celiac disease cases go undiagnosed because many physicians are not familiar with the disease or the way it presents itself. "Many people with celiac do not manifest severe symptoms," he says.

Other research appears to support Dr. Murray's findings. It is estimated, for example, that 1 in 4,700 Americans have been diagnosed with celiac disease. However, a study in which random blood samples from the Red Cross were tested for celiac disease markers suggests that as many as 1 in every 250 Americans may have it; more recent studies indicate prevalence may be as high as 1 in 133 across the nation, and even as high as 1 in 100 in children in a major metropolitan area. "We're learning that celiac disease appears to be primarily an urban/suburban phenomenon and more common in Caucasians than in any other ethnic group," says Dr. Murray. More than 90 percent of the diagnoses made in Dr. Murray's study are in Caucasians. "Celiac disease is thought to be rare in Asian and sub-Saharan African ethnic groups though no one knows for sure as those populations have not been subject to detailed study."

According to Dr. Murray, over the past 10 years, because of increased awareness and new and improved blood tests, many more people are being diagnosed. His study also has found patients can be overweight or even obese and have celiac disease, "which flies in the face of it being a malabsorption disease." Celiac disease is also an explanation for anemia and osteoporosis and is linked to people with type 1 diabetes. "We're finding that 30 percent of those being diagnosed with celiac disease are either overweight or obese, that weight loss is only a symptom in half the cases we see, and that the disease affects women more than men two-to-one." Also, Dr. Murray's findings indicate that most recent diagnoses are being made in people 45 years and older.

PATIENT PROFILE

As for the Traffs, they are very grateful that everyone in their family has been tested, and that by eating gluten-free, they can control the disease. “As a result of Emily’s diagnosis 10 years ago, we know how to eat gluten-free,” says Mr. Traff, who, since being diagnosed, has cut back on going out to lunch at work because he feels uncomfortable asking people in restaurants if their food contains gluten or not. “It’s more an annoyance than anything else.” And this is a healthy way to look at it.

The NIDDK fosters research on celiac disease. Research studies solicited by the Institute have yielded insights into the pathogenesis, genetics, and prevalence and diagnosis of celiac disease. Furthermore, many recent findings in celiac disease–including the greater than expected prevalence in the U.S., insights into the underlying causes of disease symptoms, and further characterization of the links between celiac and other autoimmune and digestive diseases–were the topic of a recent meeting of the statutory Digestive Diseases Interagency Coordinating Committee, a federal group led by the NIDDK, that promotes information exchange and agency collaborations geared toward combating digestive diseases. As a result of discussions at this meeting, the NIDDK is planning an “NIH Consensus Development Conference” on celiac disease. The NIH convenes these conferences to address complex issues of medical importance to health care providers, patients and the general public. The goal for the June 2004 conference is to rigorously assess the state of the science and medical practice for celiac disease and to identify the most pressing clinical research questions for pursuit in the near future. Through these efforts, the Institute hopes to reach a better understanding of celiac disease, and to facilitate improved rates of diagnosis and treatment, and the development of prevention strategies for this serious condition.