Management of Inflammatory Bowel Disease

Burton I. Korelitz
Norman Sohn

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Burton I. Korelitz, M.D.
Chief, Section of Gastroenterology
Lenox Hill Hospital
Cornell University Medical College
New York, New York

Norman Sohn, M.D.
Associate Physician
Lenox Hill Hospital
Department of Surgery
Clinical Assistant Professor of Surgery
Cornell University Medical College
New York, New York

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CONTRIBUTORS

Daniel Adler, M.D.
Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

Theodore Bayless, M.D.
Professor of Medicine
The Johns Hopkins University
Clinical Director
The Meyerhoff Digestive Diseases–Inflammatory Bowel Disease Center
The Johns Hopkins Hospital
Baltimore, Maryland

Zane Cohen, M.D.
Professor, University of Toronto
Head, Department of Colorectal Surgery
Toronto General Hospital
Toronto, Canada

Steven M. Faber, M.D.
Past Fellow in Gastroenterology
Lenox Hill Hospital
New York, New York

Joseph B. Felder, M.D.
Fellow in Gastroenterology
Lenox Hill Hospital
New York, New York

Michael S. Frank, M.D.
Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

Myron D. Goldberg, M.D.
Associate Physician
Section of Gastroenterology
Assistant Chief
Gastrointestinal Endoscopy Unit
Lenox Hill Hospital
New York, New York

Bette Harig, M.D.
Attending Physician
Department of Radiology
Lenox Hill Hospital
New York, New York

Arthur D. Heller, M.D.
Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

Henry Janowitz, M.D.
Chief Emeritus
Division of Gastroenterology
Department of Medicine
Mount Sinai Medical Center
New York, New York

Marvin A. Kaplan, M.D.
Adjunt Physician
Section of Psychiatry
Lenox Hill Hospital
New York, New York

Albert B. Knapp, M.D.
Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

Burton I. Korelitz, M.D.
Chief
Section of Gastroenterology
Lenox Hill Hospital
Cornell University Medical College
New York, New York

Michael P. Krumholz, M.D.
Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

Gregory V. Lauwers, M.D.
Fellow
Department of Pathology
Memorial Hospital
New York, New York

Raul N. Lugo, M.D.
Adjunct Surgeon
Lenox Hill Hospital
New York, New York

Robert A. Mendelsohn, M.D.
Fellow in Gastroenterology
Lenox Hill Hospital
New York, New York

Mark A. Peppercorn, M.D.
Associate Professor of Medicine
Harvard Medical School
Physician, Beth Israel Hospital
Section of Gastroenterology
Department of Medicine
Boston, Massachusetts

Daniel H. Present, M.D.
Clinical Professor of Medicine
Mount Sinai School of Medicine
Attending Physician
Section of Gastroenterology
Department of Medicine
Mount Sinai Medical Center
New York, New York

David B. Sachar, M.D.
Professor of Medicine
Mount Sinai School of Medicine
Director, Division of Gastroenterology
Department of Medicine
New York, New York

Norman Sohn, M.D.
Associate Physician
Lenox Hill Hospital
Department of Surgery
Clinical Assistant Professor of Surgery
Cornell University Medical College
New York, New York

Stephan R. Targan, M.D.
Professor of Medicine
University of California at Los Angeles
Director, UCLA Center for Health Sciences
Inflammatory Bowel Disease Research and Clinical Center
Los Angeles, California

Jerome D. Waye, M.D.
Clinical Professor of Medicine
Mount Sinai School of Medicine
Chief, Gastrointestinal Endoscopy Unit
Lenox Hill Hospital
New York, New York

Michael A. Weinstein, M.D.
Associate Physician
Department of Surgery
Lenox Hill Hospital
New York, New York

Audrey Woolrich, M.D.
Assistant Adjunct Physician
Section of Gastroenterology
Lenox Hill Hospital
New York, New York

PREFACE

The rationale for grouping ulcerative colitis with Crohn's disease (inflammatory bowel disease) has historical support. The medical literature included descriptions of both diseases in the latter half of the 19th century, both cause inflammation of the colon, they share many symptoms, in some instances the differential diagnosis may be very difficult, and the cause of each remains unknown. Furthermore, one member of a family may have Crohn's disease, and another have ulcerative colitis. Both processes are prone to the late complication of carcinoma at a site of previous involvement. Finally, the investigators and students of one disease usually have contributed to understanding of the other disease as well.

The prevalence of Crohn's disease is remarkable when we consider that 60 years ago, as the classic description from Mt. Sinai Hospital was being prepared, the disease was rare. Although the cause remains elusive, we must acknowledge the natural course, complications, choices of drug therapy and both their positive and negative effects, and the risks of surgical intervention, including the likelihood of recurrence and its own subsequent complications. Therapy must try to combat this disease as skillfully as possible, with consideration of indications and timing of drug and surgical intervention. In this regard, the choice forms of management have been controversial even among the most experienced.

The incidence of ulcerative colitis seems to be stable. Nonsurgical management has improved, however, and urgent surgery is much less often required. This has provided many patients the opportunity to have pouches shaped by the surgeon on an elective basis. Successful

nonsurgical management also has created the opportunity for greater likelihood of development of carcinoma of the rectum or colon. These considerations also introduce controversy.

Burton I. Korelitz, M.D.
Norman Sohn, M.D.

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PART 1

Overview and Etiology

Chapter 1

Recent Developments in Inflammatory Bowel Disease

Burton I. Korelitz

There have been many developments in *inflammatory bowel disease* (IBD) during the past 4 years. First, however, what has not changed?

1. The causes of both Crohn's disease and ulcerative colitis remain unknown.
2. Evidence for an infectious cause, which dominated the scene a few years ago, has really not been sustained.
3. Crohn's disease is not cured by any form of surgery; that remains a fact.
4. Many resections continue to be performed for perirectal abscesses and fistulas, small bowel obstruction, and toxic megacolon despite the efficacy of minor operative procedures and nonoperative techniques.
5. The role of antibiotics in the treatment of Crohn's disease has not yet been submitted to any trials.

What is it that has changed?

1. New epidemiologic factors have been identified that influence cause and course, and these are challenging.
2. Provocation of IBD by nonsteroidal anti-inflammatory drugs has become recognized.
3. New types of colitis, such as collagenous and microscopic colitis, have been defined.
4. The mechanism of diversion colitis is now being explained, and it is of particular pertinence in Crohn's disease.

5. The need for surgery in ulcerative colitis has been decreased.
6. As a corollary to the preceding, more patients retain the colon and are at risk of development of carcinoma.
7. The need for surgery in Crohn's disease has been at least postponed if not reduced; therefore we see less malabsorption and less short bowel syndrome.
8. The risk of cancer complicating long-standing Crohn's disease, particularly when it involves the colon, is increasing and is approaching that of ulcerative colitis.
9. The role of both oral and rectal 5-aminosalicylic acid (5-ASA) preparations is becoming better established, the first not only for ulcerative colitis but also for Crohn's disease.
10. New steroids that are absorbed but have no glucocorticoid effect, and others not absorbed at all, are now available for trial.
11. Utilization of immunosuppressive drugs has increased as experience with efficacy and toxicity has accumulated. The role of 6-mercaptopurine (6-MP) in treatment of Crohn's disease has been established, and its use in treatment of resistant cases has now been acknowledged by gastroenterologists all over the country. Cyclosporine has arrived, as have methotrexate and hydroxychloroquine sulfate (Plaquenil).
12. The role of surveillance for dysplasia in carcinoma has become better established, and the clinical recommendations based on these findings are being clarified.
13. The early enthusiasm resulting from the introduction of the ileo-pouch-anal anastomosis for ulcerative colitis has now been tempered to some extent. There is renewed enthusiasm for some of the older procedures. The best choice of operation for the individual patient is being sought.
14. Experience has led us not only to new approaches in therapy but also to recognition of errors that have occurred in the past.

Chapter 2

Progress in Understanding the Pathogenesis of Inflammatory Bowel Disease: Infectious and Immunologic Factors

Stephan Targan

Advances in understanding the cause, genetic factors, and infectious process of inflammatory bowel disease (IBD) have been made recently. These advances have identified new directions for study of the cause of, and new treatments for, IBD.[13a] Potential contributors to the pathogenesis of IBD include elements that might predispose to, trigger, and perpetuate the disease. Tissue damage might be due to a direct attack by the mucosal immune system on a specific target, such as the surface, or glandular, epithelial cell. A nonspecific outcome of disordered mucosal immune regulation, with uncontrolled overreactivity to environmental antigens based on a defective down-regulation of this response, may perpetuate the damage. Genetic predisposing factors might operate at the level of the "target" cell or at the level of the mucosal immune system.

Evidence to suggest genetic predisposing factors in these diseases is based on the percentage of concordance in monozygotic twins and dizygotic twins. In Crohn's disease, 67% of monozygotic twins are concordant, vs. only 3% of dizygotic twins. Among twins with ulcerative colitis, 27% of monozygotic twins are concordant, and no dizygotic twins are concordant.[18] The concordance among monozygotic twins, then, is greater than among dizygotic twins. There was no concordance among mixed pairs. Given the evidence of genetic predisposition, studies have begun in an attempt to demonstrate linkage. Linkage refers to the exist-

ence of two loci located so close together on chromosomes that they are inherited as a unit.[18]

Demonstrating HLA linkage in IBD is particularly complicated. In work performed previously, linkage analyses of IBD and HLA were limited to samples of affected sib-pairs. Furthermore, the various forms of these diseases could reflect a genetic heterogeneity that greatly limits the power of the sib-pair method. Geneticists have recently developed a new linkage method for extended pedigrees, which employs the study of affected relative pairs.[18] This method searches for shared alleles among affected relatives. Since the chance of concordance decreases the more distantly related pairs of patients with disease may be, fewer patients or pairs are required to establish significance. A significant association could be made within as few as one family if concordance among third cousins can be determined.

This method has been applied to families of patients with IBD. Recent genetic investigations have determined an HLA linkage to the presence of IBD in families with multiple affected members. The fact that 20 years of prior research have not yielded consistent findings regarding linkage is due to the likelihood that these diseases are genetically heterogeneous. The evidence points to forms of IBD that can be demonstrated to be linked to HLA, and forms of IBD in which no linkage can be determined (Rotter et al, unpublished data).

The HLA region has been identified in IBD. Candidate genes for IBD have been advanced. Genetic studies have defined an HLA (HLA-DR, DQ haplotype) and C3 (C3F related) abnormality to be associated with Crohn's disease (H. Toyoda, unpublished data). An HLA (HLA-DR2 haplotype) may be associated with ulcerative colitis. Using subclinical markers, family studies of patients with Crohn's disease have defined C3 dysfunctional and intestinal permeability to be increased in family members of patients with Crohn's disease. Antibodies to epithelial antigens are increased in a very large number of family members of patients with IBD; suggesting this represents a common infectious exposure and not an underlying genetic susceptibility. Family studies will soon be performed to investigate the relationship of colonic mucins and antineutrophil cytoplasmic antibodies in ulcerative colitis.

The implication of the inconsistency of genetic data among various groups is that genetically distinct forms of the disease exist. This signals the need to begin considering subgroups of IBD in future investigations. The development of "reagent grade" patients is required to perform such studies adequately. Such reagent grade patients can be determined by analysis of all available clinical and subclinical markers, and then groups of individuals with like profiles considered individually in