Meeting Minutes

Department of Health and Human Services
National Institutes of Health
National Commission on Digestive Diseases

November 6, 2006

I. CALL TO ORDER

The Chairman of the National Commission on Digestive Diseases (NCDD), Stephen P. James, called to order the second meeting of the Commission at 9:00 a.m. on Monday, November 6, 2006 in Salons E-G of the Marriott Crystal Gateway, Arlington, Virginia.

A. ATTENDANCE – COMMISSION MEMBERS PRESENT

STEPHEN P. JAMES, M.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)
BRUCE R. BACON, M.D., St. Louis University
BARBARA L. BASS, M.D., The Methodist Hospital, Houston, Texas
RICHARD S. BLUMBERG, M.D., Brigham & Women's Hospital
JOHN M. CARETHERS, M.D., University of California, San Diego
MAURICE A. CERULLI, M.D., New York Methodist Hospital
EUGENE B. CHANG, M.D. University of Chicago
MITCHELL B. COHEN, M.D., Children's Hospital Medical Center, Cincinnati, Ohio
MARGARET M. HEITKEMPER, Ph.D., R.N., University of Washington
DAVID A. LIEBERMAN, M.D., Oregon Health Sciences University
NANCY J. NORTON, B.S., International Foundation for Functional Gastrointestinal Disorders
PANKAJ J. PASRICHA, M.D., University of Texas Medical Branch
DANIEL K. PODOLSKY, M.D., Massachusetts General Hospital
KENTON M. SANDERS, Ph.D., University of Nevada School of Medicine
ROBERT S. SANDLER, M.D., M.P.H., University of North Carolina
JOANNE A.P. WILSON, M.D., Duke University Medical Center

COMMISSION MEMBER ABSENT

JANE M. HOLT, National Pancreas Foundation, Boston

***EX OFFICIO* MEMBERS PRESENT**

ALEXIS BAKOS, Ph.D., R.N., National Institute of Nursing Research (NINR)
BETH P. BELL, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)
BROOKS D. CASH, M.D., MC, USN, National Naval Medical Center
NANCY EMENAKER, Ph.D., R.D, National Cancer Institute (NCI) [for John Milner, PhD, NCI]
DAVID P. GOLDMAN, M.D., M.P.H., United States Department of Agriculture (USDA)
RAJ K. GOYAL, M.D., VA Boston Healthcare System
GILMAN GRAVE, M.D., National Institute of Child Health and Human Development (NICHD)
BRIAN HARVEY, M.D., Ph.D., Food and Drug Administration (FDA)
JAY H. HOOFNAGLE, M.D., NIDDK
DENNIS LANG, Ph.D., National Institute of Environmental Health Sciences (NIEHS)
SUSAN MEIKLE, M.D., M.S.P.H., Office of Research on Women's Health, Office of the Director [for Lisa Begg, Dr.Ph.H., R.N.)
MICHAEL ROGERS, Ph.D., National Institute of General Medical Sciences (NIGMS)
ANNETTE ROTHERMEL, Ph.D., National Institute of Allergy and Infectious Diseases (NIAID)
SAM ZAKHARI, Ph.D., National Institute on Alcohol Abuse and Alcoholism (NIAAA)

ADDITIONAL PRESENTERS IN ATTENDANCE

ELIAS ZERHOUNI, M.D., Director, National Institutes of Health
JAMES (JAY) EVERHART, M.D., M.P.H., Branch Chief; Director; Epidemiology and Data Systems Program Project Officer, NIDDK
DANITA BYRD-HOLT, Project Manager, Social and Scientific Systems, Inc.
MEGAN MILLER, Ph.D., Health Science Policy Analyst, Office of Scientific Program and Policy Analysis, NIDDK
ROBERT HAMMOND, Ph.D., Executive Director, NCDD

B. ATTENDANCE – NIH STAFF AND GUESTS

In addition to Commission members, others in attendance included NIH staff representatives and interested members of the public. Attendees included the following:

Sara Arnold, Health and Medical Counsel of Washington
Anne Bicha, American Gastroenterological Association
A.J. Bownas, the Hill Group
Clarice Brown, Social & Scientific Systems, Inc.
Michelle Cissell, M.A.Cissell Consulting
Leslie Curtis, NIDDK
Carol Feld, NIDDK
Winnie Feldman-Lindauer, Celiac Sprue Association
J. Michael Hall, American Liver Foundation
Eleanor Hoff, NIDDK
Michael Kalutkiewicz, American Gastroenterological Association
Carina May, the Hill Group
Helyn Oscanyan, the Hill Group
Stacey Poole, TAP Pharmaceuticals
Sharon Pope, NIDDK
Jeff Ricchetti, American Gastroenterological Association
Constance Ruhl, Social & Scientific Systems, Inc
Asad Umar, NCI
Rucha Vyas, Digestive Diseases National Coalition
Anne Wright, Circle Solutions, Inc.

II. WELCOME, APPROVAL OF JUNE 12 MINUTES, AND TODAY'S GOALS

Dr. Stephen James, NCDD Chairperson, welcomed all attendees to the second meeting of the National Commission on Digestive Diseases. Appointed members of the Commission introduced themselves and identified the working group(s) that each would be chairing. Dr. James reminded everyone that each member of the Commission has signed a conflict of interest form. Questions about the conflict of interest policy can be directed to Dr. James. Members were reminded that rosters of each working group would be posted on the NCDD public website as they are approved. The minutes of the June 12, 2006 NCDD meeting were unanimously approved.

The goal of the meeting was to review progress made since the June meeting, mainly related to formation of 13 working groups and identification of areas of overlap among the groups. In addition, staff preparing the burden of disease report discussed the process for gathering and analyzing data for the report. Finally, members were given directions on organizing and assembling information from their working groups into a succinct and coherent report.

III. REMARKS FROM THE NIH DIRECTOR

Dr. Elias Zerhouni, Director of the National Institutes of Health, spoke to the group regarding his reasons for chartering the NCDD in 2005 and his expectations for how the Commission's work will fit into the broader NIH vision for biomedical research and public health. Digestive diseases impose an enormous public health burden because of the number of organs that are affected, the wide spectrum of conditions,

and the diverse underlying mechanisms of disease that are involved. The Commission's process, much like the one that led to the NIH Roadmap, will define a group of short-, medium-, and long-term objectives. The resulting strategic plan will be used as a guide across the NIH to shape digestive diseases research.

The NIH is now facing its third consecutive year of below inflation budget increases or, in 2006, a slight decrease. Flattening of the budget requires NIH to balance its many scientific portfolios and allocate resources as well as possible. Moreover, it is more important than ever to communicate to Congress and the public the return on its investment in biomedical research. The doubling of the NIH budget from FY 1999-2003 stimulated a dramatic increase in research capacity in the U.S., both in terms of research facilities as well as in the number of new scientists and new fields of study, such as genomics, proteomics, and computational biology. The Commission must understand the context of their efforts in relation to the overall NIH budget and make strong arguments that justify the investment in digestive diseases research.

The NIH attempts to maintain a portfolio that is balanced with respect to fundamental vs. applied science, high-risk/high impact research, and the need to support new investigators while also maintaining existing innovative programs. Dr. Zerhouni challenged the Commission to promote research to transform medicine, protect new investigators, improve communication about the return on NIH investment, and broaden the NIH vision of what can be achieved through its research programs. He cautioned the group to not allow current budget constraints to limit the scope of their vision.

The Commission was urged to consider the "science of the science" or the environment in which digestive diseases research evolves. The scope and scale of scientific issues now requires cross-disciplinary planning and collaboration to explore new fields of research. Researchers and funders must be willing to assume failure, which is an expected outcome of leading edge science. Most importantly, public support for research depends on the ability of the NIH to articulate a compelling vision of the future that is relevant to the landscape of public health in terms of chronic disease, health disparities, aging of the population, and other critical issues.

The NIH message to Congress and the public is that we are in a transformational era that is leading to a new system of predictive, personalized, pre-emptive, and participatory medicine. The Commission must be visionary in its planning and help to define the health care system 15 years into the future. How GI diseases will be detected, how health care delivery will occur, and how patients and communities will be empowered to take more responsibility are issues that must be considered when defining the evidence base that must be developed to support the changing health care environment.

Over the past several years, the age at which investigators obtain a tenure-track position and receive their first R01 grant has steadily risen. To address the need to protect and support new investigators, the NIH has created the "Pathway to Independence Award" program that provides up to 2 years of mentored-support for postdoctoral fellows followed by 3 years of independent, R01-like funding for those who secure a tenure-track position. The Commission should propose ways to encourage new ideas and new people to enter into the digestive diseases research field.

In summary, Dr. Zerhouni strongly urged the Commission to look for synergies between the research plan for digestive diseases and the overall NIH vision for the future of medicine. The plan must promote cross-cutting, innovative research and identify opportunities to translate basic research into clinical applications. In the post-doubling era, careful planning and allocation of resources is more important than ever. The advice and input of the Commission will be critical for translating the vision into new tools, ideas, and concepts that will advance the fundamental understanding of biology and, in turn, transform health and medicine in the 21st century.

In response to questions from Commission members, Dr. Zerhouni noted:

- To ensure that a diversity of scientific disciplines is represented in the Pathway to Independence Award program, applications are reviewed by clusters of institutes with shared interests (e.g. neuroscience). Program staff in each cluster are aware of research and personnel gaps within their portfolios and help maintain a balance in the overall program. A related issue is that the limited budget for FY2006 will make it difficult for investigators to obtain continuing support for grants that are up for their first competitive renewal.
- Between "big science" projects and individual investigators grants, programs of an intermediate scale are needed that allow investigators from multiple fields to collaborate on complicated research questions. Dr. Zerhouni advocated the need for more research on the best model to promote multi-investigator, collaborative projects that are innovative and high-risk. The NIH has created an Office of Portfolio Analysis and Strategic Initiatives that will track and evaluate new funding mechanisms such as the Director's Pioneer Award and team science efforts. In addition, the NIH Roadmap process has developed a multi-PI grant process that recognizes and rewards multiple researchers for equal intellectual contributions.
- Roadmap initiatives are designed to address high risk/high impact ideas—for example, nanotechnology—that would not otherwise be funded or do not fit into the mission of a single institute or center. However, these programs are expected to last no more than 5-10 years at the most. The NIH solicits new ideas from the research community every few years to ensure that the Roadmap is tackling emerging issues in science. Knowledge management tools are being developed that will simplify the ability to analyze multi-disciplinary portfolios, such as digestive diseases research or angiogenesis research, across the campus. These tools will help NIH to recognize and integrate over-arching themes that can impact biomedical research as a whole.

IV. WORKING GROUP UPDATES

Working group (WG) chairs[1] were asked to present on: the major points of the background/introduction to the chapter; the scientific scope of the chapter; areas of potential overlap with other chapters; progress made on the working group timeline; and lessons learned or anticipated challenges. A list of overlap areas will be distributed to working group chairs to share with their committees.

Dr. James noted that, although this meeting will focus on background and the classification of relevant diseases and research areas, the strategic plan is ultimately intended to be a forward-looking outline of important research goals, opportunities, and hurdles. Many chapters encompass a wide array of topics, so all working groups will need to capture their main issues and recommendations in a succinct manner.

The Chairs' working group updates are summarized below in the order of their presentation at the meeting.

WG4: Cancers of the Digestive System

Because of the size and scope of digestive cancers research, members of this working group will chair subgroups to solicit input from experts in the wider research and clinical communities. Background to this chapter will include: epidemiology of each cancer area (incidence, prevalence, burden of disease, risk factors, and natural history); known or hypothesized pathogenic pathways for initiation of each cancer (progression from a benign state; genes involved; patient presentation and progression); and current means for prevention, cure, or control of the cancer.

[1] A list of working groups and Chairs can be found in the appendix of these minutes. Complete rosters of the working groups are available at http://www.niddk.nih.gov/federal/ncdd/list-wking-groups.htm.

The scope of the chapter (and organization of the subgroups) includes: basic mechanisms of digestive cancers (e.g. cell cycle regulation, apoptosis, angiogenesis); esophageal cancer (squamous and adenocarcinoma, but not initiation of Barrett's metaplasia); stomach cancer (adenocarcinoma); pancreatic cancer (primarily adenocarcinoma, as well as neuroendocrine tumors); colorectal neoplasia (precursor lesions and adenocarcinoma); "orphan" cancers of the small intestine or cancers involving multiple areas of the digestive tract (e.g. small intestinal adenocarcinoma, lymphomas, gastrointestinal stromal tumors).

This working group has finalized its roster and is completing pre-call work in preparation for the first conference call. The major challenge for this group is the large scope of the chapter which encompasses multiple common cancers that affect the U.S. population.
The Commission noted the importance of inviting input from experts outside of mainstream cancer research, for example from fields such as stem cell biology or developmental biology, as well as interacting with large programs such as the cancer genome project. Experts in behavioral psychology, nursing science, and related fields can help address the impact of behavioral interventions on cancer screening, symptom management, nutraceuticals, and other issues.

WG10 Diseases of the Pancreas
The major diseases covered by this working group are acute pancreatitis, chronic pancreatitis (including cystic fibrosis), and other cystic lesions. Disorders of the pancreas are among the top ten digestive diseases and accounted for an estimated $2.4 billion in healthcare costs in 2000.

Acute and chronic pancreatitis are distinct in terms of etiologies, clinical presentations, natural history, approaches to treatment, and causes of death. The major etiologies of acute pancreatitis are alcohol or gallstones, although the pathogenesis is not well understood. In a subset of cases, death results from necrotizing pancreatitis and multiple organ failure. The chapter will address these issues as well as antibiotic treatment, prevention of infection, and the role of endoscopy. The clinical manifestations of chronic pancreatitis are abdominal pain and pancreatic insufficiency. The natural history of this disease is not well defined, although many patients develop malabsorption and diabetes. The major etiology is alcohol, although some idiopathic cases can be attributed to genetic mutations, cystic fibrosis, and autoimmunity. Chronic pancreatitis is a major risk factor for pancreatic cancer. Recently, a variant cystic fibrosis phenotype has been identified in which the classic lung and intestinal manifestations of CF are absent, but patients exhibit pancreatic insufficiency and chronic pancreatitis. Pancreatic cysts, including cystic neoplasms, also fall within the scope of this chapter.

The chapter will cover : basic pancreatic biology; mechanisms of acute pancreatic injury and complications; mechanisms of chronic pancreatitis and complications; epidemiology, natural history, and genetics of pancreatic disease in children and adults; diagnosis and treatment of acute pancreatitis; diagnosis and treatment of chronic pancreatitis; and cystic neoplasms. The working group has submitted a membership roster for approval.

WG11 Diseases of the Liver and Biliary Systems
An estimated 5-6 million people in the U.S. have chronic liver disease or cirrhosis and more than 20 million have gall bladder disease. Liver diseases are among the leading causes of death in the U.S. and deaths from chronic viral hepatitis, cirrhosis, and hepatocellular cancer are rising.

Liver and biliary diseases that will be covered by this working group include: acute and chronic viral hepatitis; alcoholic liver disease; nonalcoholic fatty liver disease (hepatic steatosis, NASH); drug-induced liver disease; autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis); inherited liver diseases (hemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease, cystic fibrosis); cancers of the liver; benign hepatic masses and cystic disease; biliary disorders;

gall bladder disease; liver transplantation; and liver diseases that are specific to children. While many pathophysiologic processes are specific to each disease, some mechanisms are common to many liver diseases. Fibrogenesis is an overarching issue that often occurs in the end stage of liver disease. Additional general issues include regeneration, oxidative stress, insulin resistance, inflammation and repair, apoptosis, portal hypertension, and others. Diagnosis, epidemiology, natural history, and treatment also vary widely among various liver diseases.

The scope of the chapter will include discussion of epidemiology and natural history; causes of chronic liver and biliary diseases; pathophysiologic mechanisms; genetics; treatment paradigms; clinical trials; liver transplantation; and pediatric liver disease.

The working group has an approved roster and has begun preparations to schedule a conference call. The major challenge is expected to be integrating the multiple, diverse diseases covered by this topic into a cohesive chapter.

The Commission urged the working group to ensure that gall bladder disease, the leading GI diagnosis, is fully covered in this chapter. In addition, the liver research community and NIH have been innovative in the establishment of consortia and networks to study pediatric and adult liver diseases. In 2004, the NIH published a Liver Action Plan that is guiding liver research directions. A discussion of the success or lack of success of programs or initiatives launched in response to the Action Plan—i.e. "lessons learned"—could be an important component of this chapter.

WG3 Infections of the GI Tract

Infections of the GI tract are a frequent cause of illness both in the U.S. and globally. Diarrheal disease is the second leading GI symptom prompting out-patient visits, and gastroenteritis is the third most frequent GI diagnosis. While the number of reported cases of infectious GI diseases remains high, progress has been made. In 2003, just over 7,600 cases of acute hepatitis A were reported, which represented a drop of 76 percent compared to previous years. Likewise, cases of enterohemorrhagic *E. coli* were down 44 percent. The availability of new vaccines and improved public awareness contributed to these declines and highlight the return on investment in research and communication.

The working group will address bacterial, viral, and parasitic pathogens that are already identified or newly emerging. Issues of special risk groups, such as immunocompromised patients or children, will be included. Preventive therapies, vaccines, probiotics, antisecretory therapies will all be considered along with the role of emerging antimicrobial resistance, public health burdens, and bioterrorism. Acute infections can develop into chronic illnesses which may include irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD) as well as non-GI sequelae like arthritis or Guillain-Barre Syndrome.

The chapter will include the following topics: bacterial pathogens; emerging pathogens; uncommon infections and diseases (e.g. Whipple's disease); viral pathogens; parasites; infections in immunocompromised hosts; vaccines; probiotics; long term sequelae of infection, including IBS; food borne illnesses; and bioterrorism. In addition, the chapter will incorporate the topics of host immune responses to infection, microbial agents in the pathogenesis of IBD, and microorganisms and development.

The working group has an approved roster and is preparing materials in advance of a conference call. The chairs might convene a brief, preliminary call to introduce the group members and stimulate their thinking about synergies among their individual areas of expertise. The Commission recommended including expertise in the field of public health and the impact of GI infections and food borne illnesses.

WG5 Inflammatory Bowel Diseases

Crohn's disease and ulcerative colitis (UC) are the most common forms of inflammatory bowel disease (IBD) and a significant source of morbidity and health care expense. Geographic and temporal variability have been noted in the prevalence and incidence of these diseases, which appear to be triggered by a combination of genetic and environmental factors. Diagnosis is often empiric and there is no definitive therapy for Crohn's disease with frequent recurrence after surgery. UC can be cured by total removal of the colon. Medical therapies include general anti-inflammatory agents or immunosuppressive drugs. The basic pathogenic paradigm is that luminal flora drive an inflammatory process due to inappropriate activation of innate and adaptive immune responses.

The scope of this chapter will include: epidemiology; genetics; microbiology of the micro flora and its relationship to disease processes; epithelial biology; innate and adaptive immune responses; a systems approach to development of an integrated understanding of these diseases; clinical studies to understand the disease, translate laboratory findings into advances for patients, and address quality-of-life issues related to the disease and treatments; and special needs and pathophysiology of the pediatric population.

This working group is in the process of finalizing its membership roster. The major anticipated challenge is the need to balance priority setting with the development of a comprehensive scientific agenda for IBD research. The group plans to explore opportunities from all sciences, such as genomics and systems biology, and define the best, innovative approaches to promoting research goals. The Commission recommended that the group discuss the availability and appropriateness of animal models of IBD as well as explore systems biology approaches that can take into account genes, environment, and the microbial flora.

WG8 Diseases of the Stomach and Small Intestine

The working group has divided this topic into three focus areas: acid/peptic disorders; diarrheal diseases, malabsorption, and maldigestion; and celiac disease and other disorders, including those affecting children. On the topic of acid/peptic disorders, the group will provide an overview of the epidemiology and burden of disease and discuss basic physiology (the role of gastric acid), *H. pylori*, NSAIDS (non-steroidal anti-inflammatory drugs) and related complications, and other diseases such as Zollinger-Ellison syndrome, Menetrier's disease, opportunistic infections (e.g. CMV, herpes simplex 1), and possibly Crohn's disease to a limited extent. The overview of diarrhea, malabsorption, and maldigestion will focus on the basic pathophysiologic mechanisms that lead to these conditions. Both acute and chronic diarrheal disorders will be covered along with nutrient disorders related to enzyme deficiencies, transport defects, and bacterial overgrowth. Finally, celiac disease will be addressed with respect to its genetics, immunology, epithelial biology, the role of gluten, and treatments and complications. Necrotizing enterocolitis, a serious complication of neonates and premature infants, and other pediatric disorders (protracted diarrhea, congenital/genetic disorders) will be discussed.

The chairs have organized subgroups for each of the main themes; these subgroups are developing goals and initiatives in anticipation of the first conference call. The Commission suggested including management of GI bleeding as an important area of discussion. In addition, it might be useful to solicit input from experts on animal models, which are lacking or inadequate for many of these disorders.

WG2 Functional Gastrointestinal Disorders and Motility Disorders

Motility disorders can affect any region of the GI tract and, with few exceptions, the causes are not known. Presentation is usually symptomatic, although parameters that can be measured include delayed gastric emptying or abnormal peristalsis times. Functional gastrointestinal disorders are associated with pain, discomfort, and related symptoms such as diarrhea, constipation, or bloating. Collectively, these disorders affect up to a quarter of the American population and account for 40 percent of GI problems for which patients seek healthcare. Functional diseases can be chronic, episodic disorders that do not increase

mortality or predispose to other medical conditions, although they can have a significant impact on quality of life. A number of potential mechanisms, including genetic predisposition, have been hypothesized.

The scope of this chapter includes multiple clinically recognized conditions that include, but are not limited to: esophageal disorders (e.g. globus, rumination syndrome); gastroduodenal disorders (e.g. functional dyspepsia, aerophagia); bowel disorders (e.g. IBS, functional abdominal bloating, constipation or diarrhea); functional abdominal pain; functional disorders of the biliary tract and pancreas; anorectal disorders (e.g. fecal incontinence, pain); pediatric disorders; and motility disorders of the esophagus, stomach, small intestine, and colon. Because of the large number of disorders, the group will highlight commonalities that can promote research progress in many areas. The group will discuss current treatments that include pharmaceutical agents, behavior modification, cognitive therapy, and other approaches. Importantly, the availability or lack of epidemiological data will be discussed, especially in relation to less common conditions.

The chairs have an approved roster and are distributing materials to working group members. A major challenge for this group is the breadth of disciplines encompassed by functional and motility disorders which will require them to reach out to experts beyond the formal working group. The Commission noted that health disparities with respect to these disorders will be an important issue to consider.

WG7 Diseases of the Oropharynx and Esophagus

Oropharyngeal disease is a substantial issue for stroke patients, up to three-quarters of whom develop post-stroke dysphagia. This condition contributes to problems with nutrition, swallowing, and quality of life and predisposes to pneumonia and aspiration, major causes of death in these patients. Moreover, dysphagia is becoming recognized as a common problem of aging. Esophageal motility disorders often lead to non-cardiac chest pain, which is among the most frequent in-patient diagnoses. Gastroesophageal reflux disease (GERD) has an enormous impact in terms of number of patients affected, medical costs, and complications including Barrett's esophagus and, in turn, adenocarcinoma. Frequent GERD, Barrett's, and obesity are major risk factors for esophageal cancer, the fifth leading cause of death from GI diseases. Many technologies for diagnosis and treatment of esophageal disease are under development, including narrow band imaging, endocytoscopy, optical coherence tomography, and others. GERD is now becoming more common in the pediatric population.

With respect to the oropharynx, the main focus of the chapter will be on swallowing disorders, which derive from either structural/anatomic defects, or functional problems due to neurological or muscular diseases. In the esophagus, the over-riding issue is GERD and its complications. Motor disorders (achalasia, diffuse esophageal spasm), sensory disorders (non-cardiac chest pain), and inflammatory and infectious disease (eosinophilic esophagitis, opportunistic infections, scleroderma) will also be covered.

The chairs are in the process of finalizing the composition of the working group. The Commission noted the importance of including a focus on pediatric issues such as swallowing problems in children with developmental disabilities. A pediatric gastroenterologist has been nominated for the working group and should provide appropriate coverage.

WG6 Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation

Obesity research is a very broad topic that is a major focus of other NIH planning groups. Thus, this chapter will handle obesity to the extent that research opportunities relate specifically to the gut, normal physiology of eating/satiety, surgical interventions for obesity (i.e. bariatric surgery and its long-term consequences), or the impact of obesity on secondary digestive organs through GERD, gallbladder disease, liver disease, or other consequences.

Intestinal failure, across the spectrum from short gut to intestinal failure to intestinal transplantation, will be another primary focus. Clinical management of patients—nutritional management, maximizing adaptation, and minimizing complications—is a key issue for discussion. Repair of the gut by stimulating epithelial growth and differentiation or regeneration will be covered. Finally, in the context of intestinal transplantation, the issues of immune tolerance and the long term physiology/function of the transplanted organ will be addressed in this chapter.

Nutrition is another large category that is being addressed by multiple NIH groups and was specifically omitted from the NCDD charter. However, nutrition will be covered in a limited way to the degree that there are specialized opportunities specifically related to the digestive system. Pediatric growth and development could be considered. In the adult, nutrition problems due to gut dysfunction caused by critical illness, surgery, or immunosuppression will be covered. In general, therapy-oriented issues may be discussed rather than general nutrition research.

The chairs are recruiting working group members. The Commission suggested including a pediatric gastroenterologist in this group.

WG9 Diseases of the Colon and Rectum

Diseases of the colon and rectum are a significant cause of physician visits and hospitalizations, particularly in the elderly. Anorectal disorders are an important factor in fecal incontinence and psychosocial disability and the leading reason for institutionalization in the aging population. The pathogenesis of many common disorders, including diverticular disease and ischemic colitis, are poorly understood. Radiation injury is becoming an increasingly common result of therapy.

The scope of the chapter will encompass: colonic mucosal injury and repair, with a focus on colonic mucosal absorption and the role of NSAIDS and other agents in increasing injury; colonic wall and the development of diverticular disease and bleeding; colon vasculature and changes that predispose to ischemia or angioectasia. Diverticular disease will be a major focus with particular attention to the interaction with gut flora, pathogenesis of inflammation, bleeding, and segmental inflammation, and clinical management. Other topics of interest include: prevention, repair and management of ischemic colitis; pathogenesis and prevention of radiation colitis; solitary colon ulcers; anorectal disease with emphasis on hemorrhoids, fissures, and fistulas, and its association with fecal incontinence. Finally, appendicitis—which is a leading cause of hospitalization—will be discussed.

The working group has a membership roster ready for approval. The Commission discussed inclusion of the late sequelae of surgical intervention for abnormal structures (e.g. imperforate anus, cloacal deformities) and other pediatric disorders, such as VATER syndrome and perforated anus, in this chapter. Angiodysplasias were also mentioned as a relevant topic.

WG12 Multi-Organ Diseases and Diseases of Abdominal Structures

The leaders of this group have begun to define the scope of this chapter. Possible topics include: surgical conditions (e.g. hernia); diseases of the mesentery (e.g. volvulus vascular problems); multi-system diseases that affect the gut, but are not considered digestive diseases (e.g. scleroderma); connective tissue disorders; genetic anomalies; rheumatologic conditions; endocrine diseases, for example diabetes as it relates to gastroparesis, fecal incontinence, the alimentary tract, and the liver; and neurologic diseases (e.g. Parkinson’s disease, stroke).

WG13 Bioengineering, Biotechnology, and Imaging

Because bioengineering, biotechnology, and imaging are relevant to virtually every digestive disease, the group has decided not to take a disease-specific approach, but rather solicit perspectives from a variety of

specialties such as radiology, engineering, mathematics, and computational science. Three main focus areas will be imaging, emerging interventional technologies, and tissue engineering relevant to the gut.

The scope of the chapter will cover luminal diseases, including approaches to surveillance and detection as well as ablation technologies. Technologies for intra-abdominal diseases will be addressed in terms of non-endoscopic approaches to disease detection and surveillance, procedural planning and guidance, and interventional technologies. Within the broad field of imaging, topics of interest include the development of virtual endoscopy, image enhancement with functional molecular markers, and image guidance for surgical planning and robotic systems. The chapter will explore opportunities in tissue engineering through the use of stem cells, design of scaffolds, and the development of strategies to enhance growth and differentiation with the ultimate goal of creating functional tissue and organ replacements. Emerging technologies like robotics, remote control devices, image guidance, molecular targets, and development of functional imaging interfaces will be important considerations. Devices, especially with respect to miniaturization, will be discussed.

This chapter will overlap with essentially all other topics. A relatively unique feature of this field—and a critical issue for discussion—is its reliance on industry and academic-industry partnerships and the allocation of private and public resources and funding to support progress. The Commission suggested including experts from the chemical biology and systems biology fields on this working group.

WG1 Overview of the Digestive System

To manage a broad range of topics, the chapter has been divided into seven main areas organized by clinical issues and related fundamental biological problems in digestive diseases research. A subchair has been assigned to each area to solicit input from a variety of experts and report back to the working group.

The main focus areas and some of the relevant biologic pathways of interest are:

- Development: factors that mediate epithelial-mesenchymal interactions; patterning factors; cryptovillus integrity and the intestinal cell niche; relation between developmental and carcinogenic pathways; and basis of congenital abnormalities and metaplastic transformation.
- Growth/Integrative Physiology: cross-talk among elements within the gut wall and integration with extra-intestinal tissues (e.g. brain); interaction between gut and other metabolic tissues; integrative responses to food intake; and coordination of neural, endocrine, and muscle factors with epithelial function.
- Digestion: role of membrane transporters in selective uptake and channeling of lipid macronutrients; dialog between host transporters and bacteria; enterohepatic circulation and metabolic regulation; metabolic channeling of FA/sterols and intestinal growth, proliferation, and carcinogenesis; and lipid transporters and antigen presentation.
- Nutrient and Fluid Absorption/Secretion: regulation of barrier function versus transport; cellular and protein diversity in creating integrated absorptive functions; adaptation of gut to surgical or inflammatory challenge; receptors an transporters controlling micronutrient and macromolecule absorption; genetic disorders of absorption; and nutrient absorption in diabetes and obesity
- Neurophysiology, Endocrine, Satiety: neurophysiology of the enteric nervous system; neurophysiology and endocrine mechanisms of gut-brain interactions; gut peptides and metabolomics in relation to diabetes, obesity, metabolic stress, and inflammation
- Microbiology/Microbiome: define bacterially-associated diseases by establishing genotypes of normal flora; bacteria as delivery vehicles; physiologic interactions between bacteria and host; comparative, evolutionary, and environmental microbial ecology; and mechanisms by which normal flora induce inflammation.
- Mucosal Immunology: mucosal immunization and vaccine development; mucosal immunoregulation and oral tolerance; epithelial barrier function and host defense; IgA and IgE responses and transport across the epithelial barrier; mucosal cell trafficking, and mucosal cytokine responses.

The working group roster has been approved. A challenge for this group will be to maintain a clinical translation orientation in the context of a basic biology perspective on digestive diseases. In addition, it will be crucial for members of this group to communicate regularly with the other disease-oriented working groups in order to minimize overlap and provide a robust, cross-cutting blueprint for understanding fundamental issues underlying the various diseases.

V. COMMISSION TIMELINE AND NEXT STEPS

A. Burden of Disease Report

Dr. Jay Everhart informed the Commission that the Burden of Digestive Diseases Report, a separate product that will be largely tabular and disease-oriented, will be published as a research paper and on the web. Because of the intersection between the report and the Commission's work, members will have an opportunity to request data for inclusion throughout the planning process. Social and Scientific Systems, Inc. (SSS) will provide data analysis, computer programming and epidemiology support for this project. SSS has worked with NIDDK for 20 years and has expertise relevant to digestive diseases.

Danita Byrd-Holt, an SSS project manager, explained to the Commission the projected timeline and process for producing the burden of disease report. The overarching goal of the report is to provide information on the frequency, health impact, and cost of major digestive diseases. SSS intends to complete a draft report by September 2007 and a final report by the end of November 2007. Importantly, the report will be generated in parallel with the NCDD working groups to ensure that the Commission has all data required for its efforts. SSS obtains information by data mining, processing, and survey analysis as well as by integrating data obtained through literature searches. Examples of measures that could be obtained include: work loss days, days of restricted activity, years of productive life lost, number of hospital stays, number of outpatient visits, number of home health care visits and episodes, incidence, prevalence, and mortality. Data sources include: National Center for Health Statistics, Agency for Healthcare Research and Quality, Medicare standard analytic files, Verispans, physician drug and diagnosis audit file, the SEER (Surveillance Epidemiology and End Results) cancer registry, and the CORI (Clinical Outcomes Research Initiative) database.

The Commission suggested that the measures should include data on procedures and interventions, which would be useful for multiple areas including the technology group. A draft list of measures will be circulated to the working groups for input. It was suggested that, to the extent possible, the list of requested data measures be consistent across all areas. However, it was acknowledged that the availability and quality of resources and data will vary widely for different diseases. The process of obtaining useful data might highlight the need for better epidemiological research and resources within specific disease areas.

B. Organization and Assembly of the NCDD Strategic Plan

Dr. Megan Miller of the NIDDK Office of Scientific Program and Policy Analysis briefed the Commission on the organization of the overall plan and the process for assembling the working group reports into a coherent package. An Executive Summary will encapsulate the research planning process and the Commission's recommendations as well as provide an overview of the NIH digestive diseases research portfolio. Each of the 13 topic-specific chapters will be organized according to a template that has been distributed to the working groups. These chapters are expected to be approximately 8-10 pages in length and include an introduction/background section, a list of recent research advances, and a list of forward-looking research goals. It will be very important for the working groups to adhere to the general structure as much as possible so that the chapters can be integrated into a cohesive plan with minimal re-working. The plan will conclude with a summary of recommendations for implementing the Commission's goals.

Dr. James emphasized that the main substance of the plan lies in the development of well-honed, prioritized research goals rather than a reiteration of current knowledge in gastroenterology. It was suggested that the Commission as a whole also discuss cross-cutting themes and develop recommendations for changing how research is conducted and moving the entire field. These recommendations could either be highlighted in the executive summary or assembled in a separate chapter. Career development, training, and education are topics that must also be addressed. For all goals, working groups are expected to give some thought to hurdles and opportunities.

C. Timeline

Following this second meeting of the NCDD, recruitment for the working groups will be completed and conference calls will be held during early 2007. Working group members are expected to submit major discussion points as bulleted items in advance of each call so that the groups' discussions can be focused. At the third NCDD meeting on June 18-19, 2007, chairs will report on the recommendations of their working groups for discussion by the entire Commission. Over the summer 2007, the Burden of Disease Report will be incorporated and a draft NCDD report will be made available for public comment. In the fall 2007, the Commission will meet for a fourth time to review and incorporate those comments, and prepare a final draft report. A final meeting will be held in spring 2008 to approve the final report for publication and discuss implementation plans.

VI. FY 2006 NIH AND OTHER FEDERAL AGENCY PORTFOLIOS

One of the Commission's charges is to describe the NIH portfolio for digestive diseases research. The Commission was provided the NCI portfolio that includes for each award: the grant mechanism, project number, project title, principal investigator name, and institution. Commission members were asked to review this information and let the coordinating staff know if there were other data elements that would be useful to their analysis.

VII. ADJOURNMENT

Dr. James thanked Commission members and all attendees for their time and participation. The second meeting of the NCDD was adjourned at 4:45 p.m., November 6, 2006.

I hereby certify that to the best of my knowledge, the foregoing summary minutes are accurate and complete

Stephen P. James, M.D.
Director, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases
Chairman, National Commission on Digestive Diseases

APPENDIX: NCDD Working Groups

1. Overview of the Digestive System (Chair: Richard Blumberg; Vice-Chair: Eugene Chang)
2. Functional Gastrointestinal Disorders and Motility Disorders (Chair: Kenton Sanders; Vice-Chair: Nancy Norton)
3. Infections of the GI Tract (Chair: Mitchell Cohen; Vice-Chair: Richard Blumberg)
4. Cancers of the Digestive System (Chair: John Carethers; Vice-Chair: Robert Sandler)
5. Inflammatory Bowel Diseases (Chair: Daniel Podolsky; Vice-Chair: Eugene Chang)
6. Intestinal Failure and Regeneration, Nutritional Disorders and Support, Surgically Modified Gut, and Transplantation (Chair: Barbara Bass; Vice-Chair: Margaret Heitkemper)
7. Diseases of the Oropharynx and Esophagus (Chair: Pankaj Pasricha; Vice-Chair: David Lieberman)
8. Diseases of the Stomach and Small Intestine (Chair: Eugene Chang; Vice-Chair: Maurice Cerulli)
9. Diseases of the Colon and Rectum (Chair: Joanne Wilson; Vice-Chair: Nancy Norton)
10. Diseases of the Pancreas (Chair: Jane Holt; Vice-Chair: Pankaj Pasricha)
11. Diseases of the Liver and Biliary Systems (Chair: Bruce Bacon; Vice-Chair: Maurice Cerulli)
12. Multi-Organ Diseases and Diseases of Abdominal Structures (Chair: David Lieberman; Vice-Chair: Stephen James)
13. Bioengineering, Biotechnology, and Imaging (Chair: Barbara Bass; Vice-Chair: David Lieberman)