Conclusion: Common Themes and Steps for Implementation

Pressing Need for a Substantial Research Effort in Digestive Diseases

Disorders of the digestive system affect the majority of the U.S. population at some time throughout life. These disorders include a large spectrum of diseases, ranging from acute, foodborne infections to chronic, debilitating diseases, such as inflammatory bowel diseases, and life-threatening conditions, such as cancer and liver failure. Some conditions, such as heartburn and constipation, are so prevalent that many may not view them as disease entities, while a large number of conditions are serious, relatively rare, and often below the radar screen of public attention.

Many decades of NIH-funded research in digestive diseases have led to a detailed understanding of the digestive system, the causes of many diseases, and improved treatments that are now the standard of care. Among the many stories of success are the discovery of *H. pylori* as a major cause of ulcer disease; development of highly effective acid-blocking drugs as treatments for ulcer and heartburn; discovery of the multiple forms of viral hepatitis and development of curative treatments and preventive programs; development of biologic therapies for inflammatory bowel diseases (IBD); and implementation of effective screening programs to prevent colorectal cancer. Dramatic technological innovations in noninvasive imaging and testing, endoscopic procedures, and minimally invasive surgery now permit rapid and accurate diagnosis and treatment of many of the most common, serious problems involving the digestive system that confront healthcare providers on a daily basis, including GI bleeding, abdominal pain, jaundice, and diarrhea.

Despite these advances, many of the current solutions for these problems remain imperfect and costly. In addition, progress on other diseases has occurred at a much slower rate, including the highly prevalent functional GI disorders, many forms of cancer of the digestive system, and pancreatitis. Acute enteric infections remain an important cause of morbidity and mortality, particularly in children in underdeveloped countries. Other conditions associated with the rising prevalence of obesity, such as non-alcoholic steatohepatitis, are likely to increase the burden of digestive diseases in the U.S.

The Director of the NIH, recognizing both the great burden of digestive diseases in the U.S. and the great diversity and complexity of basic, translational, and clinical research approaches that could be brought to bear on the problem, chartered the National Commission on Digestive Diseases to make recommendations to the NIH for future research on digestive diseases, which are described in this long-range research plan.

Common Themes

Although the Commission’s research plan contains a large number of goals and specific objectives, common themes transcend many of these recommendations. These themes include:

1. A focus on major scientific disciplines that are the engine for creating new knowledge;
2. Approaches to the organization of research efforts, such as multidisciplinary basic or clinical research teams and networks, that are required for effective translation of laboratory findings for the benefit of patients with digestive conditions.
Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases

(3) the development of important research resources that provide infrastructure necessary for modern scientific discovery; and (4) efforts that must be undertaken to ensure the availability of a highly specialized workforce to conduct digestive diseases research of the future. It is the position of this Commission that strong support by NIH for coordinated research planning efforts to address these common themes is critical for the continued success of digestive diseases research and, as will become apparent, may be more broadly applicable to many other areas of health and disease-oriented research. Maintaining current momentum and facilitating new research approaches for these common themes by all parties in the research process will encompass the major strategies needed for implementing the research plan. These strategies are not described in any specific order, since all are thought to be of high priority.

Theme 1: Increase the Fundamental Knowledge Base for Understanding Health and Digestive Diseases.

Basic and translational biomedical research is the foundation and core of NIH-supported digestive diseases research. The diverse research programs supported by NIH have provided a robust and steady stream of new knowledge about the normal, healthy digestive system and how it is perturbed in diseases. Research discoveries have provided critical data necessary to develop better ways for preventing, diagnosing, treating, or curing digestive diseases. Steps that are needed to ensure that this process continues are encompassed in the strategies listed below.

Strategy 1.1: Elucidate the molecular basis of biologic and pathologic processes in the digestive system.

Many advances in digestive diseases research have emerged from detailed studies of the molecules, cells, and pathways that underlie health and are perturbed in disease processes. Extensive additional work is needed to obtain a comprehensive understanding of the many cell types in the digestive system, including their normal development and senescence, cell-cell communication, and function as part of whole organs, systems, or organisms. Increasingly, understanding complex conditions, such as the functional GI disorders, will require integration of knowledge about the digestive system with other systems, particularly the central nervous system, and increased understanding of the biologic basis of symptoms and behaviors. These approaches will be the foundation for the discovery of potential targets for intervention in disease processes with drugs or biologics. Increasingly, studies of cell and molecular biology will use not only currently available techniques, but also more complex, integrative systems biology approaches to understand the biology and pathobiology of the digestive system.

Strategy 1.2: Define the genetic basis of digestive diseases.

Medical research has entered an era where comprehensive analysis of whole genomes of organisms will facilitate the discovery of the genetic basis of not only classic genetic diseases, but also of the role of common genetic variation in complex non-Mendelian diseases. For example, recent ground-breaking discoveries concerning the genetics of IBD will likely propel and transform research in numerous areas of translational and clinical research in IBD; parallel approaches offer great potential for advances in many other digestive diseases. The complete unraveling of risk alleles, gene-gene interactions, and gene-environment interactions in the pathogenesis of diseases will undoubtedly be challenging, but the expected benefits of this line of investigation are considerable. These benefits include a better understanding of critical pathways in pathogenesis, clues to potential environmental factors, and potential clinical research advances, including diagnostic
tests, new therapeutic agents, and improved understanding of genetic variability in responses to medicines (pharmacogenomics). In addition, studies of genetics and modifications that influence gene activity (epigenetics) are central to understanding cancers of the digestive system.

**Strategy 1.3: Understand the role of microbes in digestive health and disease.**

The normal human GI tract exists in symbiosis with the complex mixture of microbes inside it, which plays an important role in the function of the digestive system. In addition, infectious agents cause substantial morbidity and mortality throughout the world as the major cause of diarrheal diseases and chronic infectious diseases, such as viral hepatitis. Microbes in the gut also probably contribute to the pathogenesis of a variety of complex disorders, including IBD. Chronic infections, such as *H. pylori* gastritis or chronic viral hepatitis, are important causes of cancer. Further microbiological research is needed to identify and fully understand the pathogenesis of infections of the digestive system, to develop effective strategies, such as vaccines, for their prevention, and to understand the role of the entire internal microbiological ecosystem in maintaining health and contributing to disease. New technologies must be developed to understand the collection of microbes and their genomes (microbiome) and to identify and understand both pathologic and health-maintaining processes caused by microbes. Prevention of diseases caused by infectious agents through vaccination has been one of the greatest contributions of medical science in modern times, but many potentially preventable infectious diseases lack vaccines. Identifying highly effective anti-microbial treatments for both acute and chronic infectious diseases of the digestive system, or ways to tip the balance toward more beneficial microbial species through the use of agents such as prebiotics or probiotics, is an equally high priority. The potential for modifying the microbiome of the digestive system to maintain health is an important new research opportunity that will be pursued through efforts such as the NIH Human Microbiome Project.

**Strategy 1.4: Harness research in immunology, inflammation, and transplantation to improve our understanding of the digestive system and its diseases.**

The digestive system is an important component of the overall immune system of the body. Its unique functions and structures—known collectively as the mucosal immune system—play a critical role in both host defense and tolerance. Many, if not most, diseases of the digestive system are characterized by immune and inflammatory components, which play a central role in disease pathogenesis. Some diseases, such as celiac disease, are characterized by loss of tolerance to ubiquitous dietary antigens. Immunity to alloantigens is a major barrier in transplantation of liver and small bowel. Immunological research has led to important advances, such as the development of protective vaccines and specific therapies, including interferon for viral hepatitis and infliximab for IBD. Further research is needed to define the specific roles of the immune system in a wide range of complex diseases, such as IBD, celiac disease, necrotizing enterocolitis, pancreatitis, viral hepatitis, autoimmune liver diseases, and pre-malignant conditions. Progress in immunological research holds promise for identifying new targets for therapies and potential approaches to disease prevention, as well as amelioration of the barriers to transplantation.
Strategy 1.5: Discover the cellular and molecular basis of development, regeneration, and aging of the digestive system.

Some components of the digestive system have an astonishing capacity for regeneration and self-repair. The one-cell-thick lining of much of the GI tract exhibits rapid turnover of cells, with continuous replacement due to progenitor cells that differentiate into multiple cell types. While hepatocytes have a long lifespan, the liver also has remarkable regenerative capacity under conditions of cell death or resection. While much research in disease pathogenesis has focused on mechanisms of cell death, less attention has been given to the role of regenerative mechanisms in disease processes until recently. Rapid progress in stem cell and developmental biology research has energized this area of biologic research in the digestive system. Relatively little attention has been devoted to changes in the digestive system that occur in aging. Research in stem cell and progenitor cell biology, developmental biology, and aging offers the potential for profound insights into many different diseases, including cancer, as well as the potential means for new cell and tissue engineering-based approaches to treatment.

Strategy 1.6: Support the development and application of new research technologies for digestive diseases research.

Many advances in digestive diseases research have directly resulted from the development of new technologies that permit investigators to approach previously insurmountable problems. The list of technologies is long and includes recombinant DNA techniques, isolation and propagation of clonal cell populations, creation of genetically modified animals, production of monoclonal antibodies, high-throughput DNA sequencing, siRNA inactivation, and high-throughput screening of molecular libraries. Not surprisingly, many of these techniques have found clinical applications. It is expected that new technologies will continue to appear. Newer technologies, such as expression arrays, high-throughput DNA sequencing, proteomics, and metabolomics, generate large amounts of data that have required parallel development of computational methods to analyze the data. High-resolution imaging techniques have revolutionized both research and clinical practice. While support for hypothesis-driven, laboratory-based investigation is the cornerstone of NIH-supported research, continued progress in digestive disease research requires the development and availability of new technologies to enable both basic and clinical research.

Theme 2: Translate Fundamental New Knowledge for the Direct Benefit of Individuals.

To achieve the long-term goals of this plan, increased attention should be devoted to translational research, that is, moving knowledge gained from basic research into patient-based clinical research in digestive diseases and then encouraging adoption of successful practices in the broader healthcare community. In contrast to the prototypic laboratory-based research project, clinical research projects typically require longer time periods to plan and execute, have substantial resource and personnel requirements and higher costs, and often encounter additional regulatory and ethical hurdles not found in animal or in vitro research. Human subjects research, particularly clinical trials, may require interaction with different government agencies, such as the U.S. Food and Drug Administration (FDA), require development of partnerships with industry, and may be subject to the limitations of the existing healthcare system. Meeting these overall requirements for clinical and translational research will require a combination of strategies.
Strategy 2.1: Refine the phenotypes of patients with digestive diseases.

Progress in understanding diseases often requires an iterative process of discovery, observation, and a more refined description of the disease, followed by additional research. A simple example of this process is the discovery and understanding of the different forms of viral hepatitis. Initially recognized only as “infectious” hepatitis, research ultimately led to a detailed understanding of the multiple different forms of hepatitis and discovery of effective treatment and prevention approaches suitable for each form. Assembling the research phenotype of subjects with a particular digestive disease requires an organized approach with common definitions for all clinical and laboratory parameters, standardized methods to obtain laboratory data, and construction of databases that include novel research parameters, such as genetic alleles or response to a new treatment. Increasingly, analysis of disease phenotypes will include not only routine clinical and laboratory observations, but also whole genome information, proteomic profiles of biofluids, serological and microbiological information, data from advanced imaging studies, and psychosocial information. Full understanding of disease processes may also require longitudinal observation of the evolution of disease over time, as in observational natural history studies or in treatment trials. Research in many complex digestive diseases will likely benefit from a concerted, organized effort to define more highly refined disease phenotypes that will underpin the discovery of the fundamental basis of digestive diseases, including symptoms and clinical manifestations, as well as new approaches for prevention and treatment.

Strategy 2.2: Discover biomarkers and surrogate markers for digestive diseases.

Biomarkers and surrogate markers are components of a patient phenotype with implications extending beyond a physiologic or pathologic parameter and providing additional insights into the disease process. Biomarkers correlate with or are predictive of diagnosis, stage, rate of progression, response to treatment, or any other clinically meaningful characteristic. A surrogate marker has the additional feature of being a predictor that can be used to assess the disease process itself and can be used as an endpoint in a clinical trial, faithfully predicting eventual clinical outcomes. Ideal biomarkers and surrogate markers should be observations that can be made noninvasively and repeatedly, with modest cost and high reproducibility. With these goals, much work on identifying biomarkers has concentrated on easily obtainable fluids, such as serum, plasma, urine, or blood, but biomarkers may include any type of observation, such as images or biophysical measurements, like measures of liver stiffness. Many digestive diseases currently have no or only a few imperfect biomarkers. The availability of robust biomarkers and, particularly, surrogate markers would greatly improve the efficiency of clinical trials and potentially lead to improvements in clinical care.

Strategy 2.3: Define the natural history and risk factors for digestive diseases through epidemiologic research.

For many digestive diseases in the U.S., simple population-based descriptive information is lacking or incomplete. Patient registries and long-term natural history studies will permit opportunities to discover many important features of disease processes, such as environmental factors, interacting co-morbidities, response to treatment, quality-of-life information, and health economics data, as well as provide information needed for design of clinical trials. New epidemiologic research is needed for many digestive diseases in order to generate new testable hypotheses, to properly design clinical trials, and to inform all stakeholders in medical policy decisions.
Strategy 2.4: Develop new, innovative technologies for clinical applications.

Research on advanced new technologies has revolutionized diagnosis and treatment of numerous digestive diseases. Among these are endoscopy-based imaging and treatment techniques, minimally invasive surgery, including robotically assisted surgery and tissue ablation, and high-resolution CT, MRI, and PET imaging technologies. Continued improvements in all of these technologies will undoubtedly provide new opportunities for clinical research and improved diagnosis and treatment. Newer technologies, such as nanotechnology, cell-based treatments, tissue engineering, and organ assist or replacement devices also offer promise for the future. Development of these technologies is often primarily supported by industry, and academia-industry partnerships should be encouraged. Additional partnership opportunities exist between the NIH and FDA to ensure that adequate research information is available for informed decision-making regarding the clinical application of new technologies.

Strategy 2.5: Develop new means to prevent, cure, or treat digestive diseases through clinical trials.

For decades, adequately powered, randomized clinical trials have been the cornerstone for evaluating the potential benefit of new drugs, biologics, devices, behavioral treatments, or combinations of these approaches to managing digestive diseases. As noted above, the design and conduct of important clinical trials is complex and often requires the participation of well-trained research teams, availability of subjects willing to participate in the research, research infrastructure, the opportunity to create new resources such as repositories and databases, industry partnerships, adherence to numerous regulatory guidelines, and adequate funding, both in dollar amount and duration. NIH should play an important role in the design and conduct of critical clinical trials, particularly when it is unlikely that the private sector alone will conduct these research trials. The newly developed Clinical and Translational Science Award program of the NIH National Center for Research Resources (NCRR) will play a vital role in academic clinical research programs. To meet the goal of improving health for all, research in digestive diseases supported by NIH must provide information about special populations, such as women, children, minorities, and other disproportionately affected populations that can be used to address health disparities.

Strategy 2.6: Bridge the gap between controlled clinical trials and dissemination of new knowledge into clinical practice.

The discovery that an intervention has efficacy in a carefully controlled, randomized clinical trial is not the final step in translation of a discovery from the laboratory bench to the bedside of a patient with a digestive condition. Further research is often required to demonstrate effectiveness in broad patient populations, to identify and overcome hurdles that prevent widespread adoption of new treatments, to determine how to use therapies in combination or sequentially with other forms of treatment, and to deal with additional post-marketing assessments of the risks and benefits of therapies. These issues may become the subject of professional practice guidelines, but all too often the evidence base is inadequate to provide sound guidance to practitioners for important questions that arise in the clinical setting. Close collaboration between practitioners, industry, NIH, and other government agencies will be required to identify the highest priority areas that require additional clinical research investments to solve these problems. NIH can facilitate this process through education and awareness campaigns and by sponsoring conferences, including consensus development conferences.
**Strategy 2.7: Support clinical research teams.**

As for basic and translational research, clinical research on digestive diseases increasingly requires the formation of teams of individuals with diverse expertise, including outstanding clinical knowledge and leadership skills; expertise in evaluation and treatment of patients; clinical trial design; statistical evaluation; training and monitoring of research support, such as study nurses and coordinators; creation of databases; expertise in the various regulatory and compliance steps needed for clinical research; and knowledge about procedures to effectively collaborate with other research partners, such as industry. Clinical research projects provide important opportunities to leverage the investment in ongoing clinical research by supporting additional ancillary clinical or basic research projects that use patient, specimen, or data resources of the parent study. Clinical research projects are also important for ensuring a continuing pipeline of clinical investigators by providing opportunities for research fellowship and career development programs.

**Theme 3: Develop Research Resources and Infrastructure.**

As indicated in the preceding themes, new technologies and translational research have revolutionized biomedical research. More than ever, the rapid application of research discoveries depends on the availability of not only expensive, complex technologies, but also the appropriate “raw materials” for research, which include various types of specimens and data and highly trained, specialized research teams.

**Strategy 3.1: Increase the availability of specimens, data, and computational methods for research in digestive diseases.**

The lack of availability of well-characterized specimens for research is frequently an insurmountable hurdle for research progress. The lack of sufficient research specimens may be due to different reasons, such as rarity of a disease, difficulty of obtaining inaccessible specimens from humans, limited financial or organizational resources to collect and maintain samples, or an array of technical issues, such as how to define, obtain, and store different types of specimens. The resources needed for research include, among others, cells, cell lines, tissues, sera, antibodies, DNA, and, in the case of human specimens, associated clinical annotations. Increasingly, innovative research involves computational analysis of complex data sets that have been produced by other investigators, exemplified by whole-genome single nucleotide polymorphism (SNP) data that describe individual genetic changes in large numbers of subjects. The NIH and other research organizations must strive to find efficient, cost-effective ways to make the necessary specimens and data sets widely available to investigators. While the cost of building and maintaining repositories is substantial, the cost of these resources is often much lower than the cost of supporting the development of multiple resources and technologies used by individual investigators.

**Strategy 3.2: Create and make available new animal models for digestive diseases research.**

For over a century, progress in biomedical research has depended on experiments conducted with animals to answer questions with approaches that are not feasible in humans or *in vitro* systems. For the foreseeable future, NIH must continue to encourage and support research using animals. A substantial fraction of current research in digestive diseases is conducted in animals. Animals provide access to well-characterized, standardized samples and the potential for detailed physiologic and pathologic observations not possible in humans, as well as
preclinical models to test the safety and efficacy of new therapeutic agents. Genetically modified animals provide the opportunity to study the role of specific genes and pathways. Animals raised in germ-free conditions enable studies of the effect of microbes on normal biology and disease processes. Important techniques, such as high-resolution whole-body imaging, are now available for research in animals. Further development is needed of noninvasive, in vivo diagnostic tools for the assessment of GI phenotypes in animal research, such as small animal MRI, ultrasound, PET, SQUID, and breath tests, among others. Research in model organisms, including worms, flies, and fish, will increasingly permit rapid identification of critical pathways, targets, and potential therapies. To this end, development and utilization of improved data mining tools will facilitate screening and comparison of large-scale genomics data from various animal models of disease. Developing, procuring, and maintaining animals for research are currently very expensive processes, and centralized investment and infrastructure are needed to ensure that such resources are available to the wider community of scientists.

**Strategy 3.3: Support team research.**

Many biomedical research projects require close collaboration of multiple, highly trained individuals with different types of expertise. Increasingly, biomedical research on digestive diseases is characterized by team science. The creation of an effective research team requires not only a vision for the research that needs to be done, but also leadership, organizational skills, stable institutional and financial support, rewards that incentivize and reward all members of the team, as well as more mundane requirements for space, time, technologies, and specimens or data. Innovative research teams of the future will include members with expertise in areas not traditionally found in many biomedical research teams, including physics, mathematics, engineering, and behavioral and social sciences. Collaboration among basic, translational, and clinical investigators will be required for rapid application of new fundamental discoveries to benefit individuals with digestive diseases.

**Theme 4: Maintain a Pipeline of Research Investigators for the Future.**

The long-term success of the Nation’s investment in digestive diseases research requires that steps be taken to ensure a steady stream of entrants into the biomedical workforce, representing the best and brightest new investigators willing to make long-term commitments to careers in research. The research training, individual fellowship, and career development programs of NIH and, more recently, the Loan Repayment Programs for Clinical and Pediatric Research have been important components of maintaining the pipeline. At the conclusion of research training and career development programs, young investigators are at a particularly vulnerable period where career choices may be strongly influenced by grant funding paylines, success rates, and the job satisfaction of their mentors. Mentorship is a critical component of the research training process that does not receive adequate support or recognition. Trainees need to have opportunities to be immersed in the activities of strong research teams where there is adequate infrastructural and educational support. The Nation needs a diverse biomedical workforce to address the numerous digestive diseases research problems of a complex society, and efforts should be taken to ensure adequate development of women and minorities in the workforce.

**Strategy 4.1: Support research training, individual fellowship, and career development programs.**

These programs should encourage innovative research programs designed to attract
outstanding young investigators, support mentors, and provide high-quality educational experiences. Success rates for funding of career awards in digestive diseases should be high enough not to discourage young investigators from choosing a research career path. Stipend and salary support should be increased to keep pace with competitive salary requirements for the different stages of training career positions. Career grants should provide competitive salary support commensurate with the academic rank of the individual.

**Strategy 4.2: Support mentorship.**

In recognition of the critical requirement for mentorship, NIH should explore a variety of potential mechanisms to incentivize and reward mentorship activities. Mentorship is essential for progress in digestive diseases research by the next generation of scientists, yet potential mentors and their institutions are not often given reasons to value mentoring over other activities with more visible benefits, such as grant awards and research publications.

**Strategy 4.3: Maintain a substantially higher success rate for R01-equivalent grants for new investigators in digestive diseases than that of established investigators.**

New investigators must have a reasonable chance of success at obtaining an R01-equivalent award, as it is currently the *de facto* standard required by academic institutions for remaining in an academic research career. This may be achieved by establishing higher paylines for new PIs or using funds set aside expressly for this purpose. NIH should provide bridging support for new investigators who have no means of research support pending review of revised applications.

**Strategy 4.4: Enhance career development educational workshops and conferences.**

Many NIH Institutes and Centers, as well as professional organizations and foundations, sponsor career development conferences and workshops that provide necessary training in the many procedures and processes—the “nuts and bolts”—of career development. These programs are widely viewed as serving an essential need, and they should be expanded to the extent that every young investigator on a digestive diseases research track is able to participate in these workshops. Additional workshop opportunities are needed for mentoring. Research conferences and workshops sponsored by NIH should encourage attendance of young investigators by providing funds specifically for this purpose.

**Strategy 4.5: Reduce the financial burden for new investigators.**

The NIH Loan Repayment Programs for Clinical and Pediatric Research may encourage career choices in research by providing additional support for loan repayment. The success rate for applicants in digestive diseases-related research fields should equal that of NIH overall. Consideration should be given to expanding the loan repayment programs to include investigators in additional research fields besides clinical or pediatric research.

**Strategy 4.6: Assure a diverse workforce.**

Programs should be encouraged to target individuals in under-represented minorities to enter careers in biomedical research with a focus on digestive diseases. Potential steps to be taken include educational programs targeted to high school and college students and dedicated stipends for individuals at later stages of research training.
Strategy 4.7: Provide short-term training in digestive diseases research.

Adoption of complex new technologies in research frequently requires in-depth training, but for a limited period of time. Training programs targeted at short-term training in new technologies for digestive diseases research should be encouraged.

Strategy 4.8: Encourage entry of PhD scientists into translational and clinical research in digestive diseases.

Both nationally and internationally, there is a large pool of young PhD scientists with training in basic scientific disciplines that could potentially be tapped to contribute to the pipeline of translational and clinical investigators in digestive diseases research. Young investigators could be encouraged to concentrate on the digestive system by development of short-term educational programs that expose individuals to research opportunities, experiences of successful PhD investigators, and funding opportunities at NIH in digestive diseases research.

The large number of goals, objectives, and challenges identified in this research plan that must be addressed to comprehensively solve the problems of maintaining digestive health and conquering the many forms of digestive disease represents a formidable challenge to all parties in the research process: the research community of investigators, study participants, professional research and patient advocacy organizations, industry, foundations, and public funding organizations, such as the NIH. It is hoped that each of these research partners will use this research plan as a scientific guidepost to identify ways to promote promising future research opportunities to address the burden of digestive disease. The NIH will continue to solicit broad stakeholder input as it oversees implementation of this long-range research plan for digestive diseases through the activities of such coordinating bodies as the Digestive Diseases Interagency Coordinating Committee.

In particular, a large number of individual steps will need to be taken by these research partners over the 10-year time horizon of the research plan to achieve its goals and objectives. The members of the Commission recognize that research progress often occurs in a “bottom up” fashion, not only rapidly outstripping the best laid efforts of scientific planners, but also as a result of the innovative ideas and initiative of individual scientists and research teams. However, it is also clear that certain types of research projects and program, as well as specific resources and infrastructure, require central, “top-down” organization led by funding institutions with the flexibility to apply optimal mechanisms to address promising research directions as they arise. Because of these considerations and others, the Commission’s recommendations are targeted primarily at the research goals that should be achieved, but not on the administrative, policy, or procedural approaches that NIH might use to achieve those goals. The Commission recommends that the NIH maintain an approach focused on the goals

**STEPS FOR IMPLEMENTATION OF THE RESEARCH GOALS**

This long-range plan for digestive diseases research from the National Commission on Digestive Diseases results from deliberations of the appointed and *ex officio* members of the Commission with the assistance of many individuals who contributed additional valuable ideas and insights. The plan describes numerous broad goals and specific objectives to improve the health of the Nation through basic, translational, and clinical research that will lead to the discovery of improved ways to prevent, treat, or cure a diverse group of conditions that affect the GI tract, liver, biliary system, and exocrine pancreas.
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.