



Helicobacter pylori adhering to the surface of the gastric mucosa. *H. pylori* are a major cause of peptic ulcer disease.

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Diseases of the Stomach and Small Intestine

SUMMARY OF RESEARCH GOALS

The impact of research on diseases of the stomach and small intestine is epitomized by the discovery of *Helicobacter pylori* and its role in peptic ulcers, which quickly revolutionized the treatment of many, though not all, patients with peptic ulcers. To capitalize on this and other advances, the Commission proposes several research goals to improve understanding of the diverse diseases that affect the stomach and small intestine and to accelerate development of effective therapies. Peptic ulcer disease (PUD) can be triggered by multiple causes in addition to *H. pylori*. Research efforts are needed to understand the mechanisms of ulcer formation and mucosal injury and to develop new approaches to prevention and treatment of ulcers, especially those associated with non-steroidal anti-inflammatory drugs (NSAIDs). Developing effective treatments for diarrhea and other maldigestive/malabsorptive diseases requires better understanding of the fundamental mechanisms of water, nutrient, and electrolyte transport in the intestine. Research on celiac disease and other autoimmune and allergic diseases that affect the digestive tract is needed to uncover the genetic and environmental triggers of such conditions and to improve methods of diagnosis and treatment. Finally, focused research efforts are critical for diseases of unknown origin, such as necrotizing enterocolitis (NEC) and eosinophilic gastrointestinal (GI) diseases, for which few effective treatment options are available.

INTRODUCTION AND BACKGROUND

Diseases of the stomach and small bowel are common and cause significant morbidity, economic hardships, and health consequences. Acid-peptic ulcer diseases alone accounted for an estimated \$2.8 billion in direct costs in 2004. Diarrheal diseases, which are major causes of morbidity and mortality on a global scale, cost the American public close to \$3.0 billion in 1998, notwithstanding the huge indirect costs associated with lost wages and work productivity. Celiac disease, an immune-mediated disorder that primarily affects the GI tract, had been considered a rare disease. However, recent studies suggest that it affects as many as 3 million Americans (roughly 1 percent of the population), indicating that the disease is widely unrecognized across the country. NEC, an inflammatory condition of the distal small bowel and colon leading to bowel necrosis, perforation, and death, affects approximately 7 percent of premature infants weighing less than 1,500 grams; about one-quarter of those infants will succumb to the disease.

Gastroduodenal disease: PUD has a lifetime prevalence of approximately 12 percent in men and 9 percent in women. A major cause of PUD, *Helicobacter pylori* colonizes the stomachs of at least half of the world's population and is a strong risk factor for gastric cancer. Successful treatment of *H. pylori* virtually eliminates the subsequent risk of developing PUD in response to this microbial pathogen. Patients may have ulcers that recur frequently, ulcers that require large doses of medication for healing, or *H. pylori*-negative duodenal ulcers that occur in the absence of NSAIDs. These drugs, which are commonly used for prevention of cardiovascular events and pain, are another important cause of PUD. GI side effects, which are the main factor limiting the use of NSAIDs, include life-threatening upper GI complications (e.g., bleeding, perforation, or obstruction), uncomplicated symptomatic PUD, and other symptoms

(e.g., dyspepsia). The proportion of ulcers due to NSAID use is beginning to approach that caused by *H. pylori*. NSAIDs are the most commonly used medication in the U.S., with regular use by 11 percent of the population and intermittent use by a much greater number of individuals. For this reason, the GI effects of NSAIDs incur a tremendous healthcare burden that is expected to rise as the population ages and the prevalence of arthritis increases. The Zollinger-Ellison syndrome (ZES) is caused by a gastrinoma (tumor of gastrin-secreting G cells), which leads to excessive production of the hormone gastrin, resulting in gastric hyperacidity. ZES may present with severe or refractory peptic ulceration, ulcers in unusual sites, ulcer complications, severe esophagitis, and/or unexplained diarrhea. Other peptic diseases include stress ulcers in critically ill patients, viral diseases in immunocompromised or post-transplant patients, ulcerations associated with cocaine and mesenteric ischemia, and inflammatory bowel diseases (IBD). Although less common, these diseases are often difficult to manage and are, therefore, inadequately treated.

Two paradigm-shifting advances in the understanding and treatment of gastroduodenal disease—the discovery of histamine H2 receptor blockers that could be used to treat peptic ulcers (among other conditions) without surgery and the discovery of *H. pylori* and its causative role in PUD—were recognized by the award of Nobel Prizes in Physiology or Medicine, in 1988 and 2005 respectively.

Diarrheal and malabsorptive/maldigestive diseases: Acute diarrheal diseases are primarily caused by food or infectious agents and, in most cases, are self-limiting. Medical intervention is usually not necessary except in the very young or elderly. Infectious diarrheal diseases on a worldwide basis cause over 2.5 million deaths per year, particularly in children in the first year of life. In 40 percent of cases of chronic diarrheal diseases (lasting more than

2 weeks), the cause cannot be identified and patients are often chronically dehydrated. No effective anti-diarrheal agents are available to treat severe or chronic diarrheal diseases. Similarly, there is an inadequate understanding and treatment of malabsorptive and maldigestive disorders, many of which cause chronic diarrhea, malnutrition, and metabolic abnormalities.

Autoimmune and allergic diseases of the bowel: Celiac disease is an immune-mediated disorder that primarily affects the GI tract of genetically predisposed individuals. The disease is caused by an aberrant immune reaction to gliadin, a gluten protein of dietary grains. It is characterized by chronic inflammation of the small intestinal mucosa that results in atrophy of intestinal villi, malabsorption, and a variety of clinical manifestations, including diarrhea, abdominal cramping, pain, and distention. Untreated celiac disease may lead to vitamin and mineral deficiencies, osteoporosis, and other extraintestinal problems. While there is no cure, considerable progress has been made in understanding celiac disease and in preventing or curing its manifestations by dietary interventions. The strong genetic predisposition to celiac disease is attributed mainly to genetic markers, known as HLA-DQ2 and HLA-DQ8, that are present in affected individuals. Glutens found in wheat, barley, and rye interact with these HLA molecules to activate an abnormal mucosal immune response that is necessary, but not sufficient, to induce tissue damage. Innate immune activation is required to induce activation of intraepithelial lymphocytes, which consequently mediate tissue damage.

Inadequate colonization of the newborn gut with commensal bacteria or a lack of exposure to neonatal infectious agents may result in an increased expression of allergic conditions (e.g.,

food allergy) and autoimmune diseases during late childhood and adulthood due to inadequate development of the mucosal immune system (e.g., lack of oral tolerance). Research suggests that early interaction of colonizing bacteria with the neonatal gut can orchestrate development of the mucosal immune system. The incidence of autoimmune diseases has increased substantially during the last few decades.

Necrotizing enterocolitis: NEC puts affected infants at risk for intestinal morbidity and poor neurodevelopmental outcome. The primary risk factors for NEC appear to be prematurity, bacterial colonization, altered vascular regulation, and enteral feeding. Since these issues are common to all premature infants, it is currently impossible to predict which infants will develop this devastating disease. Mucosal injury is believed to be caused by a breach in the intestinal mucosal barrier, leading to bacterial translocation and activation of an inflammatory cascade. There is also evidence of an exaggerated immune/inflammatory response to pro-inflammatory stimuli. No specific treatment is available, and supportive measures are often inadequate because of the rapid progression of NEC after diagnosis. Despite many advances in the care of premature infants, the incidence of NEC has remained remarkably constant over the past 4 decades.

Eosinophilic gastrointestinal disorders (EGIDs): EGID, originally thought to be a rare condition, has been diagnosed with increasing frequency over the last decade. Clinical manifestations include vomiting, abdominal pain, malabsorption, GI obstruction, and ascites. The cause is unknown, but the disease has been associated with allergic symptoms. The diagnosis of eosinophilic gastroenteritis requires a histologic demonstration of markedly increased numbers of eosinophils in the GI tract.

RECENT RESEARCH ADVANCES

***Helicobacter pylori* infection and resulting peptic diseases**

Eradication of *H. pylori* significantly decreases peptic ulcer risk and likely reduces gastric cancer risk in infected individuals without pre-malignant lesions. However, only a small percentage of colonized persons ever develops symptomatic disease. The identification of certain host and *H. pylori* genotypes that synergistically augment the risk for gastric cancer was an important step that may permit physicians to focus diagnostic and eradication strategies in high-risk populations to reduce the risk of pathologic outcomes.

Bone marrow-derived stem cells and formation of gastric tumors associated with chronic mucosal inflammation

Circulating bone marrow-derived stem cells may contribute to the formation of gastric tumors within *H. pylori*-inflamed mouse gastric mucosa. This concept has opened up new avenues for exploring the pathogenesis of microbially induced gastric cancer, as well as other malignancies that arise within the context of chronic inflammation.

Pathogenesis of Zollinger-Ellison syndrome

Key research advances in ZES are the identification of the *MEN 1* gene product menin, the finding that this protein interacts with numerous transcription factors, and the generation of mouse models of *MEN 1*. This basic research characterizing the *MEN 1* gene complements recent studies demonstrating that ZES within the context of *MEN 1* is frequently due to multifocal duodenal gastrinomas with mutations in specific menin domains. These tumors are difficult to localize and remove, and such patients tend to be more refractory to treating the consequences of hypergastrinemia and hyperacidity.

Cyclooxygenases in the pathogenesis of peptic diseases associated with NSAIDs

The identification of the role that cyclooxygenases (COX-1, COX-2) play in regulating NSAID-induced GI injury led to the development of agents that selectively inhibit specific pathways (e.g., COX-2) in order to reduce GI toxicities associated with the use of traditional non-selective NSAIDs. Although COX-2 inhibitors can reduce side effects in the GI tract, studies have demonstrated an increase in cardiovascular morbidity and mortality associated with these agents. This has reinforced the strategy of combining a potent acid-suppressing agent with NSAIDs in high-risk patients to prevent ulcer bleeding.

Gene defects in diarrheal, malabsorptive, and maldigestive diseases

The major proteins that participate in transport across the intestinal epithelium of several nutrients (e.g., sodium, potassium, chloride, D-glucose, L-amino acid, and heavy metals) have been identified. Some diarrheal, malabsorptive, and maldigestive diseases are now understood to result from genetic mutations in these proteins. These diseases include D-glucose/D-galactose malabsorption, congenital chloridorrhea, congenital sodium diarrhea, Menke's disease, and congenital lactase deficiency. Progress has been made in understanding how these proteins work in cell, experimental, and some animal intestinal epithelial models.

Intestinal regulatory systems, such as enteroendocrine cells, in intestinal digestion and absorption

Malabsorption can result from defects or abnormalities in integration of intestinal functions. For instance, children with a mutation in neurogenin-3, an intestinal transcription factor, fail to develop enteroendocrine cells, which are believed to be essential for paracrine and

juxtacrine regulation of mucosal function. As a consequence, congenital malabsorption plus diarrhea results even when a fat-free diet consisting of oral rehydration solution is consumed. Thus, integration of digestive and absorptive functions is a critical aspect of normal physiology.

The intestinal microflora in health and disease

New technologies to study the normal human intestinal microflora have revealed the complexity and diversity of the enteric microflora, many species of which cannot be cultivated by standard techniques. These advances are redefining our understanding of how luminal bacteria contribute to bacterial overgrowth, intestinal malabsorption or maldigestion, mucosal inflammation, and diarrheal diseases. New research suggests that alterations in composition of the human microflora have a role in obesity.

Improved oral rehydration solutions

Oral rehydration solutions (ORS) have been used effectively to treat acute and infectious diarrheal diseases, reducing deaths from acute diarrhea worldwide from 12 million to less than 2 million per year. In the past several years, the effectiveness and patient acceptability of ORS have been improved by lowering the osmolarity of ORS. Adding poorly hydrolyzable starch (e.g., corn starch) to promote colonic salt and water absorption is an important advance.

Intestinal barrier function in health and disease

Research on the function and regulation of tight junctions has led to a better understanding of their roles in health and disease. Diseases of junctional proteins can lead to changes in localization or function, which affect cell polarity, localization of plasma membrane

proteins, and permeability of the paracellular pathway. In addition, changes or defects in tight junctions are important mechanisms that can underlie or contribute to microbial pathogenesis and mucosal inflammation (e.g., IBD).

Pathogenesis and management of celiac disease

Intestinal intraepithelial lymphocytes, IL-15, and natural killer receptors have been recognized as key mediators of the effector phase of celiac disease and the development of enteropathy. This finding suggests that therapies designed to block specific innate immune responses can be developed to treat celiac disease.

Because the human intestinal tract is deficient in the secretion of prolyl endopeptidases, digestion of dietary gluten in the small intestine is incomplete. As a consequence, relatively large proline-rich gluten peptides are generated that can uniquely bind to the HLA-DQ2 and HLA-DQ8 major histocompatibility proteins with subsequent activation of immune mechanisms leading to tissue damage. Thus, strategies to supplement diet with enzymes that can fully digest these large gluten peptides are being developed as a useful adjunct to the gluten-free diet in the treatment of celiac disease.

Many gluten peptides can activate celiac disease, their proportion and types determined by the specificity of tissue transglutaminase for deamidating those peptides. This has led to an algorithm for predicting candidate disease-activating peptides in the dietary grains known to cause celiac disease. This information can be used to uniquely engineer grains deficient in potentially disease-activating gluten peptides.

Prevalence and phenotype of celiac disease

For many years, celiac disease was thought to be uncommon in this country. However, several

studies have now shown that celiac disease is very common, estimated to afflict about 3 million people in the U.S. or about 1 in 133 people. It is estimated that 1 in 22 individuals who have a first degree relative with the disease also has celiac disease. Celiac disease can present in different ways, making diagnosis difficult in some individuals. The basis for different clinical presentations or phenotypes is poorly understood.

Intestinal immaturity

Prematurity is the greatest risk factor for NEC rather than any particular insult, which suggests that the fundamental issue may be intestinal immaturity. Studies have focused on identifying aspects of intestinal immaturity that explain the unique susceptibility of the premature infant to NEC. The exquisite susceptibility for the initiation of inflammation in the immature intestine compared to the mature intestine due to inadequate regulation of NF- κ B signaling provides an explanation for the high prevalence of NEC in premature infants compared to more mature individuals. In addition, immature intestinal vascular regulation contributes to this disease.

Pathogenesis of necrotizing enterocolitis

The intestinal microflora and its relationship to the mucosal immune system are emerging as important components of pathophysiologic processes that cause acute disease, such as NEC in the premature infant, as well as

long-term autoimmune and allergic disorders, such as type 1 diabetes, IBD, and asthma. Innate immune and genetic mechanisms also contribute to the risk of developing NEC. TLR4 on intestinal epithelium contributes to activation of inflammation in NEC. Single nucleotide polymorphisms have been identified in key inflammatory mediator genes that could contribute to ethnic disparity in various neonatal outcomes, including NEC.

Several clinical studies have shown efficacy of probiotics in treating NEC in the premature infant. Other agents, including platelet-activating factor acetylhydrolase, epidermal growth factor, heparin-binding epidermal growth factor, and erythropoietin, have been tested in animal models of NEC and also show promise as therapeutic candidates for this disease.

Eosinophils in enteric diseases

An accumulating body of clinical evidence supports a pro-inflammatory role for eosinophils as damaging white blood cells in intestinal diseases. Eosinophils accumulate in the GI tract during allergic inflammation, acid injury, infections, and IBD in response to chemokines. Involvement of eosinophils in altering intestinal motility and disrupting the intestinal barrier with subsequent diarrhea and protein loss is likely related to release of specific mediators, including granule proteins and other biologically active mediators.

Research Goal 8.1: Understand mechanisms and improve treatment of *H. pylori* diseases.

H. pylori has been categorized as a Class 1 carcinogen for stomach cancer and is a major risk factor for PUD. Several important issues remain unresolved, and there have been reports that *H. pylori* is inversely related to other diseases, such as esophageal disease and asthma. Research now must be directed toward obtaining a better understanding of the cellular and molecular basis of *H. pylori*-associated diseases, particularly in defining the role of chronic mucosal inflammation. Knowledge of the pathogenesis of *H. pylori* will enable the rational development and testing of novel therapeutics and optimization of existing treatments. Importantly, with the falling prevalence of *H. pylori*, the proportion of idiopathic ulcers is likely to increase; the cause of this significant minority of ulcers is a new focus of investigation.

Objectives:

- Profile the microbial, molecular, cellular, and epidemiological features of *H. pylori*-induced gastric carcinogenesis and PUD to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.
- Define the relationship between *H. pylori* and GERD complications and assess the consequences of prolonged PPI use.
- Develop noninvasive technologies to screen for *H. pylori*-induced pre-malignant lesions.
- Develop prevention strategies based on mechanisms of *H. pylori*/host interactions that lead to pre-malignant/malignant lesions and evaluate their effectiveness in at-risk populations.

Research Goal 8.2: Reduce and prevent NSAID peptic diseases.

Peptic diseases caused by NSAID usage could be reduced or prevented entirely by identifying at-risk patients, improving patient and physician education on the potential complications of NSAIDs, and developing more effective and safe countermeasures. To reach this goal, research is needed to understand the risks associated with long-term use of NSAID and PPIs and to identify the populations that are most likely to suffer adverse effects. The causes of idiopathic ulcers may be heterogeneous. A careful assessment of the proportion of such ulcers that are due to surreptitious NSAID use would aid in the identification of at-risk individuals. Researchers have already demonstrated that inhibition of COX-1 is not sufficient for abrogating GI damage induced by NSAIDs. Furthermore, 5-lipoxygenase inhibitors appear to protect against NSAID-induced injury. By exploiting these and other advances, better drugs to treat NSAID-associated acid-peptic diseases or reduce the risk of complications can be developed.

Objectives:

- Define pathogenic mechanisms that regulate NSAID-induced injury.
- Develop population-based screening and pharmacogenomic approaches for identification of individuals at risk for NSAID-induced peptic ulcer disease as a basis for subsequent intervention.
- Educate patients and physicians regarding risk factors and improve adherence to appropriate strategies for decreasing NSAID-associated GI complications.
- Determine long-term risks of chronic NSAID usage and PPI therapy, including the risk of neoplasm.
- Design anti-inflammatory agents of comparable or higher efficacy to traditional NSAIDs, but which lack traditional GI side effects and cardiovascular toxicity.

¹⁵ Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.

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Research Goal 8.3: Define the genetic, bacterial, and host factors that regulate epithelial and inflammatory cell responses to injury in gastric mucosa.

The mechanisms that underlie gastric mucosal responses to pathogens and injurious agents are incompletely understood. By defining the genetic, molecular, and cellular bases for gastric mucosal injury and repair, novel therapies can be developed to prevent or more rapidly recover from acid-peptic diseases.

Objectives:

- Elucidate genetic, bacterial, and host factors that regulate or affect gastric mucosa response to pathogens and stress.
- Understand mechanisms of mucosal cytoprotection and wound healing.
- Develop novel therapies that promote mucosal cytoprotection and wound healing.

Research Goal 8.4: Understand the basis of rare gastric cancers, develop effective measures for earlier and more accurate diagnosis, and develop effective treatment strategies. (See also Goal 4.12.)

More information regarding the carcinogenic process of less common gastric cancers, such as gastrinomas, would accelerate the development of strategies for early diagnosis and for more effective treatment. For example, improved understanding of the correlation between mutations in the *menin* gene and patient phenotypes would help in the development of effective treatment strategies that are tailored to subgroups of patients. Identifying other genetic loci that regulate the development of gastrinomas would also improve the classification of patient and disease sub-types.

Objectives:

- Develop more sensitive methods for detecting gastrinomas and metastases.
- Develop a reliable mouse model of gastrinoma that mimics features of ZES, specifically duodenal tumors.

Research Goal 8.5: Determine the genetic, molecular, and integrated physiologic bases of intestinal water, nutrient, and electrolyte transport.

Despite the prevalence and other impacts of diarrheal diseases, their disease mechanisms are not well understood. Experimental models to probe the genetic, molecular, and integrated physiologic bases of intestinal water, nutrient, and electrolyte transport are inadequate. Most knowledge has been gained at the cellular and membrane level, where key transporter molecular and their associated regulatory signaling pathways have been partially elucidated. Currently available molecular and genetic approaches make it possible to unravel the complexities of protein and molecular interactions involved in enterocyte transport, although the cost of using these technologies may be prohibitive. Noninvasive methods are needed to study *in vivo* the function and regulation of intestinal absorptive and digestive processes, including visualizing the signal transduction pathways and genes involved in normal absorption/digestion and their integration (in humans and animals). This line of research will lead to better understanding and treatment of diarrheal diseases, particularly chronic diarrhea, for which treatment is often purely symptomatic and limited.

Objectives:

- Identify and characterize proteins involved in intestinal transport function, such as fatty acid transport proteins and transport proteins in the basolateral membrane of sodium absorptive cells involved in moving amino acids, sodium, chloride, or heavy metals into blood, as well as

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signaling molecules and accessory proteins that regulate the activity, expression, trafficking, membrane abundance, and degradation of these transport proteins.

- Understand the processes that allow coordination of motility, absorption, and secretion in the intact intestine of animal models and humans. Determine how changes in sodium absorptive and chloride secretory processes are integrated with changes in tight junctions.
- Determine the proteome of the intestinal sodium absorptive cell and chloride secretory cell, including the subcellular proteome of brush border and basolateral membrane under normal conditions and in diarrhea and malabsorption.
- Characterize the effects of knocking out enteroendocrine cells on the development of the gut and on integrative aspects of absorptive, secretory, and digestive functions of the intestine. Determine how maldigestive states affect normal gut development and differentiation of the genes involved in nutrient digestion and transport.
- Identify bacteria that are present in the normal human small intestine and colon and the changes that occur in bacterial overgrowth, Crohn's disease, microscopic colitis, eosinophilic enteritis, celiac disease, other malabsorptive diseases, lactase deficiency, and obesity.
- Determine the contribution of paracellular transport of luminal materials to intestinal disease, characterize how tight junctions limit specific molecule movement, and understand the integration of cellular and paracellular movement and regulation of movement.

Research Goal 8.6: Improve treatment, prevention, and diagnosis of malabsorptive and diarrheal diseases.

Clinically, the prevalence and impact of acute diarrheal diseases on the elderly must be

ascertained. Improvements are needed in treatment, prevention, and diagnosis of malabsorptive and diarrheal diseases. Developing noninvasive methods to study normal digestive and transport processes, as well as their regulatory systems and integration, is crucial for research in this area. Likewise, new approaches to studying patients with these conditions would enhance our understanding of small bowel bacterial overgrowth and diarrheal, maldigestive, and malabsorptive disorders. Finally, research is needed to understand the causes, pathophysiology, and treatment of chronic diarrheal diseases and to develop clinically useful imaging and diagnostic technologies.

Objectives:

- Determine the causes of chronic diarrheal diseases in the 40 percent of patients in whom no specific cause is identified; it is expected that some will be due to polymorphisms and/or mutations in intestinal transporters. Determine the epidemiology of acute diarrhea in the elderly, including mortality.
- Develop preventive measures to limit the incidence of acute diarrheal diseases. Evaluate the role of non-hydrolyzable starch-based ORS in treatment of acute diarrhea in adults and children in developing countries and the U.S.
- Develop clinically useful imaging and diagnostic techniques to examine digestive processes and abnormalities in diarrheal and malabsorptive diseases.
- Test new anti-chloride-secretory and pro-sodium-absorptive drugs in animal models of acute diarrheal diseases. Conduct clinical trials to test these agents in patients with acute diarrhea.
- Develop gene therapy targeting intestinal epithelial cells and pharmacologic agents capable of blocking or augmenting pathways that control intestinal gene expression as part of future treatment strategies for chronic diarrheal and malabsorptive/maldigestive diseases.

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Research Goal 8.7: Understand pathogenic mechanisms of celiac disease, autoimmune diseases, and allergic diseases of the digestive system.

Identification of molecular pathways supporting the critical role of innate immunity has transformed our understanding of the pathogenesis of celiac disease. It is now evident that the interplay between adaptive and innate immunity is critical at all steps of the disease. Furthermore, several observations suggest that transglutaminase is in an inactive state in the intestinal mucosa of patients with the disease. The events leading to transglutaminase activation remain poorly understood. Finally, the role of antibodies and immune complexes in initiation and development of celiac disease have not been sufficiently investigated. Our understanding of genetics, host responses, and tissue injury in response to gluten has increased substantially, but is far from complete. A major limitation in studying celiac disease is the lack of suitable animal models.

A good understanding of disease pathogenesis in autoimmune and allergic disorders of the bowel is lacking. Potential contributors to these diseases that warrant further exploration include risk factors, gut development, innate and adaptive immunity, the enteric microflora, and intestinal barrier function.

Objectives:

- Define the early innate events and the interplay between innate and adaptive immunity in celiac disease pathogenesis.
- Elucidate the events leading to transglutaminase activation and define its role in celiac disease pathophysiology, both as an autoantigen and as a modifier of toxic gluten peptides.
- Define mechanisms and events that link the generation of large gluten peptides and the ultimate development of pathogenic T cell populations.
- Define the role of antibodies and immune complexes in celiac disease.
- Define the potential role of intestinal microflora in the pathogenesis of celiac disease and autoimmune and allergic disorders of the bowel.
- Define signaling pathways (e.g., protease, MLCK, enteric toxins, cytokines) that are involved in the regulation of intestinal permeability under physiologic and pathophysiologic conditions.
- Distinguish between the effects of the IL-23 and IL-12 pathways in the pathogenesis of chronic GI inflammation.
- Determine the basis of refractory celiac disease.

Research Goal 8.8: Improve screening, diagnosis, prevention, and treatment of celiac disease and of autoimmune and allergic disorders of the bowel. Characterize and define the mechanisms underlying the association of celiac disease with autoimmune and neurological diseases. (See also Goal 2.11.)

Celiac disease is common, but often unrecognized until severe enteric and systemic complications occur. Furthermore, the clinical presentations of celiac disease are diverse and may be linked to different effector mechanisms. For instance, immune complexes may underlie the pathogenesis of dermatitis herpetiformis and gluten-associated neurological diseases, whereas pathologic T cells mediate epithelial cell destruction and enteropathy. In addition, subclinical presentations of celiac disease remain poorly characterized. In particular, several lines of evidence suggest that the presence of anti-transglutaminase antibodies does not imply the presence of intestinal lesions and enteropathy. Conversely, gluten-induced innate events may lead to epithelial cell alterations associated with clinical symptoms in the absence of anti-transglutaminase antibodies. Finally, celiac disease is strongly associated with other organ-specific autoimmune diseases, particularly type 1 diabetes. The molecular mechanisms underlying

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this association remain poorly understood. Many physicians and medical staff members are unaware of the prevalence and clinical manifestations of celiac disease. A better understanding of the seemingly protean nature of clinical, histological, and immunological presentations of celiac disease will help improve the diagnosis and treatment. Novel and effective therapeutic and preventive strategies are now possible through the insights gained over the past few years of research on disease pathogenesis.

Allergies and hypersensitivity to food are common, yet poorly understood. In some cases, allergies to foods, such as nuts or shellfish, can be life-threatening and require immediate medical attention. Molecular and immune mechanisms that underlie food allergies are not well understood and are inadequately studied.

Objectives:

- Develop a more complete understanding of the pathogenesis of celiac disease, including the role of immune, epithelial, microbiological, environmental, and host factors, as well as its relationship to other autoimmune diseases.
- Identify novel biomarkers, including additional genetic risk factors, to predict the development of autoimmune disease in high-risk patients and to determine severity of illness and response to treatment.
- Identify environmental triggers of celiac disease.
- Identify new, noninvasive methods to diagnose celiac disease.
- Develop non-dietary methods to treat celiac disease.
- Establish the safety/efficacy and benefits of therapeutic interventions that improve intestinal barrier function in patients with autoimmune diseases and identify the autoimmune pathologies (GI and non-GI) that may benefit from such interventions.
- Identify the mechanisms underlying food allergies and develop simple and accurate tests to identify food allergy or hypersensitivity.

Research Goal 8.9: Understand the pathogenesis of necrotizing enterocolitis and the unique susceptibility of the premature infant, including genetic susceptibility, microflora, and immune/inflammatory processes.

The exquisite susceptibility for inflammation of the immature intestine compared to the mature intestine provides an explanation for the high prevalence of NEC in premature infants compared to more mature individuals. The intestinal microflora and its relationship to the immature mucosal immune system are emerging as important components of pathophysiologic processes that cause acute disease, such as NEC, in the premature infant, but may also play a role in intestinal maturation. Several studies suggest that manipulation of the intestinal microflora with probiotics is beneficial. Despite a paucity of information on deleterious side effects, there is concern that introducing live microbes might result in long-term complications. Studies have suggested that Toll-like receptor (TLR) ligands or other non-live microbial components provide benefits similar to those of live bacteria without deleterious effects, but additional investigation is needed.

Objectives:

- Develop models of immature gut relevant to the development of NEC.
- Investigate the development of intestinal host defense mechanisms and the intestinal immune system relevant to NEC.
- Define normal patterns of bacterial colonization in the healthy premature infant relevant to NEC.
- Understand the role that appropriate microbial balance plays in intestinal development.
- Identify mechanisms responsible for probiotic effects on acute gut injury in premature infants.

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Research Goal 8.10: Develop novel predictive, therapeutic, and preventive approaches for necrotizing enterocolitis.

Although several compounds have recently shown promise in the prevention of NEC in rat and mouse models of the disease, many hurdles remain to testing these agents in human infants. Nonetheless, several agents warrant further investigation in clinical settings. Development of predictive biomarkers, including polymorphisms or other parameters, for at-risk infants is a priority. Improved understanding of predisposing genetic or other biomarker traits will enhance identification of at-risk infants and could lead to improved approaches for preventing and treating this disease.

Objectives:

- Complete phase I and phase II trials in the U.S. of promising therapeutic interventions to assess tolerability and dosing strategy in premature infants, including platelet-activating factor acetylhydrolase, probiotics, and factors found in human milk.
- Develop other novel therapies or preventive measures based on discoveries made in understanding NEC pathophysiology and causes.
- Investigate the mechanisms behind and possible interventions to prevent the poor neurodevelopmental outcomes of infants with NEC.
- Investigate the role in NEC development of clinical practices, such as the use of H₂ blockers, opioids, indomethacin, umbilical catheters, treatment of patent ductus arteriosus, and feeding patterns.
- Develop programs to encourage breast milk feeding of premature infants.

Research Goal 8.11: Determine the genetic bases, mechanisms, natural history, and clinical phenotypes of eosinophilic gastrointestinal disorders and identify/develop novel therapeutic compounds.

It is now recognized that eosinophils play an important role in inflammatory diseases of the upper GI tract. However, the mechanisms by which eosinophils disrupt normal GI physiology and cause disease are incompletely understood. Defining genetic profiles, understanding the natural history of disease, and developing more specific and effective treatments for EGIDs are critical research goals.

Objectives:

- Define the genetic bases, epidemiology, and natural history of EGIDs.
- Define clinical phenotypes of EGIDs (e.g., allergic, non-allergic, or autoimmune) and develop novel animal models and reagents to study eosinophilic GI inflammation.
- Define cellular and molecular pathways that regulate eosinophil-dependent tissue remodeling.
- Identify and develop novel agents for treatment of EGIDs, such as anti-IL-5 antibody, anti-CCR3 receptor antibody, and imatinib.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Animal models: Development of robust animal and cell models would accelerate scientific progress on both normal gastric and small intestinal physiology, as well as the pathophysiology underlying a wide spectrum of diseases that affect these organs. Research areas that would benefit from experimental models that faithfully replicate human disease include *H. pylori*-induced gastric cancer and ZES, intestinal transport, malabsorption, maldigestion, celiac disease, autoimmune and allergic diseases of the bowel, and NEC. In addition, development and optimization of animal models to study infection, morphologic interpretation of lesions, imaging technology, basic cellular processes such as endocytosis, migration, and ion transport in intestine, and drug testing will foster innovative research approaches to understand and treat GI diseases. Related resources, such as improved organ cultures, organotypic culture technologies, and *H. pylori* strain repositories, would also strengthen the field.

Clinical research collaboration: For less common diseases (e.g., gastrinomas, genetic diarrheal disorders) or complex disorders (e.g., dyspepsia, celiac disease, IBD, NEC), single institutions lack sufficient numbers of cases, biospecimens, research resources, or therapeutic capabilities. The establishment of multicenter, systems biology-based consortia or networks of healthcare professionals to share materials and information and increase statistical power would accelerate research in these diseases. For example, the lack of information on cost-effective prevention of *H. pylori* or NSAID-induced injury could be addressed through interdisciplinary, population-based, endoscopic, multi-institutional studies to identify *H. pylori*-infected populations at greatest risk for gastric cancer and to determine the prevalence and natural

history of pre-malignant lesions. Mechanisms to coordinate research and management of a range of diseases (e.g., rare gastric tumors, ZES, dyspepsia, chronic diarrheal and malabsorptive diseases, NEC, celiac disease, and eosinophilic gastroenteritis) would secure the critical mass of cases needed for scientific advancement. Such multicenter networks could pool biosamples and patient data and implement guidelines for clinical practice. Small conferences would support clinical and scientific interactions that could spark innovative approaches to research on these diseases.

Central research resources: The establishment of centralized resources, including databases, patient registries, and biosample repositories, would support and facilitate multicenter collaborations. The creation of databases, with an emphasis on enrollment of minority gastric cancer patients, and specimen and tissue banks would fill an important gap. Large-scale biology approaches could be developed to identify protein-protein interactions as well as pH and calcium homeostasis within sodium-absorptive, chloride-secretory, and enteric endocrine cells during digestion and in diarrheal diseases. Similarly, development of centralized repositories of clinical data and samples (e.g., serum, intestinal tissue, cDNA) from celiac disease or eosinophilic gastroenteritis patients could be used by investigators across the country to gain insights on the pathogenesis of these diseases and to explore alternative treatments. A similar repository for autoimmune patient samples or databases on families with high incidence of autoimmune diseases would serve as valuable resources for clinical and basic science investigators in the field. Indeed, research on many diseases of the stomach and small intestine would benefit from the availability of centralized, accessible resources for patient samples and data.

Physician communication and education:

Inadequate interaction and communication occurs between adult and pediatric clinicians who treat diseases of the stomach and small intestine. Small conferences could promote interactions between adult and pediatric clinicians to define the natural history of these diseases. In addition, there is poor adherence to guidelines or “best practices” (e.g., protective strategies in high-risk NSAID users) in treatment of acid-peptic diseases. Programs could be developed that determine causes, make appropriate recommendations, develop mechanisms to disseminate recommendations, assess whether recommendations are being followed, and assess alterations in outcomes (quality-of-care). Because celiac disease is so prevalent but under-recognized, educational campaigns, such as the NIH Celiac Disease Awareness Campaign, have the potential to increase awareness of this disease among healthcare professionals.

Innovative technologies: Experimental tools and models to study gastric and intestinal epithelial physiology and diseases, including peptic diseases, *H. pylori* pathogenesis, diarrhea, malabsorption, development, inflammation, and pediatric disorders are lacking. Investment in infrastructure to develop proteomic approaches to study GI disease would promote progress across the field. The development of new methods to target epithelial cells or GI tissues with siRNA,

expression vectors, or integrative models of gut absorptive and digestion function in humans would open up new avenues of research. Technology and scientific methods for evaluation of microbial ecology are rapidly emerging, but communication between basic scientists developing the technology and clinical scientists who are able to bring these technologies to the patient could be enhanced. Finally, refinement of genomic and proteomic techniques to identify biomarkers using human intestinal samples would be useful in many intestinal diseases, including NEC.

Drug development: Many intestinal diseases lack effective therapies. Therefore, new drug development, which is an expensive and time-consuming endeavor, could benefit from collaboration between academia and the pharmaceutical and biotechnology industries. For example, the dearth of anti-diarrheal drugs could be addressed by developing programs, possibly through partnership with industry, to better understand diarrheal pathogenesis and to develop novel therapeutic compounds. High-throughput screening of anti-diarrheal drugs that inhibit chloride secretion and/or stimulate sodium absorption could result in the identification of promising compounds. Similarly, collaboration with industry to develop specific microbes (probiotics) or microbial products that stabilize the intestinal mucosal immune system and mutual funding of multicenter trials could accelerate the search for therapies for NEC.