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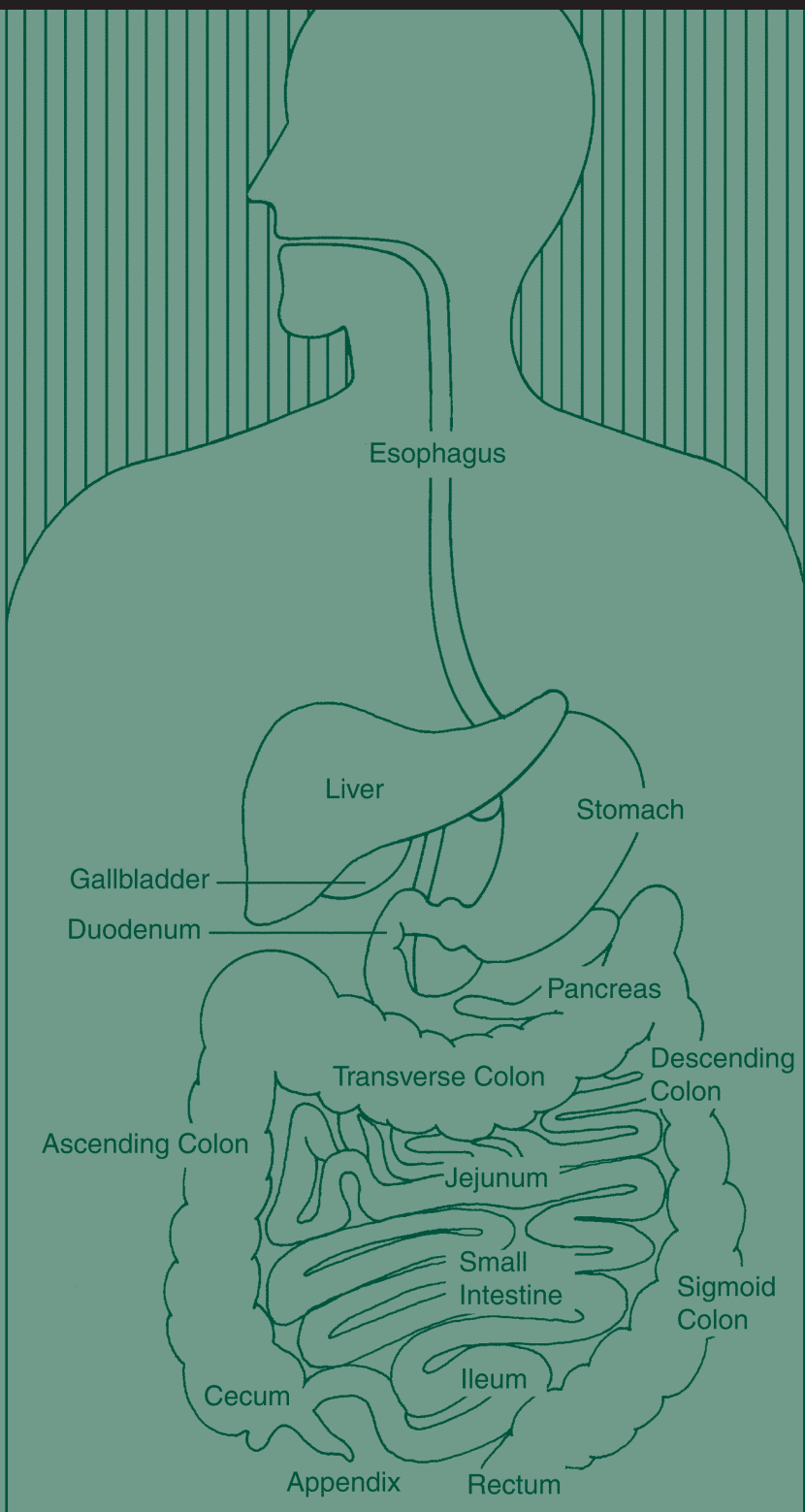
Opportunities and Challenges in Digestive Diseases Research:

Recommendations of the National Commission on Digestive Diseases



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Recommendations of the National Commission on Digestive Diseases

U.S. Department of Health and Human Services
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Executive Summary

BURDEN OF DIGESTIVE DISEASES IN THE UNITED STATES

The digestive system can be affected by a wide diversity of acute and chronic diseases or conditions that, collectively, place a substantial burden on the U.S. healthcare system. At least 60-70 million Americans are affected each year by digestive diseases at a cost that exceeds $100 billion in direct medical expenses. Annually, about 10 percent of hospitalizations and 15 percent of in-patient hospital procedures are attributed to the treatment of digestive diseases. An additional 105 million visits to doctors' offices related to digestive diseases occur each year. These diseases are associated with significant mortality, morbidity, and loss of quality of life, and they frequently impact patients' ability to work or engage in everyday activities. More than $44 billion in indirect costs from disability and mortality are associated with digestive diseases each year. Digestive diseases in general can affect individuals of any age, race or ethnicity, gender, or socioeconomic status, although some diseases disproportionately affect certain populations. All of these factors provide opportunities and challenges for the National Institutes of Health (NIH) as it develops and supports research programs aimed, ultimately, at reducing the significant public health burden of digestive diseases.

NATIONAL COMMISSION ON DIGESTIVE DISEASES

The National Commission on Digestive Diseases was chartered by Elias A. Zerhouni, M.D., Director of the NIH, on July 26, 2005, in response to congressional report language accompanying the FY 2005 appropriations bills in the House and Senate for the Departments of Labor, Health and Human Services, and Education, and Related Agencies. The Commission was tasked with reviewing the state of the science in digestive diseases research and developing a 10-year plan for digestive diseases research that is consistent with the NIH mission and aimed at improving the health of the Nation through research. The Commission was comprised of 16 members, including academic researchers, medical professionals, and patient advocates, who were appointed by the NIH Director after a public nomination process. In addition, 22 representatives of NIH Institutes and Centers, as well as other Federal agencies involved in digestive diseases research, served as *ex officio* members of the Commission. Stephen P. James, M.D., Director of the Division of Digestive Diseases and Nutrition of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, chaired the Commission. Working groups composed of experts in diverse areas of digestive diseases research were formed to aid the Commission in identifying major scientific advances and formulating high-priority research goals.

This report, entitled *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*, presents the Commission's long-range plan for digestive diseases research. The Commission offers recommendations in many broad areas of scientific inquiry of relevance to digestive diseases, including fundamental biology of the digestive system, as well as disease-oriented research topics, such as: epidemiology; environmental factors; genetics; mechanisms; diagnosis; causes; treatments; behavioral, social, and psychological factors; health disparities; prevention; and cures. The Commission developed specific research goals in each of the following 12 scientific topic

areas: research on the basic biology of the digestive system; functional gastrointestinal disorders and motility disorders; infections of the gastrointestinal tract; cancers of the digestive system; inflammatory bowel diseases; intestinal failure and regeneration, nutritional disorders and support, surgically modified gut, and transplantation; diseases of the oropharynx and esophagus; diseases of the stomach and small intestine; diseases of the colon and rectum; diseases of the pancreas; diseases of the liver and biliary system; and bioengineering, biotechnology, and imaging. In addition, the Commission identified a set of high-priority, common themes for which coordinated research planning efforts would accelerate progress across the digestive disease research field by fostering the development and utilization of state-of-the-science technologies, tools, and resources to increase fundamental knowledge, improve translation of research advances into applications for human diseases, and ensure a robust pipeline of talented researchers focused on the challenges of digestive diseases. Collectively, the Commission's recommendations will provide scientific direction for the NIH and all parties engaged in digestive diseases research as they address opportunities and priorities in digestive diseases research over the next decade.

NIH SUPPORT FOR DIGESTIVE DISEASES RESEARCH

NIH Funding and Coordination of Digestive Diseases Research

Twenty NIH Institutes, Centers, and Offices support digestive diseases research on a variety of topics with a total expenditure of more than $1.2 billion in FY 2007. The NIH research portfolio encompasses basic, translational, and clinical research and training on the digestive system for normal states and disease conditions and supports extramural researchers and institutions, as well as intramural laboratories. To aid in the development of the recommendations in this research plan, lists of grants and other awards comprising the NIH portfolio for digestive diseases were provided to members of the Commission and to each working group.

In addition to the direct funding of digestive diseases research, the NIH coordinates research programs within the agency and with other Federal agencies with an interest in digestive diseases through the Digestive Diseases Interagency Coordinating Committee (DDICC). The DDICC brings together representatives from multiple NIH Institutes and Centers that fund digestive diseases research, as well as from other agencies, including the Agency for Healthcare Research and Quality, the Food and Drug Administration, the Department of Defense, the Centers for Disease Control and Prevention, the Department of Veterans Affairs, the Health Resources and Services Administration, and the Department of Agriculture. The NIH also promotes communication and collaboration within the digestive diseases research community through the support of conferences and workshops on relevant topics. Finally, the NIDDK-led National Digestive Diseases Information Clearinghouse provides informational materials and other resources with the goal of increasing knowledge and understanding of digestive diseases within the healthcare community and the general public.

Advances in Digestive Diseases Research

Digestive diseases research supported by the NIH and other public and private organizations has resulted in many breakthrough discoveries that have advanced our understanding of digestive system biology and function, as well as improved the health and quality of life of many people with digestive diseases.

Examples of research advances include:

- Molecular signaling pathways have been uncovered in intestinal crypt progenitor cells that are responsible for continual regeneration of the intestinal lining. Understanding these pathways gives researchers new insights into the genetic basis of colorectal cancer, as well as processes such as normal intestinal development and inflammation.

- Researchers have discovered that neural stem cells persist in the gut after birth. Stem cells from other sources also may have potential for generating replacement neurons in the gastrointestinal (GI) tract. Stem cell research holds promise for future clinical applications in digestive disease therapy.

- The development and licensing of two rotavirus vaccines is an important advance in the prevention of rotavirus infections, the leading cause of severe diarrheal disease and dehydration in infants and young children. Similarly, research to develop and test vaccines for hookworm, schistosomiasis, and amebiasis has the potential to make a global impact on the prevention of these infectious diseases.

- New endoscopic imaging techniques have improved detection of a variety of cancers in high-risk patients, such as squamous esophageal cancer, pancreatic ductal and other cancers, and cancers of the GI lumen. Research to discover genetic risk factors for GI cancers has enabled better risk assessment of individuals with a family history of these cancers.

- Progress has been made in identifying genes that increase susceptibility to inflammatory bowel diseases. By studying the mechanistic processes associated with these genes, researchers can develop better models of disease risk, improve methods to predict the course of disease, and develop more targeted therapies for inflammatory bowel diseases.

- Advances in surgical techniques to lengthen the intestine have enhanced the management of infants and children with refractory short bowel syndrome. Intestinal lengthening procedures such as serial transverse enteroplasty and the Bianchi procedure lead to improved intestinal function and nutrient absorption in these patients.

- Risk factors for Barrett's esophagus are being better defined. Researchers are finding that this disease is not as closely associated with chronic heartburn symptoms as once thought. Obesity and central adiposity, in particular, appear to be important risk factors for Barrett's esophagus. New high-resolution imaging techniques are being developed that have the potential to identify early cancers in these patients.

- The identification of the microbe *Helicobacter pylori* as a cause of peptic ulcer disease quickly led to the use of antibiotics to effectively treat ulcers. Likewise, research on the role of cyclooxygenases in non-steroidal anti-inflammatory drug (NSAID)-induced GI injury led to the development of new strategies to reduce the GI toxicity associated with some NSAIDs and prevent ulcer bleeding in high-risk patients.

- Researchers using modern genetic techniques have discovered that the human gut microflora are far more complex than once thought. The feces of healthy subjects contain thousands of bacterial species, most of which are novel, uncultivated organisms. Research to characterize the relative abundance of different microbes in obese and lean individuals could lead to the development of techniques to manipulate the microflora as a means to alter body weight.

- Progress in endoscopic ultrasound technology has dramatically improved the ability to visualize changes in pancreatic structure and allowed for the possibility of early diagnosis

of chronic pancreatitis. This technique also provides clinicians with the means to obtain tissue for histologic diagnosis of chronic pancreatitis without the need for surgical resection of the pancreas.

- The development of an effective vaccine against the virus that causes acute hepatitis B and its use in successful vaccination programs represent a major advance that has contributed to a significant reduction in the incidence of this disease in the U.S. Moreover, the introduction of tests that can detect the presence of hepatitis B and C viruses in blood has nearly eliminated their transmission through blood donation.

- Development of the video capsule endoscope has revolutionized imaging of the small bowel mucosa and facilitated the evaluation of common disorders, such as Crohn's disease, idiopathic inflammatory diseases of the small bowel, and malignancy. Occult bleeding from the small bowel may now be identified, addressing a longstanding clinical dilemma prior to this technology.

RECOMMENDATIONS OF THE NATIONAL COMMISSION ON DIGESTIVE DISEASES

Development and Organization of the Long-Range Research Plan of the National Commission on Digestive Diseases

This research plan describing opportunities and challenges in digestive diseases research was developed by the Commission through a collaborative, transparent process that involved multiple opportunities for engagement of the research, clinical, and patient communities with an interest in digestive diseases. The full Commission held five public meetings throughout the duration of its charter to develop and discuss the structure and content of the research plan. In addition, working groups comprising additional experts in each scientific topic area were convened to advise the Commission on the current state of the science in digestive diseases research and to identify high-priority research goals to be addressed over the next decade. A near-final draft of the research plan was posted online for public comment before being approved by the Commission and submitted to the NIH Director and the Congress.

The Commission's recommendations are organized into 12 scientific topic areas that categorize digestive diseases by common etiology, mechanism, affected organ system, or other considerations. For each topic area, the Commission has provided: an overview of common diseases or conditions; a review of significant research advances; a description of high-impact, forward-looking, science-based research goals; and a discussion of major barriers to research progress and steps to overcome those challenges. The goals, which are not prioritized, each include a list of specific objectives that represent more discrete, shorter-term steps toward achieving the overall goal. Although it was not possible to explicitly address every digestive disease that affects the human population, the Commission noted that many of the research recommendations are expected to have a broad impact on diseases of the digestive system, including those not explicitly mentioned. In addition, it should be noted that diseases of the oral cavity and general aspects of nutrition research (not related to digestive diseases and their treatment) were not considered in the development of this research plan.

High-Impact Goals for Digestive Diseases Research

With the assistance of its working groups, the Commission identified high-priority research goals that, if pursued over the next decade, have the potential to expand our understanding of digestive system biology and accelerate the

development of new strategies for prevention, diagnosis, treatment, and cure of digestive diseases. These major research goals are summarized below:

- **Research on the Basic Biology of the Digestive System**
  The Commission proposes multiple research goals to achieve the overarching mission of understanding the basic biologic underpinnings of the structurally and functionally complex digestive system. Developing new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system may provide new approaches to understand the pathogenesis and develop new therapies for digestive diseases. Uncovering the mechanisms that control development and differentiation of the digestive tract before birth and in neonatal life could generate new insights for regenerative therapies to treat digestive cancers and other diseases, as well as provide new insights into disease pathogenesis. Studying the fundamental mechanisms of digestion could point to new strategies for treating disorders of nutrient and fluid absorption, secretion, and metabolism. The enteric nervous system links the digestive system and the brain and controls motility within the GI tract. Research on the function and organization of the enteric nervous system will enable a better understanding of gut motility in digestive health and disease. The intestinal microflora are essential to normal digestive function; studying the composition and activity of commensal organisms in healthy individuals could reveal important links between alterations in the microflora and human disease. Finally, the mucosal immune system is a critical component of the body's defenses against disease. Understanding the mechanisms by which this system operates could lead to new vaccination strategies or other approaches to prevent or treat infectious diseases that affect the digestive system.

- **Functional Gastrointestinal Disorders and Motility Disorders**
  Functional GI disorders and motility disorders, such as irritable bowel syndrome, functional dyspepsia, and gastroesophageal reflux disease, take a significant toll on the health and well-being of many Americans. The Commission offers several research goals designed to improve our understanding of normal motility and secretory activities of the GI tract, discover the physiologic changes that lead to disease, and develop more effective therapies to prevent, treat, or reverse these disorders. Research efforts are needed on the numerous systems and processes that may be impaired in functional GI and motility disorders, including brain-gut interactions, the enteric nervous system, interstitial cells of Cajal and smooth muscle cells, pain and sensory mechanisms, the gut mucosa and musculature, the intestinal microflora, and immune and inflammatory responses. It is important to define how factors such as genetic differences, age, sex, and gender influence a person's susceptibility to these disorders. Many individuals with diabetes develop GI motility disorders, such as gastroparesis and constipation. As the rate of diabetes continues to rise in the U.S., research on how diabetes affects the GI tract is increasingly important. Ultimately, research to discover the basic mechanisms of disease must be translated into new technologies, pharmacological therapies, and behavioral strategies to effectively treat all patients afflicted with functional GI and motility disorders.

- **Infections of the Gastrointestinal Tract**
  GI infections can be caused by many types of microbes, including bacteria, viruses, protozoa, and helminths. The Commission recommends research goals that are focused on identifying disease-causing microbes, understanding what distinguishes those organisms from the normal microflora of the human GI tract, and using that knowledge

to develop safe, effective therapies to prevent and treat intestinal infections. Developing new, more efficient diagnostic methods to identify specific organisms is critical for rapid treatment and for understanding the epidemiology of infectious disease outbreaks. Research is needed to develop better treatments, including vaccines, that address both the infectious agents themselves, as well as the long-term effects of GI infection in the gut and other organ systems throughout the body. The human GI tract is colonized from birth with microorganisms that are essential for normal growth and digestive function. Research on the nature and function of the human microflora could suggest strategies to manipulate these beneficial microbes to combat pathogenic organisms. Collectively, achievement of these goals has the potential to reduce the public health burden of infectious diseases in the U.S. and globally.

- **Cancers of the Digestive System**
  Recognizing the substantial public health impact of digestive system cancers, the Commission recommends several research goals targeted at improving the detection, prevention, and treatment of these diseases. Research is needed to develop more efficient screening tools to predict and detect digestive tract cancers and pre-malignant conditions that frequently progress to cancer. These efforts would be bolstered by identifying health disparities that influence an individual's susceptibility to digestive system cancers or their response to treatment. Understanding the underlying mechanisms common to all digestive cancers and identifying biomarkers to detect disease or predict response to treatment would accelerate the search for safe, effective therapies. In order to develop targeted strategies for cancer detection, prevention, and treatment, it is critical that researchers identify the genetic risk factors that predispose an individual to a specific form of digestive cancer, such as esophageal cancer, pancreatic cancer, gastric cancer, colorectal cancer, or certain rare GI cancers. Together, these research goals aim to improve the health and lives of people at risk for or living with digestive cancers.

- **Inflammatory Bowel Diseases**
  Inflammatory bowel diseases (IBD) are a diverse group of digestive tract disorders of often unknown origin and complex disease management. Given the potentially severe impact of these diseases on patients' quality of life, cancer risk, growth and development in childhood and adolescence, and other serious health issues, the Commission proposes a set of research goals that are intended to accelerate progress on understanding, preventing, and effectively managing these diseases in all patients. An urgent research goal is the development of objective criteria for IBD diagnosis and risk evaluation, based on phenotypic and genetic characteristics, which would enable reliable subclassification of patients and their diverse constellations of symptoms. Such validated criteria could facilitate clinical evaluation and disease management approaches that are tailored to individual needs and that improve the efficiency of clinical trials to test new therapies. Strategies to prevent or control IBD that could be tested include modulation of the intestinal microflora or the mucosal immune system. These and other therapeutic approaches are targeted at maintaining the health of the intestinal mucosa and stimulating regeneration and repair in patients with IBD. In addition, finding ways to alleviate the unique developmental challenges faced by children with IBD is a particularly important goal in this research area.

- **Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation**
  Loss of intestinal function can occur through surgical removal of tissue or diseases that

impair digestion or cause tissue death. The Commission recommends research goals that, if pursued, would increase understanding of the natural mechanisms of growth, differentiation, and adaptation in the GI tract and use that information to better treat patients with GI diseases. Research is needed on the development of new treatment strategies for short bowel syndrome and intestinal failure, including innovative approaches to optimizing intestinal transplantation and post-transplant survival. GI tract surgeries, including bariatric surgeries for weight loss, are frequently associated with nutritional or hormonal complications. An important research focus is improving nutritional support for surgical patients and others with digestive diseases who rely on parenteral or enteral nutrition to sustain life, including premature infants with necrotizing enterocolitis. Achieving these research goals would markedly enhance the quality of life and health of many patients with digestive diseases or injury who are unable to properly absorb nutrients through their GI tract.

- **Diseases of the Oropharynx and Esophagus**
  Because normal functioning of the oropharynx and esophagus can be compromised by a wide spectrum of diseases, the Commission suggests a number of research goals that address the diverse etiologies and potential treatments for these disorders. Research to understand the neuromuscular biology of the oropharynx and esophagus is critical to developing therapies for conditions like swallowing disorders brought on by stroke, premature birth, non-erosive reflux disease, and other motility disorders that affect this portion of the GI tract. Similarly, more studies are needed to identify better therapeutic targets for gastroesophageal reflux disease (GERD), among the most common diagnoses for a digestive disorder in the U.S. GERD is also associated with increased risk for Barrett's esophagus and esophageal cancer. Thus, research is needed to uncover the risk factors and mechanisms of disease progression in order to develop more effective prevention and treatment strategies. The emergence of eosinophilic esophagitis and other inflammatory diseases of the esophagus over the last decade highlights the need for research to define the clinical course of these poorly understood diseases and design rational therapies to reverse them. Progress toward these research goals will help to reduce the significant economic toll that these diseases, particularly GERD, take on individuals and the U.S. healthcare system.

- **Diseases of the Stomach and Small Intestine**
  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 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. 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 and eosinophilic GI diseases, for which few effective treatment options are available.

- **Diseases of the Colon and Rectum**
  The colon and rectum are susceptible to a variety of diseases and conditions that can impair their primary functions of maintaining water balance and eliminating wastes. The Commission's proposed research goals are aimed at understanding mechanisms of colonic injury, repair, and function so that prevention and treatment strategies for these disorders can be optimized. Key topics for research on colonic diseases are elucidating the role and composition of the gut microflora and manipulating this microbial community to restore health. Studies are also needed to establish the basis for structural defects like diverticular disease and vascular disorders, such as colonic ischemia and angioectasias. Better means of detection and treatment would improve the health and quality of life of elderly individuals who are most affected by these conditions. Research is urgently needed on anorectal disorders, including anal fistulas, hemorrhoids, and fecal incontinence, which lack a firm evidence base concerning the causes and effective management strategies for these common, but poorly studied, conditions. Research on ways to prevent and treat radiation injury of the colon would alleviate this treatment-induced complication of pelvic cancer therapy. Finally, appendicitis can be fatal if undiagnosed and untreated. Research on the risk factors for onset and progression of appendicitis would further reduce the burden of this condition, especially in children.

- **Diseases of the Pancreas**
  The exocrine pancreas, which produces and secretes multiple enzymes necessary for digestive function, is vulnerable to a variety of disorders that, collectively, affect more than 1 million Americans each year. The Commission recommends a series of research goals that are focused on the most prevalent of these disorders—acute and chronic pancreatitis and their sequelae. Pancreatitis can be triggered by many possible causes, including gallstones, alcohol abuse, certain medications, autoimmunity, and diseases such as cystic fibrosis, or it may be of unknown etiology. Research is needed to identify the biologic and genetic factors that increase a person's susceptibility to acute pancreatitis and/or the transition to chronic disease. The development of innovative diagnostic, preventive, and therapeutic approaches to pancreatitis has the potential to reduce the burden of this disease in both children and adults. Equally important is the need to understand the mechanisms of pancreatic pain, a highly prevalent complication of all forms of pancreatitis that is difficult to treat and severely erodes the quality of life of patients with pancreatic disease. Research to understand the risk factors for and mechanisms of progression to pancreatic cancer is particularly critical for patients who develop pancreatitis at a young age and are, therefore, at a corresponding increased lifetime risk for pancreatic cancer.

- **Diseases of the Liver and Biliary System**
  Major research goals relating to diseases of the liver and biliary system were set forth in the trans-NIH *Action Plan for Liver Disease Research*, which was released in 2004. Taking that effort into consideration, the Commission proposes research goals that are intended to complement and reinforce the comprehensive recommendations made in the *Action Plan*. Understanding normal liver and biliary function and development will provide a solid foundation for new approaches to detect, prevent, and treat liver and biliary diseases. Although the burden of some forms of viral hepatitis has decreased in recent years due to efforts such as the development of vaccines and antiviral therapies, more work is needed

to find safe, effective means for prevention and treatment of all forms of acute and chronic viral hepatitis, as well as human immunodeficiency virus (HIV)-associated liver disease. Hepatic steatosis (fatty liver disease) is an increasingly common form of liver disease in the U.S. Research to discover the basic mechanisms underlying steatosis will point to new therapeutic strategies. Similarly, research is needed to uncover the genetic bases and fundamental cellular mechanisms of a range of disorders, including drug-induced liver disease, autoimmune diseases of the liver, childhood syndromes and other hereditary liver diseases, cirrhosis, liver cancers, and gallstones. More knowledge of all of these conditions will accelerate the search for new means of prevention, diagnosis, and treatment, such as improved procedures for liver transplantation, to reduce the burden of liver and biliary diseases in the U.S.

- **Bioengineering, Biotechnology, and Imaging**
  The luminal structure of the gastrointestinal tract and the inherent regenerative capacities of many cell types within the organs of the digestive system afford significant opportunities for the development of innovative technologies and approaches to the diagnosis and treatment of digestive diseases. The Commission recommends several research goals that are intended to capitalize on emerging technologies and facilitate medical and surgical care of digestive disease patients. Ready access to much of the digestive tract is permitted by endoscopic or minimal access approaches for biopsy or resection of tissue. Research is needed to evaluate the risks and benefits of such procedures compared to conventional surgical techniques. Advances in stem cell biology and regenerative medicine could be applied to foster the repair and regeneration of diseased tissue within the digestive system. Innovative scaffolds to guide the growth of complex digestive organ structures will need to be developed in order to realize the potential of promising tissue engineering approaches. The development of advanced imaging technologies and interactive simulators that allow surgeons to plan and practice procedures using patient-specific images would reduce the risk of trauma to healthy tissue during treatment. Collectively, these research goals will lead to innovative technologies that have the potential to significantly improve patient outcomes and enhance treatment efficacy for many digestive diseases.

CONCLUSION

Pressing Need for a Substantial Research Effort in Digestive Diseases

Disorders of the digestive system affect the majority of the U.S. population at some time throughout life. Many decades of NIH-funded research in digestive diseases have led to a detailed understanding of the digestive system, the causes of many diseases, and improved treatments that are now the standard of care. Examples of research advances that have reduced the burden of digestive diseases include: the discovery of *H. pylori* as a major cause of ulcer disease; discovery of the multiple forms of viral hepatitis and development of curative treatments and preventive vaccines; and implementation of effective screening programs to prevent colorectal cancer.

Nonetheless, the current solutions for the prevention, diagnosis, or treatment of digestive diseases are often imperfect and costly. In addition, progress on many digestive diseases, such as the functional GI disorders, pancreatitis, and others, has occurred at a much slower rate. Conditions associated with the rising prevalence of obesity, such as non-alcoholic steatohepatitis, are likely to increase the burden of digestive diseases in the U.S. The Director of the NIH, recognizing both the great burden of digestive

diseases in the U.S. and the diversity and complexity of basic, translational, and clinical research approaches that could be brought to bear on the problem, chartered the National Commission on Digestive Diseases to make recommendations to the NIH for future research on digestive diseases.

Common Themes

While developing its recommendations for goals and objectives within the 12 topic areas, the Commission noted recurring themes that transcend much of digestive disesases research. The Commission notes that strong support by NIH and other participants in the research process for coordinated research planning efforts to address these common themes will be critical to the continued success of digestive diseases research.

- **Theme 1: Increase the fundamental knowledge base for understanding health and digestive diseases.** Basic and translational research provides essential knowledge about the normal, healthy digestive system and how it is perturbed in disease. Research to elucidate the molecular basis of biologic and pathologic processes in the digestive system is needed to form the basis for discovery of new drugs to intervene in disease processes. Identifying genes and gene-environment interactions that influence susceptibility to disease will lead to better understanding of mechanisms of disease and new strategies for diagnosis and personalized medicine. As researchers increasingly appreciate the complexity of the microflora populating the human gut, new technologies will be needed to fully characterize this microbial community and understand its role in health and disease. Research in fields such as immunology, developmental biology, and stem cell biology are needed to gain insights into the pathogenesis of many digestive diseases. Finally, continued progress in the digestive diseases research field depends on the development and application of new technologies, including development of animal models, high-throughput DNA sequencing, proteomics, high-resolution imaging, and many others.

- **Theme 2: Translate fundamental new knowledge for the direct benefit of individuals.** Increased efforts in translational research will be needed to achieve the long-term goals of this research plan and move the knowledge developed through basic research into routine clinical practice. Translational research would be facilitated by collaborative efforts to better define patient phenotypes and to identify biomarkers that can be used to predict disease or response to treatment. Epidemiologic research through patient registries and natural history studies would generate new, testable hypotheses and aid in the design of clinical trials. Academia-industry partnerships should be encouraged to foster the development and validation of new technologies for clinical research and treatment. Translation of research from the bench to bedside requires both the implementation of adequately powered, randomized clinical trials as well as efforts, such as education and awareness campaigns, to ensure that the results of successful trials are readily adopted in clinical practice. All of these efforts rely on the formation and support of teams of individuals with the diverse expertise needed to effectively design, implement, and evaluate clinical research studies and clinical trials.

- **Theme 3: Develop research resources and infrastructure.** New technologies have revolutionized biomedical research, including the digestive diseases research field. Often, these technologies are expensive and require access to well-characterized specimens and data, as well as highly-trained research expertise. Developing resources to increase access to patient biosamples or

data is especially critical to promote research on rare digestive diseases for which few patients are seen by individual investigators or at specific medical centers. Equally important is the creation and dissemination of a variety of animal models for basic and preclinical research on digestive diseases. At all stages of research, support for diverse, multidisciplinary teams of scientists is crucial for the optimal development and application of new technologies and resources for digestive diseases research.

- **Theme 4: Maintain a pipeline of research investigators for the future.** In the long-term, continuing progress in digestive diseases research relies on attracting the best and brightest new investigators and supporting their efforts to launch sustainable, productive research careers. A variety of approaches are needed to foster new investigators, including research training, fellowship, and career development opportunities, as well as incentives for more established investigators to serve as mentors. Higher paylines for new investigators applying for an R01-equivalent grant and loan repayment programs are important mechanisms for retaining researchers at a vulnerable stage in their careers. Efforts should be made to encourage the entry of under-represented minorities into digestive diseases research. Finally, research training and education opportunities could be developed to train researchers in the use of complex new technologies and to encourage PhD scientists to pursue translational and clinical research on digestive diseases.

Steps for Implementation of Research Goals

This research plan of the National Commission on Digestive Diseases describes numerous, far-ranging, long-term goals and specific objectives to improve the health of the Nation through basic, translational, and clinical research that will lead to the discovery of improved ways to prevent, treat, or cure a diverse group of conditions that affect the GI tract, liver, biliary system, and exocrine pancreas. The goals, objectives, and challenges identified in this research plan represent a formidable challenge to all parties in the research process. It is hoped that these partners will use this research plan as a scientific guidepost to identify promising future research opportunities to address the burden of digestive disease. The NIH should continue to solicit broad stakeholder input as it oversees implementation of this long-range research plan for digestive diseases through the activities of coordinating bodies, such as the Digestive Diseases Interagency Coordinating Committee and other entities.

A large number of individual steps will need to be taken by the many partners engaged in digestive diseases research over the 10-year time horizon of this research plan to achieve its many complex goals and objectives. The members of the Commission recognize that research progress often occurs in a "bottom up" fashion, not only rapidly outstripping the best laid efforts of scientific planners, but also as a result of the innovative ideas and initiative of individual scientists and research teams. However, it is also clear that certain types of research projects and programs, as well as specific resources and infrastructure, require central, "top-down" organization led by funding institutions with the flexibility to apply optimal mechanisms to address promising research directions as they arise. Thus, the Commission recommends that the NIH maintain an approach focused on the goals set forth in this research plan that includes a substantial and balanced portfolio of programs with three major elements: strong support of investigator-initiated research project grants; initiatives designed to strategically address special needs and opportunities; and programs that ensure a pipeline of new investigators to meet the continuing needs of digestive diseases research in the future.

Introduction

DIGESTIVE DISEASES: OVERVIEW AND PUBLIC HEALTH BURDEN

The digestive system is a complex, multi-organ structure that performs many vital functions, including nutrient absorption and waste disposal. The tubular gastrointestinal (GI) tract includes the mouth, esophagus, stomach, small intestine, colon or large intestine, rectum, and anus. The luminal surface along much of this tract is lined with cells that either secrete substances that aid in breaking down ingested food or that absorb nutrients and water into the bloodstream for distribution throughout the body. The layers of muscles and associated nerves that surround the lumen propel food and waste through the system for eventual elimination. Even in healthy individuals, the digestive tract is colonized by thousands of microbial species that play a role in normal digestion and help maintain proper nutrition. Solid organs of the abdominal cavity also contribute to the digestive process. The pancreas secretes enzymes into the small intestine to help break down proteins, fat, and carbohydrates. The liver and biliary system (bile ducts, gallbladder) secrete bile into the small intestine to aid in the digestion of fat. In addition, the liver processes nutrients absorbed by the small intestine into forms that can be used by the body and detoxifies potentially harmful substances.

Diseases of the digestive system comprise an exceptionally diverse array of disorders and conditions. Conditions such as acute pancreatitis, appendicitis, and foodborne gastrointestinal infections develop suddenly and usually resolve in a relatively short time. Other disorders, including inflammatory bowel diseases and non-alcoholic steatohepatitis, are chronic and may be controlled, but not yet cured. Dysregulation of the immune system or inflammation can lead to celiac disease, Crohn's disease, eosinophilic esophagitis, or related conditions. Similarly, disorders such as Hirschsprung's disease, irritable bowel syndrome, and intestinal pseudoobstruction are associated with dysfunction of the nervous system or musculature of the GI tract. Digestive diseases can be caused by infectious agents, such as viral hepatitis or ulcers due to infection with *Helicobacter pylori*, or may be treatment-related, such as radiation proctitis, short bowel syndrome due to surgical resection of the gut, or ulcers caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs). Cancer can develop along any part of the luminal gut or in the solid organs of the digestive system. Conditions named in this section are only a few examples of the many diseases that impact the digestive system.

The burden of digestive diseases on the U.S. healthcare system is substantial. At least 60 to 70 million Americans are affected each year by digestive diseases at a cost that exceeds $100 billion in direct medical costs. Annually, about 14 million hospitalizations—10 percent of the total—and 15 percent of all in-patient hospital procedures are attributed to treatment for digestive diseases. In addition, 105 million visits to doctors' offices occur each year for digestive diseases, frequently in response to symptoms such as abdominal pain, diarrhea, vomiting, or nausea. Prescription drugs for the treatment of certain digestive diseases such as gastroesophageal reflux disease rank among the most commonly used pharmaceutical drugs in the U.S.

On a personal level, digestive diseases are associated with significant mortality, morbidity, and loss of quality of life. Digestive diseases,

including cancer, are named as a primary cause of death for approximately 236,000 people in the U.S. each year. Moreover, digestive diseases can severely affect patients' quality of life and cause significant disability even for conditions that are not immediately life-threatening. Debilitating symptoms—such as chronic pain, discomfort, bloating, diarrhea, constipation, incontinence, social stigma, or embarrassment—that are associated with many GI disorders can impact patients' ability to work or engage in everyday activities. Collectively, these diseases account for over $44 billion in indirect costs associated with disability and mortality each year.

Although digestive diseases in general can affect individuals of any age, race or ethnicity, gender, or socioeconomic status, some diseases disproportionately affect certain populations. For example, necrotizing enterocolitis occurs only in newborns, while diverticular disease is most frequently diagnosed in the elderly. The rate of some infectious GI diseases such as *H. pylori* and hepatitis B—both of which increase the risk of digestive cancers—is substantially higher among certain groups that emigrate from areas where these diseases are endemic, such as parts of Asia. Autoimmune diseases like celiac disease and inflammatory bowel diseases are more common in women. African Americans have a higher incidence of pancreatic cancer than any other racial/ethnic group in the U.S. and have a poorer prognosis at diagnosis. These and other significant health disparities provide both opportunities and challenges for research to reduce the public health burden of digestive diseases.

NIH-SUPPORTED DIGESTIVE DISEASES RESEARCH

Advances and Opportunities

Decades of research in digestive diseases have significantly contributed to a reduction in the burden of many of these diseases on individual and public health. The cumulative efforts of scientists working to uncover the fundamental principles of digestive health and disease have been translated into clinical settings to develop and validate new disease-screening protocols, effective prevention strategies, including vaccines, and innovative behavioral, pharmacological, and surgical treatments.

The incidence of acute hepatitis B has plummeted in the U.S. due in part to the introduction of a vaccine to the virus that causes this disease. The development of tests that detect the presence of hepatitis B and C viruses in blood has nearly eliminated their transmission through blood donation, further reducing the public health threat of viral hepatitis. Likewise, the annual number of deaths from colorectal cancer has been declining in recent years. This decrease may be partially attributable to the availability of cost-effective screening techniques that improve the likelihood of detecting the disease at an early stage when it is more responsive to treatment. Research on inflammatory bowel diseases (IBD) supported the development of biologically based therapies, including multiple monoclonal antibodies directed against tumor necrosis factor (TNF), that have provided relief for many IBD patients who did not respond to other treatments. Finally, the discovery that ulcers can be caused by *H. pylori* infection quickly led to the realization that many ulcer patients can be cured by antibiotics.

These and other advances have truly revolutionized the care of many digestive disease patients or those who are at risk for developing digestive diseases. However, the burden of digestive diseases in the U.S. remains significant, and the sheer number and variety of these illnesses highlight the crucial need for ongoing attention to these diseases through a vigorous research effort. For example, very little is known about the causes of functional GI disorders, and individuals affected by these conditions have few treatment options.

Likewise, patients with chronic pancreatitis often experience severe pain that is difficult to treat and can substantially reduce quality of life. Cancer of the digestive system remains an important cause of cancer-related death in the U.S. For these patients and the millions of other Americans afflicted with acute or chronic digestive diseases, the National Commission on Digestive Diseases sought to identify the most critical needs and promising opportunities in digestive diseases research that have the potential, if pursued, to advance the understanding of all forms of digestive diseases and alleviate the burden of these diseases.

Digestive Diseases Research Funding

Progress in digestive diseases research has benefited from strong support from the National Institutes of Health (NIH) in recent years. Twenty NIH Institutes, Centers, and Offices currently support digestive diseases research on a variety of topics with a total expenditure of more than $1.2 billion in fiscal year 2007 (Table 1).

The NIH research portfolio includes funding for studies of fundamental mechanisms of digestive system development and function, as well as basic, translational, and clinical research on the digestive system in normal states and disease conditions. NIH research is funded through grants, awards, contracts, and fellowships to extramural researchers and institutions for research and training, as well as support for intramural laboratories. To aid in the development of this long-range research plan, lists of grants and other awards comprising the NIH portfolio for digestive diseases were provided to members of the Commission and to each working group.[1]

Table 1: NIH Expenditures for Digestive Diseases Research FY 2007 (in dollars)

NIH Institute, Center, Office or Fund*	FY 2007
NCI	395,479,000
NIDDK	331,021,000
NIAID	273,792,000
NIDCR	83,650,000
NIEHS	32,865,000
NCRR	26,481,000
NIAAA	24,124,000
NHLBI	15,477,000
NICHD	14,705,000
NINDS	9,446,000
NCCAM	9,253,000
ROADMAP	8,014,000
NINR	2,638,000
NIA	1,900,000
FIC	1,234,000
NIDA	1,055,000
OD	910,000
NIBIB	794,000
NIMH	550,000
NHGRI	506,000
NCMHD	194,000
TOTAL NIH	**1,234,088,000**

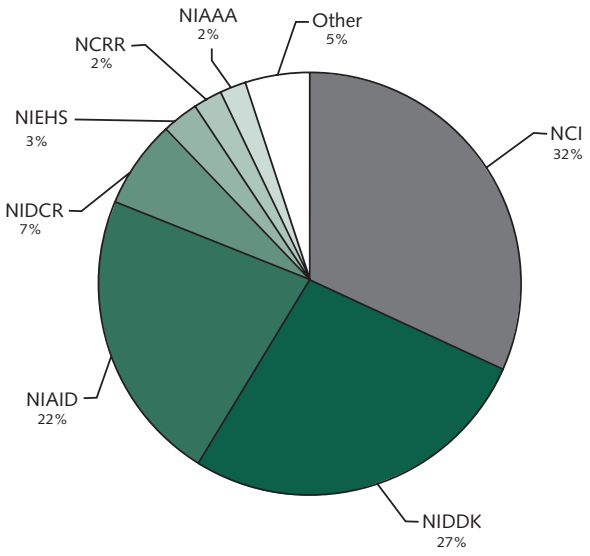
**See text for full titles of acronyms.*

[1] *Table 1 provides the most recent NIH funding data (FY 2007) as of the completion of this research plan in spring 2008. The Commission's charter required a scientific overview of NIH-funded research and research-related activities. In response to that mandate, the Commission and its working groups were provided with the most recently available, aggregate funding data and lists of digestive diseases-related NIH research awards during the course of their discussions and development of research goals, which took place in 2006-2007. The FY 2006 award list used by the Commission will be made available on the Commission's website at http://NCDD.niddk.nih.gov.*

Institutes and Centers accounting for the majority of the NIH portfolio for digestive diseases research and research training (Figure 1) include:

- National Cancer Institute (NCI, 32 percent)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, 27 percent)
- National Institute of Allergy and Infectious Diseases (NIAID, 22 percent)
- National Institute of Dental and Craniofacial Research (NIDCR, 7 percent)
- National Institute of Environmental Health Sciences (NIEHS, 3 percent)
- National Center for Research Resources (NCRR, 2 percent)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2 percent)

Figure 1: NIH Awards for Digestive Diseases Research by Institute or Center (FY 2007)



Other NIH Institutes, Centers, and Offices that support digestive diseases research and research training include:

- National Heart, Lung, and Blood Institute (NHLBI)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Center for Complementary and Alternative Medicine (NCCAM)
- NIH Roadmap for Medical Research (ROADMAP)
- National Institute of Nursing Research (NINR)
- National Institute on Aging (NIA)
- Fogarty International Center (FIC)
- National Institute on Drug Abuse (NIDA)
- NIH Office of the Director (OD)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Institute of Mental Health (NIMH)
- National Human Genome Research Institute (NHGRI)
- National Center on Minority Health and Health Disparities (NCMHD)

Coordination and Communication of Digestive Diseases Research

In addition to its direct role in funding digestive diseases research, the NIH engages in significant efforts to coordinate research programs within the agency and with other Federal agencies that share a common interest in combating digestive diseases. The Digestive Diseases Interagency Coordinating Committee (DDICC) is the primary mechanism for Federal digestive diseases research coordination. The DDICC brings together representatives from multiple NIH Institutes and Centers that fund digestive diseases research, as well as from other agencies, including the Agency for Healthcare Research and Quality, the Food and Drug Administration, the Department of Defense, the

Centers for Disease Control and Prevention, the Department of Veterans Affairs, the Health Resources and Services Administration, and the Department of Agriculture, to discuss and coordinate digestive diseases-related research activities across the Federal Government. The Liver Disease Subcommittee of the DDICC coordinates liver and biliary diseases research across the NIH and other Federal agencies, including efforts to implement the trans-NIH *Action Plan for Liver Disease Research.*

The NIH also promotes communication and collaboration within the digestive diseases research community through the support of conferences and workshops. For example, the NIH convened a state-of-the-science conference on prevention of fecal and urinary incontinence in adults to assess the scientific evidence relevant to understanding the epidemiology, risk factors, burden of illness, prevention strategies, and research priorities for these serious medical conditions. Other conferences have focused on diverse topics relevant to digestive diseases including: gastrointestinal microbiota and pre/probiotics research; nuclear receptors in liver and digestive disease; improving long-term outcomes for pediatric liver transplantation; acute liver failure; alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences; screening and outcomes in biliary atresia; and management of hepatitis B. Many of these conferences and workshops are jointly sponsored by multiple NIH Institutes and Centers, other Federal agencies, and private, professional, or patient advocacy organizations.

The National Digestive Diseases Information Clearinghouse[2] was established by NIDDK in 1980 to increase knowledge and understanding about digestive diseases among people with these conditions and their families, healthcare professionals, and the general public. This service includes distribution of public information materials on a variety of digestive diseases, referrals to health professionals, and a reference collection on health education publications.

GENESIS OF THE NATIONAL COMMISSION ON DIGESTIVE DISEASES AND ITS LONG-RANGE RESEARCH PLAN FOR DIGESTIVE DISEASES

Charter for the National Commission on Digestive Diseases

Elias A. Zerhouni, M.D., Director of the National Institutes of Health, chartered the National Commission on Digestive Diseases on July 26, 2005, based on a mutual interest in advancing digestive diseases research shared by the NIH and the Congress. The establishment of the Commission responds, in part, to congressional report language accompanying the FY 2005 appropriations bills in the House and Senate for the Departments of Labor, Health and Human Services, and Education, and Related Agencies. The Commission was charged with two main tasks: (1) to conduct an overview of the state of the science in digestive diseases research exclusive of diseases of the oral cavity, and (2) to develop a 10-year plan for digestive diseases research that is consistent with the NIH mission and aimed at the ultimate goal of improving the health of the Nation through research. The Commission's primary focus has been to identify compelling research opportunities that, if pursued, would improve the lives and health of individuals affected by digestive diseases.

The long-range research plan developed by the Commission, entitled *Opportunities and Challenges in Digestive Diseases Research:*

[2] *The National Digestive Diseases Information Clearinghouse is accessible online at: http://digestive.niddk.nih.gov/.*

Recommendations of the National Commission on Digestive Diseases, will serve as an important guide to help define NIH priorities for digestive diseases research over the next decade. Thus, the plan encompasses many broad areas of digestive diseases research that are relevant to the NIH mission, including fundamental biology of the digestive system and disease-oriented research topics such as: epidemiology; environmental factors; genetics; mechanisms; diagnosis; causes; treatments; behavioral, social, and psychological factors; health disparities; prevention; and cures. Opportunities identified by the Commission span basic, translational, and clinical research, including clinical trials in children, adults, and in special populations such as high-risk groups or the disadvantaged. The plan also addresses issues related to research training and education of investigators in digestive diseases research fields. Finally, this research plan identifies challenges to its optimal implementation and proposes cross-cutting, innovative disciplines, technologies, and resources that would create research synergies and promote progress in digestive diseases research.

Development and Organization of the Commission

Appointment of Commission Members and Formation of Working Groups

The NIH Director appointed 16 Commission members who included extramural researchers from academic institutions across the country, medical professionals, and patient advocates (Appendix 2). These members were selected from more than 100 names submitted through a nomination process that was open to the entire research community and the general public. In addition, 22 *ex officio* members representing NIH Institutes and Centers, as well as other Federal agencies with an interest in digestive diseases research, served on the Commission (Appendix 2). The Commission was chaired by Stephen P. James, M.D., Director of the Division of Digestive Diseases and Nutrition of the NIDDK, which is the lead entity for coordination of digestive diseases research at NIH.

Shortly after the Commission's establishment, the members created "working groups" of additional external experts to provide input to the Commission for developing the individual chapters of the research plan. Therefore, a second public nomination process was undertaken to solicit suggestions for members of each working group. Approximately six to ten members were chosen for each group based on their expertise and knowledge of current research related to the working group topic. Members included individuals from recently convened groups, such as the Liver Disease Subcommittee of the DDICC and NCI's GI-related Progress Review Groups, in order to complement and build upon those efforts. Due to the scientific nature of the working group reports, members were primarily researchers and healthcare providers with expertise in digestive diseases research (Appendix 2). Working group members served in an advisory role to the Commission, and each working group was led by a Chair and Vice Chair selected from among the members of the Commission.

A Collaborative and Inclusive Research Planning Process

Once the full Commission was seated, it met five times and communicated extensively via conference calls and emails to conduct business in pursuit of its mission. All meetings were open to the public and advertised in advance by notification through the *Federal Register* and through the Commission's public website,[3] as well as by updates sent to all major

[3] *The website of the National Commission on Digestive Diseases can be accessed at: http://NCDD.niddk.nih.gov.*

digestive disease organizations. Summaries of meeting proceedings were also posted on the Commission website for the information of the public. Commission meetings included:

June 12, 2006 (Arlington, VA) – At its first meeting, the Commission received its charge from Griffin Rodgers, M.D., then Acting Director of the NIDDK, on behalf of the NIH Director, Dr. Zerhouni. The Commission members also discussed plans by the NIH to update epidemiologic data on the burden of digestive diseases in the U.S. Representatives from NIH Institutes and Centers and other Federal agencies provided an overview of digestive diseases research activities being carried out within each organization. With this background in mind, the Commission deliberated on the overall structure of the final long-range research plan and defined general issues to be addressed in each chapter. The list of chapters for the research plan and the appointment of chairs for the corresponding working groups were finalized by ongoing communication after the meeting.

November 6, 2006 (Arlington, VA) – The primary purpose of this meeting was to review progress reports from each working group. The chairs of each group described: the major points of the background/introduction for each topic-specific chapter; the scientific scope of the chapter; areas of potential overlap with other chapters; and progress made on naming the working group members and developing material for the research plan. Commission members identified potential gaps in the proposed outline for each chapter and resolved overlap issues among chapters with related interests. In addition, Dr. Zerhouni addressed the Commission on the importance of its task in relation to the broader NIH vision for biomedical research and public health, as well as the current challenges being faced by NIH research programs.

June 18-19, 2007 (Arlington, VA) – This meeting focused on identifying the highest-priority research goals, objectives, and challenges, as well as major cross-cutting themes, for inclusion in the long-range research plan. It was necessary for the Commission to carefully review the many excellent research goals proposed by the working groups and determine which would potentially have the most impact on digestive diseases if pursued by the NIH. Thus, the Commission focused on developing a set of recommendations for high-priority goals that would be wide-ranging, yet manageable, in scope. Based on discussions at this meeting, working group chairs were charged with drafting a chapter for inclusion in the long-range research plan. Elizabeth Wilder, Ph.D., Acting Associate Director of the Office of Portfolio Analysis and Strategic Initiatives (OPASI) in the NIH Office of the Director, updated the Commission on progress and planning for the NIH Roadmap for Medical Research, which provides virtual "incubator space" for NIH programs of cross-disciplinary relevance or complexity. The Human Microbiome Project, launched in 2007, is an example of a Roadmap program that is of key importance to advancing digestive diseases research. Following the meeting, the presentation materials were posted on the Commission's public website.

November 19, 2007 (Rosemont, IL) – At this meeting, Dr. Griffin Rodgers, Director of NIDDK, commended the Commission on its work to date and encouraged continued public involvement in the development and implementation of the research plan for digestive diseases. The Commission was also provided an update of progress on the development of a report on the burden of digestive diseases in the U.S. Most importantly, the Commission reviewed and discussed a draft of the entire long-range research plan for the purpose of re-organizing potential overlapping or duplicative research goals and filling in gaps in the research plan.

Based on discussions at this meeting, the members made final changes to their assigned draft chapters and prepared the research plan for a public comment period. In the interim, the presentation materials from this meeting were posted on the Commission's public website.

May 16, 2008 (San Diego, CA) – At its fifth and final meeting, the Commission reviewed the near-final draft research plan that incorporated suggestions submitted during the public comment period. The Commission discussed the feasibility of prioritizing its recommendations without detracting from the inclusive nature of the research plan, which addresses multiple digestive diseases. Mechanisms or organizational structures for overseeing the implementation of the recommendations for research set forth in the plan were also considered. The Commission received an update on data developed for the report on the burden of digestive diseases in the U.S. Finally, Dr. Rodgers presented each appointed member of the Commission with a certificate signed by Dr. Zerhouni and Dr. James in recognition of their efforts over the previous 2 years. In response to discussions at this meeting, final additions and revisions were made to the recommendations for the research goals, and the Commission voted to approve the research plan in August 2008.

Working Group Meetings

In addition to the public meetings of the Commission, each working group engaged in one or two conference calls to discuss and prioritize research advances, goals for future research, and major challenges and steps that would be needed to achieve the research goals. Working group members consulted informally with additional experts and colleagues from the scientific, medical, and patient communities to ensure that the final long-range research plan draws upon a broad range of perspectives and expertise. Finally, each working group had an opportunity to review and comment on a draft of the chapter for their assigned topic.

Public Comments

A draft of the long-range research plan was posted on the Commission's website in spring 2008 for a 30-day public comment period. Comments and suggestions received from members of the research community, patient advocacy and professional organizations, and the public at large were reviewed by the Commission and incorporated into the final research plan as appropriate before transmittal to the NIH Director and the Congress.

Organization of the Long-Range Research Plan

This long-range research plan for digestive diseases is intended to be comprehensive, yet manageable, in size and scope. While acknowledging the vast number of digestive diseases and conditions that affect human health, the Commission chose an organizational structure for the research plan that categorizes diseases by common etiology, mechanism, affected organ system, or other considerations. Although there are numerous common and rare digestive diseases that have a serious impact on the daily lives and health of people throughout the Nation, it was not possible to mention every digestive disease by name in this research plan. Rather, the Commission noted that many of the recommendations are expected to have a broad impact on diseases of the digestive system, including those not explicitly mentioned. The Commission also acknowledged that many research topics or disease areas would be relevant to more than one theme within the research plan. To limit redundancy, topics were assigned to a single chapter as much as possible, with some cross-referencing where appropriate. For example, colorectal cancer research is addressed

primarily in the disease-oriented chapter on *Cancers of the Digestive System* rather than in the organ-based chapter on *Diseases of the Colon and Rectum*. Therefore, readers are encouraged to view this research plan in its entirety in order to locate all relevant text on a given topic.

Topic-specific areas chosen for organizing content with the long-range research plan are:

- *Research on the Basic Biology of the Digestive System:* Basic developmental biology and function of the digestive system, including growth and integrative physiology, digestion and metabolism, nutrient and fluid absorption and secretion, neurophysiology and motility, endocrinology and satiety, microbiology and microbial-host interactions, and mucosal immunology.

- *Functional Gastrointestinal Disorders and Motility Disorders:* Functional diseases for which no anatomic abnormality can be discerned and diseases associated with neuromuscular dysfunction, including irritable bowel syndrome, functional dyspepsia, gastroesophageal reflux disease (GERD), gastroparesis, chronic intestinal pseudoobstruction, and others.

- *Infections of the Gastrointestinal Tract:* Diseases caused by virulent bacteria, viruses, or other parasites that infect the digestive system, such as *E. coli*-associated diseases, cholera, *C. difficile* infection, and others.

- *Cancers of the Digestive System:* Cancers of the esophagus, stomach, pancreas, colon and rectum, and rare GI cancers.

- *Inflammatory Bowel Diseases:* Diseases associated with chronic inflammation of the GI tract, including ulcerative colitis and Crohn's disease.

- *Intestinal Failure and Regeneration, Nutritional Disorders and Support,*[4] *Surgically Modified Gut,*[5] *and Transplantation:* Conditions arising from challenges to the physical integrity of the GI tract, including short bowel syndrome, intestinal failure, intestinal transplantation, and surgically modified gut, as well as nutritional support strategies for patients with these conditions.

- *Diseases of the Oropharynx and Esophagus:* Disorders affecting the oropharynx and esophagus, including swallowing disorders (dysphagia), GERD, Barrett's esophagus, achalasia, eosinophilic esophagitis, and others.

- *Diseases of the Stomach and Small Intestine:* Disorders affecting the stomach and small intestine, including peptic ulcer disease, diarrheal diseases, celiac disease, necrotizing enterocolitis, eosinophilic GI disease, and others.

- *Diseases of the Colon and Rectum:* Disorders affecting the colon and rectum, including diverticular disease, fistulas, fecal incontinence, colonic ischemia, angioectasias, appendicitis, radiation proctitis, and others.

- *Diseases of the Pancreas:* Disorders affecting the pancreas, including acute and chronic pancreatitis, cystic lesions of the pancreas, and cystic fibrosis.

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[4] *The topic of nutrition was not explicitly included in the Commission's charter because research planning in this area is overseen by the existing NIH Nutrition Coordinating Committee within the Division of Nutrition Research Coordination, NIH. Nonetheless, nutritional issues and nutrition science are critically important to many digestive diseases topic areas and are addressed in the research plan as appropriate.*

[5] *Obesity, which is a major public health threat in the U.S., was not specifically chosen as an overarching topic for the Commission's research plan because it is addressed by the existing NIH Obesity Research Task Force, which released its* Strategic Plan for NIH Obesity Research *in August 2004. However, the relationship of obesity and digestive diseases is incorporated into the research plan as appropriate, for example with respect to challenges and opportunities in bariatric surgery.*

- *Diseases of the Liver and Biliary System:*[6] Disorders affecting the liver and biliary system, including viral hepatitis, fatty liver disease, drug-induced liver disease, autoimmune liver diseases, liver transplantation, liver cancer, gallstones, and others.

- *Bioengineering, Biotechnology, and Imaging:* Development of innovative techniques and state-of-the-art technologies for detection, diagnosis, and treatment of digestive diseases, including endoscopic techniques, imaging modalities, minimally invasive surgical procedures, tissue engineering and regenerative medicine, and simulation training.

Each topic-specific chapter in the long-range research plan addresses one of the major topic areas identified by the Commission and is organized along a common format with the following sections (except the chapter on *Diseases of the Liver and Biliary System,* which presents this information in a slightly different format due to its relationship to the trans-NIH *Action Plan for Liver Disease Research*):

- *Summary of Research Goals:* Major, high-priority research goals are summarized at the beginning of each chapter.

- *Introduction and Background:* An overview of the topic, common conditions and their disease burden, epidemiology, current understanding of pathogenesis and natural history, and current means of control, cure, and/or prevention are provided.

- *Recent Research Advances:* Research findings that have had a significant impact on digestive diseases research, patient health, or the ability to do future research that could benefit patients are highlighted. These advances do not represent a comprehensive survey of all progress in digestive diseases research, but are meant to indicate major, paradigm-shifting discoveries that point to new opportunities for further investigation.

- *Goals for Research:* High-impact, forward-looking, research-oriented goals are described that capitalize on new opportunities and challenges in digestive diseases research. Collectively, the research goals in each chapter represent those identified by the Commission as the highest-priority aims to be achieved in digestive diseases research over the next 10 years. The goals are numbered solely for ease of future reference and are not listed in priority order. Each goal includes a short list of specific objectives that represent more discrete, shorter term steps toward achieving the overall goal.

- *Major Challenges and Steps To Achieve the Research Goals:* Barriers to conducting research and to achieving the group of goals for each topic area are described. In addition, this section identifies important steps that, if taken, would help overcome these barriers and accelerate progress toward realizing the research goals.

Finally, the Commission's research plan concludes with a summary of common themes and steps for implementation that were identified by multiple working groups as important research goals and challenges. These common themes are broadly applicable to many digestive diseases or questions in basic biology of the digestive system. In particular, the Commission recognized the

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[6] *A major strategic planning effort in the area of liver and biliary system diseases was accomplished with the release of the trans-NIH* Action Plan for Liver Disease Research *in December 2004. The Commission working group assigned to this area was charged with identifying research opportunities that build on, rather than duplicate, recommendations from the* Action Plan. *The* Action Plan *is accessible online at: http://liverplan.niddk.nih.gov/.*

fundamental importance of finding ways to achieve and sustain a robust pipeline of trained investigators with knowledge of and a commitment to digestive diseases research. Many topic-specific chapters identify specialized areas of research training or recruitment that would help to sustain the investigator pool in specific fields of research. In addition, a working group of Commission members developed goals and recommendations for research training, education, and the recruitment of new investigators to digestive diseases research; these recommendations are described in the *Conclusion: Common Themes and Steps for Implementation* chapter.

The steps proposed to aid in implementation of the research address current gaps in scientific knowledge and critical opportunities for NIH research and training efforts over the next decade that have the potential to impact multiple areas of digestive diseases research. Pursuing these opportunities will allow the NIH and the research community to find innovative solutions to reduce the toll that digestive diseases take on the health and quality of life of individuals throughout this Nation.

Photomicrograph showing expression of the *Lgr5-lacZ* reporter gene in the base of small intestinal crypts in adult mice. Through this type of research, scientists have been able to identify stem cells within the adult intestine that are capable of forming the cell types needed to continually renew this organ throughout life.

Image courtesy of Dr. Hans Clevers. Reprinted by permission from MacMillan Publishers Ltd: Nature*, 449:1003-1007, copyright 2007.*

Research on the Basic Biology of the Digestive System

SUMMARY OF RESEARCH GOALS

The Commission proposes multiple research goals to achieve the overarching mission of understanding the basic biologic underpinnings of the structurally and functionally complex digestive system. Developing new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system may provide new approaches to understand the pathogenesis and develop new therapies for digestive diseases. Uncovering the mechanisms that control development and differentiation of the digestive tract before birth and in neonatal life could generate new insights for regenerative therapies to treat digestive cancers and other diseases, as well as provide new insights into disease pathogenesis. Studying the fundamental mechanisms of digestion could point to new strategies for treating disorders of nutrient and fluid absorption, secretion, and metabolism. The enteric nervous system links the digestive system and the brain and controls motility within the gastrointestinal (GI) tract. Research on the function and organization of the enteric nervous system will enable a better understanding of gut motility in digestive health and disease. The intestinal microflora are essential to normal digestive function; studying the composition and activity of commensal organisms in healthy individuals could reveal important links between alterations in the microflora and human disease. Finally, the mucosal immune system is a critical component of the body's defenses against disease. Understanding the mechanisms by which this system operates could lead to new vaccination strategies or other approaches to prevent or treat infectious diseases that affect the digestive system.

INTRODUCTION AND BACKGROUND

Understanding the basic biologic functions of the digestive system, which includes the GI tract, pancreas, biliary system, and liver, is of fundamental importance to the diagnosis and treatment of all diseases related to these organ systems. This research plan of the National Commission on Digestive Diseases therefore begins with an overview of several areas of biology that have broad and overarching relevance for diseases covered in subsequent chapters of this research plan. These overarching biologic pathways include those related to the following topics that have seen enormous growth in scientific knowledge, poising them to lead to future therapies. They include: development (e.g., cancer and normal/abnormal development of cells and tissues of all organ systems); growth and integrative physiology (e.g., multi-organ diseases); digestion and metabolism (e.g., intestinal failure, lipid disorders, and pancreatic insufficiency); nutrient and fluid absorption and secretion (e.g., diarrhea and malabsorption); neurophysiology and motility (e.g., irritable bowel syndrome [IBS], obesity, and metabolic syndrome); microbiology and the microbiome (e.g., infectious diseases); and mucosal immunology (e.g., inflammatory bowel diseases [IBD] and vaccines against enteric pathogens). To accomplish the goals of this chapter, three themes of common importance to these areas of investigation need to be addressed: the identification, characterization and manipulation of intestinal epithelial stem cells; development of techniques to characterize and manipulate the human intestinal microflora; and delineation of and methods to target inflammatory pathways of the intestines, stomach, pancreas, and hepatobiliary system.

Development: Congenital malformations, IBD, certain malabsorption syndromes, epithelial metaplasia, disorders of motility, and bowel cancers are all related to development of the embryonic gut. GI development has long been a priority for the NIH, which supported visionary research leading to improved understanding of endoderm specification, patterning, stem cell kinetics, and crypt-villus organization. This field is now in a position to dissect the molecular basis of GI development, which holds enormous promise for understanding pathophysiology and therapy.

Growth and integrative physiology: The digestive system is a complex collection of organs that facilitates the intake, processing, and absorption of food and water while maintaining an effective barrier from the external environment. It is highly flexible and responds to varying nutritional and disease states by altering its structure and function. Understanding the mechanisms that lead to gut growth and remodeling in health and disease is, therefore, critical for development of therapeutics to treat a wide variety of digestive problems, including intestinal failure and obesity. Maintenance of digestive health requires integration of gut physiology with the functions of other tissues and systems, including hormones, the brain and peripheral nervous systems, and the immune system.

Digestion and metabolism: In the last several years, increased understanding of many pathways involved in intestinal nutrient absorption has resulted from our expanding knowledge of the hierarchy of membrane transporters with distinct substrate specificity, as well as a refined understanding of their subcellular itineraries and regulation. Researchers have identified intracellular acceptor molecules and nuclear hormone receptors that participate in metabolic channeling, as well as nutrient sensing, and that signal through both import and export pumps. Finally, the signaling dialogue between the host and the microbiome has been

explored. Together, these advances have yielded enormous implications for understanding and enhancing the relationship between nutrition and digestive health.

Nutrient and fluid absorption and secretion: Using both functional and genetic approaches, many membrane transport proteins mediating intestinal salt, solute, and water transport have been defined over the past 10 years. While there will be a continuing need to identify the proteins mediating and regulating absorption and secretion, the real challenge of the next decade is to leverage this information about the building blocks of fluid and nutrient movement into an integrated view of epithelial function. Given the centrality of the epithelial cell to a wide range of digestive diseases and responses to disease, such information has broad and enabling implications.

Neurophysiology and motility: In recent years, much knowledge has been gained about neural-hormonal control of gut functions and energy homeostasis. Unraveling the complexity of signaling between diverse cells in the enteric nervous system (ENS) provides the cellular and molecular basis for understanding many disorders in which the ENS plays a role. Characterization of the neurobiology of brain-gut interactions provides the necessary conceptual framework for developing new treatments of functional GI diseases and motility disorders. Understanding the mechanisms governing nutrient sensing and peptide secretion by enteroendocrine cells allows investigators to exploit these pathways in the development of new agents to combat obesity and diabetes. A better understanding of the molecular mechanisms leading to disease and age-related apoptotic cell death provides hope for preventive and/or regenerative therapy. Finally, the revelation that neural crest stem cells persist in the adult gut and undergo changes in self-renewal suggests that neuron replacement therapy can become a reality.

Microbiology and microbial-host interactions: The microbial population that normally inhabits the human GI tract, especially the colon, is one of the densest microbial populations known (approximately 10^{12} per gram of intestinal contents), accounting for at least 30 percent of the volume of colon contents. This highly complex population, containing thousands of bacterial species, is acquired shortly after birth and persists in the colon throughout life. The colonic microflora have a major impact on human health that includes a role in human nutrition, stimulation of mucosal cell turnover, suppression of intestinal pathogens such as *Clostridium difficile*, and as a reservoir for antibiotic resistance genes. Members of the microflora are also significant causes of post-surgical infections and infections in cancer patients. Less clearly established are a number of suspected, but still unproven, links to such conditions as IBD, colon cancer, and obesity. Despite its importance, little is known about either the composition or functions of this vast microbial community within the human intestine.

Mucosal immunology: The mucosal immune system encompasses a constellation of specialized cells and structures that enable the function of the immune system at the site of its greatest exposure to the microbial environment: the mucosal tissues of the intestines and their affiliated structures. Understanding the many unique functions of this system will lead to a better understanding of mucosal infections, including HIV infection, may permit the development of mucosal vaccines, and may lead to better treatments for immunologic diseases of the mucosa, such as IBD and celiac disease.

RECENT RESEARCH ADVANCES

Digestive System Development

Development of the crypt-villus axis

The critical roles of the Wnt, Notch, Hedgehog, BMP, Lgr5, and FGF signaling pathways have been elucidated in intestinal crypt homeostasis and in distinguishing the functions of crypt progenitors and the intestinal epithelial stem cell from those of differentiated villus epithelial cells. These advances provide important insights into the genetic basis of colorectal cancer—the second leading cause of U.S. cancer deaths—and to epithelial stem cell homeostatic mechanisms, as well as to normal development and inflammation. It is increasingly clear that Wnt signaling maintains proliferative capacity and lack of differentiation in crypts; its absence permits differentiation in villi; and constitutive Wnt activity is responsible in large part for dysregulated cell proliferation in colorectal and other GI tumors.

Mechanisms that pattern the undifferentiated embryonic gut tube into individual digestive organs

The GI tract and its evaginated derivatives (liver, pancreas, and biliary system) are a paradigm for inductive tissue interactions in development and, in particular, epithelial-mesenchymal interactions in organogenesis. Recent studies help define how undifferentiated endoderm is specified during embryogenesis in response to extraneous signals and the activities of tissue-restricted transcription factors and indicate how these activities combine to confer tissue- and organ-specific properties. The identity of some tissue-restricted transcription factors that regulate gut development is known, though many others remain to be discovered. There is also growing, though still limited, understanding of chromatin states that distinguish the precursors of some embryonic digestive organs. In parallel, cancer biologists are gaining a better understanding of epithelial-stromal (mesenchymal) interactions in neoplasia; thus, the principles of developmental interactions in digestive organs are likely to extend into the realm of tumor biology.

Growth and Integrative Physiology

Molecular events underlying intestinal growth and adaptation

Significant progress has been made in understanding changes in gene expression and cell signaling pathways that are induced by the loss of intestinal mass, such as occurs during bowel resection and other gut injuries and during the adaptive response that follows injury. Maintenance of intestinal homeostasis during development and adult life requires a proper balance among cell proliferation, apoptosis, and differentiation and involves interactions between epithelial and other cell types in the intestinal wall, including mesenchymal cells, such as fibroblasts. Understanding the molecular pathways that mediate normal intestinal growth and the response to injury and how extrinsic stimuli, such as nutrients, affect their activity is crucial for development of interventions to maintain intestinal mass and function. In particular, studies to elucidate the stem cell niche response following gut resection or injury (e.g., from ischemia, radiation, or trauma) may provide novel therapeutic targets to enhance gut mass and function.

Regulation of intestinal growth: roles of nutrients, trophic factors, and neurohumoral signaling

Evidence from animal models and human subjects with short bowel syndrome suggests that intestinal adaptive growth is regulated by several key hormonal mediators, including

glucagon-like peptide-2 (GLP-2), insulin-like growth factor-1 (IGF-1), epidermal growth factor, and growth hormone. However, their mechanisms are still poorly understood, including the involvement of other cell types besides enterocytes in the intestinal growth-stimulating effects.

Integration of brain-gut signaling, metabolism, and mucosal biology in the regulation of body mass

Considerable progress has been made in understanding how the presence of nutrient stimuli in the gut lumen is sensed by endocrine cells and nerves. This information is crucial in the normal digestive processes that occur in the gut and may be altered in disease. The presence of luminal nutrients is also important in the short-term regulation of food intake. Evidence from rodent models and human studies suggests that two GI hormones, CCK and PYY, are involved in the regulation of food intake via activation of neural substrates in the brain-gut axis. Moreover, long-term changes in the macronutrient content of the diet can alter the sensitivity of the brain-gut axis and may lead to changes in body mass.

Role of the nervous system in GI inflammation

Research has provided new insights into neuroimmune relationships that may facilitate translation of basic science into therapeutic applications, particularly with regard to GI inflammatory diseases. One example is the cholinergic anti-inflammatory pathway, which modulates release of pro-inflammatory mediators in models of colitis, ischemia-reperfusion, postoperative ileus, and pancreatitis. Neuronal signaling pathways in the gut are affected by inflammation; studies suggest that changes in function of the mucosal serotonin transporter and other neural pathways may underlie the altered motility, secretion, and sensation seen in inflammatory gut disorders.

Digestion and Metabolism

Diversity in genetic pathways for absorption of cholesterol and other sterols

An enterocyte membrane transporter (NPC1L1) specific for intestinal cholesterol uptake has been identified. Research has also advanced the understanding of the sensing and discrimination of subtle structural differences between cholesterol and plant sterols (sitosterol) and identification of sterol efflux pumps (ABCG5/G8) that minimize entry of plant-derived cholesterol mimics into the systemic circulation through selective export into the lumen. The basolateral cholesterol efflux-pump, ABCA1, has been identified, and its importance in the production of plasma HDL has been defined. Collectively, these advances have greatly expanded our understanding of the complexities of whole body cholesterol homeostasis in health and disease.

Hierarchy of ligands and receptors for intracellular signaling or metabolic compartmentalization of nutrients

The role of nuclear hormone receptors (FXR, LXR, PPARs) and other transporter/acceptor proteins (FABPs/FATPs) in energy sensing and in the maintenance of weight has been uncovered. In addition, new information concerning the metabolic compartmentalization of fatty acids (DGAT1/DGAT2) and mono-glycerides (MGAT1/MGAT2) has provided novel targets for obesity treatment. Finally, the development of innovative systems to probe the dialogue between the host and luminal bacteria has expanded understanding of the relevance of the luminal bacterial environment to digestive and absorptive functions.

Novel functions for genes involved in intestinal lipid absorption

Conserved pathways in intestinal and hepatic lipid absorption have been implicated in lipid antigen presentation and innate immunity. In particular, emerging data strongly suggest that the microsomal triglyceride transfer protein is responsible not only for lipidation of the export protein apoB, but also for lipid antigen presentation by the major histocompatibility molecule CD1d. In addition, research indicates that apolipoproteins involved in lipid export (apoE) also participate in lipid antigen presentation by CD1 molecules. Also noteworthy is the discovery that the peptide transporter, hPEPT1, may play a role in bacterial peptide presentation.

Nutrient and Fluid Absorption and Secretion

Blurring of classical boundaries of absorptive and secretory cell types

The intestinal epithelium is composed of a variety of cell types that are intermingled in a single layer that serves as a primary barrier separating the gut lumen from the body. Studies of intestinal epithelial development have revealed new pathways that regulate the balance among these different cell types, most notably Wnt signaling in regulating epithelial proliferation, as well as Math-1 and Gfi in regulating the census of secretory cell types. The molecular pathway for intestinal epithelial differentiation to absorptive cell types has yet to be established. With the constellation of absorptive and secretory proteins being defined, there is also increased interest in distinguishing gradations of function. Recent studies have revealed fluid and sodium absorptive functions in the structures of the colonic crypt that challenge our understanding of how the intestinal epithelium works in health and disease.

Epithelial barrier function

Researchers are investigating the molecular basis for the regulation of barrier function. Elucidation of the function of claudins, occludin, and other tight junction proteins is progressing rapidly. The coordinated action of TNF-α on barrier function and absorptive transporters, without effect on chloride secretion, is a new and important facet of intestinal regulation. Specialized mechanisms by which intestinal epithelial cells actively contribute to body defense through secretion of antibacterial peptides and repair of a disrupted epithelial layer are being defined. Complementary to understanding the barrier is research on the molecular basis of cellular water transport. Cloning of water channel (aquaporin) molecules in 1991 opened the door for advances in understanding cell and tissue fluid transport and led to the awarding of the 2003 Nobel Prize in Chemistry. Research on water channels sets the stage for understanding the pathways regulating barrier function versus fluid transport function.

Gut factors and epigenetic regulation of food intake and energy metabolism

The discovery of non-mutational regulation of gene expression that can be passed through generations has ushered in an era of new understanding about disease predisposition. For example, studies have shown that the offspring of European women undergoing starvation during World War II are predisposed to a higher incidence of diabetes. These observations validate a need for more studies to evaluate this mode of regulation. The study of nutrient absorption is now integrating data on the regulation of food intake (satiety). Ghrelin is a recently discovered peptide hormone that displays strong growth hormone-releasing activity and has a stimulatory effect on food intake and digestive function while reducing energy expenditure. Research on ghrelin has

led to new insights into how this hormone produced by the stomach connects the endocrine control of nutritional homeostasis through the brain-gut interactions.

Characterization of iron absorption

It is widely recognized that iron homeostasis in the body is almost exclusively regulated at the level of intestinal iron absorption because, while tissues such as the liver can readily store iron, the ability to excrete excess iron is poor. However, research on iron overload and iron deficiency syndromes has uncovered proteins originating from the liver and intestine that play a key role in the regulation of iron absorption in the intestine. Hepcidin and hephaestin were the first proteins to be ascribed a role in iron absorption. Other proteins that underlie genetic disorders of iron transport, including HFE and hemojuvelin, might also be involved. Exploiting these discoveries will require a more integrated approach to understanding intestinal absorptive function than we can currently pursue, as well as a stronger understanding of the cell types mediating absorption and their response to stimuli.

Neurophysiology and Motility

Diversity in the structure and functional organization of the enteric nervous system

In addition to nerve and smooth muscle cells, normal functioning of the ENS requires participation of the interstitial cells of Cajal (ICC), glial cells, and enteroendocrine cells. It would not be possible to generate the motor program stored in the ENS without patterned electrical activity and synaptic connectivity provided by the ICC. These findings have implications in human physiology and pathophysiology as abnormal networks of ICC have been reported in patients with a variety of motility disorders. Glial cells play an important role in synaptic transmission plasticity and immune protection. The neurotrophic factors that are produced by glial cells have strong anti-apoptotic effects on colonic epithelial cells, which may be responsible for their protective actions during mucosal inflammation. Understanding the cellular elements within the ENS will be critical to understanding its physiology and pathophysiology.

Brain-gut interactions in the pathogenesis of functional bowel disorders

Progress on functional GI disorders, such as IBS, can be attributed to a better characterization of the neurobiology of brain-gut interactions. The corticotropin-releasing factor (CRF) signaling pathway is the best described brain-gut circuit closely related to the pathogenesis of IBS. A CRF receptor antagonist directed at normalizing a sensitized CRF system holds great promise for the treatment of IBS and cyclical vomiting syndrome. Another major advance is the ability to image the living human brain, making it possible to investigate the role of genetic factors and receptor physiology on the pathophysiology of symptoms and, thus, to provide a more precise endpoint to evaluate therapeutic interventions. Finally, characterization of the 5-hydroxytryptamine (5HT, also known as serotonin) receptor signaling system in the ENS may be important for the pathogenesis of a subset of IBS and represents an important target for new therapeutic approaches.

Stem cell technology for neuron regenerative therapy

Neural crest stem cells have been shown to persist in the adult gut and to undergo changes in self-renewal. Cell-intrinsic differences

between stem cells from different regions regulate the generation of neural diversity. These exciting revelations suggest a new mechanism for regeneration of intestinal neurons after injury or disease. Further efforts should be directed toward identifying molecules and pathways that promote neural proliferation and differentiation in the gut and/or guide the growth of enteric axons to their targets.

GI tract in the regulation of satiety and energy homeostasis

Recognition of the pivotal role of gut hormones in glucose homeostasis has opened up new therapeutic options for the treatment of obesity and type 2 diabetes mellitus. Most importantly, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) promote insulin biosynthesis and islet beta cell survival. GLP-1 also inhibits glucagon secretion and gastric emptying and induces satiety. The multiple actions of these gut hormones have been exploited to develop novel therapeutics in the treatment of diabetes and disorders of energy homeostasis. Rational manipulation of the neuroendocrine pathways regulating appetite may be used to treat obesity. Another exciting finding is that gut microflora may contribute to the pathophysiology of morbid obesity through differing capacities to harvest energy from the diet, which suggests that the gut microbiome may be a biomarker, a mediator, and/or a new therapeutic target for people suffering from obesity.

Microbiology and Microbial-Host Interactions

Genomic analysis of the microbial population of the human colon

Testing hypotheses about the effects of the colonic microflora on human health has been hampered by the need to rely on cultivation-based methods for characterizing the microflora, an approach that is both time-consuming and unreliable. A newly available molecular approach, the amplification and sequencing of bacterial 16S rDNA and possibly other highly conserved genes, makes it possible to characterize the intestinal microflora more quickly and accurately. Researchers can now assess the species composition and contributions of the microflora to causation or exacerbation of such health problems as IBD, colon cancer, and obesity.

Moving from species composition to microflora function

Taking a "census" of the bacteria that are present in the colon at any particular time is important, but the species identity of a microbe does not usually reveal its metabolic potential. The metabolic potential of a microbial population can now be assessed by genome sequence analysis of cultivated members of the microflora and metagenomic analysis of the entire bacterial population. In addition, a better understanding of important bacterial products such as enzymes, toxins, and hormone-like compounds will make it possible to assess the role of bacteria in intestinal diseases at the molecular level.

Composition and functions of colonic end-product users: the archaea and sulfate-reducing bacteria

Although research on the human colonic microflora has focused on the numerically predominant populations and clinically significant minor populations, such as the *Enterobacteriaceae* and *Enterococci*, further studies have demonstrated the importance of a minor population that consists of fermentation end-product users, such as the methanogenic archaea and sulfate-reducing bacteria. For their carbon and energy needs, these microbes use hydrogen and carbon dioxide from the

fermentation of dietary polysaccharides and sulfate from fermentation of host-produced polysaccharides, including mucins and mucopolysaccharides. Such characteristics may increase the efficiency of the colonic fermentation of polysaccharides, and their products, such as methane and sulfide, are likely to have significant effects on the human body.

Horizontal gene transfer among human colonic bacteria

It is now known that bacteria in the colon interact genetically and metabolically with each other. Bacteria, unlike humans and other mammals, do not experience species limitations and are, therefore, able to transfer DNA across species, genus, and phylum lines. These transfers can involve antibiotic resistance and toxin genes that might contribute to intestinal disorders, but the extent or types of genes transferred is unknown.

Mucosal Immunology

Role of the intestinal microflora in the maintenance of mucosal immune homeostasis

The mucosal immune system is unique in that it lies in close proximity to an enormous consortium of commensal organisms that play multiple roles in maintaining gut homeostasis, including the prevention of colonization by pathogens and the promotion of epithelial cell repair following damage. These organisms are separated from mucosal lymphoid elements by a single layer of epithelium and overlying mucus that prevents wholesale entry of the bacteria. Nevertheless, it has been shown that commensal organisms do enter the mucosa via Peyer's patches and are taken up by dendritic cells (DC) in these lymphoid structures. An additional mode of entry of commensal organisms is via DC in the lamina propria, which extend processes between epithelial cells and take up organisms. This process is enhanced in epithelium exposed to Toll-like receptor (TLR) ligands. Such limited commensal uptake leads to the production of IgA antibodies, which function to reduce further bacterial uptake by coating organisms and preventing colonization. It also leads to the induction of regulatory T cells that control T cell responses to commensal antigens in the mucosal lumen and, thus, prevents the mucosal microflora from inducing inflammation.

Role of epithelial cells in mucosal host defense and inflammation

Intestinal epithelial cells produce chemokines and cytokines that initiate innate immune cell responses and, thus, set up a first line of defense against the intrusion of harmful organisms into the mucosa. Many of these responses are induced by TLRs and nucleotide oligomerization domain-LRR receptors interacting with microbial components. Epithelial cells also produce substances such as thymic stromal lymphopoietin (TSLP) that influence DC function and, thereby, determine the nature of T cell differentiation that occurs in relation to mucosal antigenic stimulation. Additionally, epithelial cells transport IgA via the polyimmunoglobulin receptor and IgG via the neonatal Fc receptor; in doing so, they carry antibacterial agents to the luminal surface and/or move immunoglobulin/antigen complexes in a bi-directional manner across the epithelium. Finally, epithelial cells produce antibacterial substances, including defensins (cryptins) and lectins that regulate the bacterial population in intestinal crypts and contribute to the development of IBD.

The role of antigen-presenting cells and other leukocytes in the mucosal immune system

Researchers are defining the biology of leukocytes and their role in innate (neutrophils,

eosinophils, and macrophages) and adaptive (DC and lymphocytes) immunity in numerous infectious, allergic, and inflammatory diseases of the gut. The DC is a key cellular player in the mucosal immune response; as such, it plays a role in mucosal host defense and in the pathogenesis of IBD. Studies of the function of the mucosal DC revealed that these cells are, as a population, unique and contain several sub-populations with unique functional properties, such as directing the differentiation of B cells into IgA-producing cells through the elaboration of B cell differentiation factors, including BAFF and APRIL. Evidence has emerged that mucosal DC may be uniquely involved in the induction of regulatory T cells in the mucosa via the production of TGF-β, in addition to the induction of Th17-producing cells via production of IL-6 and TGF-β. Thus, DC control the balance of effector cells and regulatory cells at mucosal sites.

Trafficking of mucosal cells to the mucosal immune system

Advances have been made in understanding how and why the mucosal immune system is unified by a cell circulation system that ensures that cells generated within the inductive areas of the system—the Peyer's patches and other lymphoid follicles—"home" back to the effector areas, the GI lamina propria and other "diffuse" mucosal areas in other organs. Early studies focused on the role of integrin/integrin receptors, particularly that of the $\alpha_4\beta_7$/MAdCAM-1 combination, in gut homing. Newer work has established that regional expression of epithelial chemokines in the small and large intestines is indispensable in the homing process. A major finding is that retinoic acid (vitamin A) acting through its receptor (RAR) induces IgA plasmablasts (T cells) to express homing receptors for the gut with regulatory capacity. It is now apparent that the traffic of cells in, around, and outside of the mucosal immune system is highly choreographed.

Mucosal unresponsiveness (oral tolerance) and regulatory T cell development

Researchers have improved our understanding of oral tolerance and the possible harnessing of its underlying mechanisms to the therapy of mucosal inflammation. A significant step came with the demonstration that, while oral tolerance could be due to exposure of mucosal cells to high doses of antigen in the absence of adequate T cell co-stimulation, it is more characteristically due to exposure of mucosal cells to low doses of antigen and the induction of regulatory T cells. Further work has established that the most important type of regulatory cell mediating oral tolerance is the "natural" regulatory T cell that develops in the thymus and is defined by its expression of surface markers, such as CD25, and a transcription factor known as FoxP3. Another regulatory cell that can develop in the mucosa and that may also mediate oral tolerance is the Tr1 regulatory cell, which lacks high-level FoxP3 expression and develops in relation to exogenous rather than self antigens. Factors that determine whether a mucosal antigenic stimulus will result in a positive immune effector response important for host defense or a negative regulatory T cell response important for maintenance of an unresponsive state and prevention of mucosal inflammation are still poorly understood, but may be due to the effects of TLR ligands.

Mucosal vaccination

Researchers have expanded our knowledge of the factors controlling the generation of both humoral (IgA and IgG) and cellular effector responses in the mucosal immune system. The follicle- and T cell-centered view of IgA-producing B cell differentiation has had to make room for a second pathway of IgA-producing B cell development, since it is clear that IgA-producing B cells develop in relation to exposure to components of the

commensal microflora in the absence of T cells, CD40 ligand, or mucosal follicles. This pathway of IgA-producing B cell development could be viewed as a more "innate" pathway, given evidence that it occurs in response to innate receptors, such as TLR receptors, and may be triggered by T cell-independent non-protein antigens. Extensive study of the mucosal adjuvant, cholera toxin, has provided important insights into the function of mucosal adjuvants. Thus, the picture that emerges is that mucosal adjuvants induce mucosal immunization, rather than tolerance, because they activate DC to express surface molecules and cytokines that activate effector T cells, rather than regulatory cells.

GOALS FOR RESEARCH [7]

DEVELOPMENT

Research Goal 1.1: Develop new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system for research and therapeutic applications.

Investigations into the origins and biology of intestinal stem cells (ISCs), mesenchymal stem cells (MSCs), and, to a lesser extent, neural stem cells (NSCs) have evolved to a point where it is possible to envisage new therapies based on stem cell biology. The identification of Lgr5, for example, as a specific functional marker for ISCs and a detailed elucidation of the regional factors that manage the ISC niche, such as those deriving from Notch and Wnt/β-catenin signaling pathways, open the possibility for the development of cell culture systems and, consequently, organ engineering with clinically relevant applications. Similarly, the recent illumination of the ways in which MSCs can be differentiated into a variety of intestinal cell types, such as neurons and endothelium, together with their unique biological properties, has important ramifications. MSCs are particularly appealing because of the relative ease by which they can be purified, manipulated, and administered for the treatment of diseases as diverse as intestinal ischemia and graft-versus-host disease. Developing methods to identify, isolate, and use ISCs for a wide variety of clinically relevant tissue engineering applications would also have enormous implications for tissue repair and organ transplantation. The advances that have been made in MSC and ISC biology need to be extended into a better understanding of NSCs, which hold similar promise for neurologically derived diseases of the gut. Finally, new stem cell technologies are needed to test hypotheses concerning the role of stem cells in cancer.

Objectives:

- Develop new markers to identify different stem cell populations of the digestive system.
- Develop new methods for isolation of stem cell populations.
- Develop new methods for cultivation of stem cell populations.
- Understand molecular pathways necessary for lineage differentiation of stem cells.
- Devise assays for characterization of specific stem cells and lineages.
- Devise animal models for development of potential therapeutic applications.

[7] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

Research Goal 1.2: Understand how particular cell and tissue niches are generated and maintained in the embryonic pancreas, liver, biliary tree, and digestive tract.

An important challenge in development and homeostasis of all tissues is to understand how a limited number of signaling pathways are able to generate enormous diversity. This question is starting to yield insights in the GI tract, where the roles of the Wnt, Notch, Hedgehog, BMP, Lgr5, and FGF pathways, among others, are being defined. Recent advances help delineate how these widely expressed signaling pathways act in concert to generate tissue- and organ-specific structures and functions, and they establish the GI tract as an exceptional model system in which to study developmental mechanisms.

Objectives:

- Apply diverse model systems to investigate aspects of gut development that are best approached through biochemical, genetic, and developmental studies in *Drosophila*, chicken, and zebrafish.
- Develop tools that permit accurately targeted genetic studies in the gut of various animal models, particularly a stable repertoire of transgenic animals that faithfully express Cre recombinase, green fluorescence protein or beta-galactosidase reporter genes, or toxigenes, ideally in inducible forms.
- Exploit the identification of intestinal epithelial stem cell markers to understand pathways governing the development of the diverse epithelial cell types that populate the intestines, stomach, pancreas, and biliary system.

Research Goal 1.3: Exploit the advanced understanding of Wnt-APC-β–catenin signaling in human epithelial function to develop new, effective treatment strategies for colorectal cancer. (See also Goal 4.11.)

The Wnt signaling pathway distinguishes the functions of crypt progenitors from those of differentiated villus epithelial cells, and its dysregulation underlies development of colorectal cancer, the second leading cause of U.S. cancer deaths. Wnt signaling maintains proliferative capacity and lack of differentiation in crypts, its absence permits differentiation in villi, and constitutive Wnt activity is responsible in large part for dysregulated cell proliferation in colorectal and some other GI tumors.

Objectives:

- Identify small molecules that interfere with distal steps in the Wnt signaling pathway for potential therapeutic use in cancer.
- Identify other signals that impinge on β–catenin stability and activity in colorectal epithelial cells and might serve as alternative targets for pharmacologic therapy.

Research Goal 1.4: Delineate specific signaling pathways, transcriptional regulation, and other interactions that mediate critical patterning events in gut endoderm, which generate and maintain its distinctive major derivatives (GI tract, liver, and pancreas).

Development and homeostasis of the developing and adult digestive system represent the outcome of interactions of cells with one another and with their surrounding matrix. Signals that emanate from these interactions drive tissue- and cell-specific transcriptional programs, and their disturbance is likely responsible for many disorders that are currently treated empirically. Improved understanding of essential signaling mechanisms will enable rational, targeted therapy.

Objectives:

- Delineate the relative contributions of specific signaling pathways and transcriptional regulators

in gut development and learn how the intersection between extrinsic and cell-intrinsic signals drives development.
- Distinguish factors whose functions are restricted to the developmental period from those that continue to influence critical activities in adult organs.

Research Goal 1.5: Translate advances from laboratory research in gut development to identify disease mechanisms and therapeutic targets for diverse GI disorders (e.g., congenital disorders, cancer).

In the long term, knowledge gained from basic research must be translated into a clear understanding of how specific developmental and homeostatic pathways are affected in individual GI disorders. Such understanding will lead to strategies for rational intervention to prevent development or progression of disease.

Objectives:
- Recognize the specific molecular defects associated with particular congenital diseases or disorders and with tissue metaplasia and cancer, especially Barrett's esophagus, gastric intestinal metaplasia, intestine-type gastric cancer, pancreatic *in situ* neoplasia and adenocarcinoma, and non-infectious hepatic disorders.
- Integrate molecular databases (e.g., gene expression, chromatin-immunoprecipitation, cis-element analyses) with functional studies (e.g., siRNA, genetically engineered animal models) to identify new pathways and to better appreciate underlying regulatory circuits.

GROWTH AND INTEGRATIVE PHYSIOLOGY

Research Goal 1.6: Define the physiologic basis for intestinal growth and adaptation and alterations with aging. (See also Goals 6.1 and 9.1.)

Maintenance of intestinal homeostasis during development and adult life requires a proper balance among cell proliferation, apoptosis, and differentiation and involves interactions between epithelial and other cell types, including mesenchymal cells such as fibroblasts. Understanding the molecular pathways that mediate normal intestinal growth and the response to injury and how extrinsic stimuli affect their activity is crucial for development of interventions to maintain intestinal mass and functional capacity. Intestinal adaptive growth is regulated by hormonal mediators, including GLP-2, IGF-1, and epidermal growth factor. Understanding the mechanisms by which these and other hormones affect gut growth is essential for developing therapies for individuals with intestinal failure, including patients who require parenteral nutrition.

Objectives:
- Determine downstream mediators of growth factor signaling that affect enterocyte proliferation and apoptosis, including the neural pathways that regulate hormone action.
- Understand cross-talk and synergism among intestinotrophic peptides, growth factors, nutrients, and other growth-promoting molecules using animal models.
- Characterize the molecular basis of stromal-epithelial interactions in gut injury and repair to identify potential therapeutic targets using transgenic models, microarrays, and proteomics.
- Develop strategies that leverage intestinotrophic mediators in the treatment of short bowel syndrome, IBD, intestinal damage induced by cancer chemotherapy, and ischemic injury.
- Develop novel methods of tissue engineering utilizing knowledge of the stem cell and its niche to create functional neomucosa.

Research Goal 1.7: Define the physiologic basis for energy balance, appetite, and satiety and their roles in obesity. (See also Goal 1.10.)

Disorders of energy balance, including obesity, diabetes, and the metabolic syndrome, are increasing in prevalence among adults and children, imposing severe personal and economic costs on individuals and society. Experimental and empirical evidence, including patient outcomes after bariatric surgery, point to neuroendocrine communication between the gut and the brain as a crucial element in understanding the pathogenesis of these disorders. Integration of the function of the brain-gut axis with other sites that regulate energy balance, including liver, pancreas, and adipose tissue, is essential to understanding the pathophysiologic basis of metabolic disorders. Understanding how the presence of nutrients in the gut lumen is sensed by endocrine cells and nerves is critical for treatment of diseases in which the signaling pathways are compromised and for the development of therapeutic strategies for the regulation of food intake and body mass. Some gut hormones (CCK and PYY) regulate food intake via activation of neural substrates in the gut-brain axis. Long-term changes in the macronutrient content of the diet can alter the sensitivity of the gut-brain axis and may lead to lasting changes in body mass.

Objectives:

- Assess the localization, expression, and regulation of gut peptide receptors and ligands influencing food intake within the gut.
- Integrate physiology with peptidomic, proteomic, metabolomic, or other technologies to identify adipokines secreted by fat cells that influence gut function and determine how signals originating from the gut affect adipose tissue biology, metabolism, and the brain-gut axis.
- Assess the synergistic or inhibitory interactions between pre- and postprandially released gut peptides influencing food intake and metabolism and examine the modulation of these interactions by dietary status and composition.
- Understand the mechanisms by which bariatric surgery leads to changes in body mass.
- Develop therapeutic interventions to mimic the effects of bariatric surgery on body mass.
- Develop effective, peripherally active substances for control of food intake and body weight, such as gut hormone-based therapies to target appetite circuits.
- Develop new assessment tools, technologies, and biomarkers to measure activity, nutrient intake, and energy balance.
- Define genetic risk alleles in order to discover critical pathways involved in obesity and satiety.
- Determine the mechanisms by which different macronutrients alter appetite and satiety.
- Understand the interrelationship of basic behavioral factors and brain-gut-nutrient axes in maintaining or changing body mass.

Research Goal 1.8: Define the physiology of neuroimmune pathways involved in inflammation.

Interactions between the nervous and immune systems play important roles in normal and disease states in the GI tract. Research has provided new insights into neuroimmune relationships that may facilitate translation of basic science into new therapies, particularly with regard to inflammatory diseases. An example is the cholinergic anti-inflammatory pathway, which modulates release of pro-inflammatory mediators in models of colitis, ischemia-reperfusion, postoperative ileus, and pancreatitis. Neuronal signaling pathways in the gut are also affected by inflammation. For example, pro-inflammatory cytokines can alter expression and function of the mucosal serotonin transporter (SERT), which affects neurohumoral signaling via serotonergic pathways. Changes in function of SERT and other neural pathways may therefore underlie the altered motility, secretion, and sensation seen in these inflammatory gut disorders. Better understanding of neuroimmune crosstalk in GI inflammatory disease is warranted.

Objectives:

- Address mechanisms responsible for neuroimmune protective and injurious states by combining expertise in neuroanatomy/neurophysiology, immunology/inflammation, trauma, nutrition, and gastroenterology.
- Understand the cause and effect relationships between inflammation and altered neural function and the functional implications of inflammation-induced changes in neural signaling.
- Understand the role of nutrition in animal models, including lipid-based diets, in neurally mediated anti-inflammatory pathways.
- Use animal models of GI inflammatory conditions to manipulate neural signaling through pharmacological, electrical, or nutritional interventions; identify mechanisms of response and effects on morbidity/mortality.
- Develop therapeutics (drugs or devices) that are based on neuroimmune pathways targeted to GI disease (e.g., IBD) and pathologies that have GI effects (e.g., shock, ischemia-reperfusion injury).

DIGESTION AND METABOLISM

Research Goal 1.9: Develop a comprehensive profile of intestinal genes that regulate mammalian absorptive functions.

Intestinal digestion, absorption, and metabolism reflect the integrated functions of many pathways, most of which are incompletely understood. For example, the single candidate cholesterol transporter, NPC1L1, accounts for most, but not all, cholesterol transport functions of the mammalian enterocyte, and there is an unanticipated redundancy with other pumps and membrane receptors. Newer murine models are needed using double, triple, and other combinatorial transgenic approaches (e.g., humanized knock-ins), coupled with targeted knock-out and knock-down technology.

Objectives:

- Extend studies of candidate genes to examine selected absorptive and metabolic pathways (e.g., cholesterol, bile acid, micronutrients) from human populations using humanized knock-ins of informative polymorphisms.
- Develop targeted approaches to obesity, hyperlipidemia, and diabetes through testing candidate small molecule inhibitors of gene function using mice and other models.
- Integrate advances in developmental biology to understand regional differentiation of intestinal absorptive functions (e.g., ileal bile acid transporter, duodenal iron absorption) and possible plasticity.
- Develop selective siRNA and other tractable knock-down methodologies for widespread use in digestive/absorptive pathway interrogation.
- Understand the dialogue between host and luminal bacteria and the signaling pathways involved.

Research Goal 1.10: Identify critical pathways in murine and other *in vivo* models to develop targets for treatment of obesity and other disorders of nutrient absorption and metabolism. (See also Goal 1.7.)

A major challenge is to transition from hypothesis-directed, mechanistic studies of known pathways into a reverse-genetic paradigm by which the etiology and complications of complex metabolic disorders, such as diabetes and obesity, can be modeled. A complete understanding of the major pathways that mediate macro- and micronutrient absorption should focus on a reverse genetics approach to transgenesis, using information from the human HapMap project to direct the study of nutrient absorption and metabolism.

Objectives:

- Design targeted therapeutics based on informative pathways that predict development of obesity, hyperlipidemia, and diabetes.
- Identify serum and tissue biomarkers that predict alterations in pathways identified above.
- Recognize the specific molecular defects associated with nutrient malabsorption, including obesity, and defective or inappropriately increased intestinal nutrient delivery.
- Define mechanisms by which metabolic pathways interface with immune function.

NUTRIENT AND FLUID ABSORPTION AND SECRETION

Research Goal 1.11: Define pathways that regulate barrier function and transport function. (See also Goal 9.2.)

Researchers are defining the molecular components of the epithelial barrier and understanding more about their regulation. The interplay between barrier function and net transport in the gut is becoming evident. Barrier and transport dysfunction is common in multiple intestinal disorders, and research in this area will improve understanding of health and disease and provide new therapeutic targets.

Objectives:

- Examine the structure and function of proteins composing tight junctions, adherens junctions, and other elements mediating the epithelial barrier.
- Identify membrane transport proteins and intracellular chaperones of micronutrient and metal ion absorption (e.g., iron, calcium, magnesium).
- Expand use of non-mammalian models to studies of gut absorptive and secretory functions (e.g., zebrafish, *C. elegans*, *Drosophila*).

Research Goal 1.12: Define molecular pathways leading to differentiated absorptive and secretory functions. (See also Goal 9.2.)

The commonalities between intestinal development and tissue remodeling after injury are striking. Both require re-establishing equilibrium among the cell types that are required for transport functions that are essential to life. Some of the essential molecular pathways promoting secretory cell types are known, but the routes to production of absorptive cell types are much less clear.

Objectives:

- Integrate information on the role of cellular and protein diversity in creating efficient absorptive and secretory function in healthy human and mouse tissues.
- Understand epithelial development and remodeling in response to injury, especially related to signals and pathways required to create a balanced population of absorptive and secretory cells.
- Apply and develop mouse models that allow fine genetic mapping of qualitative trait loci related to complex traits and multifactorial genetic disorders of absorption and secretion.
- Develop a proteome fingerprint of cell types important to gut absorptive and secretory functions and define the functional meaning of these profiles.

Research Goal 1.13: Develop means to measure and manipulate epithelial function.

As we develop greater understanding about epithelial cell function and adaptation to different conditions, either experimental or disease-based, it is important to take advantage of advanced models and techniques to translate key findings to the human condition and to benefit from broad, interdisciplinary approaches.

Objectives:

- Develop advanced mutant mouse models (e.g., tissue-specific, knock-in, inducible mutations, humanized models, superior gene transfer methods for GI tissues) to study human proteins that mediate or regulate nutrient and fluid absorption and secretion.
- Understand the molecular and functional adaptation of individual epithelial cells of the intestine to challenge (e.g., surgery, inflammation, diabetes, obesity, or experimental manipulation).
- Develop a conceptual basis and technical approaches for direct translation between human and animal studies of barrier, absorptive, and secretory processes in living tissues (e.g., imaging, molecular diagnostics, and therapeutics).
- Foster interdisciplinary teams among clinical research, basic biomedical research, engineering, and computational fields.

NEUROPHYSIOLOGY AND MOTILITY

Research Goal 1.14: Define the basic cellular and molecular mechanisms responsible for neural activation, integration, and regulation in the ENS.

The ENS regulates motor patterns in the GI tract. This division of the autonomic nervous system has been mapped extensively in a few animal models, but important mechanistic questions remain about the organization and function of enteric neurons and glial cells. Additional studies characterizing neural reflexes, neural plasticity, growth and development, and stem cell biology are needed to allow therapeutic control of enteric neural function.

Objectives:

- Understand the ionic and cellular regulatory mechanisms responsible for enteric nerve cell activation, synaptic transmission, integration, and motor pattern development.
- Characterize the molecular phenotypes of the different classes of enteric neurons (i.e., sensory, interneurons, and motor neurons). Develop unique biomarkers to allow evaluation of the state of specific classes of enteric neurons during the development of GI motor disorders.
- Determine how enteric neurons function as a network to generate motor patterns, respond to luminal contents, produce stereotypical gut reflexes, generate sensory signals, and adapt to conditions like inflammation or stress.
- Understand the development of the ENS and how adult neural stem cells might facilitate repair of a defective ENS resulting from developmental defects or pathophysiologic damage.
- Understand the role of glial cells in maintaining the structure and integrity of enteric ganglia and in regulating the functions and health of enteric neurons.
- Understand how inflammatory cells and mediators influence neural activation and integration.

Research Goal 1.15: Understand the structure, function, and regulatory mechanisms responsible for motility in the GI tract.

The ENS exerts control over smooth muscle cells to develop patterns of contractile responses, such as peristalsis, segmentation, tonic contraction, retroperistalsis, and others. ENS control is superimposed upon spontaneous activity of the musculature (so-called "myogenic" activity of smooth muscle tissues) and contributions from a variety of additional regulatory systems. A more complete understanding is needed of the interactions of the ENS with smooth muscle cells and the mechanisms responsible for regulation of contractile behavior in order to develop targeted therapies to improve motor function.

Objectives:

- Understand the molecular signaling pathways responsible for generation of tonic and phasic contractions in GI muscles and how these pathways are altered in pathophysiologic conditions.
- Clearly define the role and mechanisms of electro-mechanical and pharmaco-mechanical coupling in generating tone and phasic contractions in GI muscles and the effects of sex hormones, inflammatory factors, and aging on these mechanisms.
- Determine the molecular basis for electrical coupling between GI smooth muscle cells and between smooth muscle cells and interstitial cells of Cajal (ICC) and the consequences of a breakdown in electrical coupling on contractile behavior.
- Determine the mechanisms and the role of calcium sensitization in response to neurotransmitters, hormones, and paracrine substances in GI contractile behavior and whether this mechanism is altered by inflammation, sex hormones, or aging.
- Determine the basis for spontaneous electrical activity in smooth muscle cells and tissues and the mechanisms for propagation of electrical activity in the generation of motor behavior of GI organs.
- Understand stretch-dependent mechanisms that regulate the excitability of GI smooth muscles and contribute to patterns such as receptive relaxation, peristalsis, and gut stasis.
- Determine the effects of inflammatory mediators on the structure, function, and phenotype of GI smooth muscle cells and ICC.

Research Goal 1.16: Develop research tools to investigate the structure and functional organization of the ENS.

The multiple constituents of the ENS are characterized by a dynamic cross-talk between the enteric neurons, glial cells, ICC, smooth muscle cells, and enteroendocrine cells. Hence, functional and structural studies need to be performed with tools that allow dynamic visualization of the activity of the relevant cells *in situ*. Characterization of receptors, channels, and signal transduction systems unique to different cell types and how they interact with luminal events are critical to understanding how information is processed in the coordination of motility, secretion, and absorption.

Objectives:

- Investigate molecular and electrophysiological characteristics of various ENS cellular components, which may be targets for new developments to treat motility disorders.
- Develop tools to visualize the state of activity of relevant cells in live tissues, organs, and systems.
- Characterize alterations in gut-based 5HT and corticotropin-releasing factor (CRF) in IBS and motility disorders, including genetic polymorphisms affecting ligands, receptors, transporters, enzymes, and/or signaling systems.
- Identify molecules and pathways that promote proliferation and differentiation of enteric neurons and/or molecules responsible for directing enteric axons to their targets.
- Define the molecular basis for chemo- and mechano-receptors in the gut to sense ingested nutrient environment and gain better understanding about interactions between nutrient and microbe-sensing mechanisms in the gut.

Research Goal 1.17: Characterize the neuromuscular phenotypes of human GI tissues.

Much has been learned in recent decades about the organization of the ENS and cellular mechanisms involved in generating normal gut motility patterns. Most information has come from studies of laboratory animals. It is important to translate this information into studies of human GI muscles to

determine the neuromuscular phenotypes driving normal human GI motility. Although access to human samples is limited, surgery for GI conditions like cancer or obesity presents an opportunity for studying human physiology.

Objectives:

- Understand the excitability and contractility mechanisms in human GI muscles. Translate knowledge obtained from animal models to human physiology.
- Understand the structure and function of the human ENS. Determine which animal models best simulate the integration and cellular phenotypes of human enteric neurons.
- Characterize motor innervation of the human muscularis and identify the major neurotransmitters, the cells that are innervated by motor neurons, and the mechanisms of post-junctional neural responses.
- Define the receptors and signaling pathways that are involved in neural, hormonal, and paracrine regulation of human GI muscle function.
- Develop methods of organ or cell culture that preserve the phenotypes of human muscle cell components. Determine methods to culture smooth muscle cells, ICC, enteric neurons, and other cellular components without dramatic changes in the native phenotype.

Research Goal 1.18: Integrate cellular events in ENS with whole system physiology and translate findings to pathophysiologic conditions.

Normal functioning of the GI tract requires different components of the ENS to operate in unison, emphasizing the importance of identifying relationships in an organismal context. Advances in neurobiology of brain-gut interaction, together with availability of new neuroimaging modalities, greatly enhance our ability to study functional GI disorders and search for new therapeutic targets. Recognition of the GI tract's crucial role in satiety signaling and control of energy homeostasis, body weight, and various metabolic systems provides a new framework to study disorders of energy homeostasis. Pathophysiologic models coupled with genomic analysis offer new opportunities to discover molecular mechanisms responsible for age-related neuron degeneration and provide avenues to reconstitute the ENS networks in diseased organs.

Objectives:

- Identify distinct brain circuits responsible for various gut functions and pain perception and characterize the signaling systems and receptors within these neural circuits using PET ligand imaging in rodent models and humans with IBS and functional dyspepsia.
- Develop contemporary techniques for probing genetic and proteomic changes that occur with age. Establish the mechanism that maintains the integrity of the ENS and its capacity to respond to altered function or "plasticity" in adulthood and old age.
- Investigate the cellular and molecular mechanisms of neural and endocrine bi-directional communication between the gut and the central nervous system (CNS) for regulation of weight and metabolic function and the associated neurohumoral events.
- Develop suitable animal models to mimic diseases of the ENS.

Research Goal 1.19: Translate knowledge of the ENS in digestive health and disease into diagnostics and therapies for human disease.

Research on the pathophysiology of human motility disorders needs to be aggressively translated into the treatment of human diseases, given the progress in research on functional GI disorders. This includes advances in neuroimaging modalities to study brain-gut interactions, efforts to unravel the complexity of energy homeostasis systems, an understanding of some of the key neural circuits in the ENS,

and knowledge of developmental biology and organogenesis, which allows for manipulation of neural stem cells in the bowel wall for replacement therapy.

Objectives:

- Determine specific gene profiles in tissues that suffer ICC or neuron loss or in tissues in the process of losing these elements and develop a molecular test to detect these pathologic changes.
- Develop neural imaging techniques to correlate individual circuits identified with symptom production in IBS patients and establish correlation with distinct genotypes through such approaches as a genome-wide search for polymorphisms and haplotypes.
- Develop neuron replacement therapy to guide the growth of enteric axons to their targets as a therapy for neural degenerative disease of the ENS.
- Characterize the molecular, cellular, and behavioral mechanisms that link changes of stored body fat to adaptive adjustments of feeding behaviors by defining the diverse blood-borne and affective neural signals that transmit information regarding nutrient status and energy stores to the brain where it is integrated with cognitive, visual, olfactory, and taste cues.

MICROBIOLOGY AND MICROBIAL-HOST INTERACTIONS

Research Goal 1.20: Determine the biologic activities of the microflora in healthy humans. (See also Goals 5.3 and 9.3.)

The normal intestinal microflora consists of a total population that is at least 10^{12} microorganisms per gram of intestinal content. This microflora achieves a mass that is equivalent to or exceeds the size of several human visceral organs, but very little is known about it. Yet, the microflora are considered to be key to the biologic basis of numerous intestinal and non-intestinal conditions, including the maintenance of physiologic homeostasis. As such, the normal intestinal microflora likely function as a separate, yet integrated, organ within humans. A major impediment to understanding this biomass is the lack of adequate methods to interrogate the composition of the intestinal microflora and its function. Evidence now exists that the normal intestinal microflora can directly influence and regulate the structure and function of the normal intestine. The specific properties and mechanisms by which the intestinal microflora accomplish this are unknown, but essential for both co-opting these mechanisms for the development of new therapeutics and for understanding disease processes.

Objectives:

- Undertake a metagenomic analysis of the microflora of healthy people and determine the extent of person-to-person or diet-related variation.
- Determine whether members of the major bacterial populations can transfer DNA to mammalian cells and test this hypothesis with *in vitro* and *in vivo* models.
- Develop a "humanized" mouse model of the microflora in which germ-free mice are colonized with the human microbiome.
- Obtain genome sequences of the gram-positive anaerobic bacteria that account for over two-thirds of the colonic microflora, but about which virtually nothing is known, for use in interpreting the metagenomic data and guiding biochemical studies of the activities of these bacteria.
- Take a census of the methanogenic archaea and sulfate-reducing bacteria found in the colons of healthy people.
- Determine whether bacterial enzymes, toxins, or hormone-like compounds affect intestinal epithelial and non-epithelial cells.
- Examine genome sequences from colonic bacteria to identify possible gene transfer events using advanced computational methods for detecting such events.
- Understand the establishment of the microflora in the neonate and the influence of breast feeding compared to commercial infant formula feeding.

Research Goal 1.21: Determine the mechanisms of host-microbial interactions that are necessary to maintain health and contribute to pathological processes in disease. (See also Goals 3.1, 5.3, and 9.3.)

For the most part, mammals live in harmony with their enteric microbes and derive health benefits that are becoming increasingly recognized. This relationship relies on a continuous exchange of molecular and metabolic signals that are essential for keeping a balance that is mutually beneficial to host and microbe. A major challenge is to better understand these complex interactions, as they are the underpinnings of both health and disease. Perturbations in host-microbial interactions can arise from numerous causes, including processes that affect human responses to microbes as well as changes in the composition or behavior of the commensal microbes themselves. These disturbances may cause or be a contributor to many diseases, including IBD, infectious gastrointestinal diseases, metabolic syndrome/obesity, IBS, colon cancer, acid-peptic diseases, and autoimmune disorders. The insights gained through further studies of host-microbial interactions will promote the discovery of new ways to maintain health, as well as to treat and prevent numerous common diseases.

Objectives:

- Determine the interrelationship of digestion, microbes, and nutrients in normal health and digestive diseases.
- Define the properties of the microflora that are associated with the maintenance and repair of the epithelial barrier.
- Determine the mechanism by which the normal intestinal microflora provides resistance against infectious pathogen invasion.
- Determine why commensal organisms generally elicit protective and anti-inflammatory responses in normal individuals, whereas pathogens elicit inflammation.
- Develop approaches to manipulating the commensal microflora subpopulations to prevent or reverse infection and inflammation.
- Design probiotics and prebiotics for maintenance or restoration of healthy microflora.
- Determine whether the composition of the microflora or microbial gene expression has a role in conditions such as IBD, IBS, colon cancer, or obesity.
- Determine whether bacterial toxins or hormone-like compounds are involved in inflammatory intestinal diseases.
- Define the role of the normal microflora in maintenance of the mucosal immune system.

MUCOSAL IMMUNOLOGY

Research Goal 1.22: Determine the role of epithelial cells in mucosal host defense and inflammation.

Epithelial cells are not passive participants in the mucosal immune response but, on the contrary, play active and perhaps key roles in the shaping and/or initiation of that response.

Objectives:

- Identify factors that regulate the expression of innate immune receptors (e.g., TLR) in epithelial cells and the effect of stimulation of these receptors on epithelial barrier function, chemokine and cytokine production, and antimicrobial peptide production.
- Elucidate the effects of factors produced by epithelial cells that affect lamina propria DC function and/or T cell differentiation, including TSLP, IL-10, and TGF-β.
- Generate mouse models expressing epithelial cell-specific deletion of key genes involved in epithelial mucosal immune function and barrier function to define the function of these genes in epithelial cell regulation of immune function.

- Characterize embryonic and adult stem cell differentiation into epithelial cells focusing on the attainment of properties that relate to epithelial immune function.

Research Goal 1.23: Understand the role of antigen-presenting cells in the mucosal immune system.

The DC is a key cellular player in the mucosal immune response and, as such, plays a major role in mucosal host defense and mucosal autoimmunity.

Objectives:

- Define the factors that influence DC maturation and function to mediate T cell effector and regulatory functions within the mucosal environment.
- Elucidate the function of DC TLR signaling with respect to positive and negative DC responses.
- Generate mouse models characterized by DC dysfunction to study the role of DCs in mucosal host defense and inflammation.

Research Goal 1.24: Understand trafficking of mucosal cells to various parts of the mucosal immune system.

Researchers have begun to establish the cellular and molecular mechanisms that ensure that cells generated within the inductive areas of the mucosal immune system "home" back to the effector areas of the system.

Objectives:

- Elucidate the factors that control chemokine-chemokine receptor interactions or other cell-cell interactions that contribute to mucosal traffic patterns.
- Generate mice that lack key components of the gut homing apparatus and, thus, allow in-depth examination of gut homing mechanisms.
- Develop a systems approach to the study of lymphocyte and DC homing that integrates the many factors that affect this process.

Research Goal 1.25: Understand mucosal unresponsiveness (oral tolerance) and mucosal regulatory T cell development.

The last decade has advanced the understanding of mechanisms governing immune unresponsiveness to antigens in the mucosal environment, particularly the function of regulatory cells that suppress responses to gut antigens (including commensal microflora and food antigens). The importance of these regulatory cells has become apparent in the study of murine models of inflammation, in which it was shown that lack of regulatory cell generation leads to colonic inflammation and possibly to allergic responses to food antigens as occurs in celiac disease and food allergies.

Objectives:

- Determine the nature of the immunological milieu of the mucosa in enhancing or retarding the development of regulatory T cell functions, such as the synthesis of TGF-β, retinoic acid, IL-35, and IL-27.
- Understand the immunological mechanisms that underlie the development of food allergies and develop methods to assess these allergies.
- Elucidate the biology of regulatory T cells with relation to the function of FoxP3 and other intra-cellular factors that control regulatory cell function.
- Develop gene therapy approaches to the enhancement of regulatory T cell function to treat chronic inflammatory states.

GOALS FOR RESEARCH

Research Goal 1.26: Understand the differentiation and function of mucosal lymphocytes and other immunologically active cells.

The intestines are in a state of physiologic inflammation that is presumed to be largely in response to the local milieu and, especially, to the presence of the commensal microflora. This state is important to mucosal defense against infections and cancer but, when dysregulated, it can result in uncontrolled inflammation.

Objectives:

- Define the unique factors that mucosalize local lymphocytes and other cell types (e.g., mast cells, mesenchymal cells) and, especially, the role of the commensal microflora.
- Determine the site of induction and factors that regulate the development of mucosal effector (i.e., Th1, Th2, Th17, and NKT cell) and regulatory pathways in intestines.
- Investigate the effect of aging on these pathways.

Research Goal 1.27: Develop mucosal vaccination strategies.

A practical aspect of studying the induction of IgA and other mucosal responses arises from the fact that the mucosal system is separated from the "systemic" immune system by the homing receptors that mandate the traffic of cells originating in the inductive sites of the system to effector sites. This implies that only mucosal immunization can effectively deal with pathogenic invasion of the mucosa. This point is particularly relevant to the prevention of HIV infection given evidence that the GI tract is a major site of initial HIV development and an important reservoir of established HIV infection.

Objectives:

- Elucidate epithelial or stromal cell factors and cytokines involved in elaboration of IgA-producing B cells.
- Understand IgG responses in the mucosal immune system and the neonatal Fc transport system.
- Develop new adjuvants that target particular aspects of the mucosal immune response.
- Develop effective vaccines for the prevention of major, epidemic, enteric viral infections.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Animal models: The current range of animal models for studying digestive diseases biology could be expanded by the development of tools that permit targeted genetic studies in various animal models within specific tissues and cell types. Validation of specific promoters and/or minigenes that drive tissue- or segment-specific gene expression in mouse and other relevant models (zebrafish, *Xenopus*, *Drosophila*) is required. Efforts to strengthen digestive disease research efforts across the scientific community might include: (1) the establishment of a coordinated system that would allow for the identification, characterization, and distribution of suitable mouse lines in a defined (e.g., C57Bl/6) background, including conditional gain- and loss-of-function alleles that can be induced in a temporally regulated manner; and (2) centralized animal resources to act as a repository of useful models. Moreover, efforts to generate novel animal models of specific GI, liver, and pancreatic disorders would accelerate research on the molecular pathophysiology of disease development. The success of translational research requires experimental approaches in animal models that can be more directly compared with human outcomes.

Therefore, equipment and chemical probes could be developed that permit parallel live tissue analyses in the human and mouse intestinal tract. The latter requires interdisciplinary research among digestive diseases researchers, chemists, and biomedical engineers.

Germ-free animal facilities: Many initiatives proposed in this research plan involve the study of live experimental animals under conditions in which the commensal microflora of the gut are strictly defined and controlled. Centralized germ-free facilities would provide qualified researchers with germ-free and/or microflora-defined mice for study under various conditions. If such facilities could develop the capability of sending these mice to distant locations, research of this sort could theoretically be conducted anywhere.

Methods to characterize the microbiome: It is critically important to develop basic tools to properly investigate and understand the composition of the normal intestinal microflora. As part of this effort, there is a need to collect and organize a curated database to accommodate large amounts of 16S rDNA and metagenomic sequence data and to develop advanced bioinformatic methods for analyzing these data. In addition, microarrays need to be developed that contain rDNA sequences from all of the major human colonic species for rapid characterization of the species composition of the colonic population.

More sophisticated analysis of sequence data, especially metagenomic sequence data, to deduce the known and undiscovered activities of the intestinal microbiome will require collaboration between experts in microbial physiology and bioinformatics. Improvements in microarray technologies could eliminate the need for any amplification step (i.e., direct sampling of community DNA in the case of the 16S rDNA array and of RNA in the case of metagenomic microarrays). Advanced computational approaches, such as codon usage algorithms, would enable researchers to detect and determine the origin of mobile elements and to systematically screen such mobile elements to ascertain what accessory genes (e.g., antibiotic resistance or toxin genes) are carried.

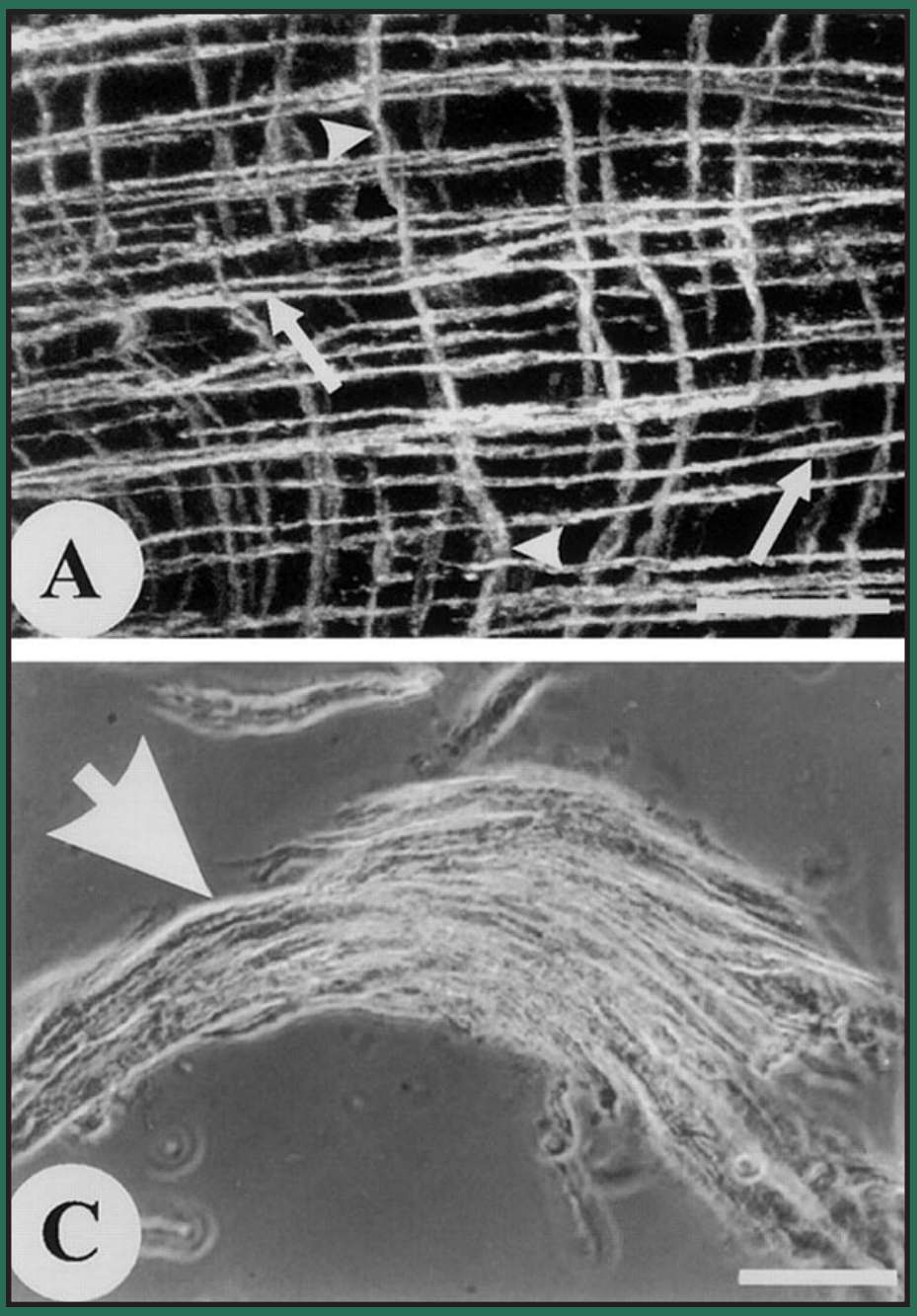
Progress in this field could be accelerated by developing microarrays that represent genes on mobile elements found in the major groups of colonic bacteria and by making these broadly available to the scientific community at a low cost. Such methodologies could also focus on defining the minor species of the microflora that have resisted cultivation to date. Finally, the development of new and better noninvasive means of quantitating the amount of energy derived from the colonic fermentation, the rate of intestinal cell turnover, and the activity of the ENS would facilitate research on the effects of the microflora in large groups of humans or animals. Noninvasive technologies, such as a swallowed capsule or MRI (e.g., to detect the fate of swallowed dyes), to monitor changes in the composition and activities of the microflora in different segments of the GI tract are priorities for development. Resources being developed under the auspices of the Human Microbiome Project, an initiative of the NIH Roadmap for Medical Research, will be critically important for meeting these challenges.

Cell lines relevant to the digestive system: Primary cells derived from humans and animal models with defined attributes would enable *in vitro* studies to characterize the signaling pathways and secretory potential of a large variety of cell types. Important cell lines to be defined and established are those related to the intestinal epithelial (and mesenchymal) stem cells, as well as native intestinal epithelial cell and DC lines. To do so, it will be important to develop better cell-specific markers. In addition, innovative techniques are required for the long-term maintenance of cells in culture under circumstances in which the cells do not undergo major changes in their characteristics. Moreover,

central facilities to acquire and maintain these cells for distribution would be helpful.

Bioinformatics: GI research would benefit from the development and implementation of novel genomic and proteomic approaches and bioinformatics databases. Investments to develop computational biologists and bioinformatics infrastructure and to foster interdisciplinary research between GI physiologists (including immunologists and bacteriologists) and computational biologists would strengthen the field. Mammalian models that provide systems biology resolution would allow integration of information from molecular regulation research directly into studies defining organismal impact without the need to create new models. For example, it might be possible to identify the role of a protein without creating a tissue-specific conditional knock-out or transgene. Centers could be developed for cell type-specific protein profiling and disease state profiling with standardized procedures and outcomes. Development of a proteome fingerprint of cell types important to various digestive disease processes, as well as to digestive development, physiology, and immunology, in mouse and humans would promote research progress. This could be augmented by the generation of large national data and tissue banks for the application of modern genomic and proteomic technologies.

Translation of genetic findings into understanding human digestive disease: Integration of genetic discovery research with studies to understand the function of newly discovered genes is required to translate basic research into opportunities to improve human health. Academia-industry dialogue could be encouraged to expand our understanding of digestive diseases in human populations. The development and coordination of regional and national databases with appropriate serum, DNA, and tissue biobanking would provide crucial resources for the entire research community.



Fluorescent and phase-contrast images of mouse stomach indicating the presence of a protein called Kit, which is found in a particular cell type involved in gastrointestinal motility known as interstitial cells of Cajal.

Image courtesy of Dr. Kenton Sanders. Used with permission of the American Physiological Society. Am J Physiol Cell Physiol *279:C529-C539, 2000.*

Functional Gastrointestinal Disorders and Motility Disorders

SUMMARY OF RESEARCH GOALS

Functional gastrointestinal (GI) disorders and motility disorders, such as irritable bowel syndrome (IBS), functional dyspepsia, and gastroesophageal reflux disease (GERD), take a significant toll on the health and well-being of many Americans. The Commission offers several research goals designed to improve our understanding of normal motility and secretory activities of the GI tract, discover the physiologic changes that lead to disease, and develop more effective therapies to prevent, treat, or reverse these disorders. Research efforts are needed on the numerous systems and processes that may be impaired in functional GI and motility disorders, including brain-gut interactions, the enteric nervous system, interstitial cells of Cajal and smooth muscle cells, pain and sensory mechanisms, the gut mucosa and musculature, the intestinal microflora, and immune and inflammatory responses. It is important to define how factors such as genetic differences, age, sex, and gender influence a person's susceptibility to these disorders. Many individuals with diabetes develop GI motility disorders, such as gastroparesis and constipation. As the rate of diabetes continues to rise in the U.S., research on how diabetes affects the GI tract is increasingly important. Ultimately, research to discover the basic mechanisms of disease must be translated into new technologies, pharmacological therapies, and behavioral strategies to effectively treat all patients afflicted with functional GI and motility disorders.

INTRODUCTION AND BACKGROUND

Functional GI and motility disorders represent common conditions seen by both primary care specialists and gastroenterologists. A functional GI disorder is characterized clinically by a constellation of symptoms that may include physiologic dysfunction such as altered GI motility and secretion, visceral hypersensitivity, and brain-gut dysregulation. A motility disorder is defined by observable disturbances in neuromuscular functioning of the enteric nervous system (ENS) and the muscularis. There is significant overlap between what have been traditionally categorized as functional disorders or motility disorders. In order to develop a more visionary research effort, some investigators believe that a new paradigm should be established that moves away from the traditional compartmentalization of functional and motility disorders and develops a more encompassing and biomechanistic framework for these diseases. The traditional delineation of "functional" versus "organic" in this area of clinical medicine is likely to be unsustainable as the pathophysiology of these diseases is discovered.

These conditions have significant impact on the American public because of their high prevalence and negative effects on quality of life, high direct and indirect costs, and the devastating consequences of the rare forms of these diseases. Irrespective of the definition or criteria applied to study their prevalence, both IBS and functional dyspepsia show prevalence rates ranging from 6-30 percent of the U.S. population. GERD, which results from disordered competence of the motor functions of the lower esophageal sphincter, affects 14-29 percent of people at least weekly and results in medication costs of $8 billion or more annually. Some patients require surgery which may be unsuccessful in at least 10 percent of patients. Estimates for prevalence of constipation range from 3-19 percent of the U.S. population with a slightly lower prevalence of diarrhea. In a burden of illness study published in 2002, GERD, IBS, and chronic diarrhea had the highest prevalence rates and each had a very significant economic burden. With respect to claims data, abdominal pain is the most frequent GI symptom reported and results in significant healthcare utilization. Thus, GI motility and sensory abnormalities result in disorders of high prevalence and constitute frequent reasons for physician consultation.

Additionally, there is a series of motility disorders whose prevalence is lower, but the impact of these disorders can be deleterious, devastating, or life-threatening. These conditions include gastroparesis (slow emptying of the stomach), chronic intestinal pseudoobstruction, Hirschsprung's disease, megacolon, and fecal incontinence. The first four appear to result from significant neuromuscular impairment, leading to impaired ability to maintain hydration, nutrition, appropriate digestion, and excretion from the gut. Fecal incontinence constitutes a significant social burden that may result in stigma, social isolation, and impaired quality of life, particularly for women.

Pathogenesis and natural history: Functional GI and motility disorders are heterogeneous and defined largely by symptoms or pathophysiologic changes. The etiologies of these disorders are not well understood. Research into the pathologic mechanisms and etiology of functional GI and motility disorders is expected to lead to major changes in the current classifications of these disorders. Dependent upon the disorder, presentation may range from altered GI motor activity, including abnormal sphincter function and/or transit (resulting in nausea, vomiting, loss of appetite, constipation, or diarrhea), to a state of heightened visceral nociception (the perception of pain, discomfort, or bloating in the gut), or a combination of both motor and

sensory symptoms. Factors that predispose patients to develop hypersensitivity may be both peripherally and centrally mediated. In animal models and human diseases, gut inflammation, gut injury, altered gut mucosal immunity, psychiatric conditions, or psychosocial factors all may modulate the reciprocal pathways between the brain and gut, inducing states of hypersensitivity. Factors leading to abnormal motor function may include reduced inhibitory neuronal activity, heightened cholinergic neural activity, loss of pacemaker cells, or abnormal responses to endocrine mediators. The specific alteration in mediators is known for only a few disorders.

Current means of control, cure, and/or prevention: The range of therapeutic agents available for the treatment of functional GI disorders and motility disorders remains limited, with no agents that can cure or prevent the disorders. The lack of agents that can cure or prevent these disorders reflects the very limited understanding of their pathologic mechanisms and etiology and, perhaps, an inappropriate grouping of patients for testing of therapies. Agents that generically speed or slow motility, or tighten or loosen sphincter tone, are used across a variety of disease states. As a class, dopamine antagonists and 5HT4 agonists function as gastroprokinetic-type agents (i.e., drugs that stimulate stomach emptying), while anticholinergics and calcium channel blockers are antispasmodics (i.e., drugs that suppress smooth muscle activity). Erythromycin has been found to have only limited use as a gastroprokinetic, even though it has a degree of motilin-like binding activity. Alosetron is a 5HT3 receptor antagonist indicated for the treatment of severe, diarrhea-predominant, female IBS patients; tegaserod, a 5HT4 receptor agonist, is indicated for female, constipation-predominant IBS patients. However, these agents are only indicated for female patients with severe disease unresponsive to first line symptomatic remedies, and both have significant labeled safety warnings. Some data suggest a role for anti-depressants in the treatment of IBS, although confirmatory, contemporary efficacy studies have either not been performed or did not demonstrate efficacy in the intent-to-treat cohort. Antibiotics and probiotics may relieve bloating, but have not been fully established as treatments for other IBS symptoms.

Whether antibiotic prophylaxis will be a successful strategy to prevent post-infectious IBS remains to be determined. Several classes of agents are in development for various functional and motility-related disorders aimed at addressing either altered states of motility or visceral hypersensitivity: corticotropin-releasing factor (CRF) antagonists, novel motilin agonists, NK antagonists, atypical benzodiazepines, kappa-opiate agonists, mu-opiate antagonists/agonists, chloride channel openers/closers, beta agonists, guanylate cyclase C agonists, other agents that act on the serotonin system, cannabinoids, and mast cell stabilizers. The range of medications being tested reflects the complexity of the control mechanisms, the redundancy of the neurohormonal mediators, and the need to more clearly understand the pivotal mechanisms underpinning the development of these syndromes.

To fully understand these diseases and develop safe and effective therapies, a major research effort is underway to address the basic mechanisms underlying the neuromuscular control, including studies of extrinsic and intrinsic nerves that control the gut, pacemaker cells and muscular mechanisms, the development of the neuromuscular apparatus, the molecular and genetic disorders associated with human disease, the afferent mechanisms that convey sensations of pain and nausea to the conscious brain, and the reflex pathways that peripherally modulate those sensations to protect the conscious brain. In addition, the social, psychological, and behavioral aspects of these diseases

are being explored, and researchers are looking for new ways to enhance disease management by improving the delivery of health care, optimizing the doctor-patient relationship, and developing medications and devices that can restore normal function or provide means to support use of the gut for nutrition, normal bowel function, and continence.

RECENT RESEARCH ADVANCES

The brain-gut axis and neurohormonal control of motor and sensory functions of the GI tract

Specific advances include an understanding that serotonin activates intrinsic and extrinsic primary afferent neurons to promote peristaltic and secretory reflexes and to modulate sensory signaling in the brain-gut axis. Identification of different serotonin receptor subtypes in the GI tract has allowed development of drugs to modulate GI motility, secretion, and sensation. Polymorphisms in the promoter region of the gene encoding the serotonin reuptake transporter (SERT) may have a role in patients with diarrhea-predominant IBS. This new understanding of GI functional mechanisms has facilitated the development of novel pharmacologic treatments for GI motility disorders, functional GI disorders, and obesity. Treatments and potential new targets for intervention include: 5HT3 receptor antagonists, 5HT4 receptor agonists, CRF antagonists, ghrelin, neurokinins, nitric oxide and other gas neurotransmitters, mu-opioid receptor modulation, cannabinoids, and mast cell stabilizers.

Role of the immune system and inflammation in GI diseases

A growing understanding of the nature and complexity of the interactions between the central nervous system (CNS), the ENS, and the immune system has led to the recognition that the arbitrary division of gut disorders as inflammatory disorders or functional disorders may be misleading. Immune activation appears to be common in GI motility disorders, although a lack of common terminology and methodology has limited comparisons between sub-groups. Immune methodology, including genetic studies, is now widely available and can be applied to the field of GI motility disorders. Abnormal physiology may be triggered by an insult or perturbation, such as an infection, and result in long-term alterations in ENS or CNS responses to subsequent stimuli. Prospective evaluations of post-infectious IBS have shown that up to 20 percent of individuals with bacterial gastroenteritis may develop symptoms of IBS or dyspepsia. Infection has been shown in epidemiological studies to confer an increased risk for development of IBS. Predictive factors show two important features relative to the pathogenesis of this disorder: (a) association of mucosal inflammation and altered mucosal immunity; and (b) association of psychosocial disturbance at time of infection. Mast cells and enterochromaffin cells have been found to be markers of mucosal immune activation in IBS in humans and in animal models. Mast cell hyperplasia is a common finding in mucosal biopsies from the large intestine of IBS patients. Changes in the mucosal immune system may also increase the excitability of neurons involved in local reflexes and central pathways in response to food antigens and chemical stimuli. Such insults to the intestine may increase mucosal permeability, rendering the mucosa more susceptible to luminal antigens and aggravating the inflammatory state.

Altered bacterial flora in functional GI disorders (including post-infectious IBS)

Luminal bacterial microflora can affect mucosal inflammation and immune function leading to neural sensitization. A rapidly growing body

of evidence suggests that important signaling pathways exist between the microflora and the gut (including signaling to enterochromaffin, immune, and nerve cells), which may contribute to normal homeostasis and may be altered in disease states such as inflammatory bowel diseases (IBD), IBS, and possibly obesity. Research on the effects of "good" and "bad" bacteria on mucosal immune function suggests the possible benefits of probiotic bacteria to either prevent or treat these conditions. Further studies are needed to determine the patient subset that might be most responsive to this type of treatment.

Interaction of stress circuitry and gut function

Researchers have shown that dysregulation of stress circuitry can affect gut function. Evidence for this link includes: (a) increased corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) reactivity to stress and increased motor and pain responses to CRH, which can be blocked by CRH antagonists; (b) increased mucosal immune activation; (c) stress-associated disruption of intestinal mucosal barrier function (i.e., increased membrane permeability, mast cell activation, and mucosal inflammation, which may lead to visceral sensitization); and (d) altered limbic system (i.e., anterior cingulate cortex) reactivity to visceral signals leading to increased pain response in functional GI disorders. The latter is enhanced by stress.

Immune response to the enteric nervous system

Autoimmune responses targeted to neuronal elements of the ENS can underlie a variety of conditions from IBS-like symptoms to chronic pseudoobstruction. Enteric inflammatory neuropathy disrupts the integrative functions of the brain-in-the-gut, including reduction in the population of inhibitory motor neurons to the musculature. Extreme loss of inhibitory motor neurons or disconnection of motor neurons with post-junctional cells manifests as disinhibitory motor disease, such as achalasia or pylorospasm in the smooth muscle sphincters, and hyperactive, disorganized contractile behavior of intestinal muscle cells, which results in pseudoobstruction. Detection of anti-enteric neuronal antibodies in the serum of patients with early symptoms of a functional GI or motility disorder may be a useful diagnostic test for inflammatory enteric neuropathy, including paraneoplastic disease associated with small cell lung cancer. Other diseases, including diabetes, cause an autoimmune-mediated visceral neuropathy probably affecting extrinsic and intrinsic nerves.

Neural stem cells (neural crest stem cells) in the gut

Researchers have discovered that neural crest stem cells persist in the gut after birth. Stem cells from other sources also show potential for giving rise to functional neurons in the GI tract. The field of directed stem cell therapy is developing and holds some promise for future clinical applications.

Development of the ENS

The molecular genetics of multiple endocrine neoplasia type 2B and Hirschsprung's disease—prototypic disorders characterized by gross and/or microscopic pathology of the ENS and associated dysmotility—have been identified. Intercellular signaling pathways involved in enteric neurodevelopment have been characterized. Mutations associated with abnormalities of neuroenteric development are known in animal models and in a spectrum of human disease processes, including:

and genetic knock-out models that have pointed to the molecular mechanisms responsible for GI neuromuscular function and disease.

Improved imaging or diagnostic techniques

Better, more quantitative, and, in many cases, noninvasive techniques have been developed to understand normal and abnormal esophago-gastric motility (e.g., high-resolution manometry, impedance manometry and impedance pH, SPECT, and MRI), to assess GI motility (e.g., stable isotope breath tests, SmartPill), and to evaluate involvement of the CNS (e.g., PET, MRI, magnetoencephalography) in functional GI disorders.

Mechanisms of obstructed defecation and fecal incontinence

Obstructed defecation and fecal incontinence present a significant burden for patients. New techniques, including the use of biofeedback, have been developed to treat these disorders with evidence from randomized, controlled trials that these treatments are effective for constipation and fecal incontinence.

Evaluation of drugs with the potential for therapy in functional bowel disorders

Many different methods are available to evaluate potential new medicines to determine whether they provide benefit in the treatment of IBS. Great strides have been made in establishing a consistent design to study new potential medicines for the treatment of IBS, including: how to collect data, how long to study treatments, and what parameters to monitor to demonstrate efficacy based on valid psychometrics and construct validity. By having a strong, consistent way to test new medicines, it is more likely that the results of studies, whether positive or negative, are accurate and, if positive, will be regarded as acceptable by regulatory agencies.

GOALS FOR RESEARCH [8]

Research Goal 2.1: Understand the molecular and cellular events that yield normal motility, sensory behavior, and integration between motility and secretory activity in the GI tract and the pathophysiology of functional GI disorders and motility disorders.

In order to identify and properly repair defects associated with GI disease, it is critical to develop a detailed understanding of the normal functioning of the gut and the brain-gut axis. Research to elucidate major signaling pathways that perform the sensory and neuromuscular functions of the GI organs or the excitability and contractile mechanisms in these organs is warranted. Studies of the physiology of ICC, which serve as pacemakers and neural mediators in the gut, may lead to new insights for methods to prevent loss of these cells or compensate for their function in functional GI disorders.

Objectives:

- Develop cell-specific markers for each cellular component involved in gut neuromuscular function and visceral sensation.
- Characterize differences in gene expression in specific cell populations in health and disease.
- Develop biomarkers that can be used to assess the health and function of specific cellular components.

[8] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

- Determine why ICC are lost in many motility disorders and how to restore this population of cells.

Research Goal 2.2: Understand the development of the GI tract and brain-gut interactions and determine how the aging process and differences in sex and gender affect gut development and function and brain-gut interactions. (See also Goal 9.7.)

The burden of many functional GI disorders varies by age and sex/gender. Studying the effects of genetics, sex, hormonal status, and aging on the development and function of cells and integrated behaviors of cells in the GI tract will provide a more complete understanding of normal GI function throughout the lifespan. This information combined with the identification of developmental or gender-specific factors that predispose the gut to motor or functional pathologies will help researchers design targeted therapies to prevent, treat, or reverse these disorders in vulnerable populations.

Objectives:

- Develop a comprehensive picture of how genetics and environmental factors affect development and maintenance of normal function of the GI tract and the brain-gut axis.
- Determine why women are disproportionately affected by functional GI and motility disorders.
- Determine how hormonal status affects the neuromuscular apparatus of the GI tract and how it might predispose the gut to abnormal motility or abnormal sensation.
- Learn the mechanisms of fecal incontinence and develop means of prevention and treatment.

Research Goal 2.3: Understand the components and functional interactions of the peripheral (autonomic and enteric) and central nervous systems in normal physiology and in functional GI and motility disorders.

The nervous system of the gut is highly complex and involves multiple cellular components, such as efferent and afferent neurons, interneurons, and glia. A primary goal for research on functional GI disorders is to distinguish the role of these nervous system cells in health and disease. Interactions between the intrinsic and extrinsic nervous systems and alterations in neural targets and effectors in functional GI and motility disorders are also incompletely understood.

Objectives:

- Define the role of the vagal homeostatic system (e.g., vagal anti-nociception, vagal anti-inflammatory reflex).
- Determine the role of the sympathetic nervous system in regulating gut and sphincter function.
- Define how neural integration is accomplished in peripheral neurons and how GI sensation integrates with central pain pathways.
- Understand the degree to which cognitive and emotional processes participate in the generation and/or symptoms of chronic functional GI disorders.

Research Goal 2.4: Understand the immune functions of the muscularis, integration between mucosal and muscle immune responses, and how inflammatory processes contribute to the pathogenesis and maintenance of functional GI and motility disorders.

The GI tract is a key point of interaction between the immune system and the environment. Many GI motility disorders are associated with immune activation. Progress in this field requires a deeper understanding of the immune function of the gut and how it relates to the development of functional GI and motility disorders. Understanding the role of inflammatory responses of resident and infiltrating immune cells (innate and adaptive immune responses) and characterizing specific populations of immune cells that either reside in or infiltrate gut tissue are important research goals. Interactions

of the immune system with intrinsic and extrinsic neurons and other cells might also influence the onset of disease. Clinical testing is warranted to evaluate the effectiveness of mast cell stabilizers and mediators on GI symptoms. With increased knowledge about immune function in the gut, researchers will be able to design new therapies to blunt the effects of inflammation-induced motility disorders and their systemic consequences (e.g., systemic inflammatory response syndrome, barrier function failure).

Objectives:

- Define mucosal functions (immune, barrier, sensing/taste) and the role of inflammation.
- Determine the interactions of pro-inflammatory immune cells and neural cells in diseases of the ENS and hypersensitivity.
- Characterize the inflammatory responses to various insults to the GI tract and develop the means to disrupt or reverse these responses.
- Characterize the effects of probiotics on mucosal-immune interactions.
- Determine the efficacy of antibiotics in prevention and treatment of post-infectious and idiopathic IBS.

Research Goal 2.5: Understand peripheral and central pain and sensory pathways and how these pathways are affected in functional GI and motility disorders.

Pain is one of the most debilitating symptoms of functional GI and motility disorders. In order to develop better treatments to combat pain, it is important to identify the ion channels expressed in nociceptive nerves and to search for specific blockers of these channels that might relieve chronic visceral pain. Understanding how generator potentials develop in nociceptive neurons and how to block or reverse the processes that lead to hypersensitivity of afferent neurons will also help researchers design new therapies. Another key issue is to determine how sensory input from the gut integrates with information from other viscera and with activity of the CNS. Progress could be made by defining how the CNS senses or processes sensory information differently in animal models and in patients with functional GI and motility disorders.

Objectives:

- Clarify enterochromaffin cell-afferent nerve terminal interactions. What are the mechanisms of afferent nerve activation and sensitization in the GI tract?
- Characterize the integration between visceral nociceptive pathways and motor pathways.
- Determine the mechanisms for GI sensation and perception of sensation and how the gain of visceral sensory pathways increases in functional GI disorders.
- Develop new agents to reduce nociception and undesirable visceral sensation.
- Characterize the sites and mechanisms of central processing of inappropriate sensation in the GI tract in normal individuals and patients with functional GI disorders.

Research Goal 2.6: Understand the noxious visceral signaling causing nausea and vomiting related to gastric neuro-electrical and/or motor dysfunction and the bi-directional brain-gut interactions.

Gastroparesis provides an archetypal disease for investigative inquiry. Chronic vomiting, a debilitating and socially isolating digestive symptom, creates potentially life-threatening disruptions in fluid and electrolyte homeostasis and compromises nutritional status. Chronic nausea remains a significant hidden disability. Nausea and vomiting usually occur in tandem and overlay with other GI symptoms as well as presenting in numerous digestive diseases. More effective treatments for nausea and vomiting would improve quality of life and physical functioning in a vast array of illnesses. A paucity of research exists

for defining peripheral noxious signaling of nausea and vomiting related to primary GI motor/sensory disturbances. Understanding normal electrophysiologic motor function would assist in unraveling the perturbed sensory signaling in postprandial nausea and vomiting, as well as the nausea and vomiting of severe gastric motor derangements as are found in gastroparesis. More research related to the autonomic nervous system and circadian patterns may provide interesting insights and lead to the development of interventions that impact the brain-gut-humoral axis.

Objectives:

- Clarify electrophysiologic normality and abnormalities, especially tachyarrhythmias, and their contribution to noxious signaling of nausea/vomiting.
- Characterize function and dysfunction of gastric and small bowel ICC and the presence, absence, and relative functional phenotypes of ICC in full thickness tissue biopsies and other GI tissue samples to identify abnormalities in slow wave generation, frequency regulation, propagation, and neural regulation.
- Characterize the impact of diet, anxiety, and sleep disruption on modulation of nausea and vomiting.
- Use animal models to understand the role of cytokines and to increase understanding of afferent signaling in nausea and vomiting.
- Determine the modulating effect of therapeutic interventions on CNS function using evidence from functional MRI (fMRI) studies.
- Understand the role of esophageal, gastric, and small bowel sensory and mechanoreceptors (in nerves, ICC, and smooth muscle cells) in the generation of nausea and vomiting.

Research Goal 2.7: Understand the role of the microflora in functional GI disorders and motility disorders.

The human microflora include the diverse collection of bacteria and other microbes inhabiting the digestive tract; little is known about the role of the microflora in health and disease. An important research focus is to understand how luminal factors such as the gut microflora, inflammation, diet, or infection influence the relative types, density, and functions of enteroendocrine cells—hormone-producing cells found throughout the lining of the digestive tract. The impact of the intestinal microflora on bi-directional brain-gut communication and the interactions between a patient's genotype and that of the microflora in their gut are key issues. Understanding these processes could provide new insights into the triggers of symptoms and symptom differences (e.g., constipation, diarrhea, or bloating) in functional GI and motility disorders.

Objectives:

- Characterize the impact of the intestinal microflora on bi-directional brain-gut communication.
- Characterize the effects of stress, diet, and infections on gut microflora.
- Determine the relationship between a patient's genotype and the microbiome.
- Determine the impact of alterations in the content of the microflora on GI function and sensation.

Research Goal 2.8: Use information from studies of animal models and cellular physiology to understand the integrated function of the musculature and the intrinsic and extrinsic nervous systems.

Animal models that mimic human disease or that recapitulate specific pathways, structures, or behaviors contributing to human disease are critical tools for understanding the relationships between cellular defects and organ- or system-level symptoms in functional GI and motility disorders. These models allow researchers to

address important questions that cannot be studied in human patients, such as how cellular elements intersect to yield tissue- or organ-level behaviors or how nerves regulate the barrier function of the mucosa. Research is also warranted to define changes in the ENS that cause inappropriate motor patterns in the gut and the contribution of the CNS to altered function in the ENS. With animal models, researchers can study how the ENS stores motor patterns and potentially translate that knowledge into new strategies to selectively change an inappropriate motor pattern to one that would be beneficial to patients with functional GI and motility disorders.

Objectives:

- Develop conceptual and/or quantitative models to demonstrate how various pathophysiologic inputs—such as stress, altered gut microflora, or neuroendocrine dysfunction—might influence motor patterns, integration between motility and secretion, and visceral sensation.
- Use animal models to determine the role of infection, metabolic disease, stress, and sex on GI phenotype, neural integration, afferent nerve sensitivity, neuro-immune responses, neuro-muscular transmission, pacemaking, and integration of information between the peripheral and central nervous systems.
- Use selective genetic models to determine the role of specific signaling pathways, neurotransmitter systems, and immune responses in normal and pathophysiologic states.
- Develop noninvasive, *in vivo* research diagnostic tools suitable for small animal research. These tools (e.g., small animal MRI, ultrasound, PET, SQUID, breath tests) could be used to screen for GI phenotypes in genetic mutants and also to test pharmacological agents.
- Develop and utilize better data mining tools for the screening and comparison of large-scale expression data in animal disease models.
- Use animal models to develop new biomarkers of gut health and function.

Research Goal 2.9: Characterize the factors in diabetes that lead to the development of functional GI and motility diseases.

Patients with long-standing diabetes are prone to development of GI motility disorders at all levels of the GI tract from the esophagus to the anorectum. These problems are increasing as obesity and cases of type 2 diabetes increase. GI complications of diabetes may be complex, severe, and substantially decrease quality of life. Common complaints include: dysphasia, premature satiety, esophageal reflux, constipation, pain, nausea, vomiting, and diarrhea. GI motility defects have traditionally been attributed to the development of autonomic neuropathy; however, recent findings suggest that additional cellular defects may also contribute to GI complications. Although few studies have addressed the changes in visceral sensory function that occur in diabetes, abnormalities in pain perception thresholds, vagal activity, and evoked brain potentials suggest that diabetes-related neural changes may be both peripheral and within the CNS.

Objectives:

- Characterize changes in neural chemical coding in the ENS and functional consequences of identifiable neuropathies associated with long-standing diabetes.
- Determine non-neuronal cells that are functionally impaired by loss or suboptimal insulin/IGF-1 signaling.
- Determine whether dysfunction or loss of neuronal and non-neuronal cells in diabetes results from poor glycemic control, loss of or defective insulin/IGF-1 signaling, or other unidentified defects inherent to the complications of diabetes.
- Develop novel biomarkers to evaluate damage to specific cellular compartments or sub-classes of enteric neurons in diabetes.
- Characterize specific motility and functional defects in animal models of both type 1 and type 2 diabetes.

Research Goal 2.10: Determine how genotype contributes to or predisposes patients to the development of functional GI and motility disorders.

A primary goal in digestive diseases research is to understand the role of genetics in the etiology, manifestations, prognosis, and therapeutic responses of patients with functional GI and motility disorders. These diseases are multifactorial and likely to be polygenic in nature. Interactions between genes and the environment also contribute to the complexities of these disorders in unknown ways. By identifying specific genetic polymorphisms or gene-environment interactions that predict disease or correlate with intermediate phenotypes (e.g., sensitivity to pain, GI transit, autonomic parameters, activity and sensory processing in the CNS), it might be possible to design early intervention strategies to prevent or blunt the development of full clinical syndromes of functional GI and motility disorders in genetically at-risk people. This may also allow targeting of therapeutics to the population most likely to receive benefit.

Objectives:

- Develop genetic epidemiological studies to discover common genetic factors that predispose patients to develop functional GI or motility disorders.
- Develop and validate endophenotypes (intermediate hereditary characteristics between the disease and the genotype) as a means of clarifying links between the genotype and the complicated phenotypes of functional GI and motility disorders.
- Utilize validated endophenotypes to clarify classification and diagnosis of functional GI and motility disorders and to foster the development of animal models.
- Utilize a pharmacogenetic approach to predict which patients might respond to specific therapies.

Research Goal 2.11: Determine the role of food in the development of functional GI and motility disorders. (See also Goal 8.8)

Growing evidence suggests that food plays an important role in the pathogenesis of GI symptoms. It is possible that specific food constituents have primary effects on gut function and sensation, rather than an intermediary effect through gut microflora. Abnormal immunologic responses to food might be linked to the development of defects in gut function and sensation and other symptoms of functional GI and motility disorders.

Objectives:

- Utilize animal models to study the influence of specific food components on gut function and gut sensation.
- Develop animal models of food allergies.
- Determine the effects of specific food components and food allergies on enteroendocrine cell populations and on the function of afferent nerve function.
- Develop patient tests to identify food allergies or hypersensitivity to food components.
- Identify and critically evaluate dietary treatments for functional GI disorders.
- Determine the role of gut taste receptors on GI function.

Research Goal 2.12: Develop new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.

Progress in alleviating functional GI and motility disorders would be spurred by the development and routine application of innovative, state-of-the-art technologies for diagnosis and treatment. Imaging approaches in both animal models and human subjects could accelerate early clinical testing and evaluation of new therapeutics and help researchers identify the most promising candidates to test in clinical trials. Improvements in noninvasive electrical recording of the GI tract for diagnostic purposes would facilitate diagnosis of patients with functional GI disorders. The development of simple, noninvasive GI motility testing modalities that can be applied on a large scale would improve

our understanding of the prevalence of these disorders in the general population. Research on the causes and mechanisms of neural hypersensitivity in relation to other functional pain disorders could make it possible to apply more general pain management strategies to functional GI disorders. Finally, a major advance in treating functional GI disorders might come from improving small bowel transplantation so that this procedure becomes as routine as kidney transplantation.

Research into the biology of stem cells will facilitate the development of stem cell-based treatments of gut disorders where smooth muscle cells, ICC, or enteric neurons are reduced, absent, or malfunctioning as in fecal incontinence, pseudoobstruction, gastroparesis, and constipation. By using stem cell biology technology and tissue engineering approaches, it may be possible to repair or replace damaged cellular or tissue components.

Objectives:

- Develop and evaluate new therapeutic pharmaceutical agents for treatment of functional GI and motility disorders.
- Develop new devices or applications of novel stimulus regimes to target vagal nerve function.
- Develop new devices, surgical techniques, or tissue replacement approaches to enhance fecal continence.
- Develop and validate standard measures for health outcomes research (e.g., primary treatment endpoints, health-related quality of life, psychosocial assessment, health behaviors, such as healthcare utilization and decreased daily function, and costs).
- Standardize behavioral treatments to make them generalizable to a broader population.
- Identify GI tract-specific stem cell populations and develop techniques to regenerate specific cell populations or tissues.

Research Goal 2.13: Evaluate therapeutic outcomes and the impact of doctor/patient interactions to determine effective treatments for functional GI and motility disorders.

Functional GI and motility disorders result from a complex and poorly understood combination of physiologic and psychological factors that can give rise to a variety of symptoms. Patient-oriented research could be pursued to define the underlying causes of the diverse symptoms of GI motility disorders. Clinical trials can be designed to compare the relative clinical effectiveness and cost-effectiveness of standard treatment approaches to innovative disease management approaches that involve novel pharmacological compounds and non-pharmacological strategies (e.g., disease education, cognitive behavioral therapy, physician education, web-based telemedicine approaches). The impact of standardized physician training programs on GI patient outcomes and cost is another important research question.

Objectives:

- Develop innovative ways to optimize healthcare delivery systems for GI disorders to enhance outcomes and reduce costs.
- Determine the elements of the healthcare provider-patient relationship that will improve healthcare outcomes, such as interview techniques, relationship-centered care, emotion management, and placebo administration.
- Determine the effect of healthcare provider education and training to enhance the provider-patient relationship on clinical outcomes, including patient satisfaction, adherence to treatment, improved symptoms, quality of life, and healthcare costs.
- Conduct randomized, controlled trials of stress management and relaxation methods, hypnotherapy, and cognitive behavioral therapy in pediatric and adult populations.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Methods to study the diversity of GI cells: Functional GI and motility disorders are complex and result from functional defects in a wide variety of cell types. At present, few well-defined animal models have been developed, and human tissues and cells are infrequently available, except from biopsies. A better understanding is required of the many cell types that produce normal GI motility and appropriate levels of GI sensation, including muscle cells, intrinsic and extrinsic neurons, glial cells, ICC, and a variety of immune cells (both resident and recruited). The development of innovative techniques to isolate and identify specific types of cells from healthy and diseased gut samples would promote progress across the field. Such techniques would allow determination of specific changes in cellular phenotype that might occur during development of a disease process and facilitate the use of state-of-the-art technologies, such as genomic and proteomic analyses.

Moreover, phenotypes of GI cells involved in motility and neural responses are not conserved adequately in cell cultures because the gut microenvironment is important to establish and maintain specific cellular phenotypes. Smooth muscle cells, for example, change radically when removed from the natural microenvironment and can no longer be considered to represent a smooth muscle phenotype within a short period in culture. Higher standards for verification of phenotypic fidelity of cultured cells need to be established. A shortage of culture models makes large-scale genomic and cell biology studies very difficult. The development of new technologies is required in order to manipulate genetic expression of GI cell types while the cells are still in their native environment. For example, enhanced spatial and temporal targeting of transgenic methodologies would enable researchers to create better, cell-specific knock-outs in GI cells. Techniques to effectively turn on and off expression of specific genes in adult animals would also facilitate research in this area.

Technologies to study the influence of the nervous system: Visceral pain is among the most debilitating symptoms of many GI disorders. Better understanding of nociception, inappropriate sensation, and sensitization of afferent neurons and pathways would enhance the development of new therapies to combat pain. Development of techniques to discriminate between different classes of afferent nerve terminals and to clearly identify nociceptive nerve terminals in living tissues should be encouraged. Dynamic imaging techniques would provide a means to study the behavior of afferent nerve terminals in the lamina propria and muscularis layers of the GI tract. A more detailed understanding of the mechanisms of generator potentials in nociceptive neurons would strengthen the field.

A better understanding of the integration between the brain-gut axis in pathophysiologic conditions and pathways of communication between intrinsic and extrinsic neurons is required. Research in this area could be enhanced by the design of: better recording methods to measure activity of the autonomic nervous system in conscious experimental animals and to correlate neural activity with motility; techniques to record from the CNS in conscious experimental animals (e.g., fMRI or PET) that correlate activity with peripheral neural activity and motility; and methods to probe the links between disorders of GI function (e.g., constipation and diarrhea) and pain and discomfort in the gut.

Systems biology approaches: The development of models or a conceptual framework that unifies disciplines related to morphology and cell biology, including anatomy, histology, histochemistry, molecular biology, and pathway

analysis, with topics relevant to physiology, such as functions of cells and integration of cellular function in tissues and organs, would enhance research to understand how cellular and sub-cellular events summate to produce whole system physiology and how cellular dysfunction contributes to pathophysiologic behaviors. Assembling and comparing databases from gene and protein expression studies of specific GI cell types in normal and pathophysiologic states might begin to reveal the many micro-defects that can lead to whole-organ or system dysfunction. Understanding specific changes in gene and protein expression that are common to specific functional GI and motility disorders might provide insights into biomarkers that can characterize these diseases more definitively. More sophisticated dynamic imaging techniques would facilitate understanding of interactions between GI cells and how discrete cellular and sub-cellular defects in genetically altered animal models contribute to function and dysfunction of tissues and organs.

Integrative biology approaches: Studies of how environmental factors and life experiences affect gut function (e.g., how stress, psychosocial co-morbidities, and impairment of CNS-ENS regulatory systems affect the gut) will help to elucidate their impact on the morphology, function, and integration of GI cells and tissues. Many integrative studies are difficult or unethical to perform on human patients. Thus, improved animal models for functional GI and motility disorders would enable researchers to explore the cause-and-effect relationship between suspected pathologic factors and the development of symptoms and disease. While it would be extremely useful to have animal models that closely mimic human diseases, much can also be learned from animals that manifest partial phenotypes (i.e., that capture specific morphologic, pathophysiologic, or behavioral aspects of human disease). A clearer understanding of what can and cannot be extrapolated from animal models to humans will help refine animal models. Complementary studies on human GI tissues and cells will enable researchers to determine whether cellular and molecular components and pathways identified in animal models are relevant to human physiology and pathophysiology. The development of better techniques for monitoring GI function, autonomic function, and brain function in genetically altered animals would increase efficiency for phenotyping animal models. In addition, genetic screens to specifically identify defective GI motility, autonomic and CNS phenotypes, and the inactivation of genes linked to defective motility phenotypes in animals would promote progress.

New model systems are required to determine the functional effects of variations in candidate genes that are reputed to alter motor and sensory functions, as well as somatization, resulting in GI tract symptoms or diseases (i.e., testing of functional genomics). Further research is also required to develop techniques that evaluate GI motility in model organisms, such as zebrafish or mice, in order to screen genes that are linked to altered bowel function. Testing human polymorphisms in vertebrate models would shed light on the consequences of genetic variation, in terms of motor and/or sensory function.

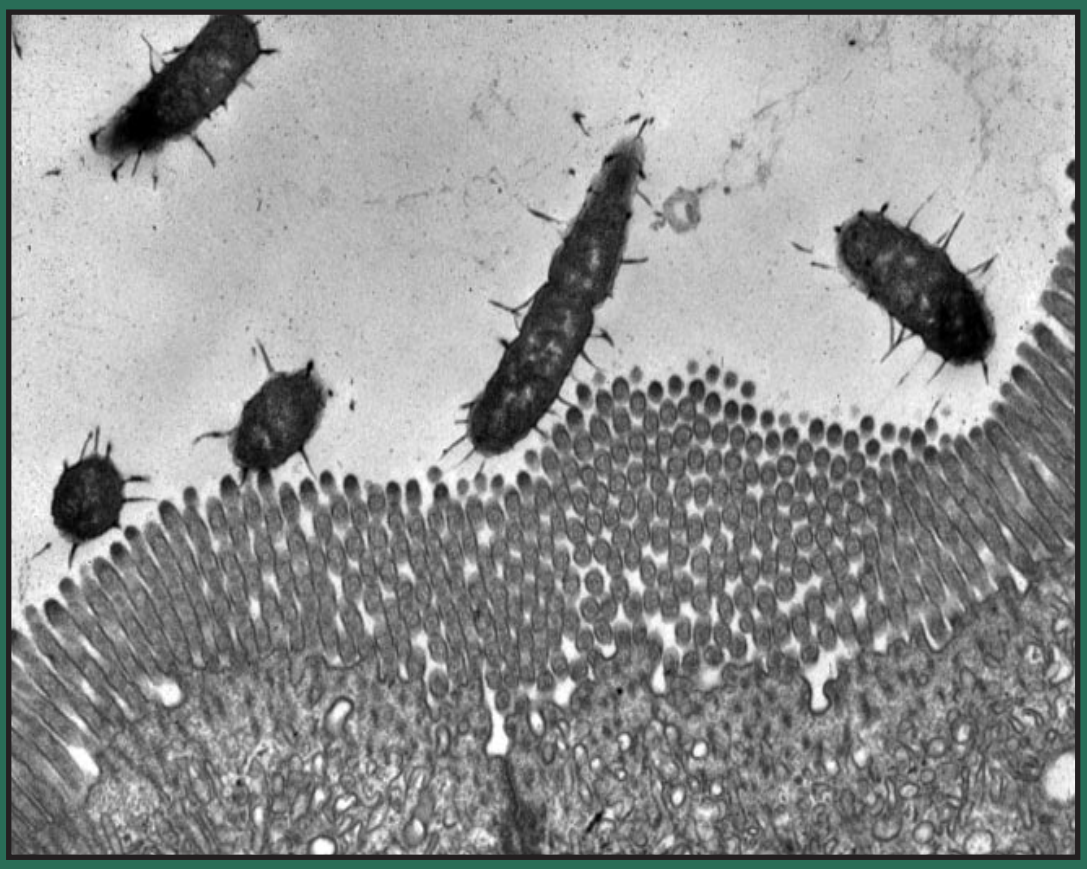
Standardized molecular definitions, biomarkers, and clinical treatments: Progress in understanding and treating GI disorders would be accelerated by the development of consensus clinical descriptions of functional GI disorders and motility disorders. Such descriptions would, in turn, enable the establishment of multicenter patient registries and tissue/reagent banks. These resources would facilitate research on the physiologic responses of human GI tissues from comprehensively phenotyped and genotyped individuals with functional GI

and motility disorders to help determine the pathophysiology and mechanisms of these disorders. Moreover, a systems biology approach would allow patient biosamples to be analyzed for genetic similarities and differences and to be used to develop biomarkers that might be used to further categorize and diagnose functional GI disorders and motility disorders.

Similarly, standardization of clinical assessments and treatments of functional GI disorders and motility disorders across patient populations and clinical research centers would be an important step toward enabling researchers to directly compare data and outcomes. Standardization of techniques and methods of analysis of brain imaging, assays for mucosal cytokines and neuropeptides, and reporting of clinical outcomes in treatment trials would all strengthen the research field as a whole.

A consortium approach would be beneficial because it would provide the large numbers of samples and controls that are required for informative studies of these disorders.

Innovative transplantation techniques: Better transplantation therapies are required, possibly based on stem cell therapies and tissue engineering. To address this challenge, more information is needed about the stem cell populations in the GI tract and how to manipulate the phenotypes of stem cell derivatives. Improvements in transplantation techniques would allow GI transplantation to become as common as with other organ systems. The development of innovative techniques to restore function within regions of GI organs through tissue engineering could also be encouraged.



Electron micrograph of enterotoxigenic *Escherichia coli* contacting microvilli on the surface of epithelial cells within pig small intestine. These organisms are a major cause of human diarrheal disease worldwide.

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Infections of the Gastrointestinal Tract

SUMMARY OF RESEARCH GOALS

Gastrointestinal (GI) infections can be caused by many types of microbes, including bacteria, viruses, protozoa, and helminths. The Commission recommends research goals that are focused on identifying disease-causing microbes, understanding what distinguishes those organisms from the normal microflora of the human GI tract, and using that knowledge to develop safe, effective therapies to prevent and treat intestinal infections. Developing new, more efficient diagnostic methods to identify specific organisms is critical for rapid treatment and for understanding the epidemiology of infectious disease outbreaks. Research is needed to develop better treatments, including vaccines, that address both the infectious agents themselves, as well as the long-term effects of GI infection in the gut and other organ systems throughout the body. The human GI tract is colonized from birth with microorganisms that are essential for normal growth and digestive function. Research on the nature and function of the human microflora could suggest strategies to manipulate these beneficial microbes to combat pathogenic organisms. Collectively, achievement of these goals has the potential to reduce the public health burden of infectious diseases in the U.S. and globally.

INTRODUCTION AND BACKGROUND

Diarrheal disease is a major cause of morbidity, with incidence rates ranging from two illnesses per person per year in developed countries to 12 or more in developing countries. Intestinal infections continue to exact an unacceptable toll on childhood and adult well-being. This is particularly true in the developing world where diarrhea has significant morbidity and mortality, especially when accompanied by malnutrition. In industrialized countries, deaths from diarrheal diseases are uncommon, but the morbidity and economic costs associated with intestinal infections remain substantial and the burden of lost productivity might exceed $19 billion per year. In recent years, developed countries in North America and Europe have experienced outbreaks of a highly toxic and antibiotic-resistant strain of the bacteria *Clostridium difficile* linked to overuse of antibiotic therapy. Although common enteric infections are not the highest priority for efforts directed at bioterrorism, research advances in infectious diseases of the digestive system could help to provide better solutions to the problem, in the event that enteric infectious agents might be used in the future as agents of bioterrorism.

Viruses, bacteria, and parasites cause protean illnesses, including acute watery diarrhea, bloody diarrhea, persistent diarrhea, chronic diarrhea, and asymptomatic infection. The etiologies of many intestinal infections remain unknown. GI infections and alterations in enteric microflora might also be related to functional GI disorders, either directly or as post-infectious phenomena such as irritable bowel syndrome (IBS). Research is also uncovering the role of specific microbes in GI inflammation, such as the ground-breaking studies linking the bacteria *Helicobacter pylori* to gastritis and peptic ulcer disease—conditions that were not previously thought to have an infectious cause—for which the 2005 Nobel Prize in Physiology or Medicine was awarded (additional information on this advance and related future research goals appear in the chapter on *Diseases of the Stomach and Small Intestine*). In addition, animal studies suggest that some species in the intestinal microflora might precipitate or perpetuate inflammatory bowel diseases (IBD) and contribute to extraintestinal manifestations of autoimmune diseases. Most recently, dramatic studies indicate that the microflora living in the intestine can have a profound impact on overall health and non-diarrheal diseases, such as obesity.

Intestinal infections pose multiple challenges. First, illness etiologies vary by geography, requiring investigative strategies that are location-appropriate. Second, accurate diagnoses are often thwarted by the polymicrobial nature of stool and the limitations of current diagnostic tools. Third, host-microbe interactions show great variability related to host-microbial genetics and host-microbial cross-talk. Enteric infections in people with the acquired immunodeficiency syndrome (AIDS), immune suppression due to organ transplants, and other immune disorders also require unique approaches.

Diarrhea continues to burden communities that lack clean water, safe food, and acceptable waste management. Underlying problems often relate to development, economic, and political issues, which are difficult for the medical community to address effectively. However, the consequences of these illnesses diminish the ability of communities to counteract these non-medical challenges. Globally, poor growth is the most important risk factor for childhood morbidity and mortality, and many children in resource-poor regions have abnormal small bowel structure and function, including crypt hyperplasia, villus stunting, hypercellular lamina propria,

decreased mucosal surface area, and increased intestinal permeability. These changes are plausibly caused by environmental exposure to contaminated food and water, but the roles of specific components of the microflora remain to be determined.

A number of promising advances in vaccination strategies have been made, including the development of effective rotaviral vaccines. Additional vaccines and other novel preventive strategies are critically needed to reduce the impact and burden of GI infections. These approaches are highly effective and provide dramatic return on investment.

RECENT RESEARCH ADVANCES

Emergence of novel agents of GI illnesses

Using the best technologies, many enteric infections remain undiagnosed. *Escherichia coli* is the most common facultative organism in the human gut, and most *E. coli* are non-pathogenic. However, a subset of *E. coli* has acquired sufficient virulence traits to cause severe human disease. Recent data demonstrate the likely etiologic role of enteroaggregative *E. coli* (EAEC) in traveler's diarrhea, persistent childhood diarrhea, and even as a cause of emergency department visits in North America. By identifying such agents, it is now possible to develop diagnostic, prevention, treatment, and complication mitigation strategies. The recognition that EAEC and other diarrheagenic *E. coli* cause disease in multiple human populations with diverse syndromes exemplifies the challenge of pathogen discovery when the agent closely resembles harmless or even beneficial microflora (e.g., commensal *E. coli*).

Emergence of enhanced virulent strains

Well-established pathogens have acquired new virulence traits. *Clostridium difficile* exemplifies a pathogen with enhanced virulence in nosocomial (hospital or other healthcare unit) and community settings, particularly those located in North America and Europe. These organisms cause increased morbidity and mortality, and development of more effective strategies to prevent and treat *C. difficile* disease should be considered a high priority.

Bacterial-host interactions

There has long been recognition that bacterial-host interactions are a two-way street, and that organisms respond to their milieu. However, specific communication mechanisms, particularly those that up-regulate virulence factors and induce injury, are poorly elucidated. Similarly, bacteria in the gut can be modulated by the host, as exemplified by adrenergic signaling to enteropathogenic *E. coli* (EPEC). This work suggests that such a mechanism might be exploited to diminish host injury.

Environment-pathogen-host interconnection

The inter-epidemic reservoir of *Vibrio cholerae* is a major source of human illness. A strong inverse association between bacteriophage "blooms" and *V. cholerae* presence in water in Bangladesh illustrates the complex interplay between the environment, bacterial control elements (e.g., bacteriophages and *V. cholerae*), and reservoirs that serve as vehicles to transmit this pathogen to humans. The intersection between reservoirs and hosts will need to be addressed to control enteric pathogens.

Mechanisms of viral pathogenesis

Novel mechanisms have been discovered for GI viral pathogenesis, including viral enterotoxins and host-pathogen interactions, such as new ways in which viral pathogens counteract the innate host response. Genetic polymorphisms have been shown to increase

non-immune mediated resistance to infection (host susceptibility) and may affect immunity to viral infections and vaccines. New animal models have led to better understanding of pathogenesis and immunity, as well as opportunities for preclinical testing of new vaccines and therapeutics. Such models include rotavirus (RV)-induced biliary atresia, RV-associated intussusception, RV-induced sterilizing mucosal immunity in mice, human RV-induced disease in rats with recurrent infection, and norovirus-induced disease in mice and piglets.

Susceptibility to infection or disease

Data have emerged linking gut disease susceptibility to changes in gut physiology. Alterations in barrier function may give rise to IBD and/or other autoimmune diseases, and acute infectious inflammatory diarrhea may predispose to IBS. Susceptibility to infection is also related to alterations in gut immunology and/or host genetics; for example, *IL8* gene polymorphisms modify clinical diarrheal disease severity.

Antiviral and intestinal parasite vaccines and therapies

The development and licensing of two new rotavirus vaccines is an important advance in the prevention of rotavirus infections, the leading cause of severe diarrheal disease and dehydration in infants and young children in both industrialized and developing countries. Genome sequencing, protein expression, and crystal structures of key proteins and viral structures inform targets for the development of new therapeutics, as well as a molecular understanding of strain diversity that may be critical for vaccine development. Virus-like particles are being studied as safe and efficient immunogens and as tools for environmental and epidemiological studies. Likewise, development and early-stage clinical testing of recombinant vaccines for hookworm and schistosomiasis, as well as identification of promising vaccine candidates for amebiasis—so-called "anti-poverty vaccine development"—are significant advances with worldwide impact.

Mechanisms of probiotic activity

The demonstration that immune and epithelial cells can communicate and subsequently discriminate between different microbial species has extended the known mechanism(s) of action of probiotics. Probiotics may exert their disease-modifying effects through one or more mechanisms that include: competitive exclusion, antimicrobial activity, enhanced epithelial barrier activity through tight junction modification and mucus production, and stimulation of anti-inflammatory mucosal and systemic effects through a number of complex probiotic-epithelial-immune cell interactions.

The progressive unravelling of these mechanisms of action has led to new credence for the use of probiotics in clinical medicine. Level 1 evidence now exists for the therapeutic use of probiotics in infectious diarrhea in children, recurrent *C. difficile*-induced infections, and post-operative pouchitis. Level 2 and 3 evidence is emerging for the use of probiotics in other GI infections, prevention of post-operative bacterial translocation, IBS, and in both ulcerative colitis and Crohn's disease. Nevertheless, it is clear that not all probiotic bacteria have similar actions or therapeutic effects.

Extraintestinal consequences of GI infection

Campylobacter jejuni is a fairly common cause of bacterial enteric infection. This organism is found worldwide and transmitted through the food supply, most typically poultry. A small subset of infected patients will develop Guillain-Barre syndrome, a severe, debilitating, potentially lethal ascending neurologic

paralysis. The chief pathogenic mechanism is believed to be induction of antibodies to the *C. jejuni* lipopolysaccharide, which also react against peripheral and central nervous system gangliosides. This is an example of autoimmune molecular mimicry following a GI infection and exemplifies the role of host defense (i.e., antibody induction) leading to host injury. It is an important paradigm applicable to a panel of additional pathogens. GI virus infection is not confined to the gut, but can spread extraintestinally; for example, rotavirus causes viremia in children and all animal models tested. Extraintestinal spread may be a general characteristic of human gastroenteritis viruses; this property was not previously appreciated based on studies with animal caliciviruses and astroviruses.

Long-term impact of enteric parasitic infection

The long-term impact on growth and cognitive function of repeated or persistent enteric parasitic infections (e.g., protozoa, helminths) has been recognized. These studies highlight how enteric parasitic diseases contribute to long-term economic and intellectual losses in resource-poor countries with implications for global development.

Bacterial communities in the gut as determinants of non-infectious diseases

The human intestinal microflora are metabolically, genetically, and antigenically diverse. Germ-free mice are protected against obesity when consuming conventional Western-style diets rich in sugar and fat, while colonized animals are not. The gut microflora are an important component of our metabolic output, and metagenomic and biochemical studies demonstrate the critical roles of the microflora in harvesting dietary calories and transferring energy in the form of calories to the vertebrate host. The relative abundance of the two major bacterial intra-intestinal divisions—Bacteroidetes and Firmicutes—is a potential determinant of host adiposity. Alterations in this microflora offer the opportunity for significant influence of extraintestinal health, such as obesity risk—an avenue that has not yet been adequately explored. Many methanogenic archaea—a group of prokaryotic and single-celled microorganisms similar to bacteria—are found in the digestive tracts of humans. The role of this community in human digestive health and disease is not well established.

GOALS FOR RESEARCH [9]

Research Goal 3.1: Elucidate the etiology, epidemiology, and pathogenesis and improve diagnostic tests for intestinal infections. (See also Goals 1.21 and 9.3.)

In the U.S., an estimated 20-40 million episodes of diarrhea occur annually in children younger than 5 years of age, and diarrheal illnesses continue to be a burden for older children and adults. Approximately 13 percent of all pediatric hospitalizations in the U.S. in this age group are for diarrheal disease. Worldwide, the number of childhood deaths from diarrhea is higher than 2.5 million per year.

Knowledge of diarrheal disease has increased remarkably during the past few decades. Numerous bacterial pathogens and an increasing number of viral pathogens have been demonstrated to cause diarrhea. However, the etiology of diarrheal disease in both developing and developed countries is unknown for 25-40 percent of all illnesses. Although diarrhea morbidity and mortality are largely related to fluid and nutrient losses, the specific etiology of intestinal infection is critically important for designing science-based prevention and control mechanisms, especially vaccination.

Classically, assigning pathogenicity to an organism has depended on identification of candidate pathogens more frequently in infected individuals than in asymptomatic controls. This approach is less informative when considering organisms that contain a repertoire of virulence loci. This is especially pertinent in view of recent data that bacterial chromosomes are mosaics, made up of horizontally acquired elements that may contain genes that are not necessarily found in all pathogens. Clearly, designation of an organism as a pathogen now requires considerably more sophisticated microbial and genomic sampling and statistical analyses than have been used previously. In addition, genotypic variability among pathogens renders some organisms more virulent than others, and the specific determinants of pathogenicity are often poorly understood for infectious agents.

Objectives:

- Understand the pathogenic mechanisms used by viruses, parasites, and bacteria in causing intestinal infection, including genotypic variability in known and putative enteropathogens.
- Understand how microorganisms interact with their environment to reach critical numbers capable of human infection and to express pathogenic factors in the intestine.
- Conduct epidemiologic investigations using modern tools to define infectious etiologies, establish the incidence of known and novel etiologic agents of diarrheal disease, and characterize the health impact of acute and persistent enteric infection in distinct subgroups of hosts, including normal and immune-compromised populations (e.g., solid organ transplant, bone marrow transplant, oncology patients).
- Develop new point-of-care diagnostics to easily and rapidly detect known microbial enteric pathogens.
- Discern correlates of protective immunity for enteric infections.
- Develop animal models to study the effects of manipulating the microbial community in the gut.

Research Goal 3.2: Improve the prevention and treatment of intestinal infections.

Provision of clean water and sanitary food are important worldwide strategies to prevent enteric infection. However, preventing enteric illness by improved hygiene is currently impractical in most developing countries. For this reason, vaccination

[9] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

against the most important GI infections has been aggressively pursued. A new generation of enteric vaccines based on either live or nonliving antigens delivered orally or by injection is in the early phases of evaluation. However, considerable technical barriers need to be overcome related to the large number of pathogens capable of causing disease and the requirement to induce immunity that is effective in the gut. It will be important to advance development of vaccines that are effective and economically accessible to those most at risk for infection and illness.

The use of probiotics (ingested microbes that can modify intestinal microbial populations in a way that benefits the host) has moved from concept to demonstration of unique benefits by specific microorganisms for a given patient population. However, the science of probiotics is still in its infancy, and scientific claims for improved outcomes, such as disease prevention and treatment, are often unsubstantiated. It is increasingly clear that benefits from probiotics are mostly mediated by the effect that intestinal microflora have on gut barrier function and host immune response. Identifying the role and mechanism of action of probiotics for treatment and prevention of diarrhea, reducing the risk of intestinal disease (e.g., necrotizing enterocolitis), and modulating host immune response to extraintestinal disease, such as allergic disease, are important potential areas of future research.

Antibiotic-associated diarrhea and colitis were recognized soon after antibiotics became available, and *C. difficile* was identified as a causative agent in the 1970s. In the last few years, *C. difficile* has been more frequent, more severe, more refractory to standard therapy, and more likely to relapse. This pattern is widely distributed in the U.S., Canada, and Europe and is now largely attributed to a new strain of *C. difficile*, designated BI/NAP1 or ribotype 027. The recent experience with *C. difficile* serves to emphasize the need for better diagnostics, early recognition, improved methods to manage severe disease and relapsing disease, and greater attention to infection control and restraint in the administration of antibiotic therapy. In addition, emerging antibiotic resistance in other GI pathogens and pathogens that use the GI tract as a portal for systemic infection (e.g., *Salmonella typhi*) is an increasing problem.

Objectives:

- Define how common conditions such as age, malnutrition, or diabetes mellitus modify mucosal innate and adaptive immunity and physiology, altering susceptibility to enteric illnesses and vice versa.
- Understand the role of host genetics in the response to GI infections.
- Understand the mechanisms of action of probiotics and prebiotics.
- Conduct appropriately designed and powered large-scale, placebo-controlled, randomized, double blind clinical trials to demonstrate safety and efficacy and substantiate the potential for novel interventions to treat or prevent enteric infections.
- Promote strategies to reduce nosocomial enteric infection, such as handwashing.
- Investigate and promote novel strategies to reduce and treat *C. difficile* infection.
- Develop new strategies for microbial killing or stasis, especially for infections in which there is emerging antimicrobial resistance.
- Advance vaccine strategies for appropriate pathogens to reduce morbidity and mortality of enteric infection. Integrate measures to control enteric parasitic infections, including vaccine distribution and potential mass treatment protocols (e.g., wide-scale de-worming, preventive chemotherapy agents).

Research Goal 3.3: Understand and modulate the long-term intestinal and non-intestinal consequences of GI infection.

Diarrhea is well-recognized as a leading cause of childhood mortality and morbidity in developing countries; however, possible long-term deficits from heavy diarrhea burdens in early childhood include delayed growth and cognitive development beyond the immediate impact of infection. It is unclear whether mechanisms such as disruption of the mucosal barrier account for these long-term sequelae of acute infection.

Similarly, long-term consequences of acute infection in developed countries include persistent IBS. Infection by pathogenic organisms leads to mucosal damage and disruption of the gut's extensive commensal microflora—factors that may lead to prolonged bowel dysfunction. Although many patients improve over the first 6 months, recovery can be slow, with approximately 50 percent still having symptoms at 5 years.

Although it is clearly a goal to reduce the burden of acute enteric infection, understanding the unintended consequences of such a strategy is critical. The hygiene hypothesis suggests that increases in chronic inflammatory disorders (e.g., allergies, IBD, and autoimmunity) in developed countries are partly attributable to diminishing exposure to organisms that were part of mammalian evolutionary history. Crucial organisms, including bacteria, helminths, and saprophytic mycobacteria, are recognized by the innate immune system as harmless or "tolerable." This recognition can trigger development of regulatory dendritic cells that may drive regulatory T cell responses to simultaneously processed "forbidden" target self-antigens of the chronic inflammatory disorders.

Objectives:

- Understand the short-term (and long-term) burden and impact of enteric infections on cognition, development, and health. Comprehensive outcome measurements should be developed to guide and standardize assessments in different populations.
- Identify biomarkers to predict the development of systemic diseases secondary to the exposure to enteric pathogens.
- Attenuate host response to specific human infections.
- Define the relationship between intestinal infection and chronic GI (i.e., IBS, IBD) and non-GI diseases.
- Conduct feasibility studies on developing vaccines or other agents against "non-pathogenic" bacteria that might trigger pathologic intestinal inflammation.
- Identify the consequences of reducing the burden of intestinal infection and/or altering the microflora, such as those anticipated by the hygiene hypothesis.

Research Goal 3.4: Understand the human microflora and microbiome in health and disease and modulate them for beneficial effects.

Microorganisms live in complex environments both *ex vivo* and *in vivo*. Current information about synergy between enteric pathogens and other organisms is limited. Many species of bacteria regulate gene expression in response to increasing cell population density; collectively, this phenomenon is called quorum sensing. Quorum-sensing bacteria produce and release signaling molecules (autoinducers) that accumulate in the environment as cell density increases. Quorum sensing is used by bacteria to communicate within the same species and across species. When a threshold stimulatory concentration of autoinducer is achieved, a signal transduction cascade is initiated that is translated into a change in behavior of the organism. Only recently has the complexity and scope of quorum sensing in bacterial regulation been appreciated. Far from being isolated entities,

GOALS FOR RESEARCH

bacteria exist in multifaceted and communicating populations. The outcome of this cross-talk can lead to either severe or attenuated infections.

The human intestine contains trillions of bacteria, hundreds of species, and thousands of subspecies. Little is known about the selective pressures that have shaped and are shaping this community's component species, which are dominated by members of the Bacteroidetes and Firmicutes divisions. Obese mice have a different microflora than non-obese mice. In addition, in contrast to mice with a gut microflora, germ-free animals are protected against the obesity that develops after consuming a Western-style, high-fat, sugar-rich diet. These observations underscore the importance of considering the intestinal microflora as an important participant in the metabolome in a supraorganismal context and perhaps as a key driver of such diseases as obesity.

Objectives:

- Develop a comprehensive understanding of the intestinal microbiome and the effect of the host genome on microbial colonization. Understand the consequences of interactions between GI pathogens and normal gut microflora for GI function.
- Develop and make accessible computational approaches and tools to assay the microbiome in the gut in a variety of disease states.
- Determine whether the microflora is altered under pathophysiologic conditions (e.g., infectious diarrhea, IBS, IBD, obesity) in animal models and in people.
- Modulate the GI microflora to prevent systemic and intestinal diseases.
- Determine whether genetically modified microorganisms can deliver therapeutic molecules to the GI tract.
- Define the composition of the gut microflora in development, including during breast feeding, formula feeding, perinatal stress, and illness early in life.
- Determine the role of prebiotics, probiotics, and symbiotics in modulating the long-term composition of the intestinal microflora in the neonatal interval and beyond.
- Define the role of archaea in the GI tract in health and disease.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Technologies to study intestinal infection: Efforts that replace archaic enteric pathogen detection technology and can identify agents across taxa would accelerate research on intestinal infections. The development of rapid and sensitive diagnostics to detect all known enteric pathogens would facilitate research and improve patient care. Other technologies that could be developed include genetic and replication tools to study viral pathogens and resources to study viral pathogens in human challenges. The development of small mammal models and *in vitro* models to study intestinal physiology, mucosal immunity, and microbial-host interactions will provide fundamental insights before trials in humans. New *in vivo* imaging systems that can be applied in animal models and humans will enhance our understanding of the pathogenesis of infectious agents.

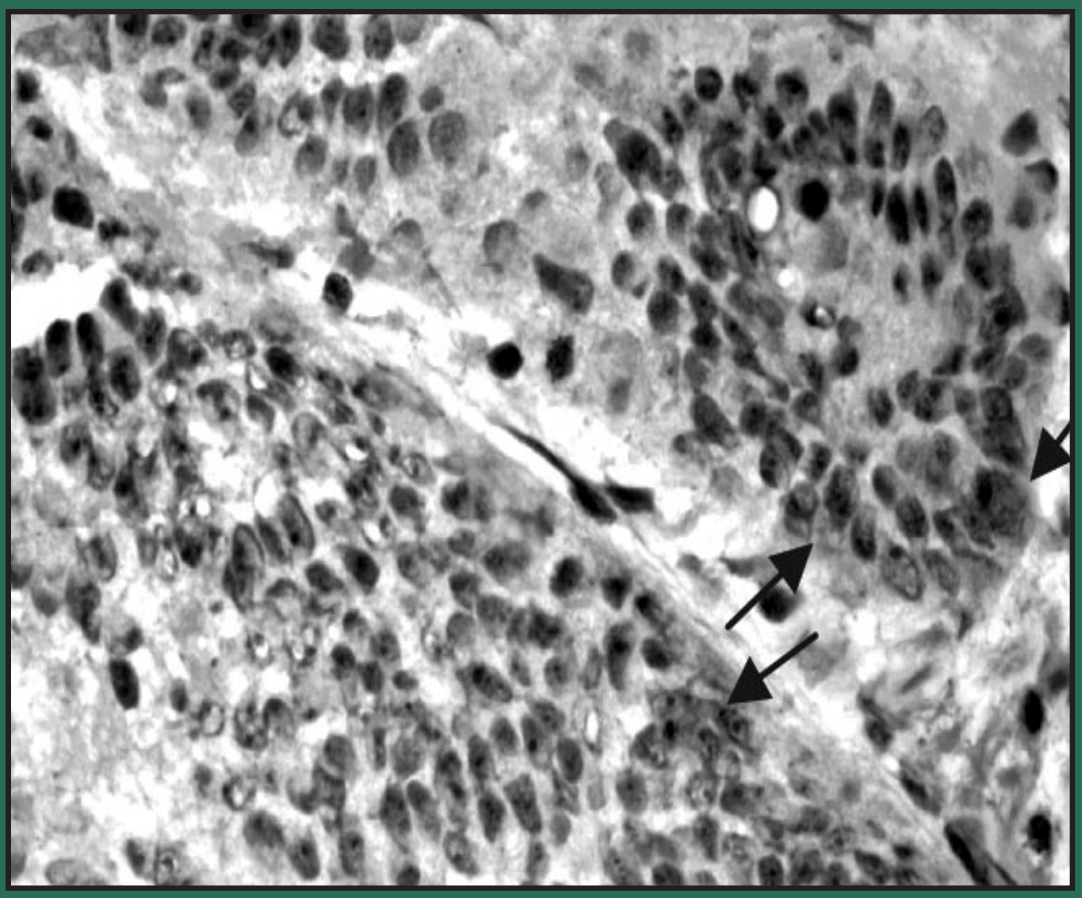
Therapeutic development for intestinal infections: Despite the effectiveness of vaccines in eliminating a subset of infectious diseases, several challenges must be

addressed to develop vaccines for enteric infections. Vaccines for some pathogens (e.g., enterotoxigenic *E. coli*, *Shigella*, *Campylobacter*, and *Norovirus* species) will require multiple or yet-to-be-defined antigens (e.g., enteroaggregative *E. coli* and *Cryptosporidium* species). Also, many oral vaccines are less immunogenic when given to malnourished persons who might need them most; vaccines that target populations in developing countries, such as those for cholera, typhoid, and parasites, will require incentives to bring them to and maintain them in global markets.

The development of new interventions, either vaccines or other methods, is hampered by insufficient knowledge of the pathways triggered by pathogens. It is possible that by establishing correlates of protective immunity for GI pathogens, we would eliminate the need for challenges or field trials to study efficacy and, thereby, speed development of licensed candidate vaccines. A final challenge is that probiotics are classified as food supplements and/or natural health products that do not require rigorous clinical evidence for efficacy; this situation directly conflicts with current and proposed uses of these agents as drugs to treat disease.

Resources for intestinal infection research: Repositories for human biologic samples, research reagents, and animal models are needed to promote progress in the field. New databases, communication networks, and scientific resources are required to develop and sustain longitudinal, large population field studies and productive international collaborations. Infrastructure and improved technology to more promptly identify infected patients would improve our understanding of the epidemiology of foodborne diseases.

Methods to modulate the human microbiome: Improved understanding of the intestinal microflora and microbiome would enhance our potential to identify novel approaches to treatment and to identify those microbes that result in long-term GI sequelae. Learning how to segregate the important variables and developing adequate bioinformatic/computational power will be required in order to make sense out of the massive data resulting from characterization of the trillions of organisms in the intestine. The formation of multidisciplinary teams of researchers in human studies would enable the field to obtain a complete picture that incorporates immune function, transcriptome, microbiology, and clinical responses. Filling the pipeline by fostering the careers of new investigators in this area is a priority. The resource development and research programs supported by the Human Microbiome Project under the auspices of the NIH Roadmap for Medical Research will be critical for research efforts to prevent and treat human intestinal infections through microbe-based approaches.



Arrows point to cells within human colon cancer samples producing a protein called CD133, which served as a marker for identifying cells that initiate colon cancer. Markers such as this one may be helpful for targeting future therapeutic approaches.

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Cancers of the Digestive System

SUMMARY OF RESEARCH GOALS

Recognizing the substantial public health impact of digestive system cancers, the Commission recommends several research goals targeted at improving the detection, prevention, and treatment of these diseases. Research is needed to develop more efficient screening tools to predict and detect digestive tract cancers and pre-malignant conditions that frequently progress to cancer. These efforts would be bolstered by identifying health disparities that influence an individual's susceptibility to digestive system cancers or their response to treatment. Understanding the underlying mechanisms common to all digestive cancers and identifying biomarkers to detect disease or predict response to treatment would accelerate the search for safe, effective therapies. In order to develop targeted strategies for cancer detection, prevention, and treatment, it is critical that researchers identify the genetic risk factors that predispose an individual to a specific form of digestive cancer, such as esophageal cancer, pancreatic cancer, gastric cancer, colorectal cancer, or certain rare gastrointestinal (GI) cancers. Together, these research goals aim to improve the health and lives of people at risk for or living with digestive cancers.

INTRODUCTION AND BACKGROUND

The digestive system, including the gut, pancreas, liver, and biliary tree, is the site of more cancers and the source of more cancer mortality than any other organ system in the body. More than 270,000 Americans develop a cancer of the GI tract each year, and half of these patients will die from the cancers (Table 2).

The burden of digestive cancers on the American population is considerable in terms of numbers of new cases, deaths, and economic costs for diagnosis and treatment. Research directed at understanding the causes of the digestive cancers will help reduce their incidence, prevent deaths, and lower healthcare costs.

Of the digestive cancers, colorectal cancer is the most prevalent, with a lifetime risk in the U.S. of 5-6 percent. Colorectal cancer is unique among cancers because it is highly amenable to screening programs that can reduce cancer mortality by early detection and, more importantly, reduce the incidence of invasive cancer by removing pre-malignant lesions. Colorectal cancer incidence and mortality have been falling over the past 2 decades for reasons that are not fully explained.

In the early 1900s, cancer of the distal stomach was the leading cause of death from cancer in the U.S. Seventy years later, gastric cancer prevalence has declined to represent the 13th leading cause of death from cancer in the U.S., but it is still ranked second worldwide. Improvements in food storage and public sanitation are considered the major reasons for the decline in these statistics, suggesting that this disease can be prevented. In 1994, the World Health Organization designated *Helicobacter pylori* as a definite carcinogen, based on the epidemiologic evidence linking the chronic gastric inflammation induced by *H. pylori* to cellular transformation in the stomach.

Esophageal cancers represent an enormous burden of morbidity and mortality worldwide. In 2002, there were an estimated 462,117 new cases and 385,892 deaths from esophageal cancer worldwide, making it the eighth and sixth leading causes of cancer and cancer mortality, respectively. Developing strategies to reduce the mortality of esophageal cancer is complicated by the fact that the two major histologic subtypes (squamous cell carcinoma and adenocarcinoma) show marked regional variation in incidence, differ substantially in etiology, and arise in different tissues. High mortality is one of the main shared characteristics of the two histologic subtypes.

Table 2. Incidence and Mortality of GI Cancers in the U.S. (2008 estimated)

Cancer Site	Overall Incidence	Male Incidence	Female Incidence	Deaths	Annual # of Deaths Divided by Incidence (%)
Esophagus	16,470	12,970	3,500	14,280	87%
Stomach	21,500	13,190	8,310	10,880	51%
Small intestine	6,110	3,200	2,910	1,110	18%
Pancreas	37,680	18,770	18,910	34,290	91%
Liver and intrahepatic duct	21,370	15,190	6,180	18,410	86%
Gallbladder and biliary ducts	9,520	4,500	5,020	3,340	35%
Colon and rectum	148,810	77,250	71,560	49,960	34%
Anus and anorectum	5,070	2,020	3,050	680	13%
Other digestive organs	4,760	1,470	3,290	2,180	46%
TOTALS	**271,290**	**148,560**	**122,730**	**135,130**	**50%**

Esophageal adenocarcinomas have been reported to be increasing in incidence in many regions of the Western world. Although esophageal cancers are less common than lung, breast, prostate, and colon cancers in the U.S., they are nevertheless the seventh leading cause of cancer death among U.S. males. Between 1972 and 2002, the incidence of esophageal adenocarcinoma in Caucasian males increased more than 600 percent, making it the most rapidly increasing cancer in the U.S., as well as in many other regions of the Western world.

Pancreatic cancer is the fourth most common cause of cancer death in the U.S., with an annual incidence of 11.4 per 100,000 men and women. Based on rates from 2002 to 2004, 1.31 percent of men and women (1 in 76) born today may be diagnosed with cancer of the pancreas at some time during their lifetime. Ninety-five percent or more of the deaths from pancreatic malignancy are due to ductal carcinomas, the most common and highly metastatic form. Less common tumor types can occur in the pancreas, but are often less lethal or even benign. The less frequent mesenchymal, hematopoietic, and endocrine tumors often share greater similarity with tumors occurring in other organs than with the pancreas-specific tumors. Pancreatic cancer is usually not diagnosed until after the disease has been manifested through clinical symptoms; as a result, only 20 percent are considered appropriate for surgical resection of the original tumor at the time of diagnosis. Even those patients whose cancer is deemed surgically resectable usually have local lymph node spread at the time of surgery, and nearly all have micro-metastatic disease that is simply undetected at presentation. The overall 5-year survival rate for pancreatic ductal cancer is less than 5 percent.

Research on digestive cancers has been generally directed toward understanding the basic biologic mechanisms of tumors. Despite major advances in this area, the research community is far from understanding how digestive cancers form, grow, and spread. An improved understanding is crucial to lowering the incidence of digestive cancers in the diverse U.S. population, identifying predictive biomarkers to prevent cancer occurrence or recurrence, and developing novel and creative approaches toward prevention or treatment strategies.

This chapter addresses digestive cancers, except liver cancer (see the chapter on *Diseases of the Liver and Biliary System*), with a focus on the four most common digestive cancers: colorectal, esophageal, gastric, and pancreatic. Rarer GI cancers (e.g., cancers affecting the small intestine, anus, gastrointestinal stromal tumors (GIST), gastrointestinal lymphomas, and carcinoids) are discussed in aggregate. The chapter outlines a set of research goals that should improve our overall understanding of basic mechanisms that are relevant to cancer etiology and prevention, as well as specific goals that are directed at individual cancer types.

RECENT RESEARCH ADVANCES

Genetic instability as an underlying mechanism of cancer

A fundamental principle underlying the formation of digestive cancers is the sequential acquisition of alterations in specific genes. These alterations lead to genetic instability that fuels the growth of cancer cells. A fraction of cancers exhibits a form of genetic instability called microsatellite instability, which is often characterized by DNA mismatch repair (MMR) enzyme deficiency. Loss of MMR functions renders tumor cells susceptible to the acquisition

of somatic mutations throughout the genome. A more common form of genetic instability is chromosomal instability, which is usually manifested by aneuploidy (a change in the number of chromosomes). For example, multiple studies have established that esophageal adenocarcinoma develops in association with chromosomal instability, which generates non-random loss of heterozygosity involving chromosomes 9p, 17p, 5q, and 18q, as well as tetraploidy (another form of altered chromosomal number) and aneuploidy. Additionally, telomere dysfunction has been shown to contribute to the onset of genetic instability in somatic cells.

Epigenetic silencing of gene expression as a mechanism in cancer formation

Chromosomal alterations or modifications have been associated with all stages of digestive tumor formation and progression. The best-characterized form of chromosomal alteration is epigenetic silencing by hypermethylation of the promoter regions of genes that have important regulatory functions in cell growth or checkpoint maintenance. Epigenetic silencing can occur during the early stages of tumor development, thus inducing the aberrant, early clonal expansion due to alterations in the various regulatory steps affected by genetic silencing. Recent studies have also suggested the presence of a unique type of cancer exhibiting the CpG island methylator phenotype (CIMP). CIMP tumors represent a clinically and etiologically distinct group of cancers that is characterized by "epigenetic instability." Lastly, a form of chromosomal modification called loss of imprinting of specific genes involved in growth regulation has been shown to predispose to cancer formation.

Cancer stem cells

Stem cells are characterized by their ability to divide asymmetrically—they can make more stem cells, a property known as self-renewal, and they can produce cells that differentiate. Recent studies support the concept that cells with properties of stem cells are integral to the development and perpetuation of human digestive cancers. Eradication of the stem cell component of a tumor may be essential to achieve stable, long-term remission or cure of cancer. Advances in the knowledge of the properties of stem cells have made the specific targeting and eradication of cancer stem cells a topic of considerable interest. The concept that GI cancers arise from hematopoietic precursor cells is a theme that was initially shown in the liver. The identification of bone marrow-derived cancer stem cells in gastric cancer is the first evidence that a luminal organ may show this property.

Cellular receptors and related signaling pathways as targets for cancer therapy

Hormones, cytokines, and growth factors control many aspects of cell proliferation, differentiation, migration, angiogenesis, apoptosis, and senescence. These chemical signals are propagated from the cell surface to intracellular processes via sequential kinase signaling, arranged in modules that exhibit redundancy and cross-talk. This signal transduction system comprising growth factors, transmembrane receptor proteins, and cytoplasmic second messengers is often exploited to optimize tumor growth and metastasis in malignancies. Thus, receptors and their signal transduction systems represent an attractive target for digestive cancer therapy, and several new drugs have been developed and shown to be effective.

Cancer genomics and proteomics

Advances in genomics, proteomics, and molecular pathology have improved the ways by which human cancers are detected, classified, staged, monitored, and treated. The

identification of genetic alterations in cancers in unprecedented detail has accelerated the understanding of the genetic basis of human cancers and provided new targets for diagnostic and therapeutic interventions.

Improvements in approaches and devices that detect and treat esophageal cancer in high-risk patients

Endoscopic imaging of squamous esophageal cancer using Lugol's solution has improved detection of this cancer in high-risk patients. Narrow band imaging and improved endoscopic magnification has enhanced the ability of the endoscope to assess areas of neoplasia without requiring topically administered contrast agents. Mucosal resection devices have been developed that permit single or multiple resections of the mucosa to allow removal of large portions of tissue for therapy and diagnosis and precise determination of the depth of invasion. Mucosal ablation devices (e.g., photodynamic therapy, thermoablation, radiofrequency ablation, cryotherapy) have been created specifically for the esophagus to ablate pre-malignant cells and, in some cases, malignant cells.

Genetic risk for gastric atrophy and cancer

Researchers have identified polymorphisms in cytokine genes that predispose individuals to gastric atrophy and cancer. This discovery underscores two important principles in gastric cancer development: that the host response (i.e., inflammation) to bacteria (presumably *H. pylori*) is essential to cancer pathogenesis; and that atrophy serves as an indicator that the mucosa is developing pre-neoplastic changes.

Mouse models that emulate human gene function in cancer

Mouse models with deleted gene function or targeted mutation similar to observed human mutations demonstrate some recapitulation of human colon cancer and include alterations of the *APC* gene, TGF-β signaling pathway, and the *PTEN* gene. New animal models of gastric cancer have uncovered a number of genetic targets that may be critical for gastric cancer formation including the cytokine receptor subunit gp130, Runx3, trefoil factor TFF1, and STAT3. New animal models of pancreatic cancer recapitulate some of the genetic and ductal abnormalities known to exist in human pancreatic cancer, including the generation of invasive ductal cancers. These highly relevant animal models may aid in the understanding of mechanisms for cancer formation and may accelerate the preclinical development and evaluation of new therapeutic compounds.

Inherited risk factors and genetic signatures for pancreatic ductal cancer

Researchers have advanced our understanding of the degree of risk acquired by members of affected families, genetic locations linked to risk (such as 4q32-34), and investigation of candidate genes that may be responsible for pancreatic ductal cancer. Special pancreatic tissue abnormalities have been found in these families, and a screening program that includes endoscopic ultrasound (EUS) has improved the detection of early and curable pancreatic lesions. In nearly 20 percent of families most affected by ductal cancer, the causative gene is now known. Approaches to treatment of ductal pancreatic cancer have taken advantage of genetic signatures of the cancer cells to test responsiveness to specific and available drugs. For example, mutations

in the *BRCA2* gene and cellular pathway are being used investigationally to assign individual patients to treatment with specific families of drugs or to explain the different responses of patients to such drugs. Also, compounds targeting cell-surface growth factor receptors are being evaluated in clinical trials based on studies showing abnormal expression of such targets in the ductal cancers.

Imaging techniques for the detection and staging of pancreatic cancer and GI luminal cancers

Advances in the quality of high-resolution CT and MRI scanners and EUS have led to a marked increase in the detection of small pancreatic cystic tumors and solid masses. EUS allows tumor features to be evaluated using complementary imaging technologies and to be directly sampled by fine-needle aspiration. Laboratory evaluation of the fluid for tumor markers (e.g., carcinoembryonic antigen), cytological evaluation of aspirated cells, and molecular analysis of suspicious cells for specific gene mutations and markers of aneuploidy represent significant advances in the early detection and diagnosis of pancreatic cancers and precancerous lesions. EUS, capsule endoscopy, double balloon enteroscopy, and improvements in the optics of endoscopes are improving detection of GI luminal cancers.

Immunologic and surgical approaches to pancreatic cancer therapy

Efforts are underway to: develop antibody therapy against specific growth factor receptors; develop and conduct clinical trials of a post-surgically administered cancer cell vaccine that generates immune responses against tumor-specific proteins; and develop new immunologic agents designed to elicit more direct immune responses against the same tumor markers. Advances in the surgical treatment of pancreatic cancer include the establishment of highly experienced pancreas cancer centers, effective reduction in the morbidity and mortality of the disease, optimal pre-surgical screening to diagnose the tumors by endoscopy and biopsy, improved planning of the surgical approach for tumors that are anatomically difficult to remove, and better means to combine surgery with radiation and chemotherapy to improve the quality and duration of life after ductal cancer surgery.

Improvements in colorectal cancer screening

Colorectal cancer is one of a small number of human cancers for which screening of the general population is cost-effective and can significantly improve outcome. Colonoscopy permits both the detection of early cancers and the removal of precursor lesions, which has the potential to reduce morbidity and mortality due to colorectal cancer. Technical advances that include CT colonography (virtual colonoscopy), fecal DNA testing for colorectal cancer, and fecal immunochemical tests provide an opportunity to improve digestive health.

Advances in genetic diagnosis of colorectal cancer

Colorectal cancer has an important familial component. Approximately one third of colorectal cancer patients have a first- or second-degree relative with colorectal cancer. Approximately 4 percent of all colorectal cancer patients have well-defined syndromic forms of colorectal cancers. Advances in understanding the genetic risk factors for colorectal cancer include improved tests for alterations in the DNA mismatch repair genes (MMR) that cause Lynch syndrome (or HNPCC); the discovery of a recessive form of familial polyposis, called *MYH*-associated polyposis; and the elucidation of "Syndrome X," which represents familial clusters of colorectal cancer that are not attributable to an inherited mutation of a known DNA MMR gene.

Chemoprevention and nutriprevention of colorectal cancer

Beginning in 1980, it was recognized that certain non-steroidal anti-inflammatory drugs (NSAIDs; beginning with sulindac) could induce the regression of adenomas in patients with familial adenomatous polyposis (FAP). Subsequently, it was shown that selective Cox-2 inhibition can significantly reduce the numbers of adenomas and carcinomas in patients who have had colorectal neoplasms in the past. However, many of these agents have unacceptable toxicities. The development of safer anti-neoplastic drugs that inhibit Cox-2 could improve treatment outcomes.

Targeted treatment for gastrointestinal stromal tumors (GISTs)

GISTs are tumors arising in the submucosa of the GI tract due to constitutively activating mutations in either the PDGFRA or KIT receptors on the interstitial cells of Cajal. Specific molecular therapies targeting the tyrosine kinase domain of PDGFRA and KIT, which were initially developed to treat certain types of leukemia, have proven to be clinically useful and superior to chemotherapy and surgery for the treatment of GISTs, although they are not curative.

GOALS FOR RESEARCH [10]

The digestive cancers represent a diverse group of disorders with respect to etiology, prevention, and treatment. The goals for research that follow include ones that are broadly applicable to digestive cancers, as well as specific goals for individual types of cancer.

Research Goal 4.1: Develop population-based strategies for screening and prevention of digestive cancers.

For some digestive cancers, such as colon cancer, technologies are available to detect pre-malignant lesions that might be used for population-based screening. Other technologies can remove these lesions, reducing the cancer risk for the patient. Clear and cost-effective utilization of the technologies will need to be evaluated. Other digestive cancer prevention strategies might target high-risk populations, such as those with family histories of cancer, GI inflammatory diseases, high-risk behaviors, or the presence of certain biomarkers.

Strategies to effectively screen and prevent digestive cancers could prove very cost-effective for society.

Objectives:

- Understand the major risk factors for digestive cancers.
- Develop risk modeling and stratification to identify high-risk populations for digestive cancers.
- Conduct large-scale trials of screening modalities to determine efficacy and cost-effectiveness and integrate effective strategies into practice.
- Improve imaging modalities to detect and/or remove pre-malignant or early malignant digestive cancers when they are more likely to be curable.

Research Goal 4.2: Ascertain the importance, detection, and natural history of pre-malignant conditions progressing to digestive cancer.

Studies to address the natural history of pre-malignant lesions that predispose to digestive

[10] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

cancers are crucial. Adenomatous polyps—detectable precursors to colorectal cancer—have been extensively studied. The importance of small adenomas is unknown, yet critical in evaluating the value of CT colonography. Rates and mechanisms for benign to malignant transformation of esophageal, gastric, and pancreatic lesions are likewise not known. The accumulation of genetic derangements required to develop the cancer and its ability to metastasize needs to be better understood. We also need to learn how adenoma, pancreatic intraepithelial neoplasia, or other precursor lesions develop from interaction with factors in the local environment. Indeed, environmental factors that are responsible for genetic derangements are largely unknown for any of the digestive cancers. Portions of the GI tract have the most diverse environmental-host interactions in the entire body, with food and waste metabolites, along with the high concentration of microbes, present intraluminally. Commensal bacteria, as well as viral, bacterial, parasitic, and other infections, may directly influence cancer risk by affecting the underlying genetics of digestive system cells. Inflammatory bowel diseases (IBD), which result from a disturbed host-environmental interaction in the gut, are associated with a marked increased risk for cancer development that is not completely understood. In addition, numerous syndromes can lead to the development of digestive cancers, such as FAP, Gardner's syndrome, Lynch syndrome, and diseases like gastroesophageal reflux disease and hepatitis.

Objectives:

- Characterize the genetic defects and clinical behaviors associated with syndromes that predispose to digestive cancers.
- Develop and study preclinical *in vitro* and *in vivo* models of digestive cancers to recapitulate the natural history seen in humans.
- Determine the natural history of pre-malignant lesions in the development of digestive cancers.
- Define the role of inflammation in digestive cancer development.
- Define the mechanisms that predispose patients with IBD for digestive cancers.
- Determine the role of the microflora in the initiation or propagation of digestive cancers.

Research Goal 4.3: Evaluate health disparities in digestive cancer etiology, risk, treatment management, and outcomes.

The U.S. population is extremely diverse, and some racial and ethnic groups have higher risks for developing digestive cancers. One factor may be single nucleotide polymorphisms (SNPs) of disease-modifying genes, but other genetic and epigenetic factors may influence race-related cancer risk. Some groups treated for digestive cancers do not have the same response rates to therapies or the same detection rates for pre-malignant or malignant conditions. Furthermore, end-of-life care varies among the groups for unknown reasons. Research to explore these racial and ethnic differences provides an opportunity to eliminate disparities in digestive cancer prevention, detection, and treatment.

Objectives:

- Conduct clinical studies on access, utilization, treatment, and outcomes of patients with digestive cancers who belong to diverse ethnic, racial, or high-risk groups.
- Understand the influence of genetic factors on cancer risk, prognosis, and response to therapy.
- Investigate the influence of gender on cancer risk, prognosis, and outcomes of patients with digestive tract cancers.

Research Goal 4.4: Improve outcomes in the care of digestive tract cancer patients.

Patients who develop digestive tract cancers are faced with surgery, chemotherapy, and radiation therapy, and may experience behavioral and social changes after their diagnosis. Improvements in

medical treatment may prolong life. Creative support systems and educational mechanisms may improve a patient's mental outlook and the management of their cancer. Side effects of chemotherapy and/or radiation are common. Therapies to counteract the side effects are not necessarily effective and can adversely influence palliation or potential cure. Completion of therapy is a goal to offer the best chance for those who are attempting cure or remission.

Objectives:

- Conduct studies to determine the optimal chemotherapy and/or radiation therapy—before or after surgery—for best long-term survival based on stage, biomarkers, or genetic make-up of the patient or patient's tumor.
- Determine mechanisms for tumor resistance to therapy and develop strategies to overcome resistance.
- Develop approaches to minimize the side effects of chemotherapy and/or radiation therapy.
- Investigate strategies to improve behaviors for optimized cancer treatment, including self-management or other modalities.

Research Goal 4.5: Develop biomarkers to detect neoplasia, target therapy, and evaluate therapeutic response in digestive cancers.

Biomarkers could be used to detect the possible presence of a disease and to select the higher risk population for screening. Additionally, biomarkers could track or predict the occurrence or recurrence of a digestive cancer or pre-malignant condition. Utilization of an ideal biomarker for each of the digestive cancers would greatly reduce costs to society and improve the ability to target high-risk individuals for diagnosis and intervention.

Objectives:

- Develop improved population-based assessment of risk for digestive cancers that can be detected in blood.
- Utilize preclinical *in vitro* and *in vivo* models of digestive cancers to ascertain biomarkers that predict tumor behavior and response to therapy.

Research Goal 4.6: Evaluate nutriceutical, probiotic, chemopreventive, and targeted therapies in digestive cancers.

All digestive cancers are associated with certain risk factors, and all cancers have accumulated genetic and epigenetic derangements that are favorable for the cancer and its cells to proliferate. Natural or target-developed compounds may be associated with reduced risk of developing a cancer, and such compounds might be effective in combating the disease once developed.

Objectives:

- Utilize preclinical *in vitro* and *in vivo* models of digestive cancers to ascertain potential effectiveness and mechanisms of preventive agents and small molecules.
- Conduct large-scale, randomized clinical trials utilizing agents or targeted therapies to determine effectiveness in prevention or treatment of digestive cancers.

Research Goal 4.7: Understand the molecular and cellular mechanisms common to all digestive cancers.

Many features of cancer must be understood broadly—how it develops, what subpopulations it affects, and what features distinguish the cancer. This information gives researchers opportunities to track the disease precisely and to determine if an intervention is effective for society or individually for the patient. Common themes from the understanding of one digestive cancer may be utilized to study other digestive cancers. For example, the basic finding of genomic instability is a key factor underpinning multiple cancers. Likewise, inflammation is a common condition that precedes

many digestive cancers. Tumor growth is influenced by the local microenvironment that helps sustain and propagate cancer cells.

Objectives

- Define genetic and epigenetic mechanisms that characterize digestive cancers.
- Characterize digestive cancer stem cells and factors in the local tumor microenvironment niche that support and propagate the cancer.
- Ascertain molecular signatures and the presence of commensal microflora for evaluation of linkage with population-based risk for digestive cancers.
- Determine the role of infection or host integration of microbes in risk for digestive cancers.

Research Goal 4.8: Determine the risk factors and pathogenesis of squamous carcinoma and adenocarcinoma of the esophagus and devise new methods for detection, diagnosis, treatment, and prevention of these diseases.

From 1979 to 2004, esophageal cancer, particularly adenocarcinoma, became one of the most rapidly increasing cancers in the U.S. Currently, the majority of afflicted persons die as the disease commonly progresses undetected until symptoms occur. Moreover, mortality from esophageal adenocarcinoma has not significantly decreased over the past decade. To address this issue, it will be important to understand how the normal esophageal lining changes to the pre-malignant lesion of Barrett's esophagus and, ultimately, into esophageal adenocarcinoma. Factors that influence this transformative process, such as acid exposure, tobacco use, and obesity and other local environmental influences on the one hand and stem cell genetic changes and chemopreventive interventions on the other hand, will be key to understanding and affecting disease pathogenesis.

Objectives:

- Perform comprehensive genetic analyses of esophageal squamous cell carcinoma and adenocarcinoma.
- Develop non- or minimally invasive imaging and/or molecular techniques to detect pre-malignant changes in the esophagus.
- Discover biomarkers for prediction and evaluation of therapeutic response in esophageal disease.
- Determine the factors that lead to trans-formation of normal esophagus to Barrett's epithelium and those that lead to further progression to adenocarcinoma, including the potential role of stem cells in the process.
- Evaluate the role of upper endoscopy and other technologies for screening and surveillance of Barrett's esophagus.
- Evaluate new techniques to ablate Barrett's epithelium, dysplasia, or early carcinoma to prevent death due to adenocarcinoma.

Research Goal 4.9: Understand the molecular profiles of various types of gastric cancer to improve risk stratification, prevention, and treatment.

Gastric cancer is not one disease. Cancers that develop in different regions of the stomach (e.g., antrum, corpus, fundus, cardia) are likely to have different risk factors and different biologic behavior. Being able to distinguish the different types of tumors is a critical and necessary step for making progress in this field. By understanding the basic biology of the various types of gastric cancer, innovative strategies for prevention and therapy can begin to be developed.

Objectives:

- Ascertain a complete molecular profiling of the histological types of gastric cancers from different locations within the stomach.

- Develop a molecular roadmap for gastric cancer development that mirrors the known phenotypes.
- Develop better tools to conduct transgenic animal studies to further our understanding of gastric mucosal biology.
- Refine risk stratification for screening and surveillance of gastric cancers.
- Improve imaging technologies for early detection of pancreatic cancer.
- Devise novel molecular therapeutics based on understanding of pathogenesis.
- Provide infrastructure to accelerate research by developing biosample, imaging, and data repositories.

Research Goal 4.10: Define the genetic and environmental factors contributing to pancreatic cancer and its precursor lesions and devise new methods for early detection, treatment, and prevention.

Pancreatic ductal carcinoma, or pancreatic cancer, has a 5-year survival rate of less than 5 percent. By the time patients have symptoms, less than 20 percent are deemed to be surgical candidates for attempted cure. Pancreatic cancer can develop in the setting of chronic inflammation and in familial pancreatic cancer syndromes and, in this small but important subset of patients, precursor lesions such as pancreatic intraepithelial neoplasms might be identified that confer risk for progression to cancer. Differentiating benign from malignant early lesions by imaging or biomarkers will be central to determining optimal patient candidates for surgical cure, which would minimize the use of surgery in those who may not require this intervention and direct better utilization of chemoradiation therapy.

Objectives:

- Define the genetic risk factors for pancreatic cancer in both familial cases and sporadic disease.
- Define environmental risk factors that contribute to pancreatic cancer.
- Define early ductal precursor lesions and factors that contribute to progression to cancer.
- Identify markers for early lesions and risk for progression to cancer.

Research Goal 4.11: Identify genetic and environmental risk factors for colon cancer and devise improved approaches for screening, early diagnosis, treatment, and prevention of colon cancer. (See also Goal 1.3.)

Because of its major impact on public health and the opportunities to further reduce the incidence and mortality of this disease, the focus on colorectal cancer should be expanded. Areas of colorectal cancer research that are particularly important include primary prevention (e.g., novel dietary approaches and viral vaccines), discovery of genes that produce hereditary colorectal cancer syndromes, understanding the natural history of pre-malignant colorectal lesions, and integrating genomics research with the clinical application of individualized medicine. Because colorectal cancer screening has been demonstrated to decrease incidence and mortality, efforts should be made to expand the use of screening, to understand the natural history, and to stratify patients by risk status. Small colon polyps have an enormous impact on clinical practice, even though the likelihood of malignancy is small, as most patients undergoing colon surveillance have only small polyps.

Objectives:

- Evaluate chemopreventive and other primary prevention strategies against colorectal cancer.
- Improve means to identify patients, characteristics of the colon, or pre-malignant lesions that give rise to the greatest risk for colorectal cancer.

GOALS FOR RESEARCH

- Determine strategies to expand the use of colorectal cancer screening in clinical practice.
- Determine the natural history of small colorectal adenomatous polyps, including factors and markers for malignant progression and potential role of chemoprevention.
- Determine the potential role of proximal hyperplastic polyps and serrated adenomas in progression to colorectal cancer.
- Understand and develop models for flat adenomas (i.e., non-polypoid colorectal neoplasia).
- Continue to develop new endoscopic, imaging, and other technologies for colorectal cancer screening.

Research Goal 4.12: Understand the etiology, natural history, prevention, and management of rare GI cancers. (See also Goal 8.4.)

The rarer GI tumors include cancers affecting the small intestine and anus, GISTs, gastrointestinal lymphomas, and carcinoids. Individually, these cancers occur less often than the organ-based cancers, but many of these occur with higher frequency in certain populations. For example, immunocompromised patients have a higher prevalence of lymphomas; those with celiac disease have a higher prevalence of small intestinal lymphomas; and anal cancers are linked to infection with human papilloma virus. Collectively, this group of tumors affects approximately 15,000 Americans annually. Because of their relatively rare occurrence, research into these conditions lags behind that for organ-based digestive cancers.

Objectives:

- Improve imaging technologies and therapeutic options to detect and remove small intestinal cancers.
- Determine predictive factors or biomarkers that more accurately predict patient outcome, such as with MALT lymphoma and *H. pylori* eradication; anal carcinoma and immunosuppression or human papilloma virus infection; or the development and behavior of intra-abdominal desmoids in FAP.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Collaborative research and centralized resources: Research on digestive system cancers would be accelerated by promoting mechanisms for collaborative research. For example, centers could be established to collect and maintain clinical information and epidemiologic data linked to a repository of biologic specimens and other data, such as gene expression profiles, SNPs, and other patient characteristics. Such multi-institutional repositories of samples and data from well-characterized patients would enable collaborative research on disparities among ethnic, racial, or high-risk groups that often cannot be performed effectively in individual clinical sites with limited patient populations. The development of high-throughput genomic and proteomic facilities to complement the current Cancer Genome Anatomy Project to profile digestive tract cancers and their subtypes would also strengthen the entire field and promote progress. Finally, the creation of high-throughput drug discovery programs based on targeted approaches to cancer biology would present an opportunity for collaboration with industry in the area of drug development and evaluation.

Technology development: The development of advanced non- or minimally invasive imaging or molecular techniques for detection of pre-

malignant changes in digestive tract cancers has the potential to improve cancer diagnosis in the early stages of the disease and dramatically reduce the burden of these diseases on individuals and the healthcare system.

Animal models: New transgenic animal models do not faithfully replicate sporadic digestive cancer occurring in the adult human. Therefore, improved, rigorously validated animal models are needed.

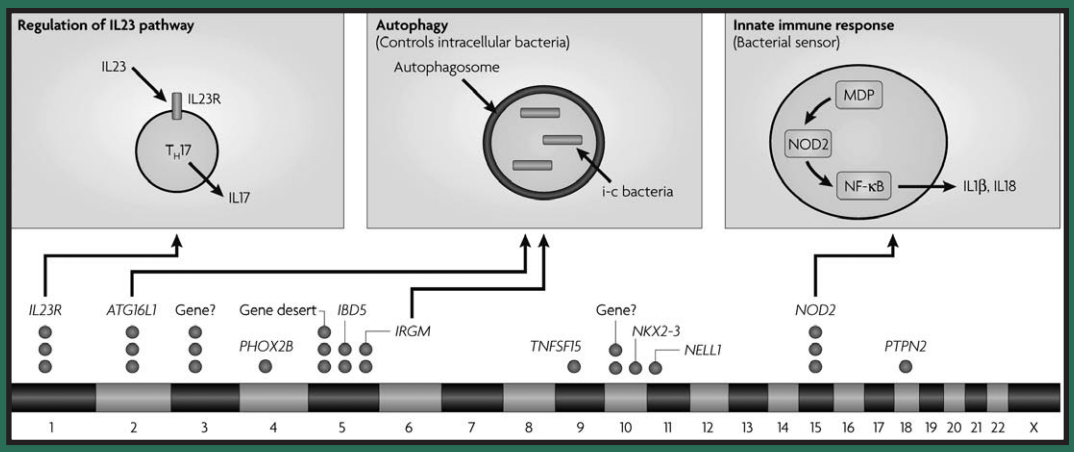

Diagram showing new genes and biological pathways associated in recent years with Crohn's disease. New approaches, such as genome-wide association studies, have identified previously unknown genetic factors and processes that influence the development of this disease, which can inform the design of future treatment strategies.

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Inflammatory Bowel Diseases

SUMMARY OF RESEARCH GOALS

Inflammatory bowel diseases (IBD) are a diverse group of digestive tract disorders of often unknown origin and complex disease management. Given the potentially severe impact of these diseases on patients' quality of life, cancer risk, growth and development in childhood and adolescence, and other serious health issues, the Commission proposes a set of research goals that are intended to accelerate progress on understanding, preventing, and effectively managing these diseases in all patients. An urgent research goal is the development of objective criteria for IBD diagnosis and risk evaluation, based on phenotypic and genetic characteristics, which would enable reliable subclassification of patients and their diverse constellations of symptoms. Such validated criteria could facilitate clinical evaluation and disease management approaches that are tailored to individual needs and that improve the efficiency of clinical trials to test new therapies. Strategies to prevent or control IBD that could be tested include modulation of the intestinal microflora or the mucosal immune system. These and other therapeutic approaches are targeted at maintaining the health of the intestinal mucosa and stimulating regeneration and repair in patients with IBD. In addition, finding ways to alleviate the unique developmental challenges faced by children with IBD is a particularly important goal in this research area.

INTRODUCTION AND BACKGROUND

Inflammatory bowel diseases comprise a set of chronic inflammatory disorders that affect different sites within the gastrointestinal (GI) tract and are not definitively attributable to any one known etiologic agent or specific precipitant. Two major forms of IBD—designated ulcerative colitis (UC) and Crohn's disease (CD)—have been empirically defined through decades of clinical experience on the basis of characteristic clinical, pathologic, endoscopic, and radiologic features. Occasionally, overlap in some features can prevent a firm diagnosis in a small proportion of patients, who are accordingly said to be affected by indeterminate colitis. Still other patients are affected by a seemingly distinct constellation of chronic idiopathic inflammation designated microscopic colitis (alternatively referred to by its two variants—lymphocytic colitis and collagenous colitis) in which the inflammatory process is milder and manifests primarily as watery diarrhea.

UC is characterized by diffuse inflammation affecting the mucosal and submucosal layers of the colon closest to the luminal surface that typically is most intense in the rectum and can extend proximally to varying degrees. In about a third of patients, the entire large bowel is affected. The inflammation eventuates in mucosal ulceration that contributes to the cardinal symptom of bloody diarrhea. While episodes of inflammatory activity can respond to therapeutic agents, additional "flares" follow with variable frequency. The chronic inflammation increases the risk of colon cancer, making surveillance for dysplasia (a form of pre-cancer) necessary even if the actual inflammatory disease remains in remission.

CD is more varied in its inflammatory process and clinical manifestations. Typically, inflammation affects all layers (referred to as "transmural inflammation"), in contrast to the superficial inflammation found in UC. CD may affect any site within the GI tract from mouth to rectum, though certain site-specific patterns are more common. The terminal ileum is most frequently affected, either alone or in conjunction with some segment of the colon. Similarly, one or more segments of the colon may be affected independent of the terminal ileum or more proximal areas of the digestive tract. In contrast to UC in which the inflammatory process is typically diffuse and continuous in extent, inflammation may be patchy and segmental in CD. Symptoms can reflect the inflammation itself or the scarring that can result (fibrostenotic disease). Often the GI tract becomes obstructed at the affected site. In many patients, the transmural inflammation can result in pathologic connections between the intestine and a variety of structures, including other parts of the GI tract, the bladder, the vagina, and the skin (most commonly in the perineal or perianal region). Many times, these connections are associated with the formation of abscesses. While CD can result in a wide range of symptoms, patients often experience the combination of abdominal pain, diarrhea, and weight loss. In pediatric patients, lack of growth is a particularly common manifestation. In addition to symptoms related directly to GI tract function, a significant minority of patients with either UC or CD also experience extraintestinal manifestations due to associated inflammation affecting the skin, eyes, joints, liver, and bile ducts. Although specific episodes or complications of CD can respond to available drugs or surgical intervention, none are curative, and disease is lifelong.

It is estimated that more than one million Americans are affected by IBD, with similar numbers for UC and CD. Prevalence is greater among some groups, including those of Ashkenazi Jewish ancestry, but the diseases are found in all ethnic and racial groups. The onset of IBD is most common in the second and third decades of life, though it can begin at any

time from infancy to the eighth decade. With onset in early adulthood, these disorders cause many decades of pain and suffering and result in significant lost productivity, in addition to the direct costs of medical and surgical care.

Research suggests that smoking increases the risk of CD, but reduces the likelihood of UC. Appendectomy early in life also appears to reduce the lifetime risk of UC, although the reason remains obscure. Family history appears to be the most significant risk factor. First degree relatives have a five- to 20-fold greater likelihood of developing IBD compared to those from unaffected families. In absolute terms, approximately 5 percent of children of a parent with IBD will develop the disease. The concordance of CD in identical twin pairs may be as high as 50 percent compared to 5-10 percent in non-identical twins, underscoring the key role that genetic inheritance plays in disease susceptibility.

Although a variety of medications are available that can control inflammation and ameliorate the resulting symptoms, none provide fully effective treatment, and almost all are associated with the risk of serious side effects. A variety of formulations that deliver 5-aminosalicylic acid (5-ASA) can be useful in treatment of mild UC and CD and may also diminish the frequency and severity of recurrence in UC. Select patient groups may respond to use of a broad spectrum antibiotic. Patients with more severe inflammation often require corticosteroids, potent anti-inflammatory agents that also carry risk of potentially severe complications, including suppression of normal immune defenses, osteoporosis, hypertension, diabetes, and others. Agents that modulate the immune system, such as azathioprine, 6-mercaptopurine, and methotrexate, are often used to minimize corticosteroid requirements and effect longer term control, but themselves can also cause serious side effects, including bone marrow suppression, pancreatitis, and liver toxicity. More recently, antibodies that target tumor necrosis factor (TNF), a key cytokine, have helped many patients who have not responded adequately to other agents. However, in addition to occasional side effects, the duration of efficacy may be limited, and a significant number of patients fail to respond. Surgical intervention plays a key role in the management of some patients. UC patients with severe disease that fails to respond to medical treatment can be "cured" by total removal of the colon, most commonly with the creation of a neo-rectum (pouch) using the terminal ileum. Surgery in CD patients is usually employed to manage a specific complication of the disease, typically involving drainage of infection and resection of an affected area. However, even when all segments apparently affected are removed, recurrence of CD over time is nearly inevitable. Unfortunately, despite extensive efforts, no effective preventive interventions have been identified for IBD.

RECENT RESEARCH ADVANCES

IBD genetic susceptibility factors

Substantial progress has been made in identifying factors that collectively appear to underlie the major forms of IBD. Research provides compelling evidence that individual risk for developing IBD depends on the inherited forms of several different genes. These genes control a variety of mucosal functions, particularly those involved in regulating the interaction with and response to luminal microflora. However, genetic inheritance alone is insufficient to lead to IBD, and actual disease depends on environmental factors, likely including the composition of the luminal microflora.

Mucosal barrier function and its functional alteration in IBD

Researchers have gained a more comprehensive—but still incomplete—understanding of the molecular basis of barrier function. Its importance in maintaining normal mucosal homeostasis and its disruption in the pathogenesis of chronic inflammatory bowel disease have been demonstrated. These advances include the composition of the tight junction and its functional regulation. Ultimately, understanding this dynamic regulation should enable strategies for enhancing the barrier to prevent IBD or restore it once damage has occurred.

Key genes conferring risk for IBD

Initial genomic screening led to the identification within the IBD1 region of *NOD2/CARD15*, a gene conferring risk for ileal Crohn's disease in many populations. More large-scale genome-wide scans using haplotypes have led to the identification of several more susceptibility genes, including those encoding the receptor for the cytokine IL-23 and ATG16L1, a protein involved in the process of autophagy and several other processes. Identification of these genes has focused mechanistic studies on the processes that they may mediate, including innate immune response to bacteria and regulation of adaptive immunity. More comprehensive understanding may allow a clinically useful definition of disease risk and prediction of disease course and response to therapy.

Commensal microflora as key drivers of intestinal inflammation

Extensive efforts have failed to consistently implicate a specific pathogen in association with IBD. However, murine models and circumstantial observations in patients provide compelling evidence that the complex variety of commensal microflora, which is innocuous in most people, is an essential driver of chronic intestinal inflammation in susceptible individuals. Thus, development of chronic colitis in murine models requires the presence of a seemingly normal microflora. Characterization of the complexity of normal microflora remains substantially incomplete, though some studies have suggested that at least one class within the microflora—designated AIEC (adherent invasive *E. coli*)—may be more common in CD.

The central role of the epithelium and dynamic interaction between epithelium and luminal bacteria

A variety of direct and circumstantial observations implicate a role for alterations of the epithelial cell compartment in the central pathogenesis of IBD. These include development of colitis in murine models resulting from genetic alterations of epithelial cell-expressed products and expression of proteins encoded by human IBD susceptibility genes in the epithelium. In addition to its role in forming the mucosal surface barrier, the epithelial cell compartment has key capabilities of innate immune response, including expression of both Toll-like receptors (TLRs) and NODs and production of effectors, such as defensins. These may be central to the functional outcome of contact and interaction with luminal microflora—both commensal populations and enteric pathogens. Alterations in these factors and processes are found in IBD.

IBD involves the loss of mechanisms that normally ensure peaceful coexistence with luminal microflora

Despite possessing a robust variety of receptor and signaling pathways that should trigger inflammation in the context of ubiquitous and constant contact with microflora, the epithelium remains in a state of "tolerance" or hyporesponsiveness. While this hyporesponsive posture allows peaceful co-existence with the

omnipresent luminal microflora, it points to important questions for further study, such as: how is this state abrogated in circumstances where inflammation may be a normal and healthy response (e.g., exposure to a true enteric pathogen); and how is it altered in the context of IBD in the absence of a specific pathogen?

Processes mediating innate immune responses and alterations associated with IBD

The finding that the IBD1 genomic region contains a gene encoding an intracellular innate immune receptor protein, as well as the characterization of the full spectrum of receptors, their signaling mechanisms, and effector mediators, underscores the importance of these pathways in mediating normal mucosal homeostasis and alterations that can lead to IBD. The former advance relates to regulation of intracellular bacterial survival and production of the antimicrobial defensin proteins, and the latter relates to altered NOD and TLR receptor forms in patients with IBD. These receptors appear to play a central role in the initial responses to luminal bacteria and, ultimately, result in chronic intestinal inflammation with downstream activation of adaptive immunity.

Processes that effect adaptive mucosal immune responses and their alteration associated with IBD

Researchers have identified several key lymphocyte populations and their cytokine products that drive ongoing intestinal inflammation through stereotypic responses. In addition to the long-recognized Th1 and Th2 responses, these are now known to include Th17 lymphocytes driven by IL-23 and capable of producing IL-17, which leads to release of pro-inflammatory cytokines by target cells and tissue injury, as well as a constellation of FoxP3-positive and -negative regulatory cells. Relative functional deficiency of the latter appears to enable the ongoing inflammation. Dendritic cells and the pivotal role they have in priming these responses have also been defined. Finally, a multitude of cytokine products of these cell populations and others have been identified and their functional effects delineated with the demonstration that many may be particularly important in the pathogenesis of IBD (including, among others: IL-1, IL-2, IL-12, IL-17, IL-23, TNF, interferon, and TGF-β).

Clinical effectiveness of mechanism-based therapeutic agents

Although therapy remains inadequate for many patients and none is curative, anti-TNF treatment has been shown to effect substantial response in some patients who do not respond adequately to other modalities. Other agents targeting mediators and mechanisms identified through recent studies on IBD pathogenesis appear promising in clinical trials.

Mediators of inflammation and tissue injury

As noted above, many cytokines have been found to mediate activation of different cell populations. These cells, in turn, produce a variety of non-peptide effectors of inflammation that include leukotrienes and other prostaglandin-derived products, as well as reactive oxygen metabolites. These appear to be among the most proximate mediators of tissue damage.

Mechanisms of mucosal tissue repair and fibrosis

Many manifestations of IBD can be traced to either failure of normal repair mechanisms to restore mucosal integrity or pathologic repair processes that result in fibrosis and loss of normal physiologic function. Key components of mucosal repair processes, including the

contribution of trefoil peptides and some select cytokines, have been identified. Alterations in the balance of production and degradation of extracellular matrix constituents, including the metalloproteinases and the factors that modify them (e.g., TIMPs), have been observed in association with fibrosis in IBD. Definition of key components of the coordinated repair response to injury and the ability to enhance repair through novel strategies for delivering recombinant proteins will play an important role in advancing understanding of IBD, as highlighted by studies of trefoil peptides. These may enable new therapeutics for IBD, complementing those targeted to inflammatory processes *per se*, which may also have particular importance as prophylactic interventions.

Murine models of colitis

Many advances in delineation of processes relevant to IBD have been made possible through the development of murine lines modified by either targeted gene deletion or transgene expression that experience "spontaneous" colitis. These animal models have been used to demonstrate that colitis can result from functional alterations in the epithelial compartment and certain immune processes. The models have also allowed researchers to explore the interaction between genetic susceptibility and environmental factors, including the role of luminal microflora.

GOALS FOR RESEARCH[11]

Research Goal 5.1: Establish an objective basis for determining clinical diagnosis, detailed phenotype, and disease activity in IBD.

Despite decades of clinical experience, diagnosis of the major forms of IBD remains dependent on empiric criteria that leave important residual uncertainty in a significant minority of patients. Further, despite the well-recognized spectrum of clinical manifestations, objective means are not available to substratify patients in order to predict the natural history of disease or likely responsiveness to different therapeutic agents that would facilitate more effective and efficient therapy. Progress in defining genotypes associated with disease susceptibility, identifying markers of immune response, identifying the central role of luminal microflora, and defining the microbiome of individuals supports the development of rigorous and prospective studies to validate objective criteria that can guide diagnosis and management. Similarly, the rapid evolution of imaging technology reflecting pathophysiologic processes provides an opportunity for functionally meaningful assessment of disease activity. Finally, identification of suitable disease markers that permit objectivity and consistency in diagnosis and subclassification of patients will facilitate and enhance the efficiency of clinical trials.

Objectives:

- Develop a comprehensive genotypic profile.
- Define informative immunophenotypic profiles.
- Develop methodology and applications for a microbiomic profile.
- Develop technology for effective anatomic and functional imaging of disease location and activity.
- Establish useful correlative and predictive biomarkers.

[11] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

Research Goal 5.2: Develop an individualized approach to IBD risk evaluation and management based on genetic susceptibility.

While significant progress has been made in identifying genetic risk factors for IBD in some broad populations, substantial limitations remain in applying these insights to individuals. Study populations to date have not delineated the relative risks within subpopulations that reflect the full diversity of people who may be affected. Most importantly, substantial gaps remain in understanding the interaction between acquired or environmental factors to determine the mechanisms leading to actual IBD development within individuals. Achieving this overall goal requires a complete understanding of the functional effects of the variant genes that have been found to confer risk of IBD, as well as a comprehensive matching of disease-associated genotypes to disease features and response to therapy. Genes that metabolize agents used in the management of IBD need to be investigated with respect to their influence in modulating response to therapy and potential toxicities. Undertaking a multi-dimensional and comprehensive study of IBD-associated genes and their products is a critical component of this goal.

Objectives:

- Complete identification of risk susceptibility genes among diverse patient populations.
- Determine the functional role of IBD-associated gene variants in pathophysiologic pathways leading to IBD.
- Determine the impact of environmental factors on disease-associated genetic variants.
- Define genetic subset/phenotype-genotype correlations.
- Identify and assess relevant pharmacogenetic variations.
- Correlate genotype (disease susceptibility and pharmacogenetics) with response to therapy and incorporate genotypes into clinical trials.
- Use genotypic variations to define disease risk.

Research Goal 5.3: Modulate the intestinal microflora to prevent or control IBD. (See also Goals 1.20, 1.21, and 9.3.)

The convergence of insights derived from experimental and clinical observations points to a central role of the luminal microflora as a driver of chronic IBD. While research proceeds in defining host factors that contribute to the development of an immune and inflammatory response that overrides the tolerance to luminal microflora found in healthy individuals, understanding of the complex populations of microbes that constitute the luminal microflora is markedly incomplete. Beyond the intrinsic complexity of the microflora, a major barrier to defining the combination of microbes and/or their products that are important in the pathogenesis of IBD in populations and individuals is the inability of current technologies to resolve this complexity. Development of large-scale sequencing and corresponding powerful computational tools is essential to understanding the role of the microflora in IBD pathogenesis. Insights derived from the application of these tools can also provide a foundation for the development of strategies for effective therapeutic manipulation of luminal microflora content, which conceptually should be free of risk for adverse side effects.

Objectives:

- Achieve a comprehensive molecular and functional delineation of the intestinal microflora in all relevant niches across different individuals/populations.
- Understand the factors that regulate the composition and functional characteristics of the intestinal microflora, including host factors (e.g., environmental, genetic, and mucosal function).
- Characterize the intestinal microflora associated with IBD by location and disease activity.
- Develop experimental tools for understanding intestinal microbiome complexity and clinical methods for characterization and monitoring of the intestinal microflora in patients.

- Develop experimental *in vivo* systems for preclinical studies of intestinal microflora therapeutic modulation.

Research Goal 5.4: Effectively modulate the mucosal immune system to prevent or ameliorate IBD.

It is axiomatic that immune activation and the production of inflammatory mediators are intrinsic to IBD, in which the presence of infiltration with cells associated with these responses is among the defining empiric criteria of these disorders. Substantial progress has been made in defining the components of mucosal innate and adaptive immune responses. However, a comprehensive understanding of these complex pathways is still needed as a foundation for understanding their activation and alteration in the context of IBD. This will require developing molecular signatures of all immune cell populations, the factors regulating their activation, and their products. The intricate interconnection among the cell populations participating in immune and inflammatory responses and the multiplicity of their products demands a systematic approach and the quantitative strategies of systems biology. Given the mounting evidence for the pivotal role of luminal microflora in IBD, it is essential to delineate the interactions among these flora, the immune response, and the factors that deregulate the processes that allow tolerance in the normal intestine. Determining the total components of the immune and inflammatory response should enable the development of strategies for focused modulation to achieve effective control of these responses without the toxicities that result from the relatively non-specific and broad immunosuppressive effects of most current therapies.

Objectives:

- Define all relevant immune cell populations by their functional characteristics and differentiation pathways.
- Define the factors regulating innate and adaptive immunity, both genetic and environmental.
- Delineate innate and adaptive immune interaction with the microbiome.
- Identify relevant inflammatory mediators in effecting IBD injury and symptomatic manifestations of IBD and mechanisms regulating inflammatory processes.
- Characterize alterations in innate and adaptive immune function in IBD, including regulatory cell populations, especially related to microbiome.

Research Goal 5.5: Sustain the health of the mucosal surface.

Normal intestinal function depends on the integrity of the mucosal surface. Research indicates that the epithelium may be intrinsically altered by genetic and other factors that play a role in the initiation of IBD. Conversely, the epithelium is the victim of the inflammatory processes that lead to mucosal ulceration, a central process underlying IBD that permits sustained activation of underlying immune and inflammatory responses. Understanding the biology of the epithelium will provide insights into the earliest and most central events that lead to the major forms of IBD and create a foundation for developing strategies to enhance the functional and physical integrity of the mucosal surface. Defining the role of the epithelium in these disorders depends on integrated study of the interaction of this surface compartment with the luminal microflora at its apical surface and the variety of cell populations within the underlying lamina propria. It is equally important to define the distinct roles of the four major cell lineages (columnar, goblet, Paneth, and enteroendocrine) that collectively comprise the epithelium, given that functional alterations in each cell type are associated with IBD. Investigating the intestinal stem cell compartment and the processes regulating the production and differentiation of cells emerging from progenitor populations is an important aspect of this goal.

GOALS FOR RESEARCH

Objectives:

- Understand the functional biology of the epithelial compartment and identify alterations in IBD.
- Identify and characterize the stem cell compartment and develop the capacity to modulate lineage specification and maturation.
- Understand the structural and functional elements of the mucosal barrier, including the role of luminal microflora and nutrients, and alterations associated with IBD.
- Define the systems biology of the intestinal mucosa, including interactions among epithelial and lamina propria cell populations, as well as integration with enteric nervous, endocrine, and vascular elements.

Research Goal 5.6: Promote regeneration and repair of injury in IBD.

In parallel with the goal of sustaining the health of the mucosal surface, effective treatment of patients with established IBD will utilize insights in mucosal biology to promote repair of injury resulting from inflammatory processes. Such therapies should aim to restore structural integrity and physiologic function to affected sites within the GI tract. For many patients, the morbidity of their disease results more from the failure of healing with ongoing ulceration or a pathologic healing response and resultant fibrosis and/or loss of mucosal function than from the effects of inflammation *per se*. Effective interventions to promote physiologic repair will depend on knowledge of the processes that contribute to tissue healing. Understanding the factors contributing to fibrosis and the mechanisms that allow remodeling of the extracellular matrix will be particularly important given the frequency at which fibrosis leads to obstruction and other morbidity. Strategies to improve functional capacity are also important for the many patients in whom the disease process leads to extensive mucosal destruction, as well as the many others who currently require extensive surgical resection.

Objectives:

- Understand normal repair processes and characterize their alteration in IBD.
- Define the impact of the intestinal microflora on tissue repair.
- Develop strategies to modulate repair processes to restore functional capacity.
- Identify mechanisms to reverse or remodel fibrotic response.
- Identify interventions that improve care of patients with surgically modified gut.

Research Goal 5.7: Provide effective tools for clinical evaluation and intervention in IBD.

While prevention of IBD is the ultimate goal, more effective tools for the evaluation of disease activity are needed to guide therapy, and more effective therapeutic agents are needed for the many patients for whom currently available modalities are ineffective or counterbalanced by adverse effects. New tools should include noninvasive modalities for rapid assessment of the distribution and intensity of inflammatory activity. Identification of early markers of inflammation, as well as markers that predict ultimate response soon after initiation of a new therapeutic intervention, will be powerful adjuncts to both routine clinical management and a means of accelerating the speed and efficiency of clinical trials of new agents. Finally, it is essential that evolving insights into the critical pathophysiologic mechanisms that lead to IBD are used to develop more specific therapeutic agents and other interventions that fill the unmet treatment needs of IBD patients.

Objectives:

- Develop and validate technologies to evaluate disease status, including biomarkers, as well as noninvasive and other novel endoscopic imaging methods.
- Develop innovative endoscopic and more physiologic surgical interventions.

GOALS FOR RESEARCH

- Develop effective and non-toxic mechanism-based pharmacologic therapies, including manipulation of the microflora.
- Develop tools for more efficient clinical development of investigational agents, including surrogate markers of response.
- Develop tools to more effectively identify pre-malignant changes in the mucosa and support interventions to reduce cancer risk.

Research Goal 5.8: Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents.

In addition to the challenges faced by adult patients with IBD, children and adolescents face distinctive clinical manifestations unique to these patient groups due to the potential impact of the disease on normal growth and development. Indeed, the lack of growth can be the most prominent manifestation in childhood, and the failure to undergo a normal growth spurt in young adolescents with IBD has potential lifelong impact. This impact extends from limitations in physical stature to difficulties in social and emotional maturation that can follow. These potentially profound effects on growth reflect a variable combination of the influence of inflammatory mediators, malabsorption resulting from mucosal injury, and poor nutritional intake. In addition to the effects of IBD, drugs used to treat the disease may have a negative impact on overall growth. Accordingly, strategies are needed to ensure normal growth and development in these vulnerable patient groups, in concert with overall efforts to treat the IBD.

Objectives:

- Develop interventions that promote normal social interactions and mental health in all children and adolescents with IBD.
- Define the mechanisms that produce growth delay in pediatric IBD patients.
- Identify approaches that enable normal growth and development within the context of pediatric IBD.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Basic mechanisms of IBD: To build on recent progress in defining IBD susceptibility genes, large-scale collaborations (national and international) would facilitate comprehensive sample acquisition, analysis of genetic loci across diverse populations, and research on well-characterized patients followed on a longitudinal basis to define genotype-phenotype correlation. Even more challenging are the current methodological limitations for the study of complex microbial populations in the GI tract. The development and dissemination of rapid, quantitative, high-throughput techniques to define individual members of complex microbial communities, robust bioinformatic tools, and metagenomic data sets with comprehensive data on provenance and host phenotype would accelerate progress in the field. New computational tools, such as *in silico* techniques for modeling microbial populations and microbial-host interactions, would enable researchers to effectively mine extremely large data sets. Initiating an intestinal microbiome project, beginning with commissioning computational tools and pilot projects, represents an important step to addressing these challenges. The establishment of the Human Microbiome Project within the NIH

Roadmap for Medical Research provides essential technologies and resources for research on the intestinal microbiome. An equally important and technically difficult hurdle is the development of techniques to isolate and sustain primary epithelial cell populations *in vitro* to enable research on these critical cell populations and their functional alteration in IBD.

Translational research: With acceleration of the discovery of susceptibility genes and basic mechanisms of immune response and epithelial function, the opportunities for translational research in the context of IBD are greater than ever. In order to realize the potential for new insights into disease processes, it is important to develop robust *in vitro* model systems, including primary cell and organ cultures, that recapitulate the complexity of intestinal mucosa and can be experimentally manipulated. Parallel development of animal models with validated clinical relevance in which response to intervention is predictive of response in humans would enable rapid progress from *in vitro* systems to animal model studies to patients. Better integration of basic and clinical research efforts is essential for more effective translational progress. Establishing consortia of investigators across institutions would expedite research to understand the functional implications of the gene variants that have been associated with IBD.

Clinical research and discovery: The lack of objective and consistent criteria for diagnosis and substratification of patients remains a significant barrier. Fully realizing the opportunities to develop and evaluate new therapies based on growing insight into IBD pathophysiology depends on establishing standards for clinical trials, including incorporation of surrogate endpoints, phenotyping, and DNA collection. Standardization of techniques for DNA sample acquisition would also foster close integration with translational studies. Overall, the potential synergies between clinical studies and translational analysis have not been realized and, thus, provide an opportunity to accelerate the assessment of basic mechanisms elucidated through study of animal models and *in vitro* systems within the context of human IBD. Equally important, development of more effective strategies for enrolling patients in clinical trials and fostering the development of a larger cadre of clinical investigators and clinical trial infrastructure would support an expanded national and international program of interventional clinical trials for IBD. Particular attention should be paid to overcoming barriers to therapeutic trials in pediatric populations, such as industry reluctance due to potential risks in these patient groups. These efforts, as well as more basic and translational research challenges, would benefit substantially from greater public awareness and understanding of IBD that can be achieved through public educational programs. Convening a clinical summit on IBD attended by investigators, all stakeholding agencies, and industry would be an initial step toward surmounting these challenges.

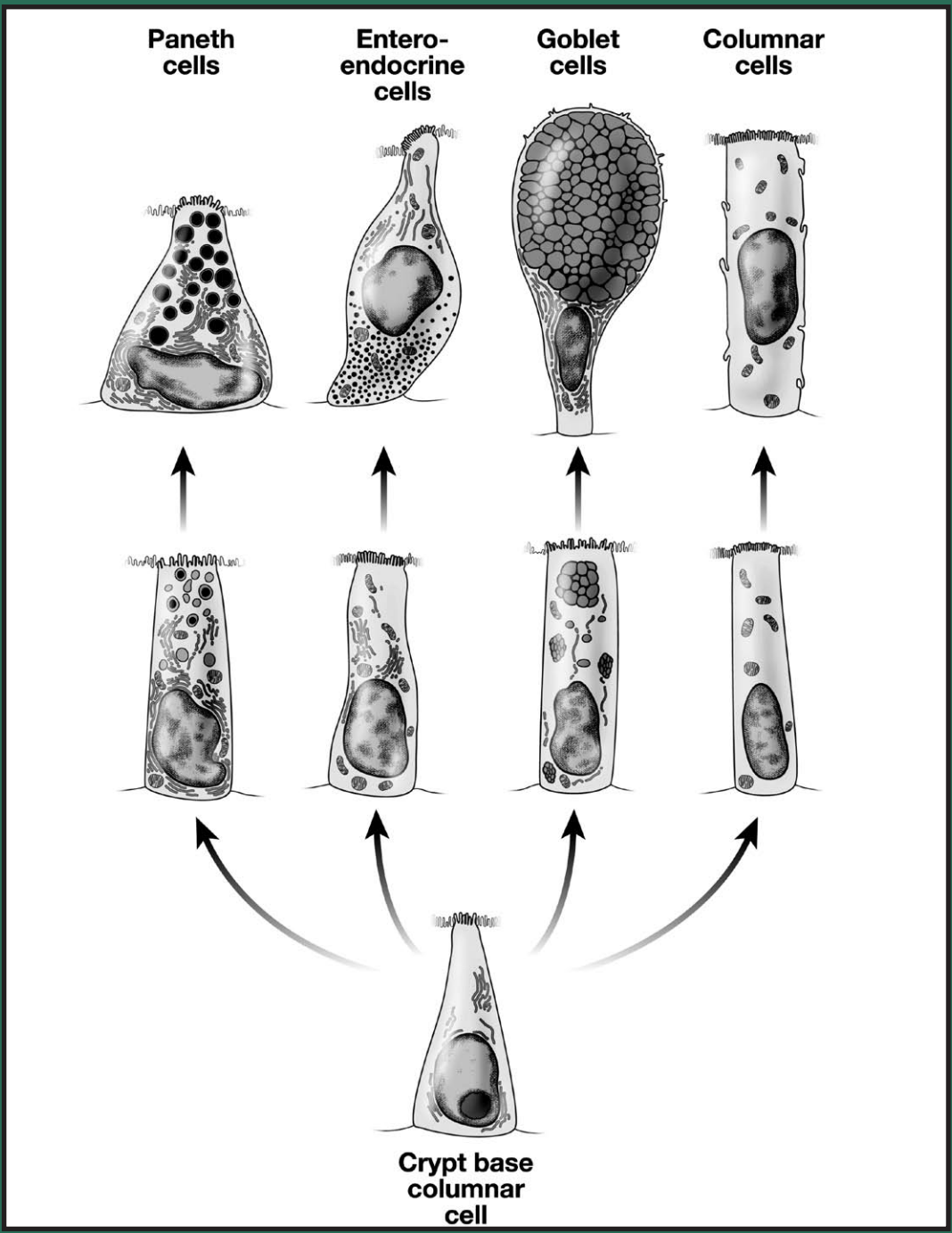


Illustration showing the proposed origin of various small bowel epithelial cell types from possible stem cells located at the base of the crypts. Stem cells play an important role in regenerating the intestinal epithelium.

Image courtesy of Dr. Nick Barker. Reprinted from Gastroenterology, *133, Barker N and Clevers H, Tracking down the stem cells of the intestine: strategies to identify adult stem cells, pp. 1755-1760, Copyright 2007, with permission from Elsevier.*

Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation

SUMMARY OF RESEARCH GOALS

Loss of intestinal function can occur through surgical removal of tissue or diseases that impair digestion or cause tissue death. The Commission recommends research goals that, if pursued, would increase understanding of the natural mechanisms of growth, differentiation, and adaptation in the gastrointestinal (GI) tract and use that information to better treat patients with GI diseases. Research is needed on the development of new treatment strategies for short bowel syndrome (SBS) and intestinal failure, including innovative approaches to optimizing intestinal transplantation and post-transplant survival. GI tract surgeries, including bariatric surgeries for weight loss, are frequently associated with nutritional or hormonal complications. An important research focus is improving nutritional support for surgical patients and others with digestive diseases who rely on parenteral or enteral nutrition to sustain life, including premature infants with necrotizing enterocolitis (NEC). Achieving these research goals would markedly enhance the quality of life and health of many patients with digestive diseases or injury who are unable to properly absorb nutrients through their GI tract.

INTRODUCTION AND BACKGROUND

The collection of topics in this chapter is linked by a common interest in the physical integrity of the gut and strategies to promote natural repair and regeneration processes in response to loss of intestinal tissue function through surgery or disease.

Intestinal growth and differentiation: At birth, the human small intestine is typically 2-3 meters in length and grows to about 6-7 meters in adults. In addition, the epithelial lining of the intestine is continually renewed as new cells mature from proliferating stem cells located at the base of the intestinal crypts. This lifelong capacity for growth and differentiation of the complex cellular structure of the intestine suggests the potential for development of regenerative cures for many digestive diseases as researchers learn how to identify, isolate, and manipulate intestinal stem cells.

Short bowel syndrome and intestinal adaptation, repair, and regeneration: SBS can occur when half or more of the small intestine is missing or not functioning properly. Infants and children can develop this condition for a variety of reasons, including congenital defects and NEC. In adults, SBS can result from surgical removal of the intestine for treatment of inflammatory, mechanical, and malignant processes, including Crohn's disease, tumors, volvulus (a twisting of the intestine that causes tissue death), bowel obstruction, traumatic injury, or other conditions. Patients with this syndrome develop diarrhea, dehydration, and malnutrition due to the inability of the intestine to absorb sufficient water, vitamins, minerals, and other nutrients from ingested food.

Patients with mild SBS are treated with dietary modification (small frequent meals), with or without anti-motility and anti-secretory medications. Patients with moderate to severe SBS often develop intestinal failure, which results when there is insufficient intestine to absorb adequate fluid to maintain hydration and/or to absorb 85 percent of required nutrients. These patients require intravenous fluids, electrolytes, or nutrients through such means as parenteral nutrition (PN)—the delivery of nutrients and fluids by vein rather than by ingestion to sustain life. Unfortunately, with prolonged use, PN is associated with life-threatening complications.

For fortunate patients without massive gut loss, SBS is a temporary phenomenon. Intestinal adaptation can occur by enlargement of the intestinal villi, an increase in crypt cell proliferation, or an increase in the diameter of the small intestine—all of which augment the surface area available for nutrient absorption. Alternatively, slowing of peristalsis—the movement of food through the digestive tract—can also help patients adapt to a shorter intestine. These processes can be facilitated with luminal nutrients and growth factors, although a much better understanding of these factors is needed to optimize this therapy. Finding ways to promote intestinal adaptation, repair, or regeneration could lead to new therapies for SBS in both children and adults. PN failure occurs in some patients from loss of venous access as a result of central vein thrombosis, recurrent severe septicemias, or development of irreversible liver disease. These patients require small bowel transplantation. A combined liver/small bowel transplant is necessary when liver failure occurs in conjunction with intestinal failure.

Intestinal transplantation: For patients with irreversible intestinal failure or those with progressive complications of PN, small intestine transplantation is the last therapeutic option. Close to 200 intestinal transplantations, either alone or in combination with other abdominal organs, are performed each year in the U.S. The short-term success of intestinal

transplantation procedures is now similar to that for other solid organs (close to 80 percent 1-year survival for host and graft) due to recent advances in immunosuppression, and recent studies suggest successful transplantation is associated with improved quality of life. Long-term survival, however, remains suboptimal.

Metabolic and nutritional consequences of surgically modified gut: With the increasing prevalence of obesity in the U.S. and worldwide, bariatric surgical procedures are becoming more common in both adults and adolescents. Different surgical procedures are used, with the most frequent being a reduction in stomach size, bypass of a portion of the small intestine, or a combination of both strategies. Many patients achieve significant weight loss in response to the surgery, although serious complications at the time of surgery, such as anastomotic leakage, pneumonia, deep vein thrombosis and embolism, or death, can occur in rare cases. Serious chronic side effects also may follow bariatric surgery procedures, including intestinal infections, food intolerance, hernia, and the need for surgical revisions or surgery for treatment of complications, occasionally resulting in intestinal loss. Nutritional deficiencies can occur due to poor absorption of food and vitamins or minerals in the modified gut. Weight loss after bariatric surgery is not wholly explained by restricted food intake, but may also involve metabolic and hormonal changes resulting from the surgery that are not yet fully understood.

Nutritional support of patients with GI disorders:[12] Patients with GI disorders often develop nutritional deficiencies due to interference with the normal digestion and absorption of food, ranging from mild deficiencies resulting from poor absorption of micronutrients to dehydration and starvation in extreme cases. Some patients, such as those with anorexia or dysfunction of the upper GI tract, can be treated by enteral feeding through a tube placed directly into the GI tract. If all gut function is lost, as for patients with moderate to severe SBS and intestinal failure or in premature infants with NEC, PN supports survival. Specialized enteral diets and gut peptide analogues, such as glucagon-like peptide-2 (GLP-2) and growth hormone, can maximize mucosal adaptation and regeneration. However, complications of PN for patients needing long-term nutritional support can include infections, chronic liver failure, loss of kidney function, metabolic bone disease, and blood clots.

RECENT RESEARCH ADVANCES

Mechanisms regulating mucosal function and growth

The mechanisms responsible for regulating mucosal function and growth have been clarified at the cellular and molecular levels, allowing for manipulation of the intestinal milieu in order to augment intestinal adaptation. For example, growth factors have been shown to enhance villus growth, stimulate enterocyte proliferation, and attenuate enterocyte apoptosis in the remnant gut following massive intestinal resection. Animal investigations, as well as preliminary studies in humans, suggest that growth factors, including GLP-2, insulin-like growth factor-1 (IGF-1), and epidermal growth factor, may help stimulate intestinal growth and development and lead to improved fluid and nutrient absorption. Collectively, these growth-stimulating phenomena in animal models are termed post-resectional adaptation. Work over the last two

[12] *The Commission considered the issue of nutritional support and its consequences for patients with gastrointestinal diseases. However, the broader topic of nutritional research planning is overseen by an existing group, the NIH Nutrition Coordinating Committee within the Division of Nutrition Research Coordination.*

decades has demonstrated that this process is influenced by a number of factors, including specific luminal nutrients, such as fiber, as well as a variety of GI and systemic hormones and peptides. These studies have demonstrated that luminal nutrients and bacteria are capable of altering gene expression profiles and absorption and digestion in enterocytes. The availability and study of isolated enterocytes and enterocyte cell lines have clarified the specific role of peptides, hormones, and matrix factors on these growth and differentiation processes.

The chronology of intestinal adaptation has demonstrated that the gut is most responsive to stimulation and augmented growth immediately following the loss of intestinal surface area. Both animal and human models demonstrate that growth hormone, but not glutamine, may enhance intestinal adaptation and improve fluid and nutrient absorption, leading to the ability to reduce PN requirements. Recent translational studies in patients with SBS-intestinal failure have shown promise for efficacy of novel agents and medications not originally developed for GI conditions. The adaptive processes of villus hypertrophy and improved fluid absorption, with the reduced need for PN, can be enhanced with GLP-2 and GLP-2 analogues. Improved chloride and fluid absorption has been reported with orally administered or transdermal clonidine.

The identification of a stem cell niche with specific responsiveness to growth factors, gut peptides, and paracrine factors has enhanced our understanding of specific molecular features of this growth adaptive process.

Surgical modification of the small intestine

Intestinal lengthening procedures have led to improved management of infants and children with refractory SBS. Intestinal dilation, bacterial overgrowth, and luminal stasis are hallmarks of chronic SBS in infants and children. Refractory to medical strategies to minimize malabsorption, it has been demonstrated that intestinal lengthening procedures, including serial transverse enteroplasty (STEP) and the Bianchi procedure to remove non-functional and dilated loops of the intestine, lead to improved intestinal function, including absorption of nutrients and liquids.

Intestinal transplant registry

Advances in intestinal transplantation have been documented by data from establishment of a voluntary international intestinal transplant registry. The registry includes virtually all intestinal, intestine/liver, and multivisceral transplants performed around the world. Expansion of the registry has allowed accurate appraisal of patient survival, graft survival, impact on survival of PN use, and other outcome data. The collaborations that contribute to the ongoing registry project have facilitated improved management of patients and development of new collaborative research projects by international centers of excellence in intestinal transplantation.

Intestinal transplantation

Intestinal transplantation, with or without the liver, has become progressively more successful in the major transplant centers, with first-year survival rates similar to orthotopic liver transplantation alone. The improvement in quality of life is substantial for patients with intestinal failure who are dependent on permanent PN. This occurs in the majority of, but not all, graft recipients. Definition of factors contributing to graft survival, optimal management of immunosuppressive regimens, improved methods to monitor rejection, and factors contributing to adaptation of the transplanted gut remain areas of active investigation. It has also been observed that intestinal transplantation can not only prevent, but also reverse, early PN-induced liver

dysfunction, thus avoiding the eventual need for combined small bowel/liver transplantation.

Candidate markers for intestinal transplant rejection without the need for tissue biopsy have been identified, including 3-0-methyl glucose absorption, serum citrulline, and calprotectin. Each may potentially serve as a surrogate for intestinal mass and/or rejection and, thus, avoid the need for frequent intestinal biopsies to identify early reversible rejection. Tolerance to the intestinal graft develops in some patients, allowing a reduction in immune suppression to a few times per week. Factors responsible for the development of tolerance are unclear and are being investigated.

Regenerative medicine for treatment of intestinal failure

Mucosal plugs from the intestinal stem cell niche have been successfully grown on bioartificial scaffolds. Placed in continuity with the native intestinal tract, these mucosal plugs have demonstrated normal proliferative patterns and the capacity to expand to fill gaps in the intestinal mucosal surface. Given the dense lymphatic tissue burden in intestinal allografts, the ideal long-term solution for patients with intestinal failure will be a regenerative medicine approach in which native intestinal tissue is expanded on a suitable scaffold and grown to a size and surface area sufficient to support enteral nutrition when placed in continuity in the GI tract. Identification of the stem cell niche and expansion of this population into a mature and differentiated mucosal surface is an important first step in this process. Identification of appropriate matrix, manipulation of the growth and differentiated environment, and strategies to induce vascularization sufficient to incorporate the tissue into the native GI tract will be required to achieve a tissue-engineered solution.

Effect of parenteral nutrition on GI development

Several strategies to reduce the negative impact of PN on developing GI organs have been identified. PN may cause choline deficiency, which has been implicated in fatty liver, an early step in liver disease. Intravenous choline supplementation may ameliorate this process. Fish-based emulsions, tumor necrosis factor (TNF) blockade, cycling of PN, and ursodeoxycholic acid administration have been reported to possibly be of benefit in the treatment of PN-associated liver disease. The timing of introduction of enteral feedings or PN in neonates and premature infants has demonstrated that there are critical windows to optimally introduce these factors to maximize GI development, infant weight gain, and growth.

Prevention and treatment of NEC

NEC remains one of the most lethal perinatal conditions of premature, low birth weight infants. Prevention is the key objective for, once established, this condition is the lead cause of intestinal failure in children. Preliminary data from trials in premature infants suggest that probiotics may be beneficial in the prevention of NEC, and granulocyte stimulating factor may reduce progression to more severe NEC. Surgical approaches have also been introduced to minimize the role of resection in the management of these patients while ensuring adequate management of abdominal sepsis in these critically ill infants.

Intestinal microflora

The application of DNA methodology to assess the resident bacteria of the gut has revealed tremendous diversity and mass of the microflora. These studies have opened

up research on the role of bacteria in the prevention and causation of intestinal disorders, including those that may lead to SBS-intestinal failure.

Animal models of bariatric surgery

A rat model of gastric banding has been developed, and bariatric surgical mouse models have also been developed. While mechanical mechanisms were once considered the primary modality of weight loss, recent advances in measurement of gut hormones, including ghrelin, polypeptide Y, and others, indicate that substantial changes in metabolic and GI hormones occur. Identification of the mechanisms underlying surgically induced weight loss in animal models could result in development of medical means to produce significant and durable weight loss, which is currently achievable only through surgery. Animal models may also allow better understanding of the long-term metabolic sequelae of bariatric procedures, including specific nutrient deficiencies, metabolic and bone disorders, management of bypassed segments, and other issues.

GOALS FOR RESEARCH [13]

Research Goal 6.1: Define mechanisms of intestinal growth and differentiation. (See also Goal 1.6.)

The intestine has the capacity to grow during childhood, renew its lining throughout life, and adapt to loss of mucosal surface area due to surgical resection or disease. By understanding these processes at a molecular and cellular level, it might be possible to develop new pharmaceutical or cell-based therapies to enhance these natural phenomena, either to (1) effect total remission or cure of disease by replacing sections of the intestine with functional tissue; or (2) promote recovery from surgery or injury by stimulating endogenous repair pathways. Researchers are focused on characterizing the mechanisms that govern lineage selection of cell phenotypes from intestinal stem cells and understanding the molecular pathways involved in intestinal adaptation.

Objectives:

- Isolate, characterize, manipulate, and expand human intestinal stem cells *in vitro*.
- Define optimal growth factors, nutrients, extracellular matrix, and milieu to enhance post-resectional adaptation in human patients.
- Develop an optimal bioartificial scaffold for neomucosal growth.
- Develop artificial intestinal constructs for replacement of diseased bowel.
- Conduct a clinical trial of exogenous factors to optimize post-resectional adaptation.

Research Goal 6.2: Develop new strategies to treat short bowel syndrome and intestinal failure.

Surgical bowel resection for conditions such as Crohn's disease or injury can lead to the development of SBS or intestinal failure, although some adaptation of the remaining tissue is possible.

[13] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

GOALS FOR RESEARCH

Studying the nutritional, hormonal, or other factors that promote adaptation could reveal new strategies for enhancing bowel recovery from surgical resection. Avoidance of SBS and intestinal failure would represent a significant therapeutic advance and relieve the significant medical and economic burden of these conditions. Further research is needed to understand why PN complications arise and how they can be prevented and/or treated.

Objectives:

- Evaluate the effect of specific micronutrients and diet on post-operative intestinal adaptation.
- Develop and validate noninvasive markers of intestinal growth and adaptation in models of SBS.
- Develop reliable, noninvasive methods to measure intestinal growth and adaptation in patients.
- Develop more effective techniques and strategies to reduce septic, metabolic, thrombotic, and hepatic complications of PN and intestinal failure.
- Define the molecular basis of radiation enteritis and of potential approaches to prevent and treat radiation enteritis and proctitis.
- Conduct a clinical trial of optimal growth factor (or synergistic combination) therapy following massive intestinal resection.
- Develop prognostic indicators for PN failure to guide the timing of intestinal transplant evaluation in optimal candidates.

Research Goal 6.3: Improve the success of intestinal transplantation.

Intestinal transplantation can be a life-saving treatment for some patients with intestinal failure who have developed potentially life-threatening complications. The success of this procedure could be improved by developing novel immunosuppressive drugs that are tailored for the unique immunological milieu of the intestine or by optimizing organ selection and preparation to minimize the risk of rejection and infection. Moreover, new techniques are needed to monitor organ rejection that would be less invasive than conventional endoscopic biopsy.

Objectives:

- Determine the role of exogenous growth factors and micronutrients post-transplantation.
- Improve methods for donor bowel preservation pre-transplant.
- Identify new targeted pathways for novel immunosuppressive therapies.
- Develop artificial intestinal conduits from native tissues and cells for autotransplantation.
- Identify biomarkers for noninvasive diagnosis of intestinal transplant rejection.
- Identify factors that diminish long-term post-transplant survival and develop appropriate countermeasures.

Research Goal 6.4: Understand and treat the metabolic and nutritional consequences of bariatric procedures and other surgical modifications of the gut.

Bariatric surgery for weight loss and other surgical modifications of the gut have metabolic and hormonal consequences that were not originally predicted based on simple resection of tissue. Researchers are working to understand the molecular bases for these phenomena and use these insights to develop non-surgical interventions to achieve the same result. Further, knowledge of these pathways could aid in the identification of biologic markers that predict which patients are most likely to benefit from bariatric or other surgeries.

Objectives:

- Identify pre-operative biomarkers to predict weight loss and metabolic correction.
- Characterize the neuroendocrine, hormonal, cytokine, and proteomic responses to bariatric procedures in animal models and humans.

GOALS FOR RESEARCH

- Characterize the long-term metabolic (vitamins, calcium, minerals, other) sequelae and changes in anorexic and orexigenic hormones in bariatric surgical patients.
- Develop non-surgical therapy that "mimics" neurohumoral sequelae of bariatric procedures.
- Develop specific dietary guidelines for patients undergoing bariatric and other surgical modifications of the gut that can effectively prevent adverse metabolic and nutritional consequences based on newly identified hormonal and absorptive abnormalities.

Research Goal 6.5: Optimize nutritional support of patients with GI disorders.

Many patients with severe GI dysfunction, including premature infants, rely on enteral or parenteral nutritional support to sustain life. Although these procedures are indispensable for many patients, they carry the risk of severe side effects and do not perfectly replicate normal digestion and absorption of nutrients. Further research is warranted to understand the impact of nutritional support protocols on patients' daily lives, to improve the nutritional value of these treatments, and to reduce the risks of adverse events.

Objectives:

- Develop and validate quality-of-life measures for patients with chronic GI dysfunction to allow assessment of the efficacy of different treatments.
- Evaluate the effect of specific micronutrients and diet on GI absorption, motility, and immunity.
- Evaluate the importance of the gut microflora in the prevention and causation of GI diseases.
- Determine optimal micronutrient requirements for patients that require long-term PN, as well as for those with catabolic illness that require PN.
- Assess the safety and potential efficacy of prebiotics, probiotics, and symbiotics in the prevention of NEC and catheter-related sepsis.
- Design and test diet formulations to prevent neonatal feeding intolerance and NEC.

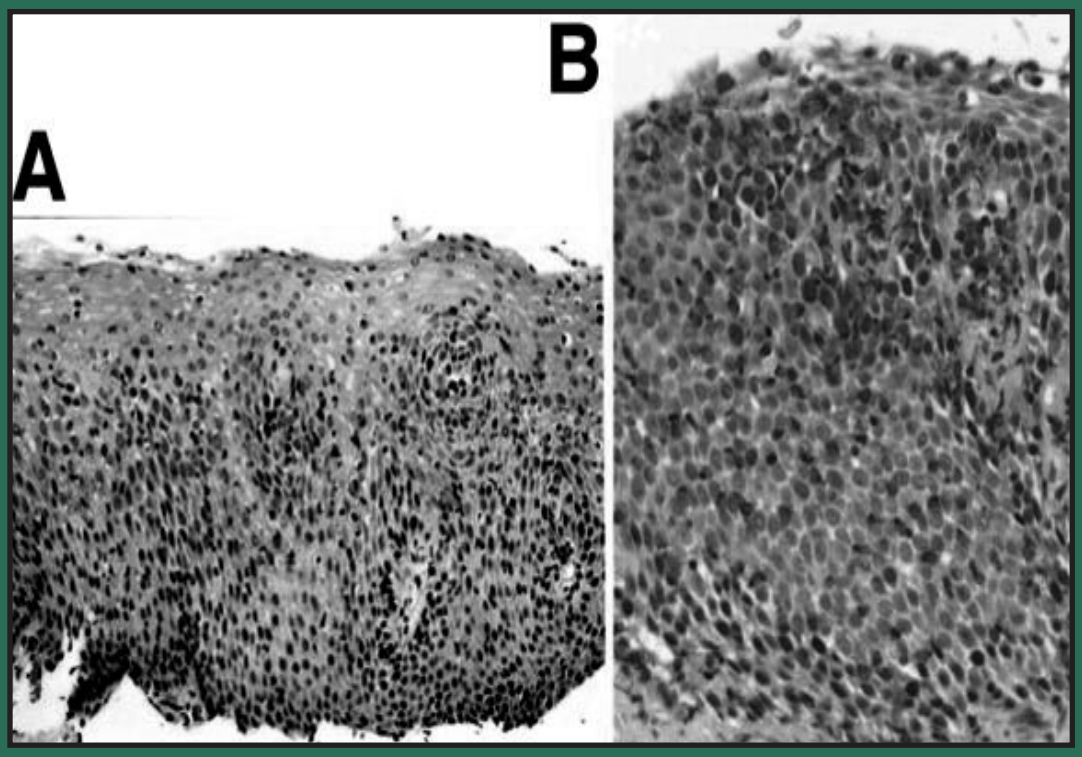
MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

National research resources: Translational and clinical research on intestinal failure and regeneration and related issues are hampered by the small numbers of patients at any single institution. In addition, many investigators have difficulty accessing human intestinal tissue at the time of resection or at regular intervals after adaptation. The establishment of multicenter clinical and basic research networks would promote progress in the field by fostering collaboration and sharing of resources. A national registry for SBS-intestinal failure patients and for those with small intestine allografts would facilitate recruitment of patients for clinical research and intervention trials. Finally, centralized tissue banks of biosamples from patients with different GI disorders or those who are undergoing bariatric surgery and follow-up would enable researchers to readily access human tissues for research, regardless of the location where the patients received care.

Standardized clinical definitions: Development of a standardized system to characterize SBS and intestinal failure in terms of anatomy, nutritional support, and complications is an important challenge for the field. Having such a system would enable

researchers to directly compare data and outcomes across studies and patient groups. Achieving consensus on data points, definitions, and outcome measures would facilitate understanding of the relative effectiveness of medical, nutritional, and surgical intervention strategies. ICD-9 codes should be created and implemented to assist in the tracking of afflicted patients. Creation of a health outcomes research consortium is one step that could be taken to promote standardization.

Advanced technologies: The difficulty in accessing the small bowel with repetitive surgical or endoscopic procedures hampers both clinical research and patient care. The development of novel, less invasive technologies to access the intestinal lumen would stimulate research on human disease. Furthermore, identification of serum or other surveillance markers would enhance the ability to care for patients with small intestinal disorders, including SBS and intestinal failure, as well as recipients of intestinal transplants.



Low (A) and high (B) power microscopic views of the esophageal epithelium in eosinophilic esophagitis, showing distinctive features of this condition, such as increased numbers of immune cells called eosinophils.

Image courtesy of Dr. Glenn Furuta. Reprinted from Gastroenterology, *133, Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment, pp. 1342-1363, Copyright 2007, with permission from Elsevier.*

Diseases of the Oropharynx and Esophagus

SUMMARY OF RESEARCH GOALS

Because normal functioning of the oropharynx and esophagus can be compromised by a wide spectrum of diseases, the Commission suggests a number of research goals that address the diverse etiologies and potential treatments for these disorders. Research to understand the neuromuscular biology of the oropharynx and esophagus is critical to developing therapies for conditions like swallowing disorders brought on by stroke, premature birth, non-erosive reflux disease (NERD), and other motility disorders that affect this portion of the gastrointestinal (GI) tract. Similarly, more studies are needed to identify better therapeutic targets for gastroesophageal reflux disease (GERD), among the most common diagnoses for a digestive disorder in the U.S. GERD is also associated with increased risk for Barrett's esophagus and esophageal cancer. Thus, research is needed to uncover the risk factors and mechanisms of disease progression in order to develop more effective prevention and treatment strategies. The emergence of eosinophilic esophagitis and other inflammatory diseases of the esophagus over the last decade highlights the need for research to define the clinical course of these poorly understood diseases and design rational therapies to reverse them. Progress toward these research goals will help to reduce the significant economic toll that these diseases, particularly GERD, take on individuals and the U.S. healthcare system.

INTRODUCTION AND BACKGROUND

The oropharynx and the esophagus can be considered the gateways to the GI tract and, as such, are critical for the digestive processes that follow. Although the two components of the oropharynx (i.e., mouth and pharynx) are relatively distinct anatomically, the oropharynx is usually considered as a unitary functional entity from a gastroenterological perspective, with its overarching purpose being to facilitate safe passage of the ingested bolus of food across the opening to the airways and into the esophagus proper. In accordance with this function, this region is under tight control of the central nervous system (CNS); its nerves and muscles are, therefore, its most critical components, with even subtle dysfunction resulting in considerable morbidity. It is not surprising, therefore, that cerebrovascular accidents (strokes) and subsequent uncoordinated nerve activity account for the vast majority of functional disturbances in this region, with only a minority related to other structural lesions. This is a huge problem: nearly 700,000 strokes per year occur in the U.S. alone, with the incidence of post-stroke dysphagia (difficulty in swallowing) ranging from 37-45 percent, even with cursory screening techniques, and as high as 64-78 percent with formal instrumental testing. Dysphagia not only leads to impairment in food intake, but also puts these patients at a 3-fold or higher risk for pneumonia. Disturbances in oropharyngeal function are also common in the elderly, perhaps independently of overt lesions in the CNS. Swallowing disorders have been reported in 30-40 percent of nursing home residents and 6.9 percent of the surveyed general population. The importance of an abnormal swallowing mechanism in the elderly is reflected by the high incidence of aspiration pneumonia in autopsy studies. A majority of patients with swallowing dysfunction will, therefore, require rehabilitation therapy.

The oropharyngeal musculature is striated, signifying its close control by cranial nerves. This pattern continues for the proximal one-third of the esophagus, after which it is replaced by smooth muscle, which is more characteristic of the rest of the GI tract and indicative of the greater influence of the intrinsic nerve cells found in the wall itself (i.e., the enteric nervous system). Despite its deceptively simple tubular form, the esophagus is in fact a complex organ. Like much of the GI tract, it is organized cross-sectionally into several concentric layers: the epithelium (which is squamous in nature, similar to the skin), the submucosa, and two principal muscle layers, with the myenteric plexus sandwiched in between. In addition, it receives extensive innervation from the vagal (cranial) and spinal nerves. Any one of these components or layers can be the primary or secondary site of a variety of diseases.

The heterogeneous nature of these organs makes them vulnerable to a considerable variety of pathologic processes and a correspondingly broad clinical spectrum that affects patients across all demographic categories. This chapter focuses on some of the diseases in these organs that have large impacts, as defined either by their socioeconomic effects or by the burden of suffering they impose on individual patients. Perhaps the most well-known and most common of these syndromes is GERD, commonly referred to as "heartburn." GERD is common worldwide, but is particularly prevalent in developed countries. The prevalence of heartburn (with or without acid regurgitation) at least once a week ranged from 14-29 percent in the U.S. population and did not differ between Blacks and Whites in a survey from Houston. In a 2004 report, GERD was the leading physician diagnosis for GI disorders, accounting for almost 7 million outpatient clinic visits. This imposes a severe economic cost, estimated to be over $11 billion in 2004. Much of this cost is related

to medications, particularly proton pump inhibitors (PPIs), for which nearly 8 million prescriptions were written per month in 2004—a number that represents more than a doubling compared to the previous 5 years. Beyond economic considerations, the most sinister health threat represented by GERD is the elevated risk for adenocarcinoma of the esophagus. The incidence of esophageal adenocarcinoma has grown dramatically in recent years, and many experts link it to the rise in GERD in the general population. This is based on the current paradigm that chronic GERD leads to Barrett's esophagus, a change in the epithelial lining of the esophagus from a squamous to an intestinal type. In some patients, such a change is associated with dysplasia, an abnormality in the appearance of the lining cells that indicates their instability and tendency to progress to cancer, which occurs in about 0.5 percent of cases per year. Disorders affecting other parts of the body have also been ascribed to GERD, including asthma, dental problems, and ear, nose, and throat disturbances (e.g., erosions, laryngitis, hoarseness, and even laryngeal cancer), but in many cases actual causality has been difficult to establish.

Another common form of esophageal cancer is squamous cell cancer, which arises at a location higher up in the esophagus and is strongly associated with smoking and alcohol intake. GERD does not appear to be a risk factor for this cancer. Unlike Barrett's esophagus, which is predominantly a disease of white males, squamous cell cancer affects African Americans disproportionately, with an incidence that is several times greater, although the incidence appears to be declining.

Another major class of disorders that affects the esophagus arises from disturbances of motility—the coordinated action of nerves and muscles that produces effective propulsion. These disorders include relatively rare conditions, such as achalasia with an incidence of approximately 1 in 100,000 per year, which are nevertheless important because of their chronic and lifelong nature. Other disorders may perhaps be more common, but are less well defined clinically and pathophysiologically. In addition, severe GERD is often associated with significant motility abnormalities of the esophagus, either as a cause or effect, and these may lead to symptoms by themselves in some patients. Abnormal esophageal motility is a consequence of some systemic disorders, notably diabetes and scleroderma or related connective tissue syndromes. Particularly in the latter, an incompetent sphincter and impaired esophageal acid clearance can lead to devastating reflux with serious consequences, such as stricture formation.

Neural changes can not only produce motility disturbances in the esophagus, but can also lead to sensory abnormalities and a hypersensitive esophagus that may account for a significant number of patients with non-cardiac chest pain. This syndrome probably results from multiple etiologies with prominent psychosocial components, akin to what has been described for other painful functional GI disorders, such as functional dyspepsia and irritable bowel syndrome. "Chest pain, not otherwise specified" is the most common inpatient GI diagnosis, with over 320,000 hospital discharges in a recent year.

Esophageal diseases affect children as well as adults. "Reflux" is extremely common in neonates and can assume pathologic proportions requiring treatment in a subset of infants. Such children are more likely to have GERD when they grow up. However, there is a paucity of good data on effective treatment in this age group. Swallowing dysfunction resulting in oral aversion, dysphagia, and regurgitation are also very common problems in neonatal and pediatric intensive care units, often associated with prematurity

and oral/pharyngeal trauma from medical devices such as endotracheal and feeding tubes. Currently, inadequate information is available on the normal development of swallowing function, the mechanisms responsible for its perturbation, and effective means to prevent and treat the same. Finally, a recently described syndrome, eosinophilic esophagitis, has been increasingly recognized in both children and adults. This condition is characterized by esophageal inflammation and infiltration by eosinophils, which are white blood cells that typically are associated with allergies and some infections. Symptoms of eosinophilic esophagitis include vomiting, abdominal pain, poor growth, difficulty with swallowing, and food impaction. This condition is often misdiagnosed as GERD. Although the underlying etiology of eosinophilic esophagitis is often unidentified, foodborne and airborne allergens have been frequently implicated. Currently, effective treatments are limited to steroids and diet restriction.

Finally, a variety of infections can afflict the esophagus, with the most common being fungal (e.g., candida) or viral (e.g., cytomegalovirus or herpes simplex virus); these are typically seen in patients with compromised immune systems, such as those with HIV-AIDS. With modern therapeutic regimens, such cases are becoming less common.

RECENT RESEARCH ADVANCES

Oropharyngeal physiology and pathophysiology

A major advance has been the systematic evaluation of the biomechanical aspects of swallowing function. In addition, recent studies have addressed the effect of bolus volume, consistency, and temperature on the swallowing apparatus. A better understanding of the biomechanical aspect of swallowing has resulted in renewed interest in devising rehabilitative approaches to swallowing disorders. Such an approach would benefit an overwhelming majority of patients with swallowing disorders. The availability of functional imaging should provide a powerful tool for manipulation of brain centers involved in swallowing to either induce or speed recovery.

Gastroesophageal reflux disease

Considerable insight has been obtained into the pathways of acid-induced injury to the esophagus. Luminal acid and pepsin initially damage the esophageal epithelium by attacking the apical junctional complex (APJ), a group of structures that control the permeability of ions and aqueous molecules passing through the intercellular space. The consequence of this is a "leaky" epithelium with dilated intercellular spaces, the latter a clinically identifiable hallmark of early acid injury to the tissue. In turn, protons and other noxious factors (e.g., pepsin) gain access to subepithelial structures, such as nerves and muscle, with several potential consequences. Neural stimulation may result in initiation and/or amplification of inflammation and generate symptoms of heartburn and chest pain. An attractive candidate for mediating these effects of protons is the vanilloid receptor, TRPV1, which is expressed by nociceptive neurons and responds to noxious stimuli, such as acid and heat. Acute, acid-induced esophagitis is reduced in animals lacking TRPV1, suggesting that refluxed acid may induce inflammation through TRPV1, possibly via neurogenic mechanisms. Muscle-produced inflammatory products may also cause dysfunction; for example, in esophageal circular muscle, production of cytokines, hydrogen peroxide, platelet-activating factor, and prostaglandin E2 results in inhibition of acetylcholine release from cholinergic motor neurons without affecting the integrity of the contractile mechanisms.

Thus, in addition to epithelial injury and symptom generation, acid reflux can alter esophageal neuromuscular function in several ways, perpetuating the process by decreasing lower esophageal sphincter (LES) tone and impairing peristalsis and acid clearance. Further, esophageal longitudinal smooth muscle function may also be affected and can contribute to both reflux and delayed clearance by creating a spatial separation of the LES and diaphragm. From the perspective of the mechanics of the esophagogastric junction (EGJ), axial motion attributable to longitudinal muscle contraction is key to the normal opening mechanism, and disordered EGJ mobility and compliance may play a role in the pathogenesis of reflux. Prolonged contraction of this muscular layer may also contribute to generation of symptoms.

Another advance in this area has been the elucidation of the neurophysiology and neuropharmacology of transient LES relaxations, a major mechanism of reflux. This has raised the prospect of mechanistically directed therapy using agents such as the GABAB agonist baclofen in treating symptomatic reflux.

Progress has also been made in understanding and managing childhood GERD, symptoms of which are reported in 8.2 percent of children ages 10-17 years. As in adults, a variety of non-esophageal symptoms have been associated with childhood GERD, including asthma, hoarseness, cough, sinusitis, and otitis media (ear infection). Natural history studies show that while symptoms improve, histopathology may remain abnormal. Initial studies show an excellent safety profile for PPI use in children, although infectious gastroenteritis and pneumonia may be more common among children using PPIs.

Finally, there has been significant clinical research, including randomized, controlled trials, on the safety and efficacy of emerging endoscopic, anti-reflux procedures, as well as surgical procedures, such as prosthetic reinforcement of the hiatus in the repair of giant hiatal hernias.

Barrett's esophagus

Barrett's esophagus can be reversed in some, but not all, patients with endoscopic treatments that either ablate or mucosally resect the epithelium. The neosquamous epithelium may have less malignant potential than the Barrett's-affected tissue it replaces. The ability to effect reversion in the mucosa suggests that there is an underlying "stem" cell, which can either revert to the normal pathway of differentiation to a stratified squamous epithelium or continue to differentiate down the specialized intestinal metaplastic pathway. Continued development of these treatments could result in the ability to prevent the progression of Barrett's esophagus to cancer and may improve healthcare utilization by decreasing expenditures on surveillance endoscopy.

Changes in gene expression likely precede the development of histologic Barrett's esophagus. For instance, the expression of a homeobox gene, *CDX2*, in esophageal epithelium leads to metaplasia and may be an early marker for Barrett's esophagus. Also, epigenetic alterations may be instrumental in the development of malignancy. Hypermethylation of the promoter regions of various tumor suppressor genes are associated with increasing degrees of dysplasia.

The demographic, anthropometric, and symptom-based risk factors for Barrett's esophagus have been better elucidated. Despite reports of the association of Barrett's esophagus with chronic heartburn symptoms, data suggest that Barrett's esophagus is relatively common regardless of whether a patient has a history of heartburn. In fact,

a substantial proportion of patients with adenocarcinoma of the esophagus have no prior symptoms of heartburn. Obesity appears to be a risk factor for Barrett's esophagus and, for any given body mass index, subjects with visceral adiposity may be at higher risk than those with higher hip to waist ratios. Multiple trophic hormones are elevated in subjects with central adiposity, which may explain the increased risk of metaplasia in this group. Preliminary data have been reported showing the influence of heritability on the development of Barrett's esophagus.

A number of novel, high-resolution imaging techniques show promise in identifying high-grade dysplasia and early cancers in Barrett's esophagus patients with moderate sensitivity and specificity. To date, these "optical biopsy" methods do not demonstrate the ability to survey large areas of Barrett's esophagus.

Eosinophilic esophagitis

Eosinophilic esophagitis is an immune-mediated inflammatory disorder that is often triggered in atopic individuals by food products or inhaled allergens. It is characterized by infiltration of the esophageal wall, including the epithelium, with mast cells and eosinophils. Clinically, the inflammatory response by mast cells and eosinophils within the esophagus results in symptoms of chest pain, heartburn, and dysphagia—the latter due either to peristaltic dysfunction or to mechanical narrowing of the lumen by a dense fibrotic reaction within the wall. Notably, infiltration of the esophagus by eosinophils has been shown to result from the release of eotaxin-3 and IL-4, IL-5, and IL-13 by squamous epithelial cells. This observation provides molecular targets for potential treatments for the condition. For instance, intravenous antibodies to IL-5 can reduce both blood and esophageal eosinophilia and improve the quality of life in patients with eosinophilic esophagitis. In 2006, a novel translational study identified the key role of eotaxin-3 in eosinophilic esophagitis. Utilizing a combination of microarray techniques, *in vivo* and *in vitro* studies, eotaxin-3 was shown to be significantly up-regulated compared to controls. Further studies showed mutation of this gene in affected patients, and basic analysis confirmed a significant role in this inflammatory process. In addition to potential molecular targets for treatment, these data add to the growing body of knowledge of the central role of the esophageal epithelium in generation of the inflammatory/allergic cascade that ultimately translates into the clinical manifestations of the disease.

Esophageal motility and "functional" disorders

The pathophysiology of achalasia has been reasonably well characterized and appears to result from a relatively selective loss of nitrergic (inhibitory) neurons supplying the muscle of the LES. However, the etiology of this process remains unknown, although there is growing evidence for a possible autoimmune process associated with antibodies directed against neuronal elements. There have been some advances in the treatment of this disorder. Botulinum toxin injections have been shown to be effective in relieving symptoms in this condition and, although the benefit is short-lived, they are valuable alternatives in patients who are not fit for more invasive forms of therapy. Pneumatic dilation has been shown to be of limited efficacy in younger patients, in whom laparoscopic myotomy appears to be the best option. This surgical approach results in less morbidity and earlier post-operative recovery than traditional, open myotomy. The demonstration that neural stem cells can be injected into the GI tract and result in recovery of nitrergic function raises hope for a true cure for this condition.

The recognition of esophageal hypersensitivity and, in particular, emerging concepts of post-inflammatory neuronal sensitization have been important in understanding the spectrum of pathophysiologic events that lead to esophageal symptom generation in patients. This includes non-cardiac chest pain and "emerging" syndromes, such as NERD.

GOALS FOR RESEARCH [14]

Research Goal 7.1: Understand the neurobiology of oropharyngeal structure and function in health and disease.

Identifying novel molecular, physiologic, and anatomic targets within the oropharynx will accelerate the development of more effective treatments and/or functional rehabilitation of stroke-induced swallowing dysfunction, a major cause of morbidity, particularly in the elderly. Similarly, understanding the processes involved in the development of swallowing function and the mechanisms by which these processes are disturbed in the neonate is very important. Currently, our approach to these problems is empirical and palliative at best, with little ability to prevent permanent disability.

In addition, this region is vulnerable to the effects of gastroesophageal reflux with consequences that potentially affect the airways in the form of laryngitis and asthma. Much needs to be learned about the pathogenesis and treatment of these problems.

Objectives:

- Develop useful animal models of oropharyngeal swallowing disorders to facilitate neuropathologic studies of central and peripheral components and evaluate the effects of interventions directed at specific molecular and/or cellular targets.
- Conduct clinical studies of recovery and plasticity with creative use of functional imaging and novel interventional techniques.
- Understand physiologic and pathologic communication between the functional components of the aerodigestive tract.
- Understand the effects of gastroesophageal reflux on the airways, including the larynx and bronchi.
- Define the effects of sleep abnormalities on upper GI tract physiology.

Research Goal 7.2: Understand the clinico-pathologic mechanisms leading to and/or associated with GERD and identify novel molecular, physiologic, and anatomic targets for more effective and rational treatment.

Although effective in the majority of patients, acid suppression is an indirect method for the treatment of GERD and its complications. Further, treatment is indefinite in duration because of the chronic nature of the disorder. Developing more effective treatments, whether they are pharmacological, endoscopic, or surgical in nature, requires a better understanding of the underlying mechanisms.

Objectives:

- Understand the clinical spectrum, outcomes, and natural history of childhood reflux and its relationship/evolution into adult patterns of disease.

[14] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

- Validate and develop more effective and/or less invasive long-term approaches to GERD and identify more precisely the clinical, anatomic, and/or functional predictors of response.
- Understand the biologic basis of gastroesophageal reflux, hiatal hernia, and GERD-associated esophageal dysmotility, including the role of biomechanical factors and longitudinal muscle.

Research Goal 7.3: Define the mechanisms responsible for esophageal injury and repair, with particular emphasis on the interactions among components of the esophageal wall.

Acute and chronic inflammation of the esophagus can lead to serious complications, such as strictures, dysmotility, and pre-malignant or malignant transformation. Esophagitis results from a complex interaction between the inciting factor and the tissue response, which involves many diverse cell types, some of which are harmful and others perhaps beneficial. A full understanding of these pathways will pave the way for more effective methods for treatment and prevention of many esophageal disorders.

Objectives:

- Elucidate mechanisms of increased permeability in the esophageal epithelium.
- Understand the role of neural and muscular elements in modulation or enhancement of esophageal injury.
- Characterize acute and chronic mechanisms responsible for esophageal epithelial squamous cell repair.
- Determine the role of foodborne, airborne, and other environmental allergens in promoting eosinophilic esophagitis and the underlying mechanisms.
- Define basic pathogenic mechanisms by which eosinophils mediate esophageal dysfunction.

Research Goal 7.4: Understand the epidemiology, natural history, and outcomes of eosinophilic esophagitis and identify targets for more rational and effective therapy.

Eosinophilic esophagitis is rapidly emerging as a significant health problem in children and adults. Since it has only been formally recognized in the last decade or so, very little is known about this disease, and much research is needed to answer fundamental questions relating to clinical course and treatment.

Objectives:

- Determine risk factors, natural history, and outcomes of patients with eosinophilic esophagitis and identify biomarkers for disease activity and progression.
- Identify novel targets and interventions for more effective and rational therapeutic approaches to eosinophilic esophagitis and other inflammatory disorders of the esophagus.

Research Goal 7.5: Understand the etiopathogenesis of Barrett's esophagus, determine risk factors associated with its progression, and identify novel targets and/or therapies for chemoprevention and treatment.

Despite several decades of research on Barrett's esophagus, this disorder continues to be a major clinical challenge. Although it is strongly associated with GERD, little is known about the biologic mechanisms by which chronic reflux leads to transformation of the esophageal lining or the particular genetic or acquired factors that predispose a given patient with reflux to this complication.

Objectives:

- Understand the initiation of Barrett's esophagus, with particular emphasis on identifying the putative stem cell involved and studying its biology.

GOALS FOR RESEARCH

- Define the contribution and etiopathogenic role of environmental (e.g., smoking) and genetic/familial factors in the development of Barrett's esophagus.
- Develop biomarkers that reliably predict dysplastic and neoplastic progression.
- Identify novel molecular targets for pharmacological approaches to restoring a stable epithelial phenotype in patients with Barrett's esophagus.
- Conduct chemoprevention studies in subjects with Barrett's based on molecular pathways identified through ongoing studies on human tissue and animal models.
- Develop better and more cost-effective tools for screening and surveillance.

Research Goal 7.6: Understand the etiology and biology of esophageal neuromuscular function in health and disease and develop more effective treatments.

Esophageal dysmotility can be primary in origin or result from several systemic diseases, such as diabetes or connective tissue disorders. In most cases, the pathologic mechanisms responsible for esophageal dysfunction remain largely unknown, leading to therapies that are generally ineffective and palliative at best. Similarly, although chest pain or discomfort of putative esophageal origin is a major drain on healthcare resources, little is known about its underlying neurobiology or potential targets for treatment.

Objectives:

- Understand the neurobiology of normal and abnormal esophageal sensation and identify novel molecular targets for more effective and rational treatment of esophageal hypersensitivity associated with disorders such as non-cardiac chest pain and NERD.
- Understand the etiopathogenesis, genetic predisposition, and risk factors for esophageal motility and functional disorders, including the roles of autoimmunity, environmental factors (e.g., viruses), relationship to GERD, genetic factors, and molecular candidates (e.g., ALADIN).
- Identify novel therapeutic targets for pharmacological, cellular (e.g., stem cell treatment), and physical (e.g., endoscopic) approaches for more effective and rational treatment for esophageal motility disorders.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Animal models: Many, if not most, disorders of the oropharynx and esophagus lack complete understanding in terms of the underlying pathobiology. This is true even of common problems, such as GERD, and is due in part to a lack of convenient and valid experimental models.

Standards for diagnosis: Challenges in less common or emerging disorders, such as esophageal dysmotility syndromes, eosinophilic esophagitis, and even Barrett's esophagus, include the small number of patients seen by any one center, the absence of uniform diagnostic criteria, the lack of generally available and reliable methods for physiologic testing, and the inaccessibility of tissue for histopathologic correlation. Further, because of variations in practice management, a true epidemiological and clinical picture of these disorders has been difficult to obtain. Such information is necessary for planning studies to elucidate pathogenic mechanisms and improve on current therapeutic strategies.

Interdisciplinary research: A major challenge affecting some disorders in this group is the lack of cross-fertilization among disciplines. This issue is best exemplified by swallowing disorders secondary to CNS pathology, an area that seems

to have "fallen through the cracks" between the neuroscience and GI specialties. In contrast to other areas of CNS, research progress in the neurobiology and pathology of the "swallowing center" and related structures has lagged. Similarly, although emerging disorders, such as eosinophilic esophagitis, initially present to gastroenterologists, research progress in understanding these conditions may require the scientific input of specialists in immunology and allergy.

Disease definitions: In diseases like Barrett's esophagus, enormous variability in disease definitions and histologic grading can be found in the literature. Even among expert centers, one group's low-grade dysplasia is another's non-dysplastic disease. A multinational consensus conference to arrive at standardized disease definitions would strengthen the field.

Validation of novel interventions: Another barrier to the advancement of knowledge in this area is that novel imaging and therapeutic techniques are disseminated prior to rigorous, multicenter testing by conflict-free groups. The result is that multiple "infant" strategies are being developed, with no effort to grade the relative value of the interventions, leading to wasted effort and unnecessary costs, as well as suboptimal patient outcomes. Direct marketing to community gastroenterologists and surgeons is occurring before rigorous testing. Emphasizing rigorous testing of this technology as part of a Request for Applications may improve this situation. Finally, in this context, it is important to point out that past attempts at limiting cancer in the setting of Barrett's esophagus have focused on subjects with chronic GERD symptoms. Increasing evidence suggests that such an approach is, at best, incomplete and flawed and, at worst, largely ineffective and cost-inefficient.

National research resources: The establishment of multicenter consortia with the ability to build large databases and patient registries would promote progress in several ways. Such resources would enable researchers to make a population-based determination of the incidence of these disorders, their etiologies, and risk factors. Researchers could also analyze the natural history of disease, including timing of onset, progression, prognosis, quality of life, cost, and healthcare utilization, and collect annotated tissue and serum specimens to study molecular and cellular mechanisms, as well as to illuminate genetic and environmental influences. Collaborative trial groups that bring together experts from relevant disciplines (e.g., immunology, oncology, and surgery) would be able to validate clinical protocols for the diagnosis and management of these patients and conduct trials of chemopreventive and therapeutic strategies. Multicenter studies could be more effective than single-site trials, which are often restricted by insufficient patient numbers.

Advanced technology: Much progress in this area could be made through technological breakthroughs, and such research and development efforts should be actively encouraged. Examples include endoscopic access for obtaining tissue samples from deeper layers of the esophagus, better physiologic tests, and less invasive and more effective anatomic and physiologic approaches to treatment. Although there is significant overlap between esophageal motility disorders and their counterparts in the rest of the GI tract, the esophagus, because of its limited length and easy access, can be viewed as a model to test hypotheses of a more general nature. An example would include the phenomenon of visceral hypersensitivity, the study of which has best been conducted in the esophagus. Similarly, if a stem cell approach will work at all, it is best tested in the esophagus, which offers a relatively easy site for local (endoscopic) delivery.

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

Image courtesy of Eye of Science/Photo Researchers, Inc.

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-κB 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.

GOALS FOR RESEARCH [15]

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-lipooxygenase 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.*

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

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.

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

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.

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.

Digitally enhanced x-ray of a human colon outlined using barium contrast material. Several diverticula, or bulges protruding from the colon wall, are visible in the distal colon.

Image Courtesy of Scott Camazine/ Photo Researchers, Inc.

Diseases of the Colon and Rectum

SUMMARY OF RESEARCH GOALS

The colon and rectum are susceptible to a variety of diseases and conditions that can impair their primary functions of maintaining water balance and eliminating wastes. The Commission's proposed research goals are aimed at understanding mechanisms of colonic injury, repair, and function so that prevention and treatment strategies for these disorders can be optimized. Key topics for research on colonic diseases are elucidating the role and composition of the gut microflora and manipulating this microbial community to restore health. Studies are also needed to establish the basis for structural defects like diverticular disease and vascular disorders, such as colonic ischemia (CI) and angioectasias. Better means of detection and treatment would improve the health and quality of life of elderly individuals, who are most affected by these conditions. Research is urgently needed on anorectal disorders, including anal fistulas, hemorrhoids, and fecal incontinence, which lack a firm evidence base concerning the causes and effective management strategies for these common, but poorly studied, conditions. Research on ways to prevent and treat radiation injury of the colon would alleviate this treatment-induced complication of pelvic cancer therapy. Finally, appendicitis can be fatal if undiagnosed and untreated. Research on the risk factors for onset and progression of appendicitis would further reduce the burden of this condition, especially in children.

INTRODUCTION AND BACKGROUND

The human colon—or large intestine—is primarily responsible for absorbing remaining water from indigestible food matter that has passed through the small intestine, maintaining the water balance in the body, and absorbing some vitamins. The final section of the luminal digestive tract—the rectum and anus—eliminates wastes from the body. Diseases involving the colon and rectum are diverse and include anatomic conditions (e.g., diverticular disease, fistulas, fecal incontinence), blood flow or vascular disorders (e.g., CI, angioectasias, hemorrhoids), conditions related to the gut microflora or immune dysfunction (e.g., inflammatory bowel disease [IBD], appendicitis), treatment-related disorders (e.g., radiation colitis), and colorectal cancer, gastrointestinal stromal tumors (GIST), carcinoids, and other cancers affecting the colon and rectum (see also the chapter on *Cancers of the Digestive System*).

Colonic mucosal injury and repair: The colon and rectum are lined with epithelial cells that absorb water and nutrients from undigested material and secrete a thick mucus layer that protects the lining from invasion by the gut microflora. Colonic epithelial cell injury requires both restitution and regeneration (proliferation). Rapid restitution of the mucosal epithelium is crucial to quickly restore the epithelial barrier, thereby limiting fluid and electrolyte losses, as well as preventing the introduction of harmful bacteria and foreign antigens. In response to colonic injury, goblet cells of the mucosa secrete a small protease-resistant peptide, termed trefoil factor 3 (TFF3) peptide.

Colonic mucosal absorption and colon vasculature: A primary function of the colonic mucosa is to absorb water and electrolytes from undigested materials before elimination. An imbalance in mucosal absorption as a result of colonic injury or disease can result in constipation or diarrhea if too much or too little water is absorbed. Chronic diarrhea can result in dehydration and malnutrition; constipation (see also the chapter on *Functional Gastrointestinal Disorders and Motility Disorders*) may lead to the development of hemorrhoids, anal fissure, or rectal prolapse.

Gut microflora: The human intestinal tract is colonized by a complex and diverse community of microbes that are essential to the normal digestive functions of these organs. Little is known about the interaction of the majority of these microbes and their role—individually and collectively—in health and disease due to technical limitations in isolating and culturing individual species in the laboratory. Advances in genomic and proteomic technologies coupled with the prior knowledge of these organisms are set to revolutionize the characterization of the gut microflora. Bacteria in the colon produce small amounts of some vitamins, including vitamins K and B, which are absorbed through the walls of the colon. Alterations in the balance of species in the gut are linked to such diverse conditions as obesity, IBD, colitis (inflammation of the colon), and sepsis. Approximately 20 percent of hospitalized patients who receive an antibiotic will become colonized by the pathogenic bacterial species, *Clostridium difficile*, and many will develop severe colitis. *C. difficile* is kept from colonizing the colon by the normal microflora, and restoration of the microflora following infection is thought to result in eradication of the pathogen, which, if proven, would indicate a vital role of the microflora in maintaining the health of the colon.

Diverticular disease: In Western society, many older people develop pockets, or "diverticula," that bulge outward from the colon wall, a condition known as diverticulosis. While some people have no symptoms of

diverticulosis, others may experience mild discomfort, bloating, or constipation. Infection or inflammation of the diverticula results in diverticulitis, a more serious condition associated with abdominal pain, bleeding, infections, perforations, or blockages. In extreme cases, abscesses may form in the colon wall, leading to peritonitis or fistulas. Diverticular disease is thought to develop as a result of a low-fiber diet and is treated by a high-fiber diet, mild pain medications, or surgery.

Ischemic colitis and angioectasias: Inadequate blood supply to the colon can lead to inflammation and injury, a condition known as ischemic colitis. The majority of cases occur in elderly patients over 60 years of age. Blood clots or low blood pressure account for some cases of ischemic colitis, although in many patients the cause is unknown. Mild cases of ischemic colitis may resolve without medical intervention. More severe cases can lead to sepsis, intestinal gangrene, or bowel perforation and require surgical care. CI is the most frequent ischemic disorder of the GI tract. Epidemiologic studies have been designed to answer the question of whether CI has a positive association with irritable bowel syndrome (IBS) or whether such an association results from medications used to treat IBS. These studies have shown that CI has an estimated crude incidence rate of 7.2 per 100,000 in the general population. Part of the difficulty in determining the incidence of CI, however, is the difficulty in diagnosing it.

Anorectal disorders: Disorders of the anus and rectum are usually not life-threatening, but can have significant impact on a person's quality of life. Anal fissures—cracks or tears in the skin of the anus—are usually superficial and easily treated. However, chronic fissures that expose the underlying muscle may require surgical intervention. An anal fistula is a pathway that develops between an anal abscess and the surface of the skin. A surgical procedure known as a fistulotomy can remove both the fistula and the original abscess. Hemorrhoids are inflamed veins in the lower rectum that may cause pain or rectal bleeding. Treatments options include over-the-counter creams, oral pain medications, or surgery to remove the tissue or cut off blood flow to the hemorrhoid. Fecal incontinence, or the inability to control the bowels, affects up to 5.5 million people of all ages in the U.S. and can be treated by dietary changes, medications, bowel training, or surgery.

Radiation colitis: Radiation therapy for cancers of the abdomen can damage the epithelial lining and blood vessels of the colon, resulting in radiation colitis. This inflammatory condition, which can develop within weeks or years after exposure to x-rays or ionizing radiation, causes symptoms that may include abdominal cramping, diarrhea, nausea, vomiting, rectal bleeding, and others. In severe cases, patients may experience complications, such as intestinal blockage, infection or abscess, nutritional deficiencies, or bowel rupture. Treatment for radiation colitis may involve changes to the diet or medications or, in very rare cases, surgery to bypass or remove the colon.

Appendicitis: Appendicitis is an inflammation of the appendix, a small, closed-end tube attached to the first segment of the colon on the lower right side of the abdomen. When the opening of the appendix is blocked, bacteria normally found in the appendix may begin to infect the walls of the organ and trigger an immune response. This blockage can occur with fecal matter, lymphoid aggregates, torsion, or a tumor with subsequent bacterial overgrowth. This leads to bacterial invasion of the appendiceal wall, inflammation, ischemia, gangrene, and perforation. Organisms typically identified include *E. coli*, *Peptostreptococcus* species, *B. fragilis*, and *Pseudomonas* species.

If left untreated, the appendix can rupture, allowing the infection to spread throughout the abdominal cavity. Appendicitis can be treated with surgical removal of the appendix and antibiotic therapy to control the infection. Approximately 325,000 cases of appendicitis occur each year in the U.S., primarily in the second decade of life.

RECENT RESEARCH ADVANCES

Effect of intestinal microflora on repair of the colonic epithelium

A greater understanding of the basic biology of TFF3 and other intestinal growth factors will advance our knowledge of how the gut responds to injury to begin the rapid repair process. In addition to restitution, the gut epithelium must also begin the process of regeneration, which involves repopulation (via proliferation) of the mucosa with new epithelial cells. The discovery that enteric bacteria promote proliferation of epithelial cell progenitors at sites of colonic mucosal injury, via their Toll-like receptor (TLR)-specific interactions with newly recruited macrophages, has proven to be a major advance in understanding the relationship among enteric microflora, the innate immune system, and epithelial repair.

Alterations in colonic sodium absorption underlie diarrheal responses in colitis

It has become clear that diarrheal manifestations of colitis are due to selective inhibition of sodium-absorptive ion transport pathways rather than activation of chloride-secretory pathways, as had been assumed in the past. Moreover, manipulation of sodium and chloride transport pathways appears to impact restoration of mucosal barrier function following injury. These findings suggest that understanding the segmental heterogeneity of ion transport pathways and their alterations during inflammation may lead to the development of new, non-immunomodulatory approaches to symptom relief and mucosal healing.

Diversity of sodium absorptive pathways and complexity of their molecular regulation

Research advances include the development of transgenic mice lacking expression of selected sodium-hydrogen exchange isoforms, coupled with new data regarding their molecular assembly as multi-protein complexes that regulate via rapid alterations in surface expression. These advances have highlighted the need for more comprehensive understanding of the factors responsible for the coordinated fine-tuning of polarized ion transporters to affect the balance of secretion and absorption in the colon during health and disease.

The influence of luminal factors on colonic mucosal absorption

Major luminal anions (e.g., short chain fatty acids [SCFAs]) and cations (e.g., ammonia) are bacterial fermentation products of dietary fiber and protein that have been shown to affect not only colonic absorptive transporter expression and function, but also mucosal growth and differentiation through genetic and epigenetic mechanisms. The recent identification of novel transporters, including MCT transporters and Rh glycoprotein transporters, illustrates the complexity of colonic handling of these substances. The presence of multiple transporters for SCFAs and ammonia suggests an important interrelationship among diet, luminal microflora, and mucosal fluid homeostasis.

Extreme diversity of the human gut microflora

Most textbooks suggest that the human colon harbors approximately 20-30 genera and 400-500 species, with a total population at least

10-fold that of somatic cells. These numbers were generated by traditional bacteriologic techniques that relied on specialized culture media to isolate, characterize, and identify individual species. Recent studies using modern genetic techniques provide a much more complex picture of the intestinal microflora. The feces of healthy subjects contain thousands of bacterial species, mostly novel, uncultivated organisms. Considerable diversity in the gut microflora exists between individual humans, suggesting the possibility that each person may harbor a distinctive repertoire of bacterial species in addition to common shared species. Adherent bacteria form a thin biofilm attached to the epithelial surface. This mucosal population differs greatly from the fecal population inhabiting the lumen and is quite diverse in different parts of the colon, suggesting considerable "patchiness" in composition.

Human and murine microbes associated with obesity

The human and mouse microflora consist of two main phyla: Bacteroidetes and Firmicutes. The former phylum includes 20 distinct genera, of which Bacteroides species are the most abundant. Firmicutes include such well-known genera as *Lactobacillus*, *Bacillus*, and *Clostridium* species. Recently, important differences were shown between the relative abundance of these two phyla in lean compared to obese humans. Obese humans had more Firmicutes and fewer Bacteroidetes than lean people. During weight loss on either a low-carbohydrate or low-fat diet, the relative composition of these two components shifted to fewer Firmicutes and more Bacteroidetes. Similar studies in obese mice showed that the microflora of obese mice were more effective at extracting calories from food, allowing increased energy recovery for the host. These important studies suggest that differences in the intestinal microflora can potentially regulate energy availability and recovery from non-digestible nutrients in the gut lumen. This revolutionary concept could be exploited to manipulate the microflora to influence body weight.

Extracellular matrix remodeling in patients with diverticulosis

Factors involved in the pathogenesis of diverticulosis include relatively low dietary fiber intake and decreased tensile strength of collagen and muscle fibers in the colonic wall as a result of aging. Research suggests that decreased tissue levels of matrix metalloproteinases, which are involved in extracellular matrix degradation and remodeling, and tissue inhibitors of metalloproteinases may contribute to the structural changes in the colonic wall seen in patients with diverticular disease.

Alteration of nervous system and smooth muscle activity in diverticulosis

Patients with diverticulosis have reduced numbers of colonic interstitial cells of Cajal and enteric glial cells, but normal numbers of enteric neurons, compared with healthy controls. These changes may decrease colonic electrical slow-wave activity, thereby resulting in delayed transit and possibly contributing to increased intraluminal pressure. In addition, these patients exhibit loss of colonic smooth muscle choline acetyltransferase activity, up-regulation of muscarinic M3 receptors, and increased *in vitro* sensitivity of the smooth muscle to exogenous acetylcholine (cholinergic denervation hypersensitivity). This finding may explain increased colonic contractility in patients with diverticulosis.

Visceral hypersensitivity in diverticular disease

Heightened visceral perception to rectosigmoid distention has been found in patients with symptomatic diverticular disease, but not in those with asymptomatic diverticulosis. Evidence suggests that the visceral

hypersensitivity may relate to release of proinflammatory mediators that sensitize enteric afferent nerve terminals and, thereby, heighten the response to noxious stimuli.

Treatment for inflammation in diverticular disease

Based on the possible role of low-grade colonic inflammation in symptomatic uncomplicated diverticular disease, trials have been undertaken of the non-absorbable antibiotic rifaximin, the anti-inflammatory agent mesalamine, and probiotic and prebiotic agents. Preliminary results suggest that these agents, particularly rifaximin and mesalamine, may reduce symptoms and prevent relapses, especially in patients with recurrent diverticulitis, although the benefit may be marginal.

Colonic vasculature injury in Crohn's disease

The cause of CI is rarely apparent, and most cases are believed to result from localized episodes of non-occlusive ischemia. A hyper-reactivity of the colonic arterial microvasculature is suggested by the approximately six-fold increased incidence in patients with IBS. A venous abnormality is suggested by the finding of increased incidence of various forms of coagulopathy in patients with CI. Segments of bowel removed for Crohn's disease show a spectrum of vascular injuries, suggesting that the pathogenesis of Crohn's disease includes multifocal infarction. Additional evidence for this hypothesis is found in the observation that the majority of granulomas in Crohn's disease form within the walls of blood vessels.

Relation of angioectasias and cardiac disease

Vascular lesions of the colon, especially angioectasias, are not an uncommon finding in the healthy elderly colon and are more commonly seen in elderly patients with major episodes of lower intestinal bleeding. Angioectasias are seen in up to 32 percent of patients with aortic stenosis, suggesting a relationship with cardiac valvular disease, perhaps via abnormal von Willebrand factor multimers, resulting in a predisposition to bleed.

Etiology and treatment of fecal incontinence

Incontinence of stool is more common than previously thought, with a prevalence of 2-15 percent, depending upon the population studied. Continence for stool is a complicated process; recent work focuses on the contribution of obstetrical injury and aging to fecal incontinence, but our understanding is still limited. New treatment modalities, including the artificial bowel sphincter and sacral nerve stimulation, show promise for patients with fecal incontinence.

Treatment of perianal fistulas

The prevalence of perianal fistulas in patients without IBD is not well described. Depending upon the location of intestinal disease, 25-50 percent of patients with Crohn's disease have perianal fistulas. The mechanism of development of perianal abscess and fistula is poorly understood. Anal fistulas may be cured with fistulotomy (unroofing the fistula tract), but the procedure carries a significant risk of fecal incontinence. For patients with Crohn's disease, the use of immunomodulators has significantly changed the treatment of perianal fistulas. For patients with cryptoglandular fistulas, new treatment modalities, including the use of fibrin glue and plugs, have been developed to cure the fistulas without the risk of fecal incontinence.

Advances in treatment of hemorrhoids

In phone surveys, 20 percent of respondents noted bothersome anal symptoms. Poor patient and provider understanding of

anorectal anatomy and pathology lead to frequent misdiagnosis and treatment of anal symptoms. Because of the pain associated with recovery from conventional hemorrhoidectomy, innovations in this treatment area have been sought. Stapled hemorrhoidectomy is a new technique for treatment of prolapsing internal hemorrhoids. Division of the internal sphincter (i.e., lateral internal sphincterotomy) is the standard surgical treatment for anal fissures. Because of the risk of post-operative fecal incontinence, new treatments have been developed, including calcium channel blockers and Botox injections.

Innovations in radiation therapy to reduce radiation proctitis

Newer techniques of radiation therapy using computer-based treatment optimization, intensity-modulated radiation therapy allow for variation in the dose in a specific field, facilitating the sparing of normal tissue (i.e., rectum) with a resultant decrease in acute radiation proctitis. Higher doses with increased efficacy have been associated with a decrease in complications. Moreover, cytoprotective agents have been found to reduce toxicity without compromising radiation efficacy. Amifostine, an agent that protects tissues from the cytotoxic actions of radiation and chemotherapy that was developed by the military for use as a radioprotectant in the event of nuclear warfare, has selective cytoprotective effects for normal tissues. Parenteral and intrarectal amifostine is effective in preventing radiation proctitis without reducing efficacy. Local agents include balsalazide, a non-absorbable salicylate that has demonstrated clinical efficacy in management of radiation injury. Sulfasalazine has not been consistently effective in clinical trials, though it is recommended by some clinicians.

Treatment for chronic radiation proctitis

Chronic radiation colitis/proctitis is most commonly characterized by rectal bleeding with mucosal pallor, multiple large telangiectasias, and strictures. Chronic injury is secondary to epithelial atrophy and fibrosis associated with endarteritis and resultant ischemia. Argon plasma coagulation has been demonstrated to decrease rectal bleeding and improve anemia within a few sessions with minimal complications. Formaldehyde has been used for several years for treatment, with recent studies demonstrating efficacy and ease of application with flexible sigmoidoscopy. Good response to single applications has been noted.

Pathophysiology of appendicitis

Fiber intake and resultant constipation have been evaluated in the pathophysiology of appendicitis. Studies of children with appendicitis showed that they have less fiber in the diet. Other studies have revealed that children in Western countries have low fiber content in their diets, which is associated with constipation. Dietary fiber intake in the young is associated with increase and maturation of microbial mass, volatile fatty acids, and lower pH. These changes in animal models correlate with fewer GI disorders. Prebiotics—non-digestible food ingredients that benefit the host by affecting the activity or growth of gut bacteria—may have a similar effect on gut microflora. Agents like inulin and fructooligosaccharides are fermentable and selectively increase the growth of bifidobacteria. These agents are fermented primarily in the proximal colon near the appendix.

A small study of patients with gangrenous and phlegmonous appendicitis showed a different cytokine profile. Researchers observed a

positive correlation of gangrenous appendicitis with Th1-mediated immunity with higher levels of interferon-γ and IL-10 when the patients were studied at least 6 months after appendectomy. Thus, individual differences in tendency toward Th1-mediated immunity with cytotoxic consequences may determine the outcome of appendicitis.

GOALS FOR RESEARCH [16]

Research Goal 9.1: Establish mechanisms of colonic injury and repair to use as a basis for development of therapeutic interventions. (See also Goal 1.6.)

The interior lining of a healthy colon regenerates continuously to replace old or damaged cells. Understanding the mechanisms that regulate this normal cellular turnover will allow researchers to develop therapies that stimulate the regenerative process to repair colonic tissues damaged by infection, inflammation, radiation, or other adverse events. Molecules such as TLRs, TFFs, and other growth factors appear to play a role in proliferation of the mucosal epithelium and represent prime candidates for drug discovery and development.

Objectives:

- Identify the specific interactions (e.g., via receptors/ligands) between enteric microflora and TLRs that promote macrophage-dependent proliferation of progenitor cells and determine which mediators released by macrophages are required for epithelial cell proliferation.
- Determine the bioavailability, safety, and efficacy of orally administered TFFs and other epithelial cell growth factors in models of mucosal injury and inflammation.
- Develop strategies for mimicking the enteric antigen/TLR interactions to promote gut healing.
- Identify other gut-specific growth factors capable of promoting colonocyte restitution and repair.
- Develop TLR agonists that mimic the protective effect of enteric bacteria.

Research Goal 9.2: Understand colonic mucosal absorption in health and disease. (See also Goals 1.11 and 1.12.)

Absorption of water and electrolytes in the colon is necessary for maintaining proper hydration of the body and recovering vital micronutrients from ingested food. Nearly all individuals throughout the lifespan experience occasional acute bouts of diarrhea or constipation. These conditions are often easily treated with lifestyle or dietary modifications or by the use of readily available over-the-counter medications. However, some people develop chronic disease that can severely affect their nutritional status and quality of life. By investigating the molecular mechanisms that govern mucosal absorption, researchers can better understand how these mechanisms break down in chronic disease and identify targets for therapeutic intervention.

Objectives:

- Survey known sodium, chloride, SCFA, and ammonia transporter expression in human colon with comparison to murine models and evaluate segmental alterations in transporter expression on varied, defined fiber, and protein diets.

[16] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

- Understand the regulation of sodium-absorptive and chloride-secretory pathways during disease and identify targets for potential therapy of diarrheal disorders and non-immunosuppressive approaches to enhance repair.
- Screen pediatric and adult U.S. populations for altered transporter complex expression and/or gene mutations in congenital and acquired constipation and diarrheal disorders, with the goal of developing individualized strategies for patients with chronic constipation or diarrhea.

Research Goal 9.3: Determine the role of gut microflora in health and disease states of the colon. (See also Goals 1.20, 1.21, 3.1, and 5.3.)

Microbes begin to colonize the digestive tract at birth and seem to have important roles in normal physiology, including digestion, nutrition, and immunity. Perturbations in the microflora have also been associated with various disease states. In some cases, overgrowth of a specific pathogenic bacterial species can cause disease, such as inflammation of the colon in response to *C. difficile* infection. Other conditions, like obesity or IBD, are associated with changes in the overall balance of different microbes. Research to characterize the gut microflora will generate new insights for therapeutic manipulation of the microflora to maintain the health of the colon and reverse disease.

Objectives:

- Establish tissue banks of mucosal biopsies to allow large-scale, chip-based comparison of adherent bacteria on the surface epithelium (biofilm) to bacteria in the normal microflora in feces.
- Compare bacterial microflora in obese and lean humans using molecular fingerprint assays and sequence analysis of cloned 16S rDNA.
- Compare colonic microflora before and after antibiotics in patients, with and without colonization by *C. difficile*, and use these data to develop a rational approach to reconstitute the microflora.
- Conduct randomized, double-blind, controlled trials to manipulate the colonic microflora in obesity as a possible adjunct therapy.

Research Goal 9.4: Establish the cause of diverticular disease and its complications, with modulation of disease.

Diverticular disease and its complications can cause significant discomfort and reduced quality of life in many elderly individuals. Understanding the risk factors for diverticulosis and its progression to diverticulitis will enable researchers to develop effective preventive strategies to reduce the burden of illness in this vulnerable population. For those patients who develop complications of diverticular disease, rigorous evaluation of medical and surgical options is needed to determine the most effective approach.

Objectives:

- Identify risk factors for diverticular disease, including genetics and lifestyle, and association with complications (specifically diverticulitis and bleeding).
- Determine whether treatment with non-absorbable antibiotics, mesalamine, prebiotics, probiotics, or other agents reduces the risk of recurrent diverticulitis and is cost-effective.
- Determine indications for surgery and the optimal surgical approach to complicated diverticular disease.
- Determine whether changes in lifestyle, especially diet, reduce the prevalence of diverticulosis and its complications (specifically, avoidance of specific dietary factors, such as seeds and popcorn) and reduce the risk of diverticulitis.

Research Goal 9.5: Understand mechanisms and develop tools for early diagnosis of colon ischemia and angioectasia.

CI is the most frequent ischemic disorder of the GI tract, yet it is very difficult to accurately diagnose. No specific tests are available to diagnose CI, except when infarction is present. Most episodes of CI resolve spontaneously and do not recur; however, approximately 25 percent of patients present with or develop irreversible disease requiring surgical intervention, and approximately 5 percent develop a chronic colitis resembling ulcerative colitis or Crohn's disease that may worsen with the standard treatment for IBD. Identifying biomarkers for early stage CI would allow earlier intervention and reduce the rate of complications.

Objectives:

- Devise a means of diagnosing CI early (i.e., before infarction ensues) and of differentiating it from other disorders by developing biomarkers for this disease process.
- Determine the underlying, proximate cause of CI, especially with regard to the behavior of colonic arteriolar and venular microvasculature, as well as the relationship of the bowel vasculature to serotonergic agents.
- Determine why angioectasias develop and understand the potential mechanisms for altered vasculature and blood flow.

Research Goal 9.6: Improve management of anorectal disorders.

Anorectal disorders are common clinical conditions, but limited basic science data exist about these disorders. While not life-threatening, the conditions may have a significant impact on a person's quality of life. The prevalence of these disorders is poorly studied, with the exception of fistulas in Crohn's disease and, recently, fecal incontinence. Limited scientific information is available on the underlying mechanism(s) of each of the conditions despite commonly accepted theories, and little is known about prevention strategies or the effectiveness of current therapeutic recommendations. Finally, new treatment modalities have been developed in recent years; however, long-term outcomes and cost-effectiveness information are not yet available.

Objectives:

- Understand risk factors and preventive strategies for anal disorders, including anal fistulas and hemorrhoids, with appropriate modification; natural history and impact of obstetrical sphincter injury; medical and neurological conditions; pelvic surgery; and the role of surgical repair of sphincter defects.
- Develop evidence-based algorithms for prevention, diagnosis, and treatment of perianal fistulas (cryptoglandular and Crohn's) and for treatment of hemorrhoids.
- Develop educational tools for providers and the public to raise awareness of anorectal disorders, including perianal abscess and fistula, and hemorrhoids, with particular focus on accurate diagnosis, initial treatment, and prevention.

Research Goal 9.7: Improve the understanding and management of fecal incontinence. (See also Goal 2.2.)

Fecal incontinence is an underreported and underappreciated condition frequently associated with shame, embarrassment, and stigma. Because of these aspects, it has been difficult to identify persons affected, risk factors, biologic causes, and social and environmental factors. Fecal incontinence has a major impact on quality of life of individuals living at home and in nursing homes, impacting people of all ages, especially women and the elderly. New treatment modalities and appropriate utilization and acceptance of prevention and management strategies are needed.

Objectives:

- Develop generally accepted definitions of fecal incontinence with longitudinal studies to identify risk factors, including medical and surgical treatments that may cause incontinence, and preventive strategies.
- Understand the existence and causes of differences in the rate and impact of fecal incontinence in different groups.
- Investigate medical and surgical treatment modalities with development of improved measures and algorithms for treatment of fecal incontinence.
- Develop evidence-based strategies for the diagnosis, prevention, and management of fecal incontinence, particularly in the aged and residents of long-term care facilities.
- Understand the direct and indirect economic and societal impact of fecal incontinence and the potential benefits of prevention and treatment interventions.
- Develop educational tools for providers and the public to raise awareness of fecal incontinence.

Research Goal 9.8: Reduce the frequency and severity of radiation injury to the colon.

Radiation colitis—damage to the colon mucosa or vasculature due to radiotherapy for abdominal or pelvic cancer—can manifest within weeks or even years after radiation exposure. Researchers are looking for ways to precisely modulate radiation dosage to maximize therapeutic effectiveness, while simultaneously minimizing or eliminating radiation-related injury to healthy colon tissue. Algorithms to accomplish this goal must allow for variation among different types and stages of cancers, as well as other patient-specific characteristics.

Objectives:

- Determine prognostic factors (e.g., genetic factors, co-morbidities) that are important in the development of chronic radiation injury.
- Determine efficacy of pharmacologic agents in prevention of radiation injury via multicenter trials with collaboration among experts in gastroenterology, oncology, and radiation oncology. Agents may have additional applications for biodefense.
- Develop evidence-based algorithms for prevention and treatment of radiation proctitis.

Research Goal 9.9: Determine causes of appendicitis and modulate the course of the disease.

The onset of appendicitis is nearly always a medical emergency. Delays in diagnosis and treatment increase the likelihood that the organ will rupture and disperse bacteria into the peritoneal cavity. The resulting peritonitis may contribute to complications, such as abscess formation, wound infection, urinary tract disorders, small bowel obstruction, or even death in a small minority of patients. Understanding the causes of appendicitis and ways to delay progression will help reduce the morbidity and mortality associated with this serious disease.

Objectives:

- Determine the effect of dietary factors, such as fiber content, prebiotics, probiotics, and bowel function (constipation), on the incidence of appendicitis, especially in children.
- Determine the role of the immune-mediated response in the histopathology and clinical course of appendicitis.
- Identify high-risk patients from an immune standpoint and develop modifications of the clinical approach to treatment of patients with different immune profiles.
- Determine the role of antibiotic therapy and other non-surgical approaches for the management of appendicitis.
- Develop improved methods for early detection of appendicitis.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Collaboration with industry: Collaboration with protein chemists and the biotechnology and pharmaceutical industries to provide sufficient quantities of TFFs and other growth factors would accelerate the testing of these factors in chronic preclinical studies and clinical intervention trials in human patients.

Research resources: Progress in the field would be aided by the establishment of centralized resources that would encourage sharing of biologic samples and patient data, as well as provide opportunities for collaborative research. A comprehensive tissue bank could be created to collect, store, and disseminate normal and diseased human colonic specimens that are defined with respect to anatomic segment and clinical data. The development of database capabilities and clinical consortia for randomized clinical trials with standardized endpoints would enable direct comparisons among clinical research outcomes. The development of a systems-based approach to the study of colonic transport using a limited number of defined cultured cell and transgenic mouse models and comprehensive expertise in cell biology, structural biology, transepithelial transport, nutrition, imaging, and computational modeling would generate a new perspective on the causes and treatments of colorectal diseases.

Research tools for the microflora: The vast and complex gut microflora present several challenges to research on the physiology of the colon and rectum in health and disease. For example, the microflora adherent to the colonic mucosa—the "biofilm"—may be more relevant than the microflora in feces. Thus, research on the microflora would benefit from the use of mucosal biopsies from colonoscopy rather than the traditional reliance on stool specimens. In addition, sensitive molecular techniques, such as PCR or microarrays, do not reliably distinguish between dead or non-viable organisms and organisms that are ingested and simply passing through the gut compared to microbes that are viable and capable of growth in the gut. The total metabolic activity (metabolome) of the microflora represents the sum of thousands of species and, in theory, could provide a less complex, quantitative approach to studying the microflora. New technology development would facilitate measurement of the metabolome of the colonic microflora. Metabolomic techniques could be developed to study the human or animal microflora *in vivo* using noninvasive methods, such as breath analysis. The use of radioactive precursors of bacterial end-products, like ammonia or hydrogen, would allow for assays of microbial metabolism.

Given the expected complexity and diversity of the microflora, the development of robust databases and software tools to analyze large amounts of data from multiple laboratories would accelerate research across the field. The Human Microbiome Project, which is being implemented through the NIH Roadmap for Medical Research, represents an important step toward meeting these challenges by providing a basic catalogue of the constituents of the stable microflora in all humans and a description of variations in the microflora that occur among individuals. The Human Microbiome Project will also facilitate the development of essential research tools and resources.

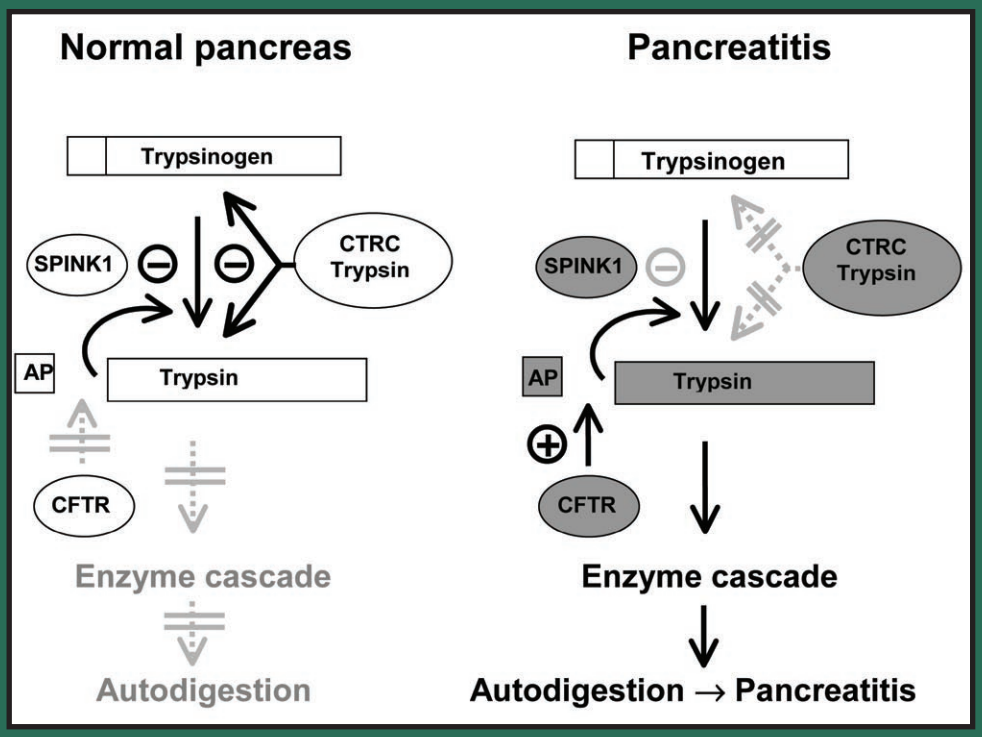
Clinical research: Diverticulosis is common in Western countries, but infrequent in underdeveloped countries. Conducting clinical research studies to compare different populations would help to define the risk factors. Clearly defining symptomatic diverticular disease and distinguishing symptomatic diverticular disease from IBS is a

difficult, but important, challenge. Prevention trials for diverticular disease will involve follow-up for several years to detect significant differences in outcomes. Similarly, intervention trials will also require long time periods, during which a method to control differences in diet among participants will be an important consideration. Central resources are especially important for diseases that are difficult to study in a single center with limited access to patients, such as radiation colitis, which generally affects an elderly population with multiple medical issues.

The frequency of anorectal disorders and interface of patients with multiple providers makes it difficult to develop an effective system of data collection for these conditions. Moreover, anal disorders often occur concomitantly, which complicates the evaluation of treatment outcomes. The field would benefit from broader understanding of the variety of anorectal disorders, the typical symptoms, and the criteria for diagnosis. Particularly for fecal incontinence, methods to overcome the reluctance of patients to discuss their symptoms and the reluctance of providers to inquire about these symptoms would improve opportunities for research and treatment. Prevention trials would require long time periods and be complex to manage.

Research on appendicitis is limited by difficulties in developing a network to study this condition in a pediatric population with an acute, self-limited disorder. Innovative approaches to research collaboration would promote progress on appendicitis. In addition, new methods are needed to obtain accurate dietary histories in patients, including children.

Animal models: Research progress could be stimulated by encouraging the development of novel animal models that faithfully mimic colonic and rectal disorders in human patients, such as diverticular disease and radiation colitis.



Proposed roles of pancreatic enzymes and other factors in normal pancreatic function compared to the pathogenesis of pancreatitis.

Image courtesy of Dr. Heiko Witt. Reprinted from Gastroenterology, *132, Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy, pp. 1557-1573, Copyright 2007, with permission from Elsevier.*

Diseases of the Pancreas

SUMMARY OF RESEARCH GOALS

The exocrine pancreas, which produces and secretes multiple enzymes necessary for digestive function, is vulnerable to a variety of disorders that, collectively, affect more than 1 million Americans each year. The Commission recommends a series of research goals that are focused on the most prevalent of these disorders—acute and chronic pancreatitis and their sequelae. Pancreatitis can be triggered by many possible causes, including gallstones, alcohol abuse, certain medications, autoimmunity, and diseases such as cystic fibrosis (CF), or it may be of unknown etiology. Research is needed to identify the biologic and genetic factors that increase a person's susceptibility to acute pancreatitis and/or the transition to chronic disease. The development of innovative diagnostic, preventive, and therapeutic approaches to pancreatitis has the potential to reduce the burden of this disease in both children and adults. Equally important is the need to understand the mechanisms of pancreatic pain, a highly prevalent complication of all forms of pancreatitis that is difficult to treat and severely erodes the quality of life of patients with pancreatic disease. Research to understand the risk factors for and mechanisms of progression to pancreatic cancer is particularly critical for patients who develop pancreatitis at a young age and are, therefore, at a corresponding increased lifetime risk for pancreatic cancer.

INTRODUCTION AND BACKGROUND

The pancreas plays a very important role in nutrient absorption via its synthesis of digestive enzymes (e.g., proteases, phosphatases, lipases, amylases, and others). The gland can be afflicted by a surprising diversity of pathologic processes leading to various diseases and clinical syndromes. Disorders of the pancreas affect more than 1 million persons in this country (1.15 million in 1998) and are estimated to result in nearly $3 billion in annual direct and indirect costs. As a group, there were 277,000 hospitalizations and 475,000 ambulatory care visits due to pancreatic diseases in 2004. Specifically, acute pancreatitis is the commonest cause of hospitalization for pancreas-related disorders in the country, accounting for 254,000 discharges, with a median charge of $13,435, and resulting in more than 2,800 deaths in 2004. CF, which interferes with pancreas function, is the most common inherited fatal disease in Caucasians, occurring in about 1 in every 3,500 births each year. This burden of disease contrasts with the relatively sparse number of researchers and actively funded proposals in this area.

The most widespread disorders of the pancreas are acute and chronic pancreatitis, or inflammation of the pancreas. In acute pancreatitis, inflammation begins abruptly and either resolves or worsens within days. About 2 percent of acute pancreatitis cases are fatal, often due to complications affecting other organs, such as the lungs, cardiovascular system, or kidneys. The most common causes of acute pancreatitis are gallstones, which traverse the bile duct and may inflame the pancreas by transiently blocking its drainage into the duodenum, and alcohol excess. Other causes include metabolic derangements, such as increased circulating triglycerides, certain medications, and invasive diagnostic tests evaluating the pancreas and bile ducts (e.g., endoscopic retrograde cholangio-pancreatography [ERCP]).

The most frequent known cause of chronic pancreatitis is also chronic alcohol abuse. Additional causes include hereditary pancreatitis due to mutations in genes that encode for key pancreatic molecules, such as trypsin or the cystic fibrosis transmembrane conductance regulator (CFTR), abnormalities of which are associated with CF and its variations. In up to 10-20 percent of cases, the cause remains unknown (idiopathic). The most frequent sequelae of chronic pancreatitis are pain, endocrine failure (resulting in diabetes mellitus), and exocrine failure (resulting in fat and protein malabsorption). Pain is present in approximately 75 percent of patients with alcoholic chronic pancreatitis, 50 percent of patients with late-onset idiopathic chronic pancreatitis, and all patients with early-onset idiopathic chronic pancreatitis. Pain is the most difficult symptom of chronic pancreatitis to treat, with many patients facing the prospect of lifelong dependence on narcotics. Our lack of knowledge about what causes pain in pancreatitis has been a serious obstacle to improving the care of these patients, leading to various empiric approaches that are often based on purely anatomical grounds, are generally highly invasive, and are not always effective. Individuals with alcoholic pancreatitis also suffer from issues of addiction to alcohol, smoking, and narcotics, which considerably complicate the care of these patients. Finally, chronic pancreatitis is associated with an increased risk for pancreatic cancer. While relatively uncommon, development of pancreatic cancer can be particularly important in those whose disease begins in childhood, such as patients with hereditary pancreatitis.

With increased use of sophisticated abdominal imaging procedures, such as high-resolution CT scan and MRI, cystic lesions of the pancreas are being recognized, often as incidental findings during investigation for other abdominal complaints. Some of these (pseudocysts) occur in the setting of

pancreatitis and may be a consequence of ductal injury. In the absence of preceding inflammation, these lesions are ominous and often neoplastic in nature. In recent years, advances in the understanding of the pathology of these cystic lesions have led to revision of the classification and nomenclature of these tumors into mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) and its variants. Both MCN and IPMN are mucinous tumors that have potential to turn malignant. While MCNs are frequently found in middle-aged women, IPMN is often seen in the elderly. Since mucinous tumors of the pancreas are precancerous, their discovery is an important health concern. They present great challenges with regard to diagnosis, treatment, and surveillance.

From a pathologic perspective, three distinct precursors to invasive pancreatic cancer have been identified, including: (1) MCNs, (2) IPMNs, and (3) pancreatic intraepithelial neoplasia (PanIN). The first two are macroscopic (i.e., generally visible on imaging techniques), while the third is microscopic in nature. All three pre-malignant processes begin as benign, noninvasive entities and progress through a series of as-yet poorly defined genetic and pathologic changes toward cancer. The link between chronic pancreatitis and pancreatic cancer and the role of PanINs in these diseases are incompletely understood.

The product of the CF gene, CFTR, is important for chloride ion transport on the apical surface of exocrine gland epithelial cells. Mutations in CFTR result in abnormally thick secretions that damage a variety of organs, including the lungs, liver, and pancreas. Pancreatic exocrine failure occurs in 85-90 percent of CF patients and results from blockade of ducts by thick mucus plugs, causing injury and fibrosis. Less frequently, diabetes will also result. In addition to the classic form of CF, patients with milder variations in the gene encoding CFTR will have residual pancreatic exocrine function, but may be at risk for recurrent pancreatitis.

Although diabetes can be considered a disorder of the pancreas, it is not considered a digestive disease in the strict sense and, although an important component of chronic pancreatitis and pancreatic cancer, will not be discussed in this research plan. Pancreatic cancer, the fourth leading cause of cancer death in the U.S., is included in the chapter on *Cancers of the Digestive System*.

RECENT RESEARCH ADVANCES

Acute pancreatitis

Researchers have recognized clearly that acute pancreatitis can affect the entire body and is associated with a systemic inflammatory response. Organ failure has been found to be a more important determinant of morbidity and mortality than necrosis or other local complications. Other important advances that are still in progress include elucidation of the complex cytokine/chemokine responses in acute pancreatitis, the development of *in vivo* models of acute pancreatitis, and understanding the nature of calcium and other cell signaling processes that mediate the physiologic and pathologic acinar cell responses.

Chronic pancreatitis

Progress has been made in understanding fibrosis events in the pancreas, particularly with regard to the role of stellate cells. With the development of valid animal models to study pancreatic pain, important molecular mechanisms and potential therapeutic targets, such as receptors and ion channels on sensory neurons (e.g., TRPV1), are beginning to be identified.

Genetic mutations and the risk of pancreatitis

Only a small subset (usually less than 5 percent) of patients with known risk factors for pancreatitis (e.g., chronic alcohol abuse or pancreas divisum) develops the disease. However, the genetic basis for this is not understood. Since the discovery in 1996 that mutations in the cationic trypsinogen gene cause hereditary pancreatitis, other genes have been implicated in apparently sporadic pancreatitis, such as recent reports concerning the role of genetic variation in the trypsin-degrading enzyme, chymotrypsin C. The frequent identification of mutations in the *CFTR* gene and the serine protease inhibitor, Kazal type 1 (*SPINK1*) gene in patients with idiopathic chronic pancreatitis and in a small proportion of the healthy population suggests that genetic predisposition may be necessary for development of disease in those with identifiable risk factors.

Recognition of autoimmune pancreatitis (AIP) as a distinct clinical entity

AIP is the pancreatic manifestation of a systemic autoimmune disorder. AIP is a form of chronic pancreatitis distinct from classically described chronic, calcifying pancreatitis. AIP has unique clinical, serologic, morphologic, and histologic features. The most frequently described presentation of AIP is that of a pancreatic mass that mimics pancreatic ductal adenocarcinoma in clinical presentation. If recognized prospectively, the inflammatory mass of AIP responds to steroid therapy, and the need for pancreatic surgery can be avoided. Interestingly, unlike usual chronic pancreatitis, AIP is a relatively painless disease despite histology showing chronic pancreatic inflammation and evidence of pancreatic edema, peripancreatic inflammation, and, in some cases, pancreatic calculi. This phenomenon is highly worthy of further study.

Pancreatic imaging

Advances in endoscopic ultrasound (EUS) technology have improved dramatically the ability to visualize even subtle alterations in pancreatic structure. These changes are visible before traditional cross-sectional imaging techniques (e.g., CT scan) show any abnormality, allowing for the possibility of diagnosing chronic pancreatitis early. However, the capability for high-resolution imaging is also the greatest drawback of this technology. Subtle alterations in structure are seen, for example, in alcoholics without pancreatitis, smokers, the elderly, and after bouts of acute pancreatitis. EUS also provides the opportunity to obtain tissue for histologic diagnosis of chronic pancreatitis without surgical resection of the pancreas.

Cystic lesions of the pancreas

A major boost to the field has come from the World Health Organization classification of cystic disorders of the pancreas, which has distilled many different types of classifications into one that determines whether or not the cells are malignant and whether or not tissue invasion has occurred. This revised system has significantly improved the ability of researchers to coordinate multiple studies. Progress in our understanding of cystic lesions of the pancreas has come from the identification of differences in diagnosis and natural history of MCN from IPMN, as well as the recognition that not all forms of IPMN require operative intervention. In addition, studies have introduced the concept of less aggressive treatment for small (less than 3 cm) cystic lesions in the pancreas. Finally, researchers have gained important new insights into the molecular mechanisms of neoplastic transformation of cystic lesions.

GOALS FOR RESEARCH [17]

Research Goal 10.1: Determine the biologic factors involved in the pathogenesis of acute pancreatitis, with particular emphasis on the mechanisms of tissue necrosis and systemic complications.

It is unclear why the majority of patients with acute pancreatitis do not develop the systemic inflammatory response syndrome or pancreatic necrosis. However, those who do will have a perilous clinical course, often complicated by organ failure and death. It is critical, therefore, to understand the biologic pathways leading to necrosis following a noxious insult. Such knowledge has the potential to identify novel and effective therapeutic targets, as well as much needed surrogate markers (clinical, hematological, or imaging) for mortality, necrosis, and systemic complications in acute pancreatitis.

Objectives:

- Understand how noxious insults, such as ethanol, gallstones, and others, initiate pancreatic injury and inflammation in adults and children.
- Understand the role of obesity, sphincter of Oddi dysfunction, and anatomic variations of the pancreas in the development of pancreatitis.
- Identify the biologic mechanisms leading to necrosis in acute pancreatitis.
- Understand the biologic mechanisms responsible for post-ERCP pancreatitis.
- Understand the role of specific cytokines and other inflammatory factors, including enteric bacteria and their products, in the development of systemic complications and multi-organ failure.

Research Goal 10.2: Understand the transition from acute to chronic pancreatic injury, particularly with respect to the role of alcohol.

Significant insight has been gained into the mechanisms by which alcohol or other insults lead to acute cellular injury. However, how these events lead to chronic inflammation and fibrosis or endocrine and exocrine cell loss remains unknown. These questions are of great clinical relevance given how often chronic pancreatitis is accompanied by enzyme insufficiency leading to malabsorption and insulin deficiency leading to diabetes.

Objectives:

- Understand how ethanol, smoking, and other putative etiologic factors contribute to chronic injury.
- Determine the biology of pancreatic fibrosis and chronic injury, including the role of stellate cells and other co-factors.
- Understand the nature and mechanism of endocrine cell loss in chronic pancreatitis.
- Understand the mechanisms of parenchymal and islet cell regeneration in response to chronic injury.
- Understand the biologic nature and importance of islet-parenchymal communication in the pancreas.

Research Goal 10.3: Understand genetic factors and their interactions with exogenous insults, with respect to pathogenesis, complications, and natural history of pancreatitis and other pancreatic disorders.

It is clear that host factors, including genetic variability, have a major influence in determining the risk for inflammation and subsequent clinical phenotype after insults, such as excessive alcohol use. Knowledge of these specific factors will be valuable in risk stratification and development of effective measures for prevention of disease. In addition, identification of these genes will provide crucial insight into the molecular mechanisms underlying pancreatitis and its complications.

[17] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

GOALS FOR RESEARCH

Objectives:

- Understand genetic factors that predispose to increased risk or severity of acute pancreatitis.
- Understand the role of genetic factors that predispose to chronic injury and/or impaired recovery from acute insults.
- Understand gene-environment interactions in the development of benign and cystic neoplasms, as well as pancreatic cancer arising in the context of chronic pancreatitis.
- Understand the genetic factors that predispose to sensitization and pain in the setting of pancreatic injury.
- Develop novel models of pancreatic disease derived from targeting of specific genes.
- Optimize nutritional strategies for the treatment of acute pancreatitis and its complications.
- Understand the effect of endoscopic approaches (e.g., stents, stone removal, and stricture formation), surgery, and radiologic interventions for the treatment of organized necrosis, pseudocysts, pain, and other complications of acute and chronic pancreatitis.
- Develop novel pharmacologic approaches for the reversal of fibrosis and prevention of islet and parenchymal cell loss, including islet cell and stem cell transplant strategies.
- Understand the role of immunosuppressive therapy for the treatment of autoimmune pancreatitis.

Research Goal 10.4: Develop and validate therapeutic interventions for treatment and/or progression of pancreatitis and its complications.

Much progress has been made in elucidating the signaling mechanisms of inflammation and fibrosis in other disease models, and several cytokines and other molecules have been identified as major players in pathogenesis. Synthetic agents directed against these targets are becoming increasingly available, and their effectiveness in modulating the acute and chronic inflammatory responses in the pancreas needs to be determined. In addition to drugs, endoscopic (e.g., placement of stents) and surgical approaches also hold promise, and their role in the management of acute and chronic pancreatitis needs to be examined rigorously through carefully conducted prospective studies.

Objectives:

- Understand the effects of specific pharmacologic therapies, including anti-cytokine agents for the treatment of acute pancreatitis, as well as the prevention and treatment of necrosis and multi-organ failure.
- Develop novel and more effective pharmacologic and/or endoscopic approaches to prevent ERCP-induced pancreatitis.

Research Goal 10.5: Understand the neurobiology of the pancreas with respect to mechanisms of pain and neurogenic inflammation.

Pain is the major symptom that drives patients to seek health care in a variety of pancreatic disorders, including chronic pancreatitis and pancreatic cancer. An understanding of how these disorders affect the sensory nerves conveying pain from the pancreas is, therefore, important for effective therapies to be developed. Further, recent investigations have suggested that communication between the pancreas and its nerves is bi-directional and that neurogenic influences can modify inflammation and perhaps influence the behavior of cancerous cells.

Objectives:

- Understand the biologic basis and mechanisms responsible for peripheral sensitization in chronic pancreatitis.
- Understand changes in central sensitization and the underlying mechanisms in patients with painful chronic pancreatitis.
- Understand the biologic basis of narcotic dependence and resistance in patients with chronic pancreatitis.

- Identify novel therapeutic targets for more effective analgesic therapy.
- Understand the mechanisms by which autonomic, spinal, and neurohormonal factors influence the course of acute and chronic pancreatitis and their complications.

Research Goal 10.6: Define the epidemiology and clinical course of acute and chronic pancreatitis, including alcoholic pancreatitis, autoimmune pancreatitis, and cystic fibrosis, through population-based studies in adults and children.

Progress in this area has been hampered by the lack of standardized approaches to diagnosis and classification and the fact that no single center sees enough cases to permit robust and generalizable conclusions. Expanding our knowledge of these issues is critical in order to develop effective estimates of the burden of disease and formulate guidelines for screening, prevention, and treatment. This gap in knowledge is particularly significant for the pediatric population.

Objectives:

- Identify reliable prognostic factors of severity of acute pancreatitis at admission that can be utilized to stratify patients who can be enrolled in studies to evaluate new therapies.
- Understand the co-factors necessary for development of fibrosis in patients with recurrent pancreatitis and the rate of disease progression in chronic pancreatitis.
- Understand the natural history of disease in patients with chronic pancreatitis due to various etiologies, including autoimmune pancreatitis.
- Understand demographic, ethnic, genetic, and environmental factors that elevate the risk of disease development and rate of disease progression.
- Develop and validate reliable measures of pain and quality of life in patients with chronic pancreatitis in adults and children.

Research Goal 10.7: Develop more accurate and useful approaches to the diagnosis of chronic pancreatitis by functional, radiologic, endoscopic, or pathologic/cytologic means.

Innovative strategies are needed for the detection of chronic pancreatitis to enable early diagnosis, predict and monitor disease activity and progression, and distinguish etiopathologic subsets, such as autoimmune or genetic pancreatitis. The pancreas is a relatively small and inaccessible organ. Direct means of evaluating pathologic changes are invasive and carry substantial risk. Most clinical information, therefore, is obtained by indirect means, including biochemical and radiological tests. Research on alternative and/or more accurate tests of form and function will be very important for future clinical progress in pancreatology.

Objectives:

- Develop and validate unequivocal criteria for diagnosis of chronic pancreatitis (histologic and non-histologic) and distinguish etiopathologic subsets, such as autoimmune or genetic pancreatitis.
- Develop novel methods, including minimally invasive biopsy techniques, to help identify patients with early chronic pancreatitis and distinguish etiopathologic subsets.
- Develop and validate novel and less invasive methods to recognize and monitor fibrosis.
- Develop and validate more accurate and convenient tests to assess and monitor pancreatic function.
- Develop and validate reliable noninvasive methods for the diagnosis and monitoring of autoimmune pancreatitis.

Research Goal 10.8: Define the role of pathologic lesions, such as pancreatic intraepithelial neoplasms, and other factors that may correlate with the risk of malignant transformation in chronic pancreatitis and cystic neoplasms and map their morphologic and molecular progression.

GOALS FOR RESEARCH

In a small but important subset of patients, pancreatic cancer develops in the setting of a cystic lesion or chronic pancreatitis. The biologic mechanisms underlying this risk remain unknown, but further knowledge in this area may offer the potential for developing effective methods of surveillance and prevention, including the use of adjuvant/neoadjuvant therapy after partial resection. This may be particularly important in patients with hereditary pancreatitis who are often very young at the onset of their disease and accumulate risk for cancer throughout their life. Other subsets that may benefit include patients with IPMN, in whom large segments of the pancreatic epithelium are vulnerable to cancerous change.

Objectives:

- Understand the epidemiology and natural history of cystic disorders of the pancreas and correlate the findings with the results of imaging and fluid analysis.
- Identify biomarkers in cystic fluid and tissue aspirates for providing unequivocal diagnoses and pathologic distinction.
- Understand the role of invasive and noninvasive methods for surveillance of patients at risk for malignancy.
- Understand the clinico-pathologic correlations involving PanINs, small cystic lesions, and IPMN.
- Understand the genetic and morphologic progression between precursor lesions and pancreatic cancer, particularly in the context of chronic pancreatitis.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Standards for diagnosis: Differences in the diagnosis and care of patients with pancreatic disease impede efforts to compare data across centers or clinical trials. The field would benefit from the development of consensus guidelines for diagnosis of chronic pancreatitis, including histologic and clinical criteria. In addition, validation of reliable tools to measure pain and quality of life in patients with chronic pancreatitis would improve patient care and enhance research efforts.

National resources for pancreas research: A significant obstacle to research progress on pancreas diseases is that relatively few patients are treated at any single center. Research could be accelerated by pooling data and biosamples and making these resources available to investigators across the U.S. through a comprehensive national database of acute pancreatitis. Such a database could be used to define mortality and morbidity and to develop reliable prognostic factors of severity at admission, which would enable stratification of patients for enrollment in clinical trials to evaluate new therapies. Similarly, a widely accessible patient registry and a repository of biologic samples for banking tissue, serum, and DNA could increase research on the basic mechanisms of onset and progression of pancreatic diseases. Establishing multicenter consortia for the study of chronic pancreatitis in adults and children would provide opportunities for collaboration among researchers with complementary expertise.

Animal models: Development and validation of animal models of both acute and chronic pancreatitis (alcoholic and non-alcoholic) and its complications would accelerate progress on understanding risk factors for this disease.

Alignment of research and clinical forces: The rapid development of endoscopic and other relatively noninvasive approaches to visualizing the pancreas provides new opportunities for building multidisciplinary research teams that include laboratory investigators, clinicians, and clinical investigators with different areas of expertise. A concerted effort to align these forces will be important in maximizing the efficiency and productivity of research efforts.

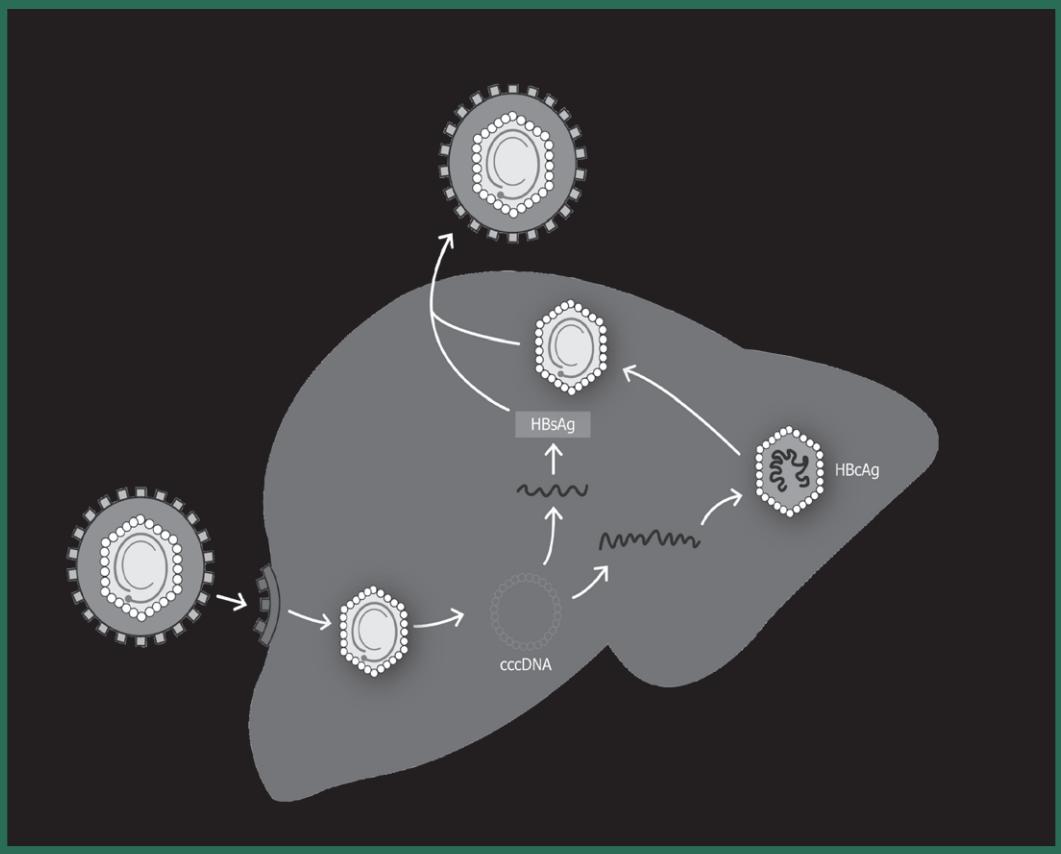


Illustration of the life cycle of the hepatitis B virus in hepatocytes. Knowledge of how hepatitis B infects the liver has aided the development of many new treatments for this disease.

Image courtesy of Dr. Edward Doo, reprinted from the Management of Chronic Hepatitis B: 2006 conference, April 2006 (http://www.niddk.nih.gov/fund/other/hbv2006/index.htm).

Diseases of the Liver and Biliary System

SUMMARY OF RESEARCH GOALS

Major research goals relating to diseases of the liver and biliary system were set forth in the trans-NIH *Action Plan for Liver Disease Research*, which was released in 2004. Taking that effort into consideration, the Commission proposes research goals that are intended to complement and reinforce the comprehensive recommendations made in the *Action Plan*. Understanding normal liver and biliary function and development will provide a solid foundation for new approaches to detect, prevent, and treat liver and biliary diseases. Although the burden of some forms of viral hepatitis has decreased in recent years due to efforts such as the development of vaccines and antiviral therapies, more work is needed to find safe, effective means for prevention and treatment of all forms of acute and chronic viral hepatitis, as well as human immunodeficiency virus (HIV)-associated liver disease. Hepatic steatosis (fatty liver disease) is an increasingly common form of liver disease in the U.S. Research to discover the basic mechanisms underlying steatosis will point to new therapeutic strategies. Similarly, research is needed to uncover the genetic bases and fundamental cellular mechanisms of a range of disorders, including drug-induced liver disease, autoimmune diseases of the liver, childhood syndromes and other hereditary liver diseases, cirrhosis, liver cancers, and gallstones. More knowledge of all of these conditions will accelerate the search for new means of prevention, diagnosis, and treatment, such as improved procedures for liver transplantation, to reduce the burden of liver and biliary diseases in the U.S.

INTRODUCTION AND BACKGROUND

Diseases of the liver and biliary system are major causes of illness and death worldwide and in the U.S. These diseases encompass a wide range of conditions, from viral hepatitis to gallstones, alcoholic hepatitis, fatty liver disease, autoimmune liver and biliary conditions, inherited and congenital disorders, liver conditions caused by toxins or medications, and liver and bile duct cancer. Collectively, diseases of the liver and biliary system rank in the top ten causes of death and accounted for over 55,000 deaths in 2004 (~2.5 percent of all deaths). Importantly, the majority of liver and biliary diseases can be accurately and easily diagnosed, and specific therapies are available for most. This optimistic assessment, however, is a recent change. Fifty years ago, most causes of liver disease were unknown, diagnosis was difficult, and only one or two rare conditions were treatable. This dramatic change in the last 50 years has been brought about by significant advances in our understanding of the liver and its diseases followed by inroads into means of prevention and cure.

Examples of important breakthroughs include: (1) discovery of the hepatitis B virus in 1964, followed by development of means for its detection, prevention, and treatment; (2) discovery of the hepatitis A virus in 1974 with subsequent development of means for diagnosis and an effective hepatitis A vaccine; (3) discovery of the hepatitis C virus in 1989, followed rapidly by means for its detection, prevention of its spread by blood transfusion, and steady improvement in treatment; (4) development of liver transplantation over the period of 1963 to 1983 with its subsequent acceptance as the standard of care for management of end-stage liver disease and liver cancer; (5) improvements in understanding how medications can cause serious liver disease, including the mechanisms by which acetaminophen injures the liver and how aspirin, when given to children during viral illnesses, can lead to fatal liver injury; (6) development of means of early detection of liver cancer at a point when resection or liver transplantation can prevent spread and prolong life; and (7) improved means of diagnosis and management of gallstones and evolution of laparoscopic surgery for cholecystectomy (removal of the gallbladder).

These advances have all been the result of progress in medical research on liver and biliary disease and have had a material effect on the frequency (incidence and prevalence) and impact (mortality and morbidity) of liver disease. Rates of death from cirrhosis and end-stage liver disease have been steadily declining in the last 15 years and are at an all-time low. Rates of acute hepatitis A, B, and C have declined by more than 80 percent in the last 20 years, and these diseases are now at historically low levels.

The changes in understanding and ability to diagnose, prevent, and treat liver disease in the last 25 to 50 years have been profound. However, the burden of liver disease in the U.S. remains an important problem. Deaths from liver and biliary disease account for approximately 2.5 percent of all deaths and have remained constant at approximately 55,000 per year for the last 10 years. Over the last decade, liver cancer incidence has increased in the U.S. at a rate second only to that of adenocarcinoma of the esophagus. Hepatitis C remains a major cause of end-stage liver disease and takes an increasing toll on medical resources. Pediatric liver disease, although rare, remains largely untreatable except with liver transplantation. Gallstone disease remains common, and surgery for gallstones is still a major health cost in the U.S. With the burgeoning epidemic of obesity throughout the world, non-alcoholic fatty liver

disease is emerging as an important new cause of significant liver disease.

These factors are the basis for a call to promote further research on liver and biliary tract structure, function, and disease. Given the recent dramatic advances in genetics and genomics research, with the completion of the Human Genome Project and with very substantial advances in cell and molecular biology, the promise of research directed at specific liver conditions is all the greater.

The preparation of this chapter was greatly aided by the availability of the 2004 comprehensive plan for research in liver and biliary diseases, the trans-NIH *Action Plan for Liver Disease Research* (http://liverplan.niddk.nih.gov). Developed by a series of 16 working groups of researchers, academicians, and lay persons involved in liver disease research, the *Action Plan* proposed a total of 214 research goals in 16 categorical areas of research. The National Commission for Digestive Diseases, in recognizing the major contribution of that plan and its updates, made extensive use of the *Action Plan* as a foundation to synthesize and update goals for research in liver and biliary diseases for this research plan. This chapter extensively cross-references the goals of the *Action Plan*, and the two documents are intended to be used in a complementary fashion by those interested in advancing liver and biliary disease research. The cross-referenced goal in the *Action Plan* is provided after the listing of each research objective in this document (by *Action Plan* chapter and goal number). In addition, the structure of this chapter, including the alignment of recent research advances with individual research goals, is meant to optimize cross-referencing with the *Action Plan* and is not an indication of priority of scientific topics.

GOALS FOR RESEARCH

MOLECULAR AND CELL BIOLOGY OF THE LIVER AND BILIARY SYSTEM (*ACTION PLAN* CHAPTER 1)

Recent Research Advance

Progress in defining molecular pathways controlling liver and biliary cells. There are numerous recent examples of continuing progress in defining the molecular pathways that control liver and biliary cell function. Two striking advances, one on hepatocyte polarity and another on regulation of cholesterol synthesis, are described here. Radixin is a major hepatocyte protein that has been shown to tether proteins such as MRP2 to the canalicular membrane; siRNA suppression of radixin results in loss of polarity, structure, and function of apical hepatocyte membranes. Studies in cell culture have further strengthened the "convergent mechanism" for feedback control of cholesterol synthesis and uptake by hepatocytes; this control is mediated by sterol-regulatory element binding proteins (SREBPs) in the endoplasmic reticulum (ER). In the presence of low levels of cholesterol, SREBPs move to the Golgi and release a transcription factor portion that up-regulates cholesterol synthetic and transporter pathways, but in the presence of high levels of cholesterol, SREBPs are bound to Scap and Insig-1 and retained in the ER, resulting in decreased transcription of target genes.

Research Goal 11.1: Define the molecules, processes, and pathways that underlie normal liver cell function, which can then be applied to understanding the cellular and molecular basis of disease processes.

The liver is the largest solid organ in the body and serves essential functions in regulating metabolism and homeostasis. The major cell of the liver is the hepatocyte, one of the body's most versatile cells, which serves to produce proteins, lipids, and complex carbohydrates, as well as to regulate energy balance, glucose and cholesterol metabolism, and to excrete foreign substances and breakdown products of metabolism, drugs, or toxins by excreting them directly into the bile or converting them to forms that can be excreted in the urine. No single test can measure the overall function of the liver and its hepatocytes, and the full range of their activity has yet to be completely described. Research on molecular and cell biology of the liver and biliary system is essential to understanding the functions of the liver, how they are altered in disease, and how they can be corrected or improved.

Objectives:

- Define how molecules are transported across membranes and to specific sites in the liver cell (cell trafficking). (Chapter 1: A3, C1)
- Fully understand the signaling mechanisms that control the activity of liver cells (signal transduction) and how these signaling mechanisms interact. (Chapter 1: A1)
- Elucidate the steps of regulation of cholesterol and lipid synthesis, transport, and excretion. (Chapter 1: A2)
- Develop a comprehensive knowledge base of the normal liver proteome, comprising an analysis of the proteins in the hepatocytes, their amino acid sequences, carbohydrate and lipid modifications, secondary and tertiary structure, interactions, and functions. A better understanding of the normal liver proteome would advance all components of knowledge about the liver and its functioning. (Chapter 1: C3)

LIVER CELL INJURY, INFLAMMATION, FIBROSIS, AND REPAIR (*ACTION PLAN* CHAPTER 2)

Recent Research Advance

Mechanisms of fibrosis. An important research advance has been the recognition that activation of hepatic stellate cells is a major factor in hepatic fibrosis. Further dissection of the pathways and cells involved in this process may provide the basis for therapeutic interventions to prevent or reverse fibrosis in the liver.

Research Goal 11.2: Understand the cellular mechanisms of liver injury, inflammation, repair, and fibrosis and develop effective means for monitoring and treating diseases caused by these processes.

Tissue injury and inflammation, repair, and fibrosis are fundamental components of all forms of acute and chronic liver diseases. Understanding the mechanisms of liver cell injury and the resulting inflammation, fibrosis, and repair will help to develop ways of preventing liver injury and reversing its effects. Liver cells die in response to inflammation or immune attack in an orderly, predetermined fashion, known as programmed cell death (apoptosis). The cellular pathways involved in apoptosis are complex, but their delineation would help in developing means to treat virtually all liver diseases. Liver cell injury is usually accompanied by inflammation and immune reactivity. Cell injury, particularly if severe and accompanied by inflammation, can lead to abnormal healing and progressive hepatic fibrosis. Understanding fibrosis and the processes that lead to cirrhosis, including how to detect fibrosis in its early stages, are major goals for research in this area.

GOALS FOR RESEARCH

Objectives:

- Delineate the steps in the process of hepatocyte apoptosis. (Chapter 2: A2a)
- Understand how liver cells produce and respond to inflammatory mediators and cytotoxic signaling mechanisms. (Chapter 2: A1a, B1)
- Develop better small animal models for liver cell injury, inflammation, repair, and fibrosis. (Chapter 2: C1)
- Develop noninvasive means of assessing liver injury and fibrosis. (Chapter 2: A3; Chapter 16: C1b)
- Translate findings about cell injury, inflammation, repair, and fibrosis to clinical diseases. Identify small molecules that might alter these processes and form the basis for translational research. (Chapter 2: B3, C2a, C3)

DEVELOPMENTAL BIOLOGY AND REGENERATION OF THE LIVER (*ACTION PLAN* CHAPTER 3)

Recent Research Advance

Identification and characterization of hepatic stem cells in fetal and adult liver. Multipotent progenitor cells have been isolated from human fetal liver that can differentiate into hepatocytes and cholangiocytes. In mice, embryonic stem cells can be induced to differentiate into hepatic lineages and can contribute to hepatic repair when transplanted into immune-deficient mice.

Research Goal 11.3: Define the molecular and cellular mechanisms underlying liver development and regeneration in health and disease and apply these findings to developing improved therapies for liver disease.

The liver has a marked ability to regenerate. Resection of half of the human liver is followed within 2-4 weeks by full restoration of the liver structure, size, and function. The process of regeneration recapitulates, in many respects, the development of the liver *in utero*. Understanding the developmental biology of the liver, how embryonic stem cells differentiate into mature and functional hepatocytes and cholangiocytes, and what processes and cellular signals initiate, promote, and conclude regeneration would aid understanding of liver disease and how the liver recovers from cell injury. Identifying signals that promote regeneration may well lead to therapies that would aid in recovery from liver injury or surgery. Such research is also likely to help identify biomarkers for regeneration and for failure of regeneration in situations such as acute liver failure or liver transplantation.

Objectives:

- Define the cellular and molecular events that underlie liver development and what processes are shared with liver regeneration. (Chapter 3: A1b, B3).
- Identify and characterize the stem cells of the liver and determine how to use such cells in gene transfer and transplant studies to correct genetic mutations that lead to inherited diseases, such as hemophilia, porphyria, alpha-1-antitrypsin deficiency, Crigler-Najjar syndrome, and other devastating diseases. (Chapter 3: A1a, C3a).
- Improve gene transfer techniques, gene transfer vectors, and means of supporting cell viability as they are directed to home to the liver (Chapter 3: B1a, C1).

BILE, BILIRUBIN, AND CHOLESTASIS (*ACTION PLAN* CHAPTER 4)

Recent Research Advance

Identification of physical and molecular regulators of bile flow. Cilia on cholangiocytes have been shown to respond to bile flow and induce increases in intracellular calcium and decreases in cyclic AMP mediated through flow receptors (polycystin-1), calcium channels (polycystin-2), and adenylyl cyclase on the cilia, providing a new model for regulation of ductal bile secretion. Fibroblast growth factor (FGF)-15 has been identified as playing an important role in gallbladder filling. FGF-15 is induced in the terminal ileum as a result of bile acid signaling through the farnesoid X receptor (FXR) and circulates in a hormonal fashion to the liver and gallbladder where it leads to gallbladder filling by acting on cyclic AMP-linked receptors on biliary smooth muscle cells. Thus, intra- and inter-cellular signals coordinate to control gallbladder filling and emptying.

Research Goal 11.4: Delineate the normal pathways of uptake, metabolism, and secretion of bile salts, bilirubin, and other biliary lipids and solutes; characterize the alterations in these pathways that participate in the pathogenesis of liver diseases; and develop means for diagnosis, treatment, and prevention of cholestatic liver disease and disorders of bilirubin metabolism.

A major and distinctive function of the liver is to make and excrete bile. Bile facilitates digestion and absorption of lipids and is also the major means of elimination of cholesterol and the breakdown products of metabolism, such as bilirubin. Persons with severe liver disease usually have altered bile formation and retention of the products of bile and bilirubin, which results in jaundice. Disruptions in the steps of bilirubin elimination and bile formation are responsible for many of the severe inherited forms of liver disease in children. Understanding the processes that lead to bile formation and excretion will provide necessary insights into diseases of the liver and how to correct them. Regulation of these pathways in health and disease might well improve liver function and aid in recovery from liver injury. Furthermore, mutations in the genes that regulate the steps in bile and cholesterol metabolism account for several severe forms of inherited liver disease that might be alleviated by altering these pathways using small molecules or gene therapy.

Objectives:

- Fully define the normal physiology and regulation of bile formation, including cholesterol synthesis and catabolism. (Chapter 4: B2a, B2b)
- Understand the pathophysiology of acquired forms of cholestatic liver disease, which disturbed processes account for the retention of bile, and how to alleviate the consequences of bile retention. (Chapter 4: A2, C1, C2)

VIRAL HEPATITIS (*ACTION PLAN* CHAPTER 5)

Recent Research Advances

New treatments for hepatitis B. In the past 5 years, new drugs that block hepatitis B virus (HBV) replication have been developed and tested, such that there are now six licensed options. The effectiveness of each of these has been characterized, and guidelines for their use have been updated. Antiviral therapy of hepatitis B has been shown to prevent disease progression.

Understanding the life cycle of hepatitis C virus (HCV). A landmark breakthrough in HCV research has been the recent growth of this virus in cell culture, which will permit more detailed studies of the entire viral life cycle, including initial infection, replication, packaging, and release of virus. Detailed

knowledge of these steps will permit identification of potential new approaches to treating the infection.

Demonstration of the efficacy and safety of a hepatitis E virus (HEV) vaccine. A landmark study conducted in Nepal has shown protective immunity against HEV infection with a three-dose schedule of a recombinant HEV vaccine.

The research goal in the area of viral hepatitis is to develop practical, safe, and effective means of prevention, treatment, and control of all forms of the disease. Viral hepatitis can be caused by any one of five viruses that infect the liver in humans, appropriately named hepatitis A, B, C, D, and E virus. Hepatitis A and E are forms of infectious hepatitis that are very contagious, occur in outbreaks of typically acute clinical courses, and are associated with poor sanitation and fecal-oral spread. Both viruses can cause severe hepatitis, but they do not cause chronic liver injury or cirrhosis. Hepatitis B, C, and D are forms of serum hepatitis that are less infectious, can cause chronic infection, are blood-borne, and are spread largely by parenteral or sexual routes. All five viruses have been identified in the last 30 years, and tests to identify infections and means of prevention with immune globulin or vaccines are available for four of them (A, B, D, and E). The incidence of new cases of viral hepatitis has been decreasing steadily in the U.S. for the last 20 years. Nevertheless, cases still occur and cases of chronic hepatitis B and C remain common causes of cirrhosis and end-stage liver disease. Full control and elimination of viral hepatitis will require several more breakthroughs in hepatitis research.

Research Goal 11.5: Develop safe and effective means to prevent and treat hepatitis C.

Progress in developing a hepatitis C vaccine has been impeded by the lack of apparent immunity from re-infection and lack of cell culture and small animal systems to study infectivity. The recent description of a cell culture propagation method for a strain of hepatitis C may help overcome these difficulties. Current therapies are effective in only half of patients and are poorly effective or too toxic for patients with advanced liver disease, patients with a solid organ transplant, or those who have other serious co-morbidities, such as renal, cardiac, or cerebrovascular disease.

Objectives:

- Develop a vaccine or specific means of prevention of hepatitis C. (Chapter 5: C3a)
- Develop safer and more effective means of treating chronic hepatitis C that can be applied to all categories of patients. (Chapter 5: B2a, B1b, C2a, C2b)
- Understand the factors underlying the differential disease burden and poorer response to therapy in African American patients with hepatitis C.
- Better understand the structure and replication cycle of the hepatitis C virus to help develop new therapeutic targets and better small molecular therapies for this disease. (Chapter 5: A3, B1a, B3a)
- Better understand the host and HCV interactions that determine viral clearance versus persistence. (Chapter 5: A2, B1a, B3a)

Research Goal 11.6: Improve strategies for use of current therapies of hepatitis B and develop new, improved treatment regimens.

Advances in hepatitis B research in the last 40 years have been impressive, but further efforts are needed for the complete control of this disease, including defining how to best use available therapies in practice. There are currently at least six licensed therapies for hepatitis B, all of which lead to improvements in the disease when given for 1-2 years; however, the optimal therapy or combinations of therapies, how they are to be

given, and for how long have yet to be identified. In addition, new classes of therapies that target other viral replication steps or elicit favorable immune responses would enhance treatment options for hepatitis B.

Objectives:

- Develop a better understanding of the pathogenesis of hepatitis B in all its forms (acute, chronic, active, inactive). (Chapter 5: B1a, B2b, B3b)
- Better define the optimal means for treatment of chronic hepatitis B. (Chapter 5: B2a, B2b, C1a, C1b, C3b)
- Understand the factors responsible for the ethnic and racial disparities in hepatitis B infection, which disproportionately affects Asian Americans in the U.S.
- Conduct clinical trials to compare multimodality therapies for hepatitis B. (Chapter 5: C1b)

Research Goal 11.7: Develop improved means to prevent and manage acute viral hepatitis.

At present, only emergency liver transplantation has been shown to be effective in management of acute liver failure due to viral hepatitis. New medical therapies are needed, as these diseases can be severe, protracted, and even fatal.

Objective:

- Develop and evaluate new approaches to therapy in all five forms of acute viral hepatitis. (Chapter 5: B2a, C1a)

HIV INFECTION AND THE LIVER (*ACTION PLAN* CHAPTER 6)

Recent Research Advance

Regimens to treat HIV/HBV co-infection. The response to therapies for chronic viral hepatitis in patients with concurrent treatment for HIV infection is different from patients with mono-infection, and there is considerably less evidence for optimal treatment regimens. Recently, tenofovir has been shown to have more potent antiviral activity against HBV than adefovir in HIV/HBV co-infected persons. The combination of tenofovir and emtricitabine is now recommended as standard of therapy for HBV/HIV co-infection.

Research Goal 11.8: Define the causes of liver disease associated with HIV and develop means to prevent and treat liver disease in HIV-infected persons.

Patients with HIV infection are susceptible to a wide range of liver diseases, and the interactions of these diseases with HIV infection and its therapies are complex and challenging. As patients with HIV infection are surviving longer as a result of effective anti-retroviral therapy, liver disease has become an increasingly important cause of morbidity and mortality. Liver disease among persons with HIV infection represents a major challenge to research. The spectrum of liver conditions among HIV-infected persons includes acute and chronic viral hepatitis; alcoholic and non-alcoholic steatohepatitis; drug-induced liver injury; autoimmune conditions of the liver; bacterial, fungal, and protozoal infections of the liver and biliary system; and liver and bile duct cancers, including lymphomas of the liver. Viral hepatitis is particularly problematic among HIV-infected persons, many of whom are in risk groups with a high rate of hepatitis B and C. The optimal approach to therapy of hepatitis C among HIV-infected persons remains unclear, and better therapies are needed.

Objectives:

- Define the prevalence and incidence of liver disease in HIV-infected persons and identify the causes of liver disease associated with HIV, as well as their means of diagnosis, prognosis, and management. (Chapter 6: B1a, B2a, B2b, B3, C3b)

- Identify the optimal approach to therapy of HCV in HIV-co-infected individuals and apply new agents active against HCV as soon as possible to this important cohort of patients. (Chapter 6: A1b, A2, C1b)

FATTY LIVER DISEASE (*ACTION PLAN* CHAPTER 7)

Recent Research Advance

Treatment of non-alcoholic steatohepatitis (NASH). In a proof-of-concept study, the administration of pioglitazone led to metabolic and histologic improvement in subjects with NASH, justifying the need for larger clinical trials, which are ongoing.

Research Goal 11.9: Understand the basic mechanisms of injury and develop means to prevent and treat non-alcoholic and alcoholic fatty liver disease.

Fatty liver disease occurs in two major forms: alcoholic and non-alcoholic, both of which are marked by accumulation of fat in the liver followed by inflammation, liver cell injury, fibrosis, and cirrhosis. Alcoholic liver disease is a major cause of illness and accounts for up to half of deaths from liver disease. Non-alcoholic fatty liver disease is a somewhat newly described problem, but appears to be the major reason for liver test abnormalities among Americans and is an increasingly common cause of significant liver disease and the need for liver transplantation. The cause of non-alcoholic fatty liver disease is unknown, but it is closely linked to obesity, diabetes, and high triglyceride levels and, thus, appears to be a part of the metabolic syndrome. There are no current means of treatment of either form of fatty liver disease, other than abstinence for alcoholic forms and attempts at weight loss for the metabolic forms of fatty liver disease.

Objectives:

- Identify the underlying pathogenesis of non-alcoholic fatty liver disease. (Chapter 7: A3, B2a)
- Elucidate the basic mechanisms of pathogenesis of alcoholic liver disease. (Chapter 7: B1a, B2a)
- Develop noninvasive means to distinguish steatosis and steatohepatitis. (Chapter 7: B2b; Chapter 16, C1b)
- Identify and test safe and effective means of treatment of both forms of fatty liver disease. (Chapter 7: B1b, B3a, B3b, C1a, C1b)

DRUG-INDUCED LIVER DISEASE (*ACTION PLAN* CHAPTER 8)

Recent Research Advance

Development of a diagnostic assay for acetaminophen toxicity. An assay for acetaminophen adducts has been developed and shown to identify 90-100 percent of cases of acetaminophen-induced acute liver failure in adults and children. These adducts are not present in cases of acute liver failure of other known causes, but are present in 12-19 percent of cases of unknown cause. Thus, some idiopathic cases of acute liver failure may be caused by unrecognized or unacknowledged acetaminophen overdose—a finding that has major therapeutic implications. The test requires further modification to become clinically useful, and its sensitivity for milder forms of acetaminophen injury requires elucidation.

Research Goal 11.10: Establish means to predict, prevent, diagnose, and treat hepatotoxicity due to drugs, herbal medications, and environmental toxicants.

Drug-induced liver disease has become an increasingly important health problem in the U.S. Liver injury from medications is rare, but can be protracted, severe, and even fatal. Indeed,

drug-induced liver disease is now the leading cause of death from acute liver failure. While medications rarely cause liver injury, the increasing use of greater numbers of medications by the American public has raised the importance of this problem. In addition, the American public has also been increasingly using herbal medications and combinations of minerals, vitamins, and natural products, many of which can cause liver injury. At the same time, there are few insights into why medications damage the liver and why hundreds or thousands of people can take a medication safely, while a rare individual gets serious liver disease. Finally, drug-induced liver disease is challenging to the physician, has many diverse manifestations, and diagnosis is often delayed or missed. For all these reasons, new approaches are needed to broaden the understanding of drug-induced liver injury and how to prevent or manage it properly.

Objectives:

- Develop reliable animal models or laboratory systems to study different forms of drug-induced liver injury. (Chapter 8: A3a, B3b)
- Elucidate the genetic basis of drug- and toxicant-induced liver injury. (Chapter 8: C1)
- Develop standardized methods to accurately diagnose drug-induced liver toxicity. (Chapter 8: A1)
- Develop predictive tests for risk of drug-induced liver injury that may allow for prevention of serious liver disease. (Chapter 8: C2b, C3)
- Develop effective means of treating drug-induced liver injury. (Chapter 8: C2a)

AUTOIMMUNE LIVER DISEASES (*ACTION PLAN* CHAPTER 9)

Recent Research Advance

Animal models of autoimmune liver diseases. Rapid research progress in autoimmune liver diseases has been significantly hindered by the absence of animal models. In the last year, three promising models for primary biliary cirrhosis (PBC) have been described, including the *Nod.c3c4* congenic mouse, the TGF-β receptor II dominant-negative mouse, and an IL-2 receptor α knock-out (-/-) mouse. Each of these mouse models develops liver disease and anti-mitochondrial antibody reactivity with specificity for PDC-E2, typical of the human autoantibody. Further work in the *Mdr2* knock-out (-/-) mouse model for primary sclerosing cholangitis (PSC) indicates that side-chain modification of ursodiol yields a bile acid with greater therapeutic activity against PSC than standard ursodiol. These and additional models under development will provide new opportunities for research into disease mechanisms that cannot be accomplished in human research.

Research Goal 11.11: Determine the etiology, pathogenesis, and potential new targets for therapy of the three major forms of autoimmune liver disease: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC).

The three major forms of autoimmune liver disease—AIH, PBC, and PSC—are distinctly different forms of liver diseases that are characterized by inflammatory destruction of hepatocytes or the biliary system and clinical features of autoimmunity. While uncommon, all are important causes of chronic liver disease that may progress to cirrhosis, liver failure, need for transplantation, or liver or biliary cancer. Current approaches to medical management are not curative and are sometimes completely ineffective. AIH has many common features of prototypic autoimmune diseases, including female predominance, typical autoantibodies, and responsiveness to corticosteroids and immunosuppressive therapies. PBC also has female predominance, typical autoantibodies, and seems to be unresponsive to standard anti-inflammatory or immunosuppressive regimens, but does respond to treatment with ursodiol. In contrast, PSC has

male predominance, is commonly associated with inflammatory bowel diseases (IBD), and is refractory to all forms of conventional therapy, including treatment of associated IBD. Syndromes of AIH and PSC may occur in early childhood, but have features that distinguish them from their adult counterparts with the same names. Many hurdles have impeded research progress in these diseases, including among others their slow, indolent clinical course, low prevalence, absence of animal models, and the great difficulty of conducting immunopathogenesis studies in human liver.

Objectives:

- Develop robust animal models to study mechanisms of liver injury associated with autoimmunity and conduct preclinical studies of novel treatments. (Chapter 9: B3b)
- Define the genetic risk alleles for each of the three major forms of autoimmune liver disease, followed by identification of physiologic pathways associated with these alleles that may contribute to understanding the pathogenesis or reveal new opportunities for therapy. (Chapter 9: B3a)
- Identify novel biomarkers and define surrogate endpoints to assist in diagnosis, assess disease activity, or predict natural history or response to different treatments. (Chapter 9: C2)
- Conduct natural history studies in childhood onset autoimmune liver diseases to refine phenotype definitions, identify genetic risk alleles, and search for potential environmental triggers. (Chapter 9: A2)

PEDIATRIC LIVER DISEASES (*ACTION PLAN* CHAPTER 10)

Recent Research Advances

Molecular basis of Alagille syndrome. Using a variety of molecular approaches, Jagged1 (*JAG1*) mutations can be identified in 94 percent of children with Alagille syndrome, and a proportion of the remaining children have mutations in the gene encoding NOTCH2, the receptor for Jagged1.

Genetic basis of diseases causing intrahepatic cholestasis in children. Studies of a number of cholestatic diseases of children have led to the identification of genetic defects in bile synthesis, formation, and secretion and in development of the biliary tree. These discoveries have also led to the development of new murine models that provide new research opportunities.

Research Goal 11.12: Determine the molecular and genetic pathways responsible for the major forms of inherited and early-onset, severe liver diseases of childhood, including biliary atresia, neonatal hepatitis, progressive familial intrahepatic cholestasis, Alagille syndrome, alpha-1-antitrypsin deficiency, neonatal hemochromatosis, and mitochondrial hepatopathies in order to devise potential new targets for therapy.

A number of liver diseases of early childhood, listed above, are often severe and lead to progressive liver failure and need for transplantation. While all of these diseases are rare, the most common—biliary atresia—is also probably the least understood. A surgical procedure, the Kasai procedure, may ameliorate the disease when performed early in life, but the majority of patients continue to have progressive liver failure, ultimately requiring transplantation. While the genetic basis is known for some of the other forms of familial diseases, current knowledge of the genes and their molecular pathways has yet to be translated into therapies for these diseases, and liver transplantation remains the only form of therapy for many patients.

Objectives:

- Define the etiology and pathogenesis of biliary atresia and identify new pathways for development of potential therapies. (Chapter 10: C3a)

- Optimize current approaches to medical and surgical therapy of biliary atresia. (Chapter 10: C1a)
- For familial childhood liver diseases, determine their genetic basis, including primary alleles and modifying alleles, which will permit development of standardized genetic tests and identification of potential pathways for development of translational therapies. (Chapter 10: A1b, B2a, C2)

Research Goal 11.13: Evaluate and improve existing adult medical and surgical therapies for treatment of children with liver diseases.

In addition to familial and congenital diseases of children that often have a severe course and present early in life, children may also be affected by diseases that are found in adults, including viral hepatitis, NASH, drug-induced liver disease, fulminant hepatitis, autoimmune liver diseases, and other genetic diseases, such as Wilson disease. While medical therapies may exist for some of these conditions, such as viral hepatitis, typically they have not been carefully validated and optimized for treatment of children. Furthermore, while liver transplantation is often successful and may be life-saving for end-stage liver diseases in children, long-term outcomes, including effects of transplantation regimens on growth, development, and cognitive function, are unknown.

Objectives:

- Conduct clinical studies to validate use of medical regimens and liver transplantation for treatment of liver diseases in children. (Chapter 10: B1b)
- Identify biomarkers and surrogate markers for assessment of children with chronic liver diseases. (Chapter 10: A1a, B3)

GENETIC LIVER DISEASES (*ACTION PLAN* CHAPTER 11)

Recent Research Advance

Unraveling the pathogenesis of hemochromatosis and iron metabolism. In the past decade, numerous research discoveries have elucidated the pathogenesis of hereditary hemochromatosis and the pathways of iron metabolism that are altered in this disease. In 1996, mutations in the *HFE* gene were shown to account for the majority of cases of hemochromatosis, which was recapitulated in murine models having deletions of this gene. Subsequently, additional proteins regulating iron metabolism were identified, and their roles in the disease were elucidated, including divalent metal transporter 1, transferrin receptor-2, hephaestin, hemojuvelin, ferroportin-1, and most recently hepcidin—a protein produced by hepatocytes that is the key regulator of iron absorption in the gut. Commercial testing for hemochromatosis is now available, and further advances in this field are likely to fully elucidate the molecular mechanisms responsible for this disease and its various manifestations.

Research Goal 11.14: Elucidate the molecular pathways responsible for hereditary forms of liver disease, including hereditary hemochromatosis, Wilson disease, the porphyrias, cystic fibrosis, polycystic liver disease, and congenital hepatic fibrosis; use knowledge of these pathways to devise novel approaches to treatment.

Hereditary hemochromatosis is the most common inherited liver disease in Caucasians, affecting approximately 1 in 200 individuals. In this disease, excess iron absorption leads to serious damage to multiple organs, including the liver, heart, pancreas, and other organs, and liver cancer. Early diagnosis and treatment with phlebotomy prevents all of the complications of this disease. Wilson disease is an uncommon cause of liver disease

due to abnormalities of copper transport and, like hemochromatosis, early recognition and treatment of the disease can prevent complications. There are five main forms of porphyria that can affect the liver, and these rare diseases can cause severe, disabling disease. Some, but not all, forms have treatments of varying efficacy. With longer survival of cystic fibrosis patients, liver disease is emerging as an important long-term complication that can lead to liver failure. Severe polycystic liver disease is an autosomal dominant condition that can lead to liver failure and is caused by genes distinct from those causing polycystic kidney disease. Collectively, for many of these diseases there has been rapid progress in identifying the molecular mechanisms responsible; however, progress has been variable in development of clinical genetic testing and development of novel, effective therapies.

Objectives:

- For each of the genetic liver diseases, define the primary genes and modifying genes and their molecular pathways that lead to disease. (Chapter 11: A1a, A3, B2a, B3, C2a)
- Accelerate translational research to identify new target pathways for treatment, including development of animal models for preclinical testing. (Chapter 11: C2b)
- For diseases having no target for drug treatment or alternative approaches to treatment, develop approaches to gene therapy to correct the underlying defect. (Chapter 11: C3b)
- Develop clinically applicable noninvasive tests to accurately measure metabolic consequences of these diseases, such as iron or copper overload. (Chapter 11: C1, C3a; Chapter 16: C1b)

LIVER TRANSPLANTATION (*ACTION PLAN* CHAPTER 12)

Recent Research Advance

Benefits and risks of living donor liver transplantation. More than 2,000 adult-to-adult living donor liver transplants (LDLT) have been performed in the U.S., yet the potential benefit to liver transplant candidates of undergoing LDLT compared to waiting for deceased donor liver transplant (DDLT) until recently was unknown. A recent large cohort study demonstrated that LDLT was associated with lower mortality than the alternative of waiting for DDLT, although this reduction in mortality of the recipient must be balanced against risks to the living donors.

Research Goal 11.15: Refine current procedures in liver transplantation, including assessment of potential transplant recipients, immunosuppressive regimens, and management of donors and recipients for living donor transplantation, and improve management of recurrent liver diseases in transplanted patients.

Liver transplantation is the standard of care for patients with end-stage liver disease or acute liver failure. The most common procedure used is deceased donor orthotopic liver transplantation, but living donor transplantation is available, particularly for children and to a lesser extent for adult transplantation. The major reason for transplantation is end-stage liver disease from any cause; other indications include acute liver failure, liver cancer, and, rarely, metabolic diseases that can be corrected with transplantation. Despite significant and continuing improvements in liver transplantation with respect to organ procurement and distribution, surgical techniques, and medical management of the transplant patient since the 1960s, a number of challenges remain in this field. Among the problems are the continuing shortage of donor organs, premature death of transplant recipients due to complications of procedures or immunosuppression, and recurrence of underlying liver disease after transplant, such as viral hepatitis or cancer. Ultimately, improvements in preventing the progression of the multiple different forms of chronic liver diseases to end-stage liver disease offers the best solution to the problems of

transplantation, but for the foreseeable future liver transplantation will continue to be an essential form of therapy that requires further improvements through research.

Objectives:

- Further refine the Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) systems to optimize allocation of livers for transplantation. (Chapter 12: A1)
- Identify biomarkers for adequate immunosuppression, active rejection, and immune tolerance. (Chapter 12: A2, C2b)
- Develop approaches to improve long-term tolerance for allografts in order to minimize the need for immunosuppressive drugs. (Chapter 12: C2a, C1a)
- Improve treatment for recurrence of underlying liver diseases, such as viral hepatitis, in transplant recipients. (Chapter 12: B2b, C3a)

COMPLICATIONS OF LIVER DISEASE (*ACTION PLAN* CHAPTER 13)

Recent Research Advance

Pathophysiology of portal hypertension. Patients with cirrhosis have a hyperdynamic state in the splanchnic bed that is caused, at least in part, by nitric oxide (NO). Vasodilation induced by NO may be mediated by vascular endothelial growth factor (VEGF). In the liver, the vasodilator response to NO is blunted, which in a rat model appears to be due to up-regulation of endothelial phosphodiesterase-5, the enzyme responsible for degrading NO. Therefore, both phosphodiesterase-5 and VEGF may be targets for therapy of portal hypertension.

Research Goal 11.16: Identify ways to prevent or ameliorate the complications of portal hypertension and cirrhosis.

The majority of patients who die of cirrhosis ultimately succumb to complications of portal hypertension, which include variceal hemorrhage, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, and hepatorenal and hepatopulmonary syndromes. Currently available techniques to diagnose and treat these complications have significant limitations and often do not significantly prolong life or eliminate the need for liver transplantation. In addition, patients with advanced liver disease may suffer from intractable fatigue and pruritus.

Objectives:

- Define in detail the pathophysiologic mechanisms that cause portal hypertension. (Chapter 13: A3a)
- Identify small molecular targets for interventions to reduce portal hypertension. (Chapter 13: B3a)
- Develop reliable, non- or minimally invasive methods to measure portal pressure and screen for esophageal varices. (Chapter 13: B3b, C3b)
- Better characterize the cause of increased susceptibility to bacterial infections in cirrhosis, particularly SBP, and determine how to manage these infections. (Chapter 13: A3b, B1)

Research Goal 11.17: Develop better means of prevention, management, and treatment of acute liver failure.

Acute liver failure is defined as the sudden onset of severe liver injury with signs of hepatic failure in a person without previous liver disease. Acute liver failure accounts for up to 2,000 deaths each year in the U.S. and typically strikes previously healthy individuals, including children and adolescents. The major cause of acute liver failure in the U.S. today is drug-induced liver injury, either due to acetaminophen or to idiosyncratic injury due to a medication or herbal preparation. Other causes include hepatitis A and B and autoimmune liver diseases. Strikingly, at least half of acute liver

failure in children and approximately one-quarter of cases in adults are due to unknown causes (idiopathic). While viruses are suspected to be the cause of idiopathic acute liver failure, the actual cause has so far eluded research investigation. Nevertheless, acute liver injury results in death or need for liver transplantation in approximately three-quarters of patients, and there are currently no therapies or means of temporary support for this dire complication of acute liver disease.

Objectives:

- Identify the cause(s) of idiopathic acute liver failure. (Chapter 10: A3)
- Develop biomarkers that more accurately reflect hepatic regeneration and reserve in acute liver failure. (Chapter 13: C2a)
- Develop non-specific, hepatoprotective therapies that improve survival or allow time for liver transplantation in acute liver failure. (Chapter 13: A1b, B2a)
- Develop and evaluate bioartificial liver support devices that improve survival in acute liver failure or allow for temporary support until a liver becomes available for transplantation. (Chapter 13: C3a)

LIVER AND BILIARY CANCER (*ACTION PLAN* CHAPTERS 14 AND 15)

Recent Research Advances

Genetic profiling of hepatocellular carcinoma (HCC). An important research advance in HCC has been the description of the molecular signatures of this form of cancer. Although in an early stage, these discoveries have diagnostic, prognostic, and therapeutic implications, in that they may eventually permit identification of new targets for therapy and stratification of patients based on their type of cancer and individualized therapies. More research is needed to fully realize the value of this advance.

Animal models of cholangiocarcinoma. Advances in diagnosis and treatment of the form of human biliary cancer known as cholangiocarcinoma have been hampered by the absence of animal models for detailed studies that are not possible in humans. Three animal models for cholangiocarcinoma have now been described that should help advance the science and therapy of this disease.

Research Goal 11.18: Develop effective strategies for early detection and treatment of hepatocellular carcinoma and cholangiocarcinoma in high-risk groups.

Malignant diseases of the liver and biliary tree can be either primary or secondary to other forms of cancer that metastasize to the liver. Primary liver cancers include the most common form, HCC, and others, including cholangiocarcinoma, hepatoblastoma, fibrolamellar carcinoma, angiosarcoma, and other rare forms. Most cases of HCC arise in the setting of other chronic liver diseases and cirrhosis; thus, patients at risk include those with many common forms of chronic liver disease, such as viral hepatitis, alcoholic and non-alcoholic fatty liver disease, and essentially any other cause of chronic liver injury. HCC is a highly lethal disease, and current diagnostic and medical treatments have limited efficacy. Liver transplantation is an option for cases having early diagnosis. Other forms of liver cancer, notably cholangiocarcinoma, have other distinctly different risk factors and clinical behaviors and, most notably, this form of cancer is a complication of long-standing primary sclerosing cholangitis.

Objectives:

- Identify new biomarkers for early detection of primary liver cancers, particularly HCC and cholangiocarcinoma. (Chapter 14: A2a; Chapter 15 C2b)

- Develop new imaging techniques that detect primary liver and biliary cancers in the setting of underlying chronic liver disease. (Chapter 14: A3; Chapter 15, A3; Chapter 16, C1b)
- Identify the cellular and molecular pathways leading to primary liver cancer in order to identify potential new targets for therapy. (Chapter 14: A2b, C2, C3)
- Identify strategies to prevent HCC and cholangiocarcinoma in high-risk populations. (Chapter 14: C1; Chapter 15: C1)

GALLBLADDER AND BILIARY DISEASE (*ACTION PLAN* CHAPTER 15)

Recent Research Advances

New approaches to prevent cholesterol gallstones. Human trials on prevention of gallstones have not yet been initiated, but several studies in animal models have suggested potential novel approaches. Fibroblast growth factor (FGF)-15, which is produced in the ileum in response to bile acid signaling through FXR, plays an important role in gallbladder filling. Lack of gallbladder filling may predispose to gallstones, which perhaps explains the link between diseases of the terminal ileum and gallstone formation. Furthermore, agonists of FGF-19 (the human homologue to mouse FGF-15) might play a role in prevention of gallstones. In another study in mice, targeted deletion of *Gpbar1*, a gene involved in regulation of cholesterol secretion, led to resistance to gallstone formation in response to a high-fat diet. Thus, inhibitors of this cell-surface receptor for bile acids may be a means of decreasing the likelihood of gallstones.

Genetic risk for gallstone disease. Researchers have identified variations in the gene encoding hepatic cholesterol transporter ABCG5/G8 that are associated with gallstone disease in human patients. Finding ways to modulate this transporter could lead to important new therapies to prevent or treat the formation of gallstones.

Research Goal 11.19: Develop better means to prevent and treat gallstones.

There are multiple diseases of the gallbladder and biliary tree, including gallstones, acute cholecystitis, acalculous cholecystitis, primary sclerosing cholangitis, biliary atresia, choledochal cysts, gallbladder cancer, and cholangiocarcinoma. However, gallstone disease is by far the most common of these conditions, affecting about 12 percent of the adult U.S. population. Gallstone disease leads to approximately 700,000 cholecystectomies per year and is one of the most costly digestive diseases for the healthcare system.

Objectives:

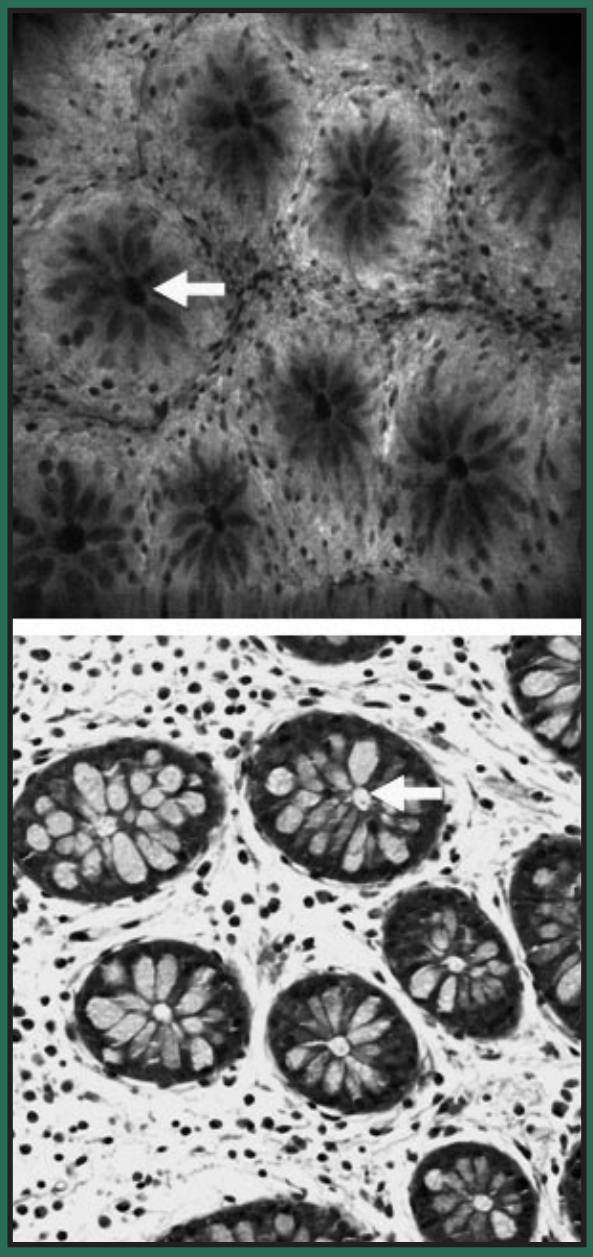
- Determine the genetic basis for increased risk and protection from gallstone disease. (Chapter 15: A1, C2a)
- Better define the pathophysiologic basis of gallstone formation, including the role of bacterial factors. (Chapter 15: B2)
- Identify biomarkers for gallstone formation. (Chapter 15: B3)
- Design approaches to prevent gallstone formation in high-risk groups. (Chapter 15: C3)

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Basic mechanisms of liver diseases: The mechanisms that trigger damage to the liver are partially known. Development of multidisciplinary and interdisciplinary collaborations between investigators interested in liver diseases and basic scientists in areas such as immunology, genetics, virology, oncology, molecular and cell biology, and other disciplines would be greatly facilitated by creating the necessary resources for collaborative studies, such as gene, liver, and serum repositories of samples from well-defined patients.

Translational research: The absence of robust animal models for many liver diseases has greatly hampered progress in understanding these diseases or preclinical testing of novel therapies. Identification of new models may allow for more rapid progress, and further studies of animal models are needed. Findings from these models need to be rapidly applied to clinical research.

Clinical research: Clinical research in liver diseases is hampered by limitations of standard criteria for case definition, need for and lack of precision in disease assessment by liver biopsy, absence of biomarkers and surrogate markers that are particularly needed for indolent diseases, and absence of a pipeline of potential new therapeutic interventions that might emerge from basic and translational research. When new approaches to treatment become available, clinical trials will often require a substantial number of research centers because of low disease prevalence. In partnership with the U.S. Food and Drug Administration, best practices for clinical trial design could be developed, along with the formation of public-private partnerships with the pharmaceutical industry to generate interest in drug development for uncommon liver and biliary diseases.



Endomicroscopy (upper) and histologic section (lower) of normal human colon crypts. New imaging technologies, such as confocal endomicroscopy, can enable more accurate diagnosis and monitoring of digestive diseases, such as colorectal cancer in high-risk patients.

Image courtesy of Dr. Ralf Kiesslich. Reprinted from Gastroenterology, *132, Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis, pp. 874-882, Copyright 2007, with permission from Elsevier.*

Bioengineering, Biotechnology, and Imaging

SUMMARY OF RESEARCH GOALS

The luminal structure of the gastrointestinal (GI) tract and the inherent regenerative capacities of many cell types within the organs of the digestive system afford significant opportunities for the development of innovative technologies and approaches to the diagnosis and treatment of digestive diseases. The Commission recommends several research goals that are intended to capitalize on emerging technologies and facilitate medical and surgical care of digestive disease patients. Ready access to much of the digestive tract is permitted by endoscopic or minimal access approaches for biopsy or resection of tissue. Research is needed to evaluate the risks and benefits of such procedures compared to conventional surgical techniques. Advances in stem cell biology and regenerative medicine could be applied to foster the repair and regeneration of diseased tissue within the digestive system. Innovative scaffolds to guide the growth of complex digestive organ structures will need to be developed in order to realize the potential of promising tissue engineering approaches. The development of advanced imaging technologies and interactive simulators that allow surgeons to plan and practice procedures using patient-specific images would reduce the risk of trauma to healthy tissue during treatment. Collectively, these research goals will lead to innovative technologies that have the potential to significantly improve patient outcomes and enhance treatment efficacy for many digestive diseases.

INTRODUCTION AND BACKGROUND

Detection, diagnosis, and treatment of digestive diseases present both challenges and opportunities for technology development given the diverse anatomy of the digestive organs. Procedural techniques and imaging strategies must be designed for both luminal and solid organs. Advances in technology require scientific collaboration among multiple clinical and scientific disciplines, including gastroenterology, surgery, radiology, engineering, mathematics, physics, computational science, and others.

Luminal structures: The most common disorders of the GI tract develop from the cells that line the intestinal lumen—the mucosa. This is the site of origin of GI cancers, benign ulcers, and a variety of inflammatory disorders that occur in all age groups. While the foregut (esophagus, stomach, and duodenum) and colorectum are readily accessible to endoscopic evaluation, the small bowel remains a vast organ that is largely inaccessible to repeat endoscopic evaluation and treatment of the luminal surface. The luminal surfaces of the colon, rectum, and foregut can be visualized, allowing abnormalities to be biopsied, ablated, or resected using endoscopic approaches or provide needed data to plan surgical procedures. New technologies for imaging the intestinal lumen have yielded improved diagnostic capability, although their therapeutic applications remain limited. CT and MRI imaging techniques have improved to evaluate structural disorders of the intestinal wall and peritoneal cavity, allowing the use of minimal access surgical technologies in lieu of conventional operative procedures.

Solid organ structures: The liver, biliary system, and pancreas remain common sites of malignant and inflammatory disorders. Enhanced application and utilization of CT, MRI, and PET imaging modalities have improved the ability to make accurate structural assessments of tumors and inflammatory processes in these organs. Endoscopic access to the pancreatic and biliary systems is now routine, allowing more accurate diagnosis and therapeutic options for patients with benign ductal disorders or with malignant conditions. Three-dimensional reconstructive imaging has improved pre-operative procedural planning to predict residual hepatic volume after resection and to more accurately stage patients with malignant tumors. Multimodality imaging of the liver, including real-time ultrasonography, has facilitated the application of ablation technologies for selective treatment of tumors in some patients. Increasing knowledge of the molecular characteristics of tumors metastatic to liver disease, such as gastrointestinal stromal tumors (GIST) and neuroendocrine tumors, enables assessment of the efficacy of chemotherapeutic agents, including imatinib or octreotide, in the management of these patients.

Imaging: Advances in imaging technology are revolutionizing the noninvasive detection of digestive diseases. Improvements in CT technology have enabled the delivery of high-resolution images for three-dimensional reconstructive imaging that mimics endoscopic observations. Emerging technologies—fusion of ultrasound and CT imaging, for example—allow precise, real-time interventions and improved procedural planning. New contrast agents and agents that reflect metabolic activity of tissues, such as PET imaging, have improved the ability to detect otherwise occult lesions in solid organs or in the peritoneal cavity.

Emerging technologies: Advances in device development have led to remarkable new tools for manipulating the GI tract and peritoneal

structures. Based on the evolution of these manipulable devices from a remote operating platform, new procedures such as natural orifice transluminal endoscopic surgery (NOTES) are being implemented in the clinic. Clinical trials are in progress to introduce an operating endoscope via the mouth for passage through the stomach wall into the abdominal cavity to remove or repair an organ. Both trans-vaginal and trans-gastric cholecystectomies (removal of the gallbladder) have been reported. Linking robotic surgical devices, whereby a surgeon manipulates fine instruments in a patient from a console with high-definition three-dimensional imaging, is increasingly applied to surgical procedures of the abdomen, with the result that surgeries can be performed with more precise and miniaturized instruments to reduce trauma to healthy tissue.

Tissue engineering/regenerative medicine: The field of tissue engineering and regenerative medicine has just begun to be explored in the GI luminal and solid organs with the goal of reconstructing functionally and structurally normal tissues. The identification of the intestinal stem cell niche provides a vital first component to this work, as this cell type will be a progenitor for growth of a new mucosal structure to replace a damaged small intestine. Similarly, the development of appropriate scaffolds on which to grow new liver cells, pancreas cells, and intestinal tissue will be necessary to create replacement organs for those patients with hepatic, pancreatic, or intestinal failure. The structural diversity and complexity of the digestive tract pose a significant challenge for the development of regenerative therapies for digestive diseases.

Simulation training: Preparing the GI endoscopy and surgical workforce for the future requires sophisticated educational platforms. The development of simulators capable of mimicking highly complex GI procedures to allow physicians and surgeons to gain needed practice and expertise before proceeding to patient procedures will foster improved patient safety and quality of care in rapidly changing new technologies. Recent advances in computational science and haptic technology have allowed the initial delivery of simulators with high-fidelity to create virtual environments for these educational purposes. As the pace of technological innovation in procedural technologies is rapid, simulators that keep pace with this change to maintain the skill sets of the gastroenterology and surgical workforce will need to be developed. Advances in technology will also enable the combination of pre-procedural, patient-specific simulation, so that a surgical team can plan and practice the procedure using images of patient-specific anatomy. It is conceivable that simulators will also be used as part of privileging programs to assess procedural competency of gastroenterologists and surgeons.

RECENT RESEARCH ADVANCES

Image-enhanced endoscopy

Advances in optical imaging have greatly expanded the sensitivity and specificity of endoscopic observations. High magnification chromoendoscopy, confocal microscopy, autofluorescence imaging, narrow band imaging, and optical coherence tomography have enhanced the ability to detect areas of mucosal abnormalities, including pre-malignant changes of dysplasia and early cancers. These technologies have allowed enhanced detection of areas of flat and depressed colorectal neoplasia, enhanced identification of Barrett's epithelium with dysplasia, and identification of dysplastic mucosa in the stomach.

Technological advances have allowed endoscopic procedures to replace more invasive surgical procedures in several complex areas of GI disease. Improved design, materials, and delivery tools for endoluminal stents have provided improved palliation for malignant strictures, refractory fistulas, and complex post-operative surgical disorders with lesser morbidity than conventional surgical approaches.

The development of operating endoscopes with multiple ports to allow improved endoscopic techniques, including suturing, injection, and manipulable instruments, has facilitated endoscopic treatment of luminal conditions that once required surgical approaches.

Effective technologies for mucosal ablation

For those areas of the GI tract amenable to endoscopic reach, a variety of ablation tools have been developed to treat benign and malignant conditions. For patients with pre-malignant disorders of the foregut and colorectum (including Barrett's esophagus and others) and those with more advanced neoplasms who are otherwise not candidates for major surgical procedures, a variety of ablation technologies, such as photodynamic therapy, radiofrequency ablation, and sclerosing agents, now offer new treatment options. For patients with GI bleeding disorders or lesions, enhanced devices and agents to treat these lesions via the endoscope have been developed, sparing patients considerable morbidity associated with major surgical procedures.

New technologies to detect colorectal neoplasia have been developed. While screening colonoscopy of the prepared colon remains the gold standard, significant advances in detection of pre-malignant and adenocarcinoma of the colon have been developed, such as the use of CT colonography (virtual colonography, colonoscopy), video capsule endoscopy, quantitative immunochemical fecal occult blood testing, and fecal DNA analysis.

Development of the endoscopic ultrasound (EUS) probe

The development of an ultrasound probe capable of being passed into the GI tract with the endoscope has made possible the examination of the mucosa, bowel wall, and adjacent organs with enhanced specificity. The ultrasound probe has revolutionized the evaluation of periampullary lesions, allowing more accurate identification and definition of pancreatic and distal biliary masses, more precise tissue sampling with fine needle aspiration biopsy, and improved staging of malignancy for pre-operative evaluation. Submucosal and mural lesions of the GI tract from the esophagus through the first portion of the duodenum—regions that were previously occult to conventional imaging and endoscopy—are readily evaluated by EUS. Intrarectal ultrasound has standardized staging of rectal cancers, allowing appropriate application of neoadjuvant strategies for patients with rectal cancer and identifying those patients amenable to local resection.

Evaluation of the small bowel lumen

The introduction of the video capsule endoscope has revolutionized imaging of the small bowel mucosa. This once hidden luminal structure is now readily evaluated for many common disorders, including Crohn's disease, idiopathic inflammatory diseases of the small bowel, and malignancy. Occult bleeding from the small bowel may be identified, addressing a long-standing, unresolved clinical dilemma prior to this technology.

Combined modality imaging and molecular imaging

Recent studies have established that FDG-PET allows identification of peritoneal and lymph node metastases for colorectal and other GI cancers. The use of specific, targeted molecular agents to silence metabolic activity of tumors has been particularly valuable in conjunction

with FDG-PET as the tracking modality. Patients with imatinib-sensitive GIST tumors or octreotide-sensitive neuroendocrine tumors exhibit molecular silencing on FDG-PET scanning, which provides a valuable marker of efficacy of these agents.

Tissue engineering/regenerative medicine (TE/RM) in the GI tract

The regenerating intestinal epithelium with its inherent stem cell population offers unique opportunities for TE/RM efforts. The most significant progress of TE/RM research in the GI tract has been in the creation of functional liver tissue. Significant advances have been made in the ability to isolate functional hepatocytes and maintain their phenotype and functionality *in vitro*; the ability to isolate biologic scaffolds that support functional hepatocytes; and in understanding the appropriate growth factors and cytokines needed to maintain hepatic growth *in vitro*.

GOALS FOR RESEARCH[18]

Research Goal 12.1: Define the optimal procedural approach for patients with digestive disorders amenable to endoscopic, image-guided, or minimal access surgery.

Innovations in minimally invasive surgery offer several potential advantages over traditional surgical techniques or endoscopic procedures. Rigorous evaluation of these new procedures is needed to determine their cost-effectiveness and efficacy in improving patient outcomes.

Objectives:

- Evaluate efficacy and outcome measures, including quality-of-life, for innovative surgical technologies.
- Perform a cost analysis of new surgical methods compared to traditional procedures.
- Conduct rigorous studies of physiologic and immunologic response to minimal access surgery to determine whether biologic advantage exists for these procedures.

Research Goal 12.2: Develop innovative technology for the diagnosis and treatment of luminal disease.

In addition to surveillance and detection of disease, endoscopic techniques are used to biopsy or resect diseased tissue. Endoscopic improvements would further reduce the risks of the procedure and augment the therapeutic applications of the technology.

Objectives:

- Develop and validate a method to perform "molecular" biopsy of luminal abnormalities in real time.
- Develop improved instrumentation for therapeutic endoscopy.
- Develop improved virtual endoscopy technology to access the luminal space of the GI tract.

Research Goal 12.3: Use tissue engineering and regenerative medicine approaches to develop innovative treatments for digestive diseases.

[18] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

Advances in stem cell biology provide an opportunity to transform the treatment of digestive diseases. The stem cell population that supports ongoing regeneration of the intestinal epithelium can be harnessed to regenerate tissues of the GI tract. To reach this goal, better understanding of the stem cell niche and development of biologically compatible scaffolds that can direct the growth of the complex structure of the GI tract are needed. The esophagus, in particular, would benefit from regenerative approaches, as there are limited surgical options for repair of this organ. The small intestine represents another prime target for stem cell-based approaches to the treatment of short bowel syndrome, inflammatory bowel diseases, and other conditions.

Objectives:

- Identify and isolate local stem cell populations in the GI tract for tissue engineering applications.
- Develop scaffolds, both naturally occurring and synthetic, to support growth and differentiation of cell populations indigenous to the GI tract.
- Develop tissue engineering and regenerative medicine methods to treat diseases of the digestive organs.

Research Goal 12.4: Expand the application and integration of imaging and procedural technologies to deliver targeted interventions with minimal tissue injury to patients with digestive disorders.

Image-guided therapeutics can accurately and specifically deliver treatments to diseased tissue and minimize damage to surrounding healthy tissue. Novel agents to visualize markers of disease must be tested and validated in human patients. New devices that facilitate noninvasive imaging and manipulation of tissues could minimize trauma to the patient and improve therapeutic efficacy.

Objectives:

- Develop new PET tracers for clinical use, including markers of proliferation, tumor-specific antigens, and markers of apoptosis and inflammation.
- Develop intraoperative high-energy gamma and beta detectors to enhance intraoperative localization.
- Develop energy delivery and real-time tracking devices to optimize local image-guided interventions.
- Develop improved devices for facilitating single port laparoscopic procedures, intraluminal procedures, and natural orifice surgeries.

Research Goal 12.5: Develop high-fidelity interactive simulators of the digestive system.

Advances in computer simulation provide an opportunity to transform technical and cognitive training in GI endoscopy and surgery. Virtual environments can be used for training, prior to initiation of patient procedures. Simulators could facilitate the acquisition of new procedural skills by physicians who have completed training and also could be used for certification and testing to ensure procedural quality.

Objectives:

- Define the optimal use of simulation in training the procedural workforce, including metrics, transference, competency assessment, and acquisition of new technologies.
- Define the value of simulation in developing new procedures to facilitate procedural design and the prediction of outcomes.
- Develop high-fidelity simulators to allow multimodality procedural rehearsal.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Translational and clinical research: A critical challenge for the field is finding ways to attract and support translational clinicians—physicians who interact with patients and can bridge the basic science questions and technologies. Training of new investigators in the area of technology feasibility and assessment could also be encouraged. In addition, enhanced support for randomized clinical trials, including studies of advanced endoscopic and other technologies, would accelerate the validation of new, state-of-the-art procedures. Increased inclusion of endoscopists and surgeons on study sections is critical for ensuring appropriate review of proposals for testing new technologies.

Academia-industry collaboration: Small technology companies working to develop imaging or intraprocedural guidance technology often do not have sufficient capitalization, and value is based primarily on a small amount of academically based intellectual property. Finding ways to foster collaboration between academia and small industry would encourage development and testing of new devices and technologies arising from translational research. Management of conflict-of-interest and intellectual property issues are key matters to address.

Regenerative medicine: The GI tract lags behind other tissues in terms of tissue engineering/regenerative medicine research. Fostering research on this topic and translation of results into clinical trials would accelerate progress in the field.

Fostering research teams: A multicenter consortium for the evaluation and treatment of luminal disease could be established. Such collaboration among expert users of advanced or novel technologies would enhance the design and execution of randomized, controlled trials in human patients. Further, the development of multidisciplinary centers for technology design, development, and testing would promote scientific investigation among relevant areas of expertise that include GI medicine and surgery, engineering, imaging, chemistry, computer science, and others. Inclusion of scientific expertise that is traditionally considered to be outside of the biomedical sciences would promote rapid progress in the field. Finally, creation of a patient registry would encourage collaboration and sharing of resources. These challenges could be addressed by a workshop to convene investigators for an early assessment of promising new technologies and to identify key questions and studies for implementation in the near future.

Conclusion: Common Themes and Steps for Implementation

PRESSING NEED FOR A SUBSTANTIAL RESEARCH EFFORT IN DIGESTIVE DISEASES

Disorders of the digestive system affect the majority of the U.S. population at some time throughout life. These disorders include a large spectrum of diseases, ranging from acute, foodborne infections to chronic, debilitating diseases, such as inflammatory bowel diseases, and life-threatening conditions, such as cancer and liver failure. Some conditions, such as heartburn and constipation, are so prevalent that many may not view them as disease entities, while a large number of conditions are serious, relatively rare, and often below the radar screen of public attention.

Many decades of NIH-funded research in digestive diseases have led to a detailed understanding of the digestive system, the causes of many diseases, and improved treatments that are now the standard of care. Among the many stories of success are the discovery of *H. pylori* as a major cause of ulcer disease; development of highly effective acid-blocking drugs as treatments for ulcer and heartburn; discovery of the multiple forms of viral hepatitis and development of curative treatments and preventive programs; development of biologic therapies for inflammatory bowel diseases (IBD); and implementation of effective screening programs to prevent colorectal cancer. Dramatic technological innovations in noninvasive imaging and testing, endoscopic procedures, and minimally invasive surgery now permit rapid and accurate diagnosis and treatment of many of the most common, serious problems involving the digestive system that confront healthcare providers on a daily basis, including GI bleeding, abdominal pain, jaundice, and diarrhea. Despite these advances, many of the current solutions for these problems remain imperfect and costly. In addition, progress on other diseases has occurred at a much slower rate, including the highly prevalent functional GI disorders, many forms of cancer of the digestive system, and pancreatitis. Acute enteric infections remain an important cause of morbidity and mortality, particularly in children in underdeveloped countries. Other conditions associated with the rising prevalence of obesity, such as non-alcoholic steatohepatitis, are likely to increase the burden of digestive diseases in the U.S. The Director of the NIH, recognizing both the great burden of digestive diseases in the U.S. and the great diversity and complexity of basic, translational, and clinical research approaches that could be brought to bear on the problem, chartered the National Commission on Digestive Diseases to make recommendations to the NIH for future research on digestive diseases, which are described in this long-range research plan.

COMMON THEMES

Although the Commission's research plan contains a large number of goals and specific objectives, common themes transcend many of these recommendations. These themes include: (1) a focus on major scientific disciplines that are the engine for creating new knowledge; (2) approaches to the organization of research efforts, such as multidisciplinary basic or clinical research teams and networks, that are required for effective translation of laboratory findings for the benefit of patients with digestive

diseases; (3) the development of important research resources that provide infrastructure necessary for modern scientific discovery; and (4) efforts that must be undertaken to ensure the availability of a highly specialized workforce to conduct digestive diseases research of the future. It is the position of this Commission that strong support by NIH for coordinated research planning efforts to address these common themes is critical for the continued success of digestive diseases research and, as will become apparent, may be more broadly applicable to many other areas of health and disease-oriented research. Maintaining current momentum and facilitating new research approaches for these common themes by all parties in the research process will encompass the major strategies needed for implementing the research plan. These strategies are not described in any specific order, since all are thought to be of high priority.

Theme 1: Increase the Fundamental Knowledge Base for Understanding Health and Digestive Diseases.

Basic and translational biomedical research is the foundation and core of NIH-supported digestive diseases research. The diverse research programs supported by NIH have provided a robust and steady stream of new knowledge about the normal, healthy digestive system and how it is perturbed in diseases. Research discoveries have provided critical data necessary to develop better ways for preventing, diagnosing, treating, or curing digestive diseases. Steps that are needed to ensure that this process continues are encompassed in the strategies listed below.

Strategy 1.1: Elucidate the molecular basis of biologic and pathologic processes in the digestive system.

Many advances in digestive diseases research have emerged from detailed studies of the molecules, cells, and pathways that underlie health and are perturbed in disease processes. Extensive additional work is needed to obtain a comprehensive understanding of the many cell types in the digestive system, including their normal development and senescence, cell-cell communication, and function as part of whole organs, systems, or organisms. Increasingly, understanding complex conditions, such as the functional GI disorders, will require integration of knowledge about the digestive system with other systems, particularly the central nervous system, and increased understanding of the biologic basis of symptoms and behaviors. These approaches will be the foundation for the discovery of potential targets for intervention in disease processes with drugs or biologics. Increasingly, studies of cell and molecular biology will use not only currently available techniques, but also more complex, integrative systems biology approaches to understand the biology and pathobiology of the digestive system.

Strategy 1.2: Define the genetic basis of digestive diseases.

Medical research has entered an era where comprehensive analysis of whole genomes of organisms will facilitate the discovery of the genetic basis of not only classic genetic diseases, but also of the role of common genetic variation in complex non-Mendelian diseases. For example, recent ground-breaking discoveries concerning the genetics of IBD will likely propel and transform research in numerous areas of translational and clinical research in IBD; parallel approaches offer great potential for advances in many other digestive diseases. The complete unraveling of risk alleles, gene-gene interactions, and gene-environment interactions in the pathogenesis of diseases will undoubtedly be challenging, but the expected benefits of this line of investigation are considerable. These benefits include a better understanding of critical pathways in pathogenesis, clues to potential environmental factors, and potential clinical research advances, including diagnostic

tests, new therapeutic agents, and improved understanding of genetic variability in responses to medicines (pharmacogenomics). In addition, studies of genetics and modifications that influence gene activity (epigenetics) are central to understanding cancers of the digestive system.

Strategy 1.3: Understand the role of microbes in digestive health and disease.

The normal human GI tract exists in symbiosis with the complex mixture of microbes inside it, which plays an important role in the function of the digestive system. In addition, infectious agents cause substantial morbidity and mortality throughout the world as the major cause of diarrheal diseases and chronic infectious diseases, such as viral hepatitis. Microbes in the gut also probably contribute to the pathogenesis of a variety of complex disorders, including IBD. Chronic infections, such as *H. pylori* gastritis or chronic viral hepatitis, are important causes of cancer. Further microbiological research is needed to identify and fully understand the pathogenesis of infections of the digestive system, to develop effective strategies, such as vaccines, for their prevention, and to understand the role of the entire internal microbiological ecosystem in maintaining health and contributing to disease. New technologies must be developed to understand the collection of microbes and their genomes (microbiome) and to identify and understand both pathologic and health-maintaining processes caused by microbes. Prevention of diseases caused by infectious agents through vaccination has been one of the greatest contributions of medical science in modern times, but many potentially preventable infectious diseases lack vaccines. Identifying highly effective anti-microbial treatments for both acute and chronic infectious diseases of the digestive system, or ways to tip the balance toward more beneficial microbial species through the use of agents such as prebiotics or probiotics, is an equally high priority. The potential for modifying the microbiome of the digestive system to maintain health is an important new research opportunity that will be pursued through efforts such as the NIH Human Microbiome Project.

Strategy 1.4: Harness research in immunology, inflammation, and transplantation to improve our understanding of the digestive system and its diseases.

The digestive system is an important component of the overall immune system of the body. Its unique functions and structures—known collectively as the mucosal immune system—play a critical role in both host defense and tolerance. Many, if not most, diseases of the digestive system are characterized by immune and inflammatory components, which play a central role in disease pathogenesis. Some diseases, such as celiac disease, are characterized by loss of tolerance to ubiquitous dietary antigens. Immunity to alloantigens is a major barrier in transplantation of liver and small bowel. Immunological research has led to important advances, such as the development of protective vaccines and specific therapies, including interferon for viral hepatitis and infliximab for IBD. Further research is needed to define the specific roles of the immune system in a wide range of complex diseases, such as IBD, celiac disease, necrotizing enterocolitis, pancreatitis, viral hepatitis, autoimmune liver diseases, and pre-malignant conditions. Progress in immunological research holds promise for identifying new targets for therapies and potential approaches to disease prevention, as well as amelioration of the barriers to transplantation.

Strategy 1.5: Discover the cellular and molecular basis of development, regeneration, and aging of the digestive system.

Some components of the digestive system have an astonishing capacity for regeneration and self-repair. The one-cell-thick lining of much of the GI tract exhibits rapid turnover of cells, with continuous replacement due to progenitor cells that differentiate into multiple cell types. While hepatocytes have a long lifespan, the liver also has remarkable regenerative capacity under conditions of cell death or resection. While much research in disease pathogenesis has focused on mechanisms of cell death, less attention has been given to the role of regenerative mechanisms in disease processes until recently. Rapid progress in stem cell and developmental biology research has energized this area of biologic research in the digestive system. Relatively little attention has been devoted to changes in the digestive system that occur in aging. Research in stem cell and progenitor cell biology, developmental biology, and aging offers the potential for profound insights into many different diseases, including cancer, as well as the potential means for new cell and tissue engineering-based approaches to treatment.

Strategy 1.6: Support the development and application of new research technologies for digestive diseases research.

Many advances in digestive diseases research have directly resulted from the development of new technologies that permit investigators to approach previously insurmountable problems. The list of technologies is long and includes recombinant DNA techniques, isolation and propagation of clonal cell populations, creation of genetically modified animals, production of monoclonal antibodies, high-throughput DNA sequencing, siRNA inactivation, and high-throughput screening of molecular libraries. Not surprisingly, many of these techniques have found clinical applications. It is expected that new technologies will continue to appear. Newer technologies, such as expression arrays, high-throughput DNA sequencing, proteomics, and metabolomics, generate large amounts of data that have required parallel development of computational methods to analyze the data. High-resolution imaging techniques have revolutionized both research and clinical practice. While support for hypothesis-driven, laboratory-based investigation is the cornerstone of NIH-supported research, continued progress in digestive disease research requires the development and availability of new technologies to enable both basic and clinical research.

Theme 2: Translate Fundamental New Knowledge for the Direct Benefit of Individuals.

To achieve the long-term goals of this plan, increased attention should be devoted to translational research, that is, moving knowledge gained from basic research into patient-based clinical research in digestive diseases and then encouraging adoption of successful practices in the broader healthcare community. In contrast to the prototypic laboratory-based research project, clinical research projects typically require longer time periods to plan and execute, have substantial resource and personnel requirements and higher costs, and often encounter additional regulatory and ethical hurdles not found in animal or *in vitro* research. Human subjects research, particularly clinical trials, may require interaction with different government agencies, such as the U.S. Food and Drug Administration (FDA), require development of partnerships with industry, and may be subject to the limitations of the existing healthcare system. Meeting these overall requirements for clinical and translational research will require a combination of strategies.

Strategy 2.1: Refine the phenotypes of patients with digestive diseases.

Progress in understanding diseases often requires an iterative process of discovery, observation, and a more refined description of the disease, followed by additional research. A simple example of this process is the discovery and understanding of the different forms of viral hepatitis. Initially recognized only as "infectious" hepatitis, research ultimately led to a detailed understanding of the multiple different forms of hepatitis and discovery of effective treatment and prevention approaches suitable for each form. Assembling the research phenotype of subjects with a particular digestive disease requires an organized approach with common definitions for all clinical and laboratory parameters, standardized methods to obtain laboratory data, and construction of databases that include novel research parameters, such as genetic alleles or response to a new treatment. Increasingly, analysis of disease phenotypes will include not only routine clinical and laboratory observations, but also whole genome information, proteomic profiles of biofluids, serological and microbiological information, data from advanced imaging studies, and psychosocial information. Full understanding of disease processes may also require longitudinal observation of the evolution of disease over time, as in observational natural history studies or in treatment trials. Research in many complex digestive diseases will likely benefit from a concerted, organized effort to define more highly refined disease phenotypes that will underpin the discovery of the fundamental basis of digestive diseases, including symptoms and clinical manifestations, as well as new approaches for prevention and treatment.

Strategy 2.2: Discover biomarkers and surrogate markers for digestive diseases.

Biomarkers and surrogate markers are components of a patient phenotype with implications extending beyond a physiologic or pathologic parameter and providing additional insights into the disease process. Biomarkers correlate with or are predictive of diagnosis, stage, rate of progression, response to treatment, or any other clinically meaningful characteristic. A surrogate marker has the additional feature of being a predictor that can be used to assess the disease process itself and can be used as an endpoint in a clinical trial, faithfully predicting eventual clinical outcomes. Ideal biomarkers and surrogate markers should be observations that can be made noninvasively and repeatedly, with modest cost and high reproducibility. With these goals, much work on identifying biomarkers has concentrated on easily obtainable fluids, such as serum, plasma, urine, or blood, but biomarkers may include any type of observation, such as images or biophysical measurements, like measures of liver stiffness. Many digestive diseases currently have no or only a few imperfect biomarkers. The availability of robust biomarkers and, particularly, surrogate markers would greatly improve the efficiency of clinical trials and potentially lead to improvements in clinical care.

Strategy 2.3: Define the natural history and risk factors for digestive diseases through epidemiologic research.

For many digestive diseases in the U.S., simple population-based descriptive information is lacking or incomplete. Patient registries and long-term natural history studies will permit opportunities to discover many important features of disease processes, such as environmental factors, interacting co-morbidities, response to treatment, quality-of-life information, and health economics data, as well as provide information needed for design of clinical trials. New epidemiologic research is needed for many digestive diseases in order to generate new testable hypotheses, to properly design clinical trials, and to inform all stakeholders in medical policy decisions.

Strategy 2.4: Develop new, innovative technologies for clinical applications.

Research on advanced new technologies has revolutionized diagnosis and treatment of numerous digestive diseases. Among these are endoscopy-based imaging and treatment techniques, minimally invasive surgery, including robotically assisted surgery and tissue ablation, and high-resolution CT, MRI, and PET imaging technologies. Continued improvements in all of these technologies will undoubtedly provide new opportunities for clinical research and improved diagnosis and treatment. Newer technologies, such as nanotechnology, cell-based treatments, tissue engineering, and organ assist or replacement devices also offer promise for the future. Development of these technologies is often primarily supported by industry, and academia-industry partnerships should be encouraged. Additional partnership opportunities exist between the NIH and FDA to ensure that adequate research information is available for informed decision-making regarding the clinical application of new technologies.

Strategy 2.5: Develop new means to prevent, cure, or treat digestive diseases through clinical trials.

For decades, adequately powered, randomized clinical trials have been the cornerstone for evaluating the potential benefit of new drugs, biologics, devices, behavioral treatments, or combinations of these approaches to managing digestive diseases. As noted above, the design and conduct of important clinical trials is complex and often requires the participation of well-trained research teams, availability of subjects willing to participate in the research, research infrastructure, the opportunity to create new resources such as repositories and databases, industry partnerships, adherence to numerous regulatory guidelines, and adequate funding, both in dollar amount and duration. NIH should play an important role in the design and conduct of critical clinical trials, particularly when it is unlikely that the private sector alone will conduct these research trials. The newly developed Clinical and Translational Science Award program of the NIH National Center for Research Resources (NCRR) will play a vital role in academic clinical research programs. To meet the goal of improving health for all, research in digestive diseases supported by NIH must provide information about special populations, such as women, children, minorities, and other disproportionately affected populations that can be used to address health disparities.

Strategy 2.6: Bridge the gap between controlled clinical trials and dissemination of new knowledge into clinical practice.

The discovery that an intervention has efficacy in a carefully controlled, randomized clinical trial is not the final step in translation of a discovery from the laboratory bench to the bedside of a patient with a digestive condition. Further research is often required to demonstrate effectiveness in broad patient populations, to identify and overcome hurdles that prevent widespread adoption of new treatments, to determine how to use therapies in combination or sequentially with other forms of treatment, and to deal with additional post-marketing assessments of the risks and benefits of therapies. These issues may become the subject of professional practice guidelines, but all too often the evidence base is inadequate to provide sound guidance to practitioners for important questions that arise in the clinical setting. Close collaboration between practitioners, industry, NIH, and other government agencies will be required to identify the highest priority areas that require additional clinical research investments to solve these problems. NIH can facilitate this process through education and awareness campaigns and by sponsoring conferences, including consensus development conferences.

Strategy 2.7: Support clinical research teams.

As for basic and translational research, clinical research on digestive diseases increasingly requires the formation of teams of individuals with diverse expertise, including outstanding clinical knowledge and leadership skills; expertise in evaluation and treatment of patients; clinical trial design; statistical evaluation; training and monitoring of research support, such as study nurses and coordinators; creation of databases; expertise in the various regulatory and compliance steps needed for clinical research; and knowledge about procedures to effectively collaborate with other research partners, such as industry. Clinical research projects provide important opportunities to leverage the investment in ongoing clinical research by supporting additional ancillary clinical or basic research projects that use patient, specimen, or data resources of the parent study. Clinical research projects are also important for ensuring a continuing pipeline of clinical investigators by providing opportunities for research fellowship and career development programs.

Theme 3: Develop Research Resources and Infrastructure.

As indicated in the preceding themes, new technologies and translational research have revolutionized biomedical research. More than ever, the rapid application of research discoveries depends on the availability of not only expensive, complex technologies, but also the appropriate "raw materials" for research, which include various types of specimens and data and highly trained, specialized research teams.

Strategy 3.1: Increase the availability of specimens, data, and computational methods for research in digestive diseases.

The lack of availability of well-characterized specimens for research is frequently an insurmountable hurdle for research progress. The lack of sufficient research specimens may be due to different reasons, such as rarity of a disease, difficulty of obtaining inaccessible specimens from humans, limited financial or organizational resources to collect and maintain samples, or an array of technical issues, such as how to define, obtain, and store different types of specimens. The resources needed for research include, among others, cells, cell lines, tissues, sera, antibodies, DNA, and, in the case of human specimens, associated clinical annotations. Increasingly, innovative research involves computational analysis of complex data sets that have been produced by other investigators, exemplified by whole-genome single nucleotide polymorphism (SNP) data that describe individual genetic changes in large numbers of subjects. The NIH and other research organizations must strive to find efficient, cost-effective ways to make the necessary specimens and data sets widely available to investigators. While the cost of building and maintaining repositories is substantial, the cost of these resources is often much lower than the cost of supporting the development of multiple resources and technologies used by individual investigators.

Strategy 3.2: Create and make available new animal models for digestive diseases research.

For over a century, progress in biomedical research has depended on experiments conducted with animals to answer questions with approaches that are not feasible in humans or *in vitro* systems. For the foreseeable future, NIH must continue to encourage and support research using animals. A substantial fraction of current research in digestive diseases is conducted in animals. Animals provide access to well-characterized, standardized samples and the potential for detailed physiologic and pathologic observations not possible in humans, as well as

preclinical models to test the safety and efficacy of new therapeutic agents. Genetically modified animals provide the opportunity to study the role of specific genes and pathways. Animals raised in germ-free conditions enable studies of the effect of microbes on normal biology and disease processes. Important techniques, such as high-resolution whole-body imaging, are now available for research in animals. Further development is needed of noninvasive, *in vivo* diagnostic tools for the assessment of GI phenotypes in animal research, such as small animal MRI, ultrasound, PET, SQUID, and breath tests, among others. Research in model organisms, including worms, flies, and fish, will increasingly permit rapid identification of critical pathways, targets, and potential therapies. To this end, development and utilization of improved data mining tools will facilitate screening and comparison of large-scale genomics data from various animal models of disease. Developing, procuring, and maintaining animals for research are currently very expensive processes, and centralized investment and infrastructure are needed to ensure that such resources are available to the wider community of scientists.

Strategy 3.3: Support team research.

Many biomedical research projects require close collaboration of multiple, highly trained individuals with different types of expertise. Increasingly, biomedical research on digestive diseases is characterized by team science. The creation of an effective research team requires not only a vision for the research that needs to be done, but also leadership, organizational skills, stable institutional and financial support, rewards that incentivize and reward all members of the team, as well as more mundane requirements for space, time, technologies, and specimens or data. Innovative research teams of the future will include members with expertise in areas not traditionally found in many biomedical research teams, including physics, mathematics, engineering, and behavioral and social sciences. Collaboration among basic, translational, and clinical investigators will be required for rapid application of new fundamental discoveries to benefit individuals with digestive diseases.

Theme 4: Maintain a Pipeline of Research Investigators for the Future.

The long-term success of the Nation's investment in digestive diseases research requires that steps be taken to ensure a steady stream of entrants into the biomedical workforce, representing the best and brightest new investigators willing to make long-term commitments to careers in research. The research training, individual fellowship, and career development programs of NIH and, more recently, the Loan Repayment Programs for Clinical and Pediatric Research have been important components of maintaining the pipeline. At the conclusion of research training and career development programs, young investigators are at a particularly vulnerable period where career choices may be strongly influenced by grant funding paylines, success rates, and the job satisfaction of their mentors. Mentorship is a critical component of the research training process that does not receive adequate support or recognition. Trainees need to have opportunities to be immersed in the activities of strong research teams where there is adequate infrastructural and educational support. The Nation needs a diverse biomedical workforce to address the numerous digestive diseases research problems of a complex society, and efforts should be taken to ensure adequate development of women and minorities in the workforce.

Strategy 4.1: Support research training, individual fellowship, and career development programs.

These programs should encourage innovative research programs designed to attract

outstanding young investigators, support mentors, and provide high-quality educational experiences. Success rates for funding of career awards in digestive diseases should be high enough not to discourage young investigators from choosing a research career path. Stipend and salary support should be increased to keep pace with competitive salary requirements for the different stages of training career positions. Career grants should provide competitive salary support commensurate with the academic rank of the individual.

Strategy 4.2: Support mentorship.

In recognition of the critical requirement for mentorship, NIH should explore a variety of potential mechanisms to incentivize and reward mentorship activities. Mentorship is essential for progress in digestive diseases research by the next generation of scientists, yet potential mentors and their institutions are not often given reasons to value mentoring over other activities with more visible benefits, such as grant awards and research publications.

Strategy 4.3: Maintain a substantially higher success rate for R01-equivalent grants for new investigators in digestive diseases than that of established investigators.

New investigators must have a reasonable chance of success at obtaining an R01-equivalent award, as it is currently the *de facto* standard required by academic institutions for remaining in an academic research career. This may be achieved by establishing higher paylines for new PIs or using funds set aside expressly for this purpose. NIH should provide bridging support for new investigators who have no means of research support pending review of revised applications.

Strategy 4.4: Enhance career development educational workshops and conferences.

Many NIH Institutes and Centers, as well as professional organizations and foundations, sponsor career development conferences and workshops that provide necessary training in the many procedures and processes—the "nuts and bolts"—of career development. These programs are widely viewed as serving an essential need, and they should be expanded to the extent that every young investigator on a digestive diseases research track is able to participate in these workshops. Additional workshop opportunities are needed for mentoring. Research conferences and workshops sponsored by NIH should encourage attendance of young investigators by providing funds specifically for this purpose.

Strategy 4.5: Reduce the financial burden for new investigators.

The NIH Loan Repayment Programs for Clinical and Pediatric Research may encourage career choices in research by providing additional support for loan repayment. The success rate for applicants in digestive diseases-related research fields should equal that of NIH overall. Consideration should be given to expanding the loan repayment programs to include investigators in additional research fields besides clinical or pediatric research.

Strategy 4.6: Assure a diverse workforce.

Programs should be encouraged to target individuals in under-represented minorities to enter careers in biomedical research with a focus on digestive diseases. Potential steps to be taken include educational programs targeted to high school and college students and dedicated stipends for individuals at later stages of research training.

Strategy 4.7: Provide short-term training in digestive diseases research.

Adoption of complex new technologies in research frequently requires in-depth training, but for a limited period of time. Training programs targeted at short-term training in new technologies for digestive diseases research should be encouraged.

Strategy 4.8: Encourage entry of PhD scientists into translational and clinical research in digestive diseases.

Both nationally and internationally, there is a large pool of young PhD scientists with training in basic scientific disciplines that could potentially be tapped to contribute to the pipeline of translational and clinical investigators in digestive diseases research. Young investigators could be encouraged to concentrate on the digestive system by development of short-term educational programs that expose individuals to research opportunities, experiences of successful PhD investigators, and funding opportunities at NIH in digestive diseases research.

STEPS FOR IMPLEMENTATION OF THE RESEARCH GOALS

This long-range plan for digestive diseases research from the National Commission on Digestive Diseases results from deliberations of the appointed and *ex officio* members of the Commission with the assistance of many individuals who contributed additional valuable ideas and insights. The plan describes numerous broad goals and specific objectives to improve the health of the Nation through basic, translational, and clinical research that will lead to the discovery of improved ways to prevent, treat, or cure a diverse group of conditions that affect the GI tract, liver, biliary system, and exocrine pancreas.

The large number of goals, objectives, and challenges identified in this research plan that must be addressed to comprehensively solve the problems of maintaining digestive health and conquering the many forms of digestive disease represents a formidable challenge to all parties in the research process: the research community of investigators, study participants, professional research and patient advocacy organizations, industry, foundations, and public funding organizations, such as the NIH. It is hoped that each of these research partners will use this research plan as a scientific guidepost to identify ways to promote promising future research opportunities to address the burden of digestive disease. The NIH will continue to solicit broad stakeholder input as it oversees implementation of this long-range research plan for digestive diseases through the activities of such coordinating bodies as the Digestive Diseases Interagency Coordinating Committee.

In particular, a large number of individual steps will need to be taken by these research partners over the 10-year time horizon of the research plan to achieve its goals and objectives. The members of the Commission recognize that research progress often occurs in a "bottom up" fashion, not only rapidly outstripping the best laid efforts of scientific planners, but also as a result of the innovative ideas and initiative of individual scientists and research teams. However, it is also clear that certain types of research projects and program, as well as specific resources and infrastructure, require central, "top-down" organization led by funding institutions with the flexibility to apply optimal mechanisms to address promising research directions as they arise. Because of these considerations and others, the Commission's recommendations are targeted primarily at the research goals that should be achieved, but not on the administrative, policy, or procedural approaches that NIH might use to achieve those goals. The Commission recommends that the NIH maintain an approach focused on the goals

set forth in this research plan that includes a substantial and balanced portfolio of programs with three major elements: strong support of investigator-initiated research project grants; initiatives designed to strategically address special needs and opportunities; and programs that ensure a pipeline of new investigators to meet the continuing needs of digestive diseases research in the future.

APPENDIX 1:
Summary List of Recommended Research Goals and Common Themes

The National Commission on Digestive Diseases recommends a series of research goals to guide the NIH and other entities in addressing scientific opportunities for digestive diseases research over the next 10 years. In addition, the Commission identified several common themes that, if addressed, would promote progress broadly across many areas of digestive diseases research. The Research Goals and Common Themes are numbered for ease of reference and are not listed in priority order.

RESEARCH GOALS

Research on the Basic Biology of the Digestive System

1.1: Develop new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system for research and therapeutic applications.

1.2: Understand how particular cell and tissue niches are generated and maintained in the embryonic pancreas, liver, biliary tree, and digestive tract.

1.3: Exploit the advanced understanding of Wnt-APC-β-catenin signaling in human epithelial function to develop new, effective treatment strategies for colorectal cancer.

1.4: Delineate specific signaling pathways, transcriptional regulation, and other interactions that mediate critical patterning events in gut endoderm, which generate and maintain its distinctive major derivatives (GI tract, liver, and pancreas).

1.5: Translate advances from laboratory research in gut development to identify disease mechanisms and therapeutic targets for diverse GI disorders (e.g., congenital disorders, cancer).

1.6: Define the physiologic basis for intestinal growth and adaptation and alterations with aging.

1.7: Define the physiologic basis of energy balance, appetite, and satiety and their roles in obesity.

1.8: Define the physiology of neuroimmune pathways involved in inflammation.

1.9: Develop a comprehensive profile of intestinal genes that regulate mammalian absorptive functions.

1.10: Identify critical pathways in murine and other *in vivo* models to develop targets for treatment of obesity and other disorders of nutrient absorption and metabolism.

1.11: Define pathways that regulate barrier function and transport function.

1.12: Define molecular pathways leading to differentiated absorptive and secretory functions.

1.13: Develop means to measure and manipulate epithelial function.

1.14: Define the basic cellular and molecular mechanisms responsible for neural activation, integration, and regulation in the ENS.

1.15: Understand the structure, function, and regulatory mechanisms responsible for motility in the GI tract.

1.16: Develop research tools to investigate the structure and functional organization of the ENS.

1.17: Characterize the neuromuscular phenotypes of human GI tissues.

1.18: Integrate cellular events in ENS with whole system physiology and translate findings to pathophysiologic conditions.

1.19: Translate knowledge of the ENS in digestive health and disease into diagnostics and therapies for human disease.

1.20: Determine the biologic activities of the microflora in healthy humans.

1.21: Determine the mechanisms of host-microbial interactions that are necessary to maintain health and contribute to pathological processes in disease.

1.22: Determine the role of epithelial cells in mucosal host defense and inflammation.

1.23: Understand the role of antigen-presenting cells in the mucosal immune system.

1.24: Understand trafficking of mucosal cells to various parts of the mucosal immune system.

1.25: Understand mucosal unresponsiveness (oral tolerance) and mucosal regulatory T cell development.

1.26: Understand the differentiation and function of mucosal lymphocytes and other immunologically active cells.

1.27: Develop mucosal vaccination strategies.

Functional Gastrointestinal Disorders and Motility Disorders

2.1: Understand the molecular and cellular events that yield normal motility, sensory behavior, and integration between motility and secretory activity in the GI tract and the pathophysiology of functional GI disorders and motility disorders.

2.2: Understand the development of the GI tract and brain-gut interactions and determine how the aging process and differences in sex and gender affect gut development and function and brain-gut interactions.

2.3: Understand the components and functional interactions of the peripheral (autonomic and enteric) and central nervous systems in normal physiology and in functional GI and motility disorders.

2.4: Understand the immune functions of the muscularis, integration between mucosal and muscle immune responses, and how inflammatory processes contribute to the pathogenesis and maintenance of functional GI and motility disorders.

2.5: Understand peripheral and central pain and sensory pathways and how these pathways are affected in functional GI and motility disorders.

2.6: Understand the noxious visceral signaling causing nausea and vomiting related to gastric neuro-electrical and/or motor dysfunction and the bi-directional brain-gut interactions.

2.7: Understand the role of the microflora in functional GI disorders and motility disorders.

2.8: Use information from studies of animal models and cellular physiology to understand the integrated function of the musculature and the intrinsic and extrinsic nervous systems.

2.9: Characterize the factors in diabetes that lead to the development of functional GI and motility diseases.

2.10: Determine how genotype contributes to or predisposes patients to the development of functional GI and motility disorders.

2.11: Determine the role of food in the development of functional GI and motility disorders.

2.12: Develop new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.

2.13: Evaluate therapeutic outcomes and the impact of doctor/patient interactions to determine effective treatments for functional GI and motility disorders.

Infections of the Gastrointestinal Tract

3.1: Elucidate the etiology, epidemiology, and pathogenesis and improve diagnostic tests for intestinal infections.

3.2: Improve the prevention and treatment of intestinal infections.

3.3: Understand and modulate the long-term intestinal and non-intestinal consequences of GI infection.

3.4: Understand the human microflora and microbiome in health and disease and modulate them for beneficial effects.

Cancers of the Digestive System

4.1: Develop population-based strategies for screening and prevention of digestive cancers.
4.2: Ascertain the importance, detection, and natural history of pre-malignant conditions progressing to digestive cancer.
4.3: Evaluate health disparities in digestive cancer etiology, risk, treatment management, and outcomes.
4.4: Improve outcomes in the care of digestive tract cancer patients.
4.5: Develop biomarkers to detect neoplasia, target therapy, and evaluate therapeutic response in digestive cancers.
4.6: Evaluate nutriceutical, probiotic, chemo-preventive, and targeted therapies in digestive cancers.
4.7: Understand the molecular and cellular mechanisms common to all digestive cancers.
4.8: Determine the risk factors and pathogenesis of squamous carcinoma and adenocarcinoma of the esophagus and devise new methods for detection, diagnosis, treatment, and prevention of these diseases.
4.9: Understand the molecular profiles of various types of gastric cancer to improve risk stratification, prevention, and treatment.
4.10: Define the genetic and environmental factors contributing to pancreatic cancer and its precursor lesions and devise new methods for early detection, treatment, and prevention.
4.11: Identify genetic and environmental risk factors for colon cancer and devise improved approaches for screening, early diagnosis, treatment, and prevention of colon cancer.
4.12: Understand the etiology, natural history, prevention, and management of rare GI cancers.

Inflammatory Bowel Diseases

5.1: Establish an objective basis for determining clinical diagnosis, detailed phenotype, and disease activity in IBD.
5.2: Develop an individualized approach to IBD risk evaluation and management based on genetic susceptibility.
5.3: Modulate the intestinal microflora to prevent or control IBD.
5.4: Effectively modulate the mucosal immune system to prevent or ameliorate IBD.
5.5: Sustain the health of the mucosal surface.
5.6: Promote regeneration and repair of injury in IBD.
5.7: Provide effective tools for clinical evaluation and intervention in IBD.
5.8: Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents.

Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation

6.1: Define mechanisms of intestinal growth and differentiation.
6.2: Develop new strategies to treat short bowel syndrome and intestinal failure.
6.3: Improve the success of intestinal transplantation.
6.4: Understand and treat the metabolic and nutritional consequences of bariatric procedures and other surgical modifications of the gut.
6.5: Optimize nutritional support of patients with GI disorders.

Diseases of the Oropharynx and Esophagus

7.1: Understand the neurobiology of oropharyngeal structure and function in health and disease.
7.2: Understand the clinico-pathologic mechanisms leading to and/or associated with GERD and identify novel molecular, physiologic, and anatomic targets for more effective and rational treatment.

7.3: Define the mechanisms responsible for esophageal injury and repair, with particular emphasis on the interactions among components of the esophageal wall.

7.4: Understand the epidemiology, natural history, and outcomes of eosinophilic esophagitis and identify targets for more rational and effective therapy.

7.5: Understand the etiopathogenesis of Barrett's esophagus, determine risk factors associated with its progression, and identify novel targets and/or therapies for chemoprevention and treatment.

7.6: Understand the etiology and biology of esophageal neuromuscular function in health and disease and develop more effective treatments.

Diseases of the Stomach and Small Intestine

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

8.2: Reduce and prevent NSAID peptic diseases.

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

8.4: Understand the basis of rare gastric cancers, develop effective measures for earlier and more accurate diagnosis, and develop effective treatment strategies.

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

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

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

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.

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

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

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

Diseases of the Colon and Rectum

9.1: Establish mechanisms of colonic injury and repair to use as a basis for development of therapeutic interventions.

9.2: Understand colonic mucosal absorption in health and disease.

9.3: Determine the role of gut microflora in health and disease states of the colon.

9.4: Establish the cause of diverticular disease and its complications, with modulation of disease.

9.5: Understand mechanisms and develop tools for early diagnosis of colon ischemia and angioectasia.

9.6: Improve management of anorectal disorders.

9.7: Improve the understanding and management of fecal incontinence.

9.8: Reduce the frequency and severity of radiation injury to the colon.

9.9: Determine causes of appendicitis and modulate the course of the disease.

Diseases of the Pancreas

10.1: Determine the biologic factors involved in the pathogenesis of acute pancreatitis, with particular emphasis on the mechanisms of tissue necrosis and systemic complications.

10.2: Understand the transition from acute to chronic pancreatic injury, particularly with respect to the role of alcohol.

10.3: Understand genetic factors and their interactions with exogenous insults, with respect to pathogenesis, complications, and natural history of pancreatitis and other pancreatic disorders.

10.4: Develop and validate therapeutic interventions for treatment and/or progression of pancreatitis and its complications.

10.5: Understand the neurobiology of the pancreas with respect to mechanisms of pain and neurogenic inflammation.

10.6: Define the epidemiology and clinical course of acute and chronic pancreatitis, including alcoholic pancreatitis, autoimmune pancreatitis, and cystic fibrosis, through population-based studies in adults and children.

10.7: Develop more accurate and useful approaches to the diagnosis of chronic pancreatitis by functional, radiologic, endoscopic, or pathologic/cytologic means.

10.8: Define the role of pathologic lesions, such as pancreatic intraepithelial neoplasms, and other factors that may correlate with the risk of malignant transformation in chronic pancreatitis and cystic neoplasms and map their morphologic and molecular progression.

Diseases of the Liver and Biliary System

11.1: Define the molecules, processes, and pathways that underlie normal liver cell function, which can then be applied to understanding the cellular and molecular basis of disease processes.

11.2: Understand the cellular mechanisms of liver injury, inflammation, repair, and fibrosis and develop effective means for monitoring and treating diseases caused by these processes.

11.3: Define the molecular and cellular mechanisms underlying liver development and regeneration in health and disease and apply these findings to developing improved therapies for liver disease.

11.4: Delineate the normal pathways of uptake, metabolism, and secretion of bile salts, bilirubin, and other biliary lipids and solutes; characterize the alterations in these pathways that participate in the pathogenesis of liver diseases; and develop means for diagnosis, treatment, and prevention of cholestatic liver disease and disorders of bilirubin metabolism.

11.5: Develop safe and effective means to prevent and treat hepatitis C.

11.6: Improve strategies for use of current therapies of hepatitis B and develop new, improved treatment regimens.

11.7: Develop improved means to prevent and manage acute viral hepatitis.

11.8: Define the causes of liver disease associated with HIV and develop means to prevent and treat liver disease in HIV-infected persons.

11.9: Understand the basic mechanisms of injury and develop means to prevent and treat non-alcoholic and alcoholic fatty liver disease.

11.10: Establish means to predict, prevent, diagnose, and treat hepatotoxicity due to drugs, herbal medications, and environmental toxicants.

11.11: Determine the etiology, pathogenesis, and potential new targets for therapy of the three major forms of autoimmune liver disease: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC).

11.12: Determine the molecular and genetic pathways responsible for the major forms of inherited and early-onset, severe liver diseases of childhood, including biliary atresia, neonatal hepatitis, progressive familial intrahepatic cholestasis, Alagille syndrome, alpha-1-antitrypsin deficiency, neonatal hemochromatosis, and mitochondrial hepatopathies in order to devise potential new targets for therapy.

11.13: Evaluate and improve existing adult medical and surgical therapies for treatment of children with liver diseases.

11.14: Elucidate the molecular pathways responsible for hereditary forms of liver disease, including hereditary hemochromatosis, Wilson disease, the porphyrias, cystic fibrosis, polycystic liver disease, and congenital hepatic fibrosis; use knowledge of these pathways to devise novel approaches to treatment.

11.15: Refine current procedures in liver transplantation, including assessment of potential transplant recipients, immunosuppressive regimens, and management of donors and recipients for living donor transplantation, and improve management of recurrent liver diseases in transplanted patients.

11.16: Identify ways to prevent or ameliorate the complications of portal hypertension and cirrhosis.

11.17: Develop better means of prevention, management, and treatment of acute liver failure.

11.18: Develop effective strategies for early detection and treatment of hepatocellular carcinoma and cholangiocarcinoma in high-risk groups.

11.19: Develop better means to prevent and treat gallstones.

Bioengineering, Biotechnology, and Imaging

12.1: Define the optimal procedural approach for patients with digestive disorders amenable to endoscopic, image-guided, or minimal access surgery.

12.2: Develop innovative technology for the diagnosis and treatment of luminal disease.

12.3: Use tissue engineering and regenerative medicine approaches to develop innovative treatments for digestive diseases.

12.4: Expand the application and integration of imaging and procedural technologies to deliver targeted interventions with minimal tissue injury to patients with digestive disorders.

12.5: Develop high-fidelity interactive simulators of the digestive system.

COMMON THEMES

THEME 1: Increase the fundamental knowledge base for understanding health and digestive diseases.

Strategies for Implementation:

1.1: Elucidate the molecular basis of biologic and pathologic processes in the digestive system.

1.2: Define the genetic basis of digestive diseases.

1.3: Understand the role of microbes in digestive health and disease.

1.4: Harness research in immunology, inflammation, and transplantation to improve our understanding of the digestive system and its diseases.

1.5: Discover the cellular and molecular basis of development, regeneration, and aging of the digestive system.

1.6: Support the development and application of new research technologies for digestive diseases research.

THEME 2: Translate fundamental new knowledge for the direct benefit of individuals.

Strategies for Implementation:

2.1: Refine the phenotypes of patients with digestive diseases.

2.2: Discover biomarkers and surrogate markers for digestive diseases.

2.3: Define the natural history and risk factors for digestive diseases through epidemiologic research.

2.4: Develop new, innovative technologies for clinical applications.

2.5: Develop new means to prevent, cure, or treat digestive diseases through clinical trials.

2.6: Bridge the gap between controlled clinical trials and dissemination of new knowledge into clinical practice.

2.7: Support clinical research teams.

THEME 3: Develop research resources and infrastructure.

Strategies for Implementation:

- **3.1:** Increase the availability of specimens, data, and computational methods for research in digestive diseases.
- **3.2:** Create and make available new animal models for digestive diseases research.
- **3.3:** Support team research.

THEME 4: Maintain a pipeline of research investigators for the future.

Strategies for Implementation:

- **4.1:** Support research training, individual fellowship, and career development programs.
- **4.2:** Support mentorship.
- **4.3:** Maintain a substantially higher success rate for R01-equivalent grants for new investigators in digestive diseases than that of established investigators.
- **4.4:** Enhance career development educational workshops and conferences.
- **4.5:** Reduce the financial burden for new investigators.
- **4.6:** Assure a diverse workforce.
- **4.7:** Provide short-term training in digestive diseases research.
- **4.8:** Encourage entry of PhD scientists into translational and clinical research in digestive diseases.

APPENDIX 2:
Rosters of the National Commission on Digestive Diseases and Its Working Groups

Chairperson

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Executive Director

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ROSTERS OF COMMISSION WORKING GROUPS

Each working group was led by a Chair and Vice Chair chosen from among the appointed members of the Commission and was composed of six to ten additional experts in each topic area who were selected after a public nomination process. Working group members were encouraged to consult informally with colleagues in the digestive diseases research community to ensure that this research plan reflects the broadest possible input. It is not possible to recognize by name all individuals who contributed to the development of this research plan through informal discussions with working group members. However, the Commission gratefully acknowledges the invaluable input of the working group members and their colleagues throughout the digestive disease research community.

Research on the Basic Biology of the Digestive System

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Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation

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APPENDIX 3:
References for Statistical and Epidemiologic Data

Everhart JE, editor. (2008) The burden of digestive diseases in the United States. U.S. Department of Health and Human Services, National Institutes of Health, Public Health Service, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office. NIH Publication No. 09-6443.

Garthright WE, Archer DL, Kvenberg JE. (1988) Estimates of incidence and costs of intestinal infectious diseases in the United States. *Public Health Rep*. 103:107-115.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Taylor M, Thun MJ. (2008) Cancer statistics, 2008. *CA Cancer J Clin*. 58:71-96.

Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. (2002) The burden of selected digestive diseases in the United States. *Gastroenterology*. 122:1500-1511.

APPENDIX 4:
Abbreviations and Acronyms

5-ASA	5-aminosalicylic acid
5HT	5-hydroxytryptamine
ABCA1	ATP-binding cassette, subfamily A, member 1
ABCG5/G8	ATP-binding cassette transporters G5 and G8
ACTH	adrenocorticotropic hormone
AIDS	acquired immunodeficiency syndrome
AIEC	adherent invasive *E. coli*
AIH	autoimmune hepatitis
AIP	autoimmune pancreatitis
ALADIN	alacrima-achalasia-adrenal insufficiency neurologic disorder protein
AMP	adenosine monophosphate
APC	adenomatosis polyposis coli
APJ	apical junctional complex
ApoB	apolipoprotein B
ApoE	apolipoprotein E
APRIL	a proliferation inducing ligand
ATG16L1	ATG16 autophagy related 16-like 1 protein
BAFF	B cell-activating factor of the tumor necrosis factor family
BMP	bone morphogenic protein
BRCA2	breast cancer type 2 susceptibility protein
CCK	cholecystokinin
CCR3	chemokine receptor 3
CD	Crohn's disease
CD1/CD25/CD40	cluster of differentiation molecules
CDX2	caudal-related homeobox 2
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CI	colonic ischemia
CIMP	CpG island methylator phenotype
CNS	central nervous system
COX	cyclooxygenase
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CT	computed tomography

DC	dendritic cells
DDICC	Digestive Diseases Interagency Coordinating Committee
DDLT	deceased donor liver transplant
DGAT	diacylglycerol acetyltransferase
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
EAEC	enteroaggregative *E. coli*
EGID	eosinophilic gastrointestinal disorders
EGJ	esophagogastric junction
ENS	enteric nervous system
EPEC	enteropathogenic *E. coli*
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangio-pancreatography
EUS	endoscopic ultrasound
FABP	fatty acid binding protein
FAP	familial adenomatous polyposis
FATP	fatty acid transport protein
FDA	U.S. Food and Drug Administration
FDG-PET	2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography
FGF	fibroblast growth factor
FIC	Fogarty International Center
fMRI	functional magnetic resonance imaging
FoxP3	forkhead box P3 transcription factor
FXR	farnesoid X receptor
GABAB	gamma-aminobutyric acid B receptor
GERD	gastroesophageal reflux disease
Gfi	growth factor independence protein
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIST	gastrointestinal stromal tumor
GLP-2	glucagon-like peptide-2
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HEV	hepatitis E virus
HFE	hemochromatosis gene
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNPCC	hereditary nonpolyposis colorectal cancer
hPEPT1	human peptide transporter 1

IBD	inflammatory bowel diseases
IBS	irritable bowel syndrome
ICC	interstitial cells of Cajal
ICD	International Classification of Diseases
IgA	immunoglobulin A
IgG	immunoglobulin G
IGF-1	insulin-like growth factor-1
IL	interleukin
Insig-1	insulin-induced gene 1
IPMN	intraductal papillary mucinous neoplasm
ISC	intestinal stem cell
LDLT	living donor liver transplant
LES	lower esophageal sphincter
Lgr5	leucine-rich repeat-containing G-protein coupled receptor 5
LRR	leucine-rich repeat
LXR	liver X receptor
MAdCAM-1	mucosal addressin cell adhesion molecule 1
Math-1	mouse atonal homolog 1
MALT	mucosa associated lymphoid tissue
MCN	mucinous cystic neoplasm
MCT	monocarboxylate transporter
Mdr2	multiple drug resistance 2
MELD	Model for End-Stage Liver Disease
MEN 1	multiple endocrine neoplasia type 1
MGAT	mannoside acetylglucosaminyltransferase
MLCK	myosin light chain kinase
MMR	mismatch repair
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein family
MSC	mesenchymal stem cell
MYH	Mut Y homolog
NASH	non-alcoholic steatohepatitis
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
NEC	necrotizing enterocolitis
NERD	non-erosive reflux disease
NF-κB	Nuclear Factor kappa-B
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute

NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NK	natural killer
NKT	natural killer T cell
NO	nitric oxide
NOTES	natural orifice transluminal endoscopic surgery
NPC1L1	Niemann-Pick C1 Like 1 protein
NSAID	non-steroidal anti-inflammatory drug
NSC	neural stem cell
OD	NIH Office of the Director
OPASI	Office of Portfolio Analysis and Strategic Initiatives
ORS	oral rehydration solution
PanIN	pancreatic intraepithelial neoplasia
PBC	primary biliary cirrhosis
PCR	polymerase chain reaction
PDC-E2	pyruvate dehydrogenase complex-E2
PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
PELD	Pediatric End-Stage Liver Disease
PET	positron emission tomography
PN	parenteral nutrition
PPAR	peroxisome proliferator-activated receptor
PPI	proton pump inhibitor
PSC	primary sclerosing cholangitis
PTEN	phosphatase and tensin homolog
PUD	peptic ulcer disease
PYY	peptide YY
RAR	retinoic acid receptor
rDNA	ribosomal deoxyribonucleic acid
RNA	ribonucleic acid
Runx3	runt-related transcription factor 3

RV	rotavirus
SBP	spontaneous bacterial peritonitis
SBS	short bowel syndrome
Scap	SREBP cleavage-activating protein
SCFA	short chain fatty acids
SERT	serotonin reuptake transporter
siRNA	small interfering ribonucleic acid
SNP	single nucleotide polymorphism
SPECT	single photon emission computed tomography
SPINK1	serine protease inhibitor, Kazal type 1
SQUID	superconducting quantum interference device
SREBP	sterol-regulatory element binding protein
STAT3	signal transducer and activator of transcription 3
STEP	serial transverse enteroplasty
TE/RM	tissue engineering/regenerative medicine
TFF	trefoil factor
TGF	transforming growth factor
TIMP	tissue inhibitor of metalloproteinases
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRPV1	transient receptor potential vanilloid 1
TSLP	thymic stromal lymphopoietin
UC	ulcerative colitis
VEGF	vascular endothelial growth factor
ZES	Zollinger-Ellison syndrome

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ACKNOWLEDGEMENTS

The National Commission on Digestive Diseases gratefully acknowledges all of the working group members (see Appendix 2) and their colleagues in the digestive diseases research and advocacy communities for their input and assistance in developing a comprehensive set of recommendations for the future of digestive diseases research.

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