CHALLENGES IN IBD RESEARCH: UPDATING THE SCIENTIFIC AGENDAS 2002

In 1990, the Crohn's & Colitis Foundation of America issued the first "Challenges in IBD Research." Since that time, the advances that have been made in the field have been nothing short of monumental. And what lies in store for the future promises to be even more impressive.

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, affects as many as one million Americans, most of whom are diagnosed before the age of 30. To date, there is still neither a cure nor a means of preventing disease in high-risk children and adults. However, thanks to enormous strides in basic science—particularly in the areas of genetics, immunology, and molecular biology—researchers now have a far more detailed grasp of the processes that lead up to inflammatory bowel disease. And that, in turn, has paved the way for the design and development of groundbreaking new therapies.

In May 2002, the Crohn's and Colitis Foundation of America (CCFA) convened a conference of leading scientists—all specialists in the field of IBD—in Phoenix, AZ. CCFA is the nation's principal organization dedicated to finding a cure for these diseases, sponsoring basic and clinical research of the finest quality. The purpose of the meeting was to define future research priorities aimed at improving current treatment options as well as devising interventions to prevent the onset and relapse of symptoms. To that end, a white paper—based on the proceedings of the conference and entitled "Challenges in IBD Research: Updating the Scientific Agendas"—has been prepared and is now being presented to the public for the first time.

INTRODUCTION

One important realization that has emerged over the past few years is that the intestine represents a unique "hive" of activity. A complex system of active communication exists among the various players in the intestine—including bacteria, immune cells, and the intestinal lining itself. When some miscommunication occurs within this elaborate network, the stage is set for an abnormal immune reaction and, ultimately, chronic intestinal inflammation. Of course, that is not the case with everyone. Only susceptible individuals—those who have a particular genetic make-up—are likely to develop IBD.

These, then, are some of the key issues:

- Who are these susceptible individuals?
- What are the genetic and molecular traits that they share that predispose them to develop IBD?

Those questions and others are best answered when clinical investigators and laboratory-based scientists work together in tandem—which is exactly what they did in order to create the latest version of "Challenges in IBD."

This close collaboration is most unusual in medicine. In the past, basic scientists (individuals who deal with physiology and the underlying mechanisms of disease) worked quite separately from clinical investigators (physicians who actually treat patients on a day-to-day basis). But newer technologies have narrowed the gap between the time a discovery in the arena of basic research is translated into a practical tool for use by physicians. Consequently, the separation between basic and clinical science has become diminished.

While identification of individuals at risk for IBD is one overriding goal, CCFA researchers intend to go even further—making prevention of disease another equally important aim. How can information regarding the origin of IBD be used to block the onset of the inflammatory process in genetically susceptible people? And how can this knowledge also be applied to prevent recurrence of disease in individuals who are in remission (a disease-free state) as a result of medical treatment or surgery?

RESEARCH PRIORITIES: THE COMBINED AGENDA

Brought together for the first time, clinicians and basic scientists dedicated to the study of IBD agreed that the following 11 avenues of research should be considered as top priorities:

- Identification of major susceptibility genes for Crohn's disease and ulcerative colitis. While most of these efforts will involve the general population with IBD, special attention should extend to specific populations such as African-Americans, Hispanics, and Asians. Other groups that also should be looked at more closely are those with onset of disease in childhood and those whose disease extends beyond the gastrointestinal tract.
- Development of specific markers, known as "surrogate markers," that can help track disease activity. These will serve as endpoints in clinical trials. They will also allow investigators and physicians to identify subclinical stages of disease (before symptoms emerge) and to determine the likely prognosis or outcome for patients.
- Development of a thorough and detailed understanding of the regulatory cells and associated pathways in the intestine.
- New clinical trials to determine effects of therapy in particular pathways of IBD—such as after surgery for Crohn's disease or in prevention of pouchitis after colectomy for ulcerative colitis. (Pouchitis may occur after some of the newer operations that eliminate the need to wear an external appliance. The surgeon uses part of the patient's small intestine to create an internal pouch for the storage of stool. If the mucosa, or lining, of this internal pouch becomes inflamed, this complication is known as "pouchitis.")
- Identification of the microbial populations within the intestine and the way in which they interact with each other (microbial ecology).
- Identification of specific microbes that stimulate inappropriate inflammatory responses in the intestine and the mechanisms by which they do so.
- Definition of descriptive terms for patients that can help in creating a molecular classification system of IBD, a system by which the diseases are defined and diagnosed by specific features or appearances that becomes standard.
- Identification of epidemiologic and environmental risk factors that contribute to the development of IBD, including the potential protective effect of smoking in ulcerative colitis and the harmful effect of smoking in Crohn's disease.
- Identification of markers for dysplasia (a pre-cancerous condition) and cancer in people with ulcerative colitis and Crohn's disease.
- Identification of host defense mechanisms, particularly by intestinal epithelial (lining) cells.
- Definition of mechanisms (on both the cellular and molecular level) that are involved in tissue injury and repair.

CLINICAL SCIENCE RESEARCH AGENDA

Although the clinical scientists who participated in the CCFA Phoenix conference are all actively involved in patient care, they also have a strong commitment to and deep interest in research. The chairs of the seven clinical science task force committees, along with the co-chairs, proposed five major directives which they felt should be viewed as priorities for research in "Challenges 2002." They are as follows:

1. The development of surrogate markers of disease activity. These markers are invaluable tools. To be most effective, they should ideally be divided into two distinct types: static ones that can help characterize particular groups or subsets of patients (differentiating them from other subsets) and those that can help track disease activity (including response to therapy) and even help forecast its course. Some surrogate markers should be traditional laboratory measurements, while others should reflect the clinical features of disease or represent specific genetic characteristics. The clinical features of disease refer to the different physical symptoms experienced by patients.

2. The design and implementation of randomized controlled trials of therapy. The postoperative course of patients with Crohn's disease represents a major area of study, and randomized controlled trials (RCTs) represent the ideal way to compare the effect of available therapies. One RCT should be conducted to

compare use of the drug azathioprine with surgical resection. Another RCT should compare three treatment approaches used for the prevention of postoperative recurrence of disease: azathioprine, placebo, and azathioprine combined with an antibiotic.

Yet another important area that would greatly benefit from an RCT is pouchitis—the complication that sometimes develops following ileoanal pouch surgery. Comparison of the use of placebo could be measured against that of a probiotic therapy (the introduction of beneficial bacteria into the intestine).

CCFA researchers intend to go even further, making prevention of disease an equally important aim

Additional proposed RCTs would evaluate the use of combinations of other current treatment regimens which are typically used alone at the present time (such as various combinations of infliximab, azathioprine, methotrexate, and mesalamine) for the induction of remission and prevention of relapse in patients with Crohn's disease and ulcerative colitis. Clinical aspects of pediatric IBD, including evaluation of both established and new treatments in the pediatric setting, should also be studied.

3. Definition of clinical descriptions of patients in order to create a molecular classification of inflammatory bowel disease. The current classification system falls short on a number of levels, leading many investigators to push for a more rigorous way to categorize and describe disease in patients. Molecular descriptors would allow for a more reproducible—and less subjective—classification system.

4. Identification of new epidemiologic and environmental risk factors for IBD, as well as further investigation into the impact of smoking on Crohn's disease. Host-environment interactions, which means your body serves as host to a variety of different bacteria depending on the environment you live in, seem to be central to the IBD process. Yet, not everyone who resides in the same area and is subject to the same exposures goes on to develop IBD. Defining the populations at greatest (and least) risk for IBD may help identify potential environmental factors that contribute to disease, as may examining trends in IBD prevalence and studying the impact of gene-gene factors. Another phenomenon worthy of further investigation is the greater number of men than women among the newly diagnosed cases of Crohn's disease.

5. Identification of biomarkers for dysplasia and cancer in patients with ulcerative colitis and Crohn's disease. Dysplasia (which indicates the presence of precancerous changes) is a significant diagnosis in people with ulcerative colitis. However, pathologists are often inconsistent in detecting and grading this particular condition—making it a completely observer-oriented, subjective measurement. This finding underscores the need for better, more objective histologic criteria. As indicators of cancer activity, these biomarkers could help identify patients who have or may develop neoplasia (cancer). These potential biomarkers could be tested in a longitudinal study, which could also measure the efficacy of various treatments aimed at slowing or halting the progression of dysplasia into cancer.

BASIC SCIENCE RESEARCH AGENDA

Basic scientists strive to understand the underlying physiologic mechanisms that keep a healthy body functioning. They also seek to discover what goes wrong with these mechanisms that subsequently leads to disease. This information offers important clues that guide the discovery of therapy. For example, the drug infliximab (Remicade®), an anti-tumor necrosis factor (TNF) substance, was developed based on the discovery that the protein TNF, which is produced by the immune system, may cause the inflammation associated with Crohn's disease. Thus, blocking TNF is beneficial in Crohn's disease.

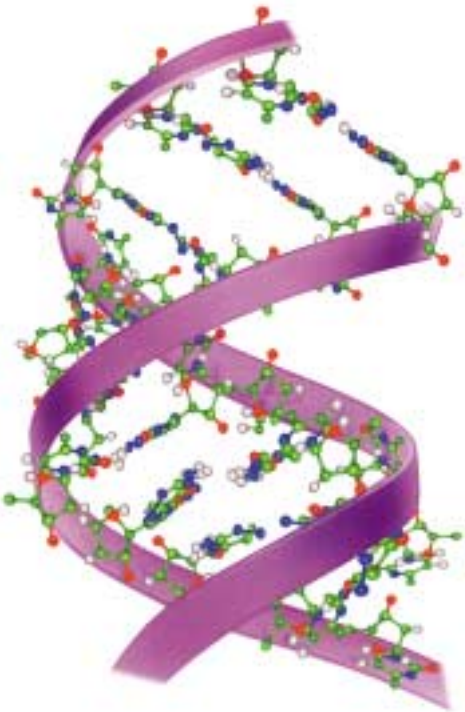
While much is known about IBD, some fundamental questions remain about what triggers various systems to malfunction and exactly what happens in the body to perpetuate the cascade of events that causes unremitting inflammation. Scientists have developed powerful new technologies to decipher these complex diseases at the level of cells, molecules, and genes. To better understand why basic scientists at the Phoenix meeting singled out certain areas, it is helpful to have a basic knowledge of what goes wrong in the body that leads to IBD.

Basic and clinical IBD scientists agreed on 11 top research priorities

The two primary systems involved in IBD are the digestive system and the immune system. The digestive system breaks food down into nutrients, which are

absorbed into the bloodstream, while indigestible food parts are eliminated. Under normal circumstances, bacteria that reside in the large intestine (colon) aid in the digestive process. Because these bacteria have a useful function, they are not disturbed by the immune system.

The role of the immune system is to seek out and destroy disease-causing bacteria, as well as viruses and other foreign invaders. This complex and intricate system involves many different types of cells and methods of attack. One of its tools is inflammation, which is a normal part of the process of injury and repair. When the site of an injury or infection becomes inflamed, that increases blood supply to the area—thereby allowing more white blood cells (the major cells of the immune system) to arrive on the scene. Once the danger has passed, the inflammation subsides and the tissue returns to normal.



In people with IBD, mechanisms in the intestine and the immune system go awry. The immune system launches an assault— most commonly in the colon—which does not go away, causing chronic inflammation and the symptoms of IBD. Genes apparently play a role in these events, too, because IBD runs in families. How ever, until recently, it wasn't known exactly which genes are responsible. Not long ago, though, a gene called NOD2 was linked to IBD, most likely by increasing susceptibility to the disease. More susceptibility genes will undoubtedly be found.

BASIC SCIENCE RESEARCH PRIORITIES

While much is known about IBD, some fundamental questions remain

Because of the complex nature of the sequence of events that occur in people with IBD, several possible targets for new therapies exist. The experts at the meeting identified seven research priorities believed to be the most important for enhancing basic knowledge about IBD, which are likely to produce results within the next five years.

1. Genetics. Identification of susceptibility genes (particularly in African-Americans, Hispanics, Asians, children, and people with certain variations of the diseases).
Crohn's disease and ulcerative colitis are partially inherited diseases, meaning that parents can pass down certain “susceptibility” genes to their children. However, just having the genes does not absolutely foretell a diagnosis of IBD. Some other, as yet unknown, factors must come into play.

But identifying susceptibility genes is a critical, and increasingly successful, area of research. In fact, one gene, called NOD2, has already been found, and work to identify others is ongoing. Susceptibility to Crohn's disease and ulcerative colitis involves a constellation of genes, and scientists now believe that at least six genes contribute to Crohn's disease; another six are responsible for ulcerative colitis. Some of the same genes may be responsible for both diseases.

Knowing these genes may lead to important improvements in diagnosis, treatment, and potentially prevention. Genetic testing may become available for identifying those at greatest risk, allowing for early treatment that may prevent or at least delay symptoms. By understanding what these genes do in the body, scientists can gain a better understanding of the disease, and it may be possible to determine what co-factor(s) set off the sequence of detrimental events of IBD.

2. Immunoregulation. Gain an understanding of how regulatory cells of the immune system tolerate beneficial bacteria under normal conditions but launch an attack against them in people who are susceptible to IBD.
Normally, the immune system does not launch attacks against the helpful bacteria that constantly reside in the colon. Cells called “regulatory cells” identify the bacteria as not harmful and suppress any attack.

Genes play a role in these events because IBD runs in families

Researchers believe that an important clue to the IBD puzzle can be obtained by investigating the biological mechanisms by which regulatory cells work. This involves identifying which cells and chemicals of the immune system are involved in the system of regulation and understanding how they communicate with one another.

It would also be helpful to understand how the regulatory cells interact with the lining of the intestine (epithelium), the bacteria, and other cells. Scientists believe, for example, that the susceptibility gene NOD2 may have a role in the function of regulatory cells. Therefore, further research is needed on the involvement of this gene. By understanding why regulatory cells fail to suppress an immune attack against bacteria in the colon, it may be possible eventually to develop treatments aimed at correcting this malfunction.

3. Signal transduction. Determination of the signaling pathways of the NOD2 gene, other susceptibility genes, and cells involved in IBD.
Signal transduction is essentially a form of communication within cells. It refers to signals sent from outside cells to inside. When substances dock onto receptors on the surface of cells, they transmit information to the inside of the cell. The transmitted information is intended to make changes to the cell's function or the expression of genes. Genetic material resides in the nucleus of all cells.

In IBD, information is transmitted that affects immune system cells, cells of the lining of the intestines, and genes, such as NOD2, that make people susceptible to IBD. Scientists believe that a more detailed understanding of how genes and IBD-related cells process signals could accelerate progress toward treating IBD.

4. Host/microbial interactions. Using rodents as models, examination of the immune response to certain types of bacteria.
As noted previously, the immune system fails to suppress an attack against bacteria in the colon. This may be due to an imbalance between "effector" T cells, which are responsible for launching an immune attack, and regulatory T cells, which stop it.

T cells of the immune system—whether initiating (effector cells) or suppressing (regulatory cells) an attack—are spurred to action by the presence of bacteria, or possibly other substances. Consequently, vital information can be gained by understanding which components of bacteria activate effector and regulatory T cells.

Research in this area can be effectively carried out in gnotobiotic rodents. These experimental animals are born and raised within a germ-free environment—thereby allowing scientists to introduce specific types of bacteria. The goal is to identify the bacteria, and ultimately their associated substances, that activate disease-causing and protective immune responses, and to understand the complex interaction between the bacteria and physiologic characteristics of the host.

5. Intestinal microecology. Identification of the bacteria that reside in the intestine.
Related to the study of host/microbial interactions, research should provide a more thorough accounting of all the species of bacteria in the intestines, in order to define which ones are the most responsible for IBD.

Many species of bacteria exist, and these differ in their ability to cause inflammation. Additionally, people, due to their genetic make-up, may differ in their individual sensitivity to various strains of bacteria.

People may differ in their individual sensitivity to various strains of bacteria

Scientists now have tools that give them a greater ability to define the populations of bacterial species in both mice and humans. These tools make it possible to know what species are present, where in the intestine they are located, and how they communicate with one another and the human body. These studies may help researchers discover which species of bacteria may be responsible for stimulating IBD.

6. Epithelial cell biology. Identification of the process by which intestinal epithelial cells interact with the immune system to prevent disease-causing bacteria and other substances from causing harm.
The layer of cells lining the intestinal wall protects the rest of the body from potentially harmful bacteria that reside inside the intestine. First, the cells are extremely close together, producing an effective barrier. Second, a layer of mucus covers the top of the cells, further hindering passage. And third, the epithelial cells send sig-

nals to immune cells, calling for an attack against harmful substances and no action against harmless bacteria.

What scientists don't know is just how the epithelium forms a functional barrier or signals the immune system, and how the epithelial cells know which bacteria are beneficial and which should be attacked. Understanding this could lead to breakthroughs in treatment methods.

7. Tissue injury and fibrogenesis (scarring). Definition of the mechanisms that cause injury to tissues and the body's methods for repairing it. The prolonged inflammation in the intestine that characterizes IBD may lead to permanent scarring of the intestinal wall. This is more common in people with Crohn's disease than in those with ulcerative colitis. By gaining a more thorough understanding of why and how this scarring occurs, it may be possible to find treatments that prevent it.

LYNNE CHRISTENSEN
AND NINA TOBIER

CHALLENGES IN IBD RESEARCH

Chairman: Charles O. Elson, MD

CLINICAL SCIENCE

Co-Chairs:
Stephan R. Targan, MD
William Sandborn, MD

Members at Large
Stephen P. Hanauer, MD
Daniel Present, MD

Task Force Chairs:
Clinical phenotyping
Marla Dubinsky, MD

Dysplasia and cancer
Teresa A. Brentnall, MD

Epidemiology and natural history
Edward V. Loftus, MD

Imaging, laboratory, serologic and genetic evaluation for diagnosis and prognosis
John D. Rioux, PhD

Medical therapy
Bruce Sands, MD

Outcome measures for clinical trials
Brian Feagan, MD

Surgical therapy
Robin S. McLeod, MD

BASIC SCIENCE

Co-Chairs:
R. Balfour Sartor, MD
Charles O. Elson, MD

Members at Large:
Stephen P. James, MD
Richard P. MacDermott, MD

Task Force Chairs:
Epithelial cell biology/barrier function
Hans-Christian Reinecker, MD

Genetics
Jerome I. Rotter, MD

Host/bacteria interactions
Richard S. Blumberg, MD

Immunoregulation
Lloyd F. Mayer, MD

Intestinal microecology
Jonathan Braun, MD, PhD

Signal transduction
Kim Barrett, PhD

Tissue injury/fibrogenesis
William F. Stenson, MD