Testimony
Before the Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives

"ASSESSING DIGESTIVE DISEASES RESEARCH AND TREATMENT OPPORTUNITIES"

Statement of

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For Release on Delivery
Expected at 11:00 am
on Thursday, July 8, 2004

Mr. Chairman and Members of the Committee: I am Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Institute that has lead responsibility for digestive diseases research at the National Institutes of Health (NIH of the Department of Health and Human Services). I am pleased to testify today regarding NIH efforts to combat digestive diseases. Through basic and clinical research studies, we can gain greater insights into the causes of these diseases, find more effective treatments, and develop prevention strategies. I am accompanied today by Dr. Stephen James, the newly appointed Director of the Institute's Division of Digestive Diseases and Nutrition. Dr. James is an expert on digestive disease research, particularly immunologically mediated diseases, including inflammatory bowel diseases.

In my testimony today, I will give you a brief overview of the public health burden of digestive diseases, the vigorous research efforts NIH has under way in this area, highlighting Crohn's disease research as an illustrative example, and closing with future directions based on our planning for research in digestive diseases.

BURDEN OF DIGESTIVE DISEASES

The digestive system is critically important to human health and well being. This complex system includes the pharynx, esophagus, stomach, liver, biliary tract, pancreas, small and large intestines, and anorectum. Thus, digestive diseases research encompasses many serious and potentially life-threatening illnesses, such as cirrhosis of the liver, inflammatory bowel diseases, hepatitis, gastrointestinal cancer, ulcers, and gallstones. This constellation of diseases also includes highly prevalent diseases such as acute gastroenteritis, gastroesophageal reflux disease (the cause of heartburn), and irritable bowel syndrome that, while generally not fatal, cause significant morbidity.

Digestive diseases and their associated long-term complications have significant social and economic consequences for the Nation. According to a report published in 2002, the estimated annual total cost for digestive diseases, in 1998 dollars, was $85.5 billion (Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C,

Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. *Gastroenterology*. 2002 May; 122(5):1500-11).

Digestive diseases rank second among all causes of disability due to illness in the United States. They result in an estimated 200,000 absences from work each day with a mean time lost of nine days. More than two million Americans are impaired to some degree by digestive diseases, limiting an estimated 1.2 million people in the type of occupation they can seek. Approximately 140,000 veterans receive payments for service-related disabilities due to digestive diseases.

The chronic nature of digestive diseases results in approximately 11 percent of all admissions to general hospitals in the United States and in 15 percent of all surgical procedures performed in this country. Approximately 200,000 deaths annually are caused by digestive diseases, including cirrhosis and other liver diseases, cancer of the digestive system, gallbladder disease, ulcers, and pancreatitis. Digestive diseases also complicate the treatment of other life-threatening conditions, such as cardiovascular disease.

In fiscal year 2003, the NIH invested nearly $1.1 billion in research on digestive diseases. The NIDDK, the National Cancer Institute (NCI), and National Institute of Allergy and Infectious Diseases (NIAID) accounted for 34 percent, 32 percent, and 17 percent of this support, respectively. Research mechanisms include regular research grants, cooperative clinical trials, epidemiologic studies and data systems, and cooperative consortia. In addition, during the period of the doubling of the NIH budget, we were able to expand the number of NIDDK Digestive Disease Research Centers from 12 to 16, as well as to add four new digestive disease Development Centers, plus a Women's Health Center (with the NIH Office of Research on Women's Health) focusing on irritable bowel syndrome. We are also vigorously supporting physician-scientists in digestive diseases through our research training and career development awards and the loan repayment program.

A statutory Digestive Diseases Interagency Coordinating Committee serves to coalesce and synergize the efforts of the many NIH Institutes and Centers that support research in this field, as well as the efforts of other Federal agencies. Intersecting

research and active collaboration are found among many NIH components. For example, NIDDK's research on the development of islet cells of the pancreas complements the NCI's work on the cellular origins of pancreatic cancer. Similarly, NIDDK and NCI have joint efforts on both Barrett's esophagus, which can be a precursor to cancer of the esophagus, and on the diagnosis, treatment, and prevention of liver cancer, which may be a consequence of infection with hepatitis virus. Hepatitis is a shared research focus of the NIDDK, NIAID, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse. The NIDDK and the National Center for Complementary and Alternative Medicine are working together to test silymarin, or milk thistle, in treatment of liver disease. These are just a few examples of the many ongoing collaborative endeavors at NIH in digestive diseases research.

The NIDDK also plays an important role in disseminating information on digestive diseases through the National Digestive Diseases Information Clearinghouse (NDDIC). The Clearinghouse develops and distributes health information for patients, the public, and health care providers to improve understanding of digestive diseases, such as Crohn's disease (http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/index.htm). The Clearinghouse is available via the web (www.digestive.niddk.nih.gov), a toll-free phone line (1-800-891-5389), e-mail (nddic@info.niddk.nih.gov), mail (NDDIC, 1 Information Way, Bethesda, MD 20892-2570), and fax (301-907-8906). Each year, the Clearinghouse meets with representatives of professional and patient-advocacy groups to share information and seek feedback. The NDDIC's most recent national meeting was held on June 10, 2004, during which Michael Dolan reported on activities at the Crohn's and Colitis Foundation of America.

INFLAMMATORY BOWEL DISEASES:
NEW DISCOVERIES AND PROMISE FOR THE FUTURE

As a major example of NIH digestive diseases research, I would like to give the committee a brief description of the paths that have been taken to realize research advances in the inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease. Ulcerative colitis is characterized by inflammation and ulceration of the inner surface of the large intestine. Crohn's disease may involve any portion of the gastrointestinal tract, but most commonly affects the lower portion of the small intestine. The lesions of Crohn's disease may penetrate through the bowel wall and lead to the formation of fistulas, which are ulcerating lesions that tunnel through the intestines of patients.

The inflammatory bowel diseases are incurable, chronic, and debilitating. They affect an estimated 1 million Americans. Many patients are diagnosed in their teens and twenties and must cope for the rest of their lives with problems that include intestinal inflammation, abdominal pain, fever, diarrhea, and rectal bleeding. In children, symptoms can progress to malnutrition and growth retardation. These problems dramatically reduce quality-of-life and require lifelong, expensive medical care. For decades, there were no truly effective medications, so that surgical removal of the affected parts of the intestine was often necessary, particularly in ulcerative colitis, which can lead to colon cancer.

Investigator-initiated basic research on the immune system, however, began to illuminate the fundamental mechanisms responsible for intestinal inflammation, leading to important therapeutic advances, particularly in Crohn's disease. Mice in which certain key genes of the immune system had been knocked out unexpectedly developed inflammatory bowel disease mimicking Crohn's disease. Importantly, bowel disease did not develop in mice raised under "germ-free" conditions in which the bacteria normally residing in the bowel are absent. Thus, the immune gene knockout alone is insufficient to cause disease, but combines with the normal gut bacteria in provoking a self-destructive immune response.

These discoveries set the stage for an ambitious long-range plan for inflammatory bowel disease research with the goals of providing more effective treatment and, ultimately, prevention. The NIDDK has pursued the plan's aims to: (1) emphasize basic research on interactions between intestinal cells and bacteria; (2) augment the pool of researchers and foster interdisciplinary research; (3) establish and enhance appropriate biological resources and data collections; and (4) develop therapeutic applications and preventive approaches as basic research progresses.

This plan was formulated with external input from patient groups, such as the Crohn's and Colitis Foundation of America, and investigator groups, such as the American Gastroenterological Association. Dr. James has worked closely with these advocacy groups to maximize efforts toward accomplishing common research goals. The plan was updated at a meeting of the NIDDK-led Digestive Diseases Interagency Coordinating Committee in April 2003. In implementing the plan, the NIDDK has deployed the full range of available mechanisms, including a robust portfolio of investigator-initiated grants and pilot-and-feasibility studies, research training grants, large program project grants, and four Digestive Diseases Research Centers that focus on inflammatory bowel disease.

Through NIH research efforts, significant improvements in therapy for Crohn's disease have resulted, most notably the development of infliximab, a drug that targets an inflammation-causing protein whose role was illuminated by the mouse gene knockout experiments. The Food and Drug Administration's (FDA) approval of infliximab was an important step forward in treating Crohn's disease. A report in the *New England Journal of Medicine* earlier this year showed that it is particularly effective in healing the fistulas. An enormous new scientific opportunity emerged in 2001 when investigators announced the unprecedented discovery of a gene that confers susceptibility to Crohn's disease. This discovery represents an important payoff of the Human Genome Project. It is also a credit to the strong foundation laid by previous NIDDK research efforts—including an emphasis on targeted, interdisciplinary collaborations among researchers from different fields. Finding this gene illuminated the potential role of abnormalities of the innate immune system—the first line of

defense against “foreign invaders”—as a cause of Crohn’s disease. This insight was then translated into a clinical trial demonstrating the potential benefit of a new treatment, GM-CSF, a natural protein in the body which boosts the function of the innate immune system. Because other genes conferring susceptibility to inflammatory bowel disease remain to be discovered, the NIDDK established a new multi-center Genetics Consortium to speed this search. The pace of discovery in genetics of IBD is accelerating, as evidenced by the publication in April of the identification of two new candidate genes involved in Crohn’s disease.

Most recently, results from a multicenter clinical trial were presented at the May 2004 meeting of the digestive diseases professional organizations. Researchers have shown that there is a benefit for Crohn’s patients in the use of a monoclonal antibody targeting the cytokine IL-12. This work emanates from the intramural research program of the NIAID.

Other clinical insights are expected to emerge from an ongoing NIDDK-funded multicenter clinical trial to investigate whether the dosing of the standard, now generic, immunosuppressive drug azathioprine can be improved. Researchers are studying new testing methods for the metabolizing enzyme and toxic metabolites of the drug. This trial is an example of the vital role NIH can play in conducting clinical trials of a treatment when there is no longer any incentive for commercial interest in such research.

Other NIDDK initiatives include the detailed study of adult stem cells of the intestine that may ultimately lead to therapies stimulating gut regeneration. We are vigorously pursuing these research areas as we evaluate and monitor progress in attaining our goals. While this example illustrates how investments in investigator-initiated basic research lead to discoveries that improve the outcomes of patients with Crohn’s disease, we recognize that we must take steps to accelerate the translation of basic science discoveries into patient benefits. For this reason, NIH and NIDDK are taking steps to bolster translational research.

INFLAMMATORY BOWEL DISEASES: TRANSLATIONAL RESEARCH OPPORTUNITIES

The NIH is strongly committed to spurring translational research in both Crohn's disease and ulcerative colitis. By translational research, we mean research to speed the movement of laboratory discoveries into research that holds promise of direct clinical benefits for patients—also called "bench-to-bedside" research. NIH Director Elias Zerhouni, M.D., has stressed the importance of this type of research in his initiative to develop a Roadmap for medical research, and the many Institutes and Centers of the NIH are also emphasizing translation research in their respective programs. At the NIDDK, for example, we have recently completed an assessment of drugs in the pipeline for several diseases within our mission, including the inflammatory bowel diseases—Crohn's disease and ulcerative colitis. One good example of translational research involves the drug rosiglitazone, which is used to treat diabetes. NIDDK-funded investigators demonstrated that this drug has anti-inflammatory effects in an animal model of IBD, and subsequently, a NIDDK-sponsored multi-center clinical trial of this drug for treatment of ulcerative colitis has been initiated and is currently in progress. There are approximately 10 new drugs under development for one or both of these diseases, as well as many new studies of existing agents. The novel therapies have emerged from a foundation of basic research supported by the public sector, with drug development steps pursued by the private sector. We are encouraged when industry builds upon NIH-funded basic research discoveries because such activity offers promise of new and more effective treatments for IBD.

We have identified roadblocks to translational research in IBD and steps that can be taken to address them, such as the development of surrogate markers of disease activity and better diagnostic tests. It is also essential to maximize the research investment in animal models of IBD, which can continue to provide insights into the underpinnings of the disease, and also serve as a source of potential genetic discoveries and a means of testing emerging new therapies. Research progress is often hampered

by the difficulty of obtaining access to human samples. To overcome this barrier, NIDDK has recently initiated a repository that will collect and make available to investigators various types of human samples, including blood, biopsies, genetic material, and datasets. Another barrier to clinical research concerns the great complexity of modern clinical trial designs. To facilitate testing of additional new treatments under development, the NIDDK convened a meeting in January 2003 that included representatives from the FDA, industry, and the investigative community, to seek improvements in the design of clinical trials, with emphasis on improving trial endpoints. We will continue to foster such proactive partnerships with the FDA and industry, and also to pursue clinical studies in needed areas that industry does not have a commercial incentive to explore.

As these highlights show, progress in IBD research reflects a convergence of public health need, scientific opportunity, stakeholder input, and the merit of research proposals submitted to the NIH for funding. While many strides have been made, we still recognize that our currently available therapies have many drawbacks and may not provide the adequate symptom relief that patients need. At the same time, however, we are encouraged by the advances being made through research and are committed to accelerating the pace of discovery and translation.

To this end, NIDDK is fostering more cross-cutting initiatives, including emphasis on harnessing powerful new technologies in genomics, proteomics, and molecular imaging to address long-standing problems. Availability of a non-invasive imaging method to assess liver scarring or fibrosis, for example, would transform the clinical management of many liver diseases which now must rely on invasive biopsies. Such cross-cutting initiatives have broad application not only to digestive diseases, but also to a wide array of other diseases within the NIH research mission. By pursuing such endeavors, we can help to maximize NIH research investments by promoting their greatest yield and application.

ENHANCING DIGESTIVE DISEASES RESEARCH

In building the digestive diseases research portfolio, we recognize the importance of input from the scientific and lay community external to the NIH. I would like to provide just a few examples.

Stakeholder input is an important dimension of our planning and program development processes. As noted previously, our joint planning efforts with the Crohn's and Colitis Foundation of America have been very productive. Another example of input that guides NIH program development can be found in the insights and recommendations we obtain from a wide range of conferences and workshops. For example, in digestive diseases, the NIH has sponsored critically important Consensus Development Conferences on hepatitis C, and we recently submitted to the Congress a report on our implementation of the recommendations we received. Just last week, June 28-30, 2004, the NIH sponsored a Consensus Development Conference on celiac disease, an immune-mediated disorder that primarily affects the digestive tract. This disease affects about 1 percent of the U.S. population but is recognized in only about one-tenth of patients using current medical practice. In addition to providing useful guidance to the NIH, we are hopeful that this conference will raise awareness of the disease among medical practitioners and the public in order to promote early, accurate diagnosis and treatment.

On a broader level, the NIH is now embarking on a new planning process for digestive diseases generally, under the auspices of the Digestive Diseases Interagency Coordinating Committee chaired by Dr. James. The first step in that process is the development of a Liver Disease Research Action Plan, in consultation with external scientific and lay experts. An open meeting provided significant input from representatives of professional organizations, patients, and the public. Six draft chapters of the Plan have already been posted on the NIDDK website for additional public comment, and remaining chapters will be posted as they are completed by the Committee. We will be following a similar planning process for other specific digestive diseases, and we believe that this planning effort will produce useful

guideposts for prioritization in NIH program development, and will help synergize cross-cutting research efforts across the NIH.

Finally, I also want to mention that on March 9, Dr. James and I were pleased to present an overview of the NIDDK digestive disease research program, recent advances, and future plans to the newly-created Congressional Digestive Disease Caucus. The Caucus was founded through the leadership of Congresswoman Sue Kelly. We are most appreciative of her commitment, as Chair of the Caucus, to increase awareness of the burden of digestive diseases and to encourage research in this important area.

Mr. Chairman and Members of the Committee, I hope that these few examples convey the firm commitment of the NIH to combating the many digestive diseases within its research mission. Through research, we seek to relieve the burden these chronic, debilitating, frustrating diseases place on individuals, families, and the Nation. I appreciate the opportunity to address the Committee on behalf of the NIH and the NIDDK, and would be pleased to respond to any questions you may have.

Allen M. Spiegel, M.D.

Dr. Allen Spiegel was appointed Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in November 1999. Before becoming Institute Director, he served as the NIDDK's Scientific Director for nine years.

Dr. Spiegel is an internationally recognized researcher and endocrinologist whose work on signal transduction helped to clarify the genetic basis of several endocrine diseases. His research showed that defects in G proteins, the intermediaries between hormone receptors and effectors, could cause inherited disease. Dr. Spiegel and a team of researchers from the NIDDK and the National Human Genome Research Institute (NHGRI) also cloned the multiple endocrine neoplasia type 1 (MEN 1) tumor suppressor gene. A mutated form of the gene causes this inherited tumor predisposition syndrome, as well as sporadic, noninherited forms of endocrine tumor.

Dr. Spiegel earned his bachelor's degree, summa cum laude, from Columbia University in 1967, and his medical degree, cum laude, from Harvard Medical School in 1971. He completed an internship and residency in internal medicine at Massachusetts General Hospital in Boston in 1973, and then came to the NIDDK's Endocrinology Research Training Program. He became a senior investigator in the Metabolic Diseases Branch; in 1985 was promoted to chief of the Molecular Pathophysiology Section; and in 1988 to chief of the Metabolic Diseases Branch.

The author of over 350 scientific papers and two books, Dr. Spiegel has received many awards recognizing his accomplishments, including the Jacobaeus Prize of the Novo Nordisk Insulin Foundation in 1990, the 1996 Komrower Memorial Lecture Award from the Society for the Study of Inborn Errors in Metabolism, and the 1998 Edwin B. Astwood Lecture Award from the Endocrine Society. He has been elected to membership in the American Society for Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the National Academies.