

# 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 diseases 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.

