INFLAMMATORY BOWEL DISEASES 1990

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INFLAMMATORY BOWEL DISEASES 1990

Proceedings of the Third International Symposium on Inflammatory Bowel Diseases, Jerusalem, September 10–13, 1989

edited by

D. RACHMILEWITZ

Hadassah University Hospital, Jerusalem, Israel

and

J. ZIMMERMAN

Hadassah University Hospital, Jerusalem, Israel

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PREFACE

The Third International Symposium on Inflammatory Bowel Diseases was held in Jerusalem during September 10-13, 1989. Four hundred physicians and scientists from 25 countries attended the meeting. The symposium was organized into five panels devoted to state of the art reviews of the latest findings and approaches on the etiology, pathogenesis, metabolic implications, clinical assessment of disease activity and the medical management of IBD. Several issues were discussed in debate form. The last panel was dedicated to discussion of three patients with computer assisted active participation of all the attendants.

In addition, 63 abstracts were presented as posters, all of which were published in the Book of Abstracts.

The organizing committee gratefully acknowledges the contributors who presented their work in clear and concise manner and the participants, whose active part in the discussions contributed to the success of the meeting.

The Jerusalem International Symposium on Inflammatory Bowel Diseases has become a tradition that will continue with the Fourth Symposium to be convened in September 1993.

Joseph Zimmerman, M.D. Daniel Rachmilewitz, M.D.

LIST OF FIRST AUTHORS

Theodore M. Bayless,
Johns Hopkins University
School of Medicine,
Baltimore, Maryland.

Michael D. Blackstone,
University of Chicago,
Chicago, Illinois.

Charles O. Elson,
Division of Gastroenterology,
The University of Alabama
at Birmingham,
Birmingham, Alabama.

Allen L. Ginsberg,
George Washington
University Clinic,
2150 Penn Avenue N.W.,
Washington DC.

Stephen B. Hanauer,
University of Chicago Hospital,
Chicago, Illinois.

Henry Janowitz,
1075 Park Avenue,
New York, New York.

Gunnar Jarneröt,
Department of Medicine,
Orebro Medical Centre Hospital,
Orebro, Sweden.

Richard A. Kozarek,
Department of Medicine,
Virginia Mason Clinic,
Seattle, Washington.

Irwin H. Rosenberg,
Tufts University,
Human Nutrition Research Center,
Boston, Massachusetts.

Jerome I. Rotter,
Division of Medical Genetics,
UCLA School of Medicine,
Cedars-Sinai Medical Center,
Los Angeles, California.

Michael J. Langman,
Department of Medicine,
Queen Elizabeth Hospital,
Birmingham, England.

J.E. Lennard-Jones,
St. Mark's Hospital,
City Road,
London, England.

James Lee Madara,
Department of Pathology,
Brigham and Women's Hospital,
Boston, Massachusetts.

Lloyd F. Mayer,
Mount Sinai Hospital,
New York, New York.

Daniel K. Podolsky,
Gastrointestinal Unit,
Massachusetts General Hospital,
Harvard Medical School,
Boston, Massachusetts.

Daniel Present,
12 East 86th Street,
New York, New York.

Daniel Rachmilewitz,
Department of Medicine,
Hadassah University Hospital,
Mount Scopus,
Jerusalem, Israel.

Robert Henry Riddell,
Department of Pathology,
McMaster University,
Hamilton, Ontario.

Michael D. Sitrin,
Section of Gastroenterology,
University of Chicago,
Chicago, Illinois.

W. Stenson,
Washington University
School of Medicine,
St. Louis, Missouri.

David B. Sachar,
Mount Sinai School of Medicine,
New York, New York.

F.G. Seidman,
Gastroenterology Division,
University of Montreal,
Ste. Justine Hospital,
Montreal, Quebec.

Walter R. Thayer,
Rhode Island Hospital,
Providence, Rhode Island.

Alan B.R. Thomson,
Department of Medicine,
University of Alberta,
Edmonton, Canada.

Guido N. Tytgat,
University of Amsterdam,
Academic Medical Centre,
Amsterdam, Holland.

IBD: THE PRESENT SITUATION AND A GLIMPSE OF THE PROMISED LAND

H.D. JANOWITZ
Mount Sinai Medical Center
Division of Gastroenterology
One Gustave L. Levy Place
New York, NY 10029

The only excuse for my opening remarks on the present situation in IBD is that my memory of our field probably goes back further than anyone in this audience, save one. Like a more exalted predecessor who hoped to reach Canaan, I have been wandering for more than 40 years in the, at times, trackless desert and I think I have caught a glimpse of the promised land.

While you share with me our mutual dismay that after so many years of effort in the laboratory and at the bedside we know so little abut the cause or causes of IBD, and have so limited a kind of medicines, it is also my assigned task to review the distance we have come in the last two-and-a-half generations, or, at the least, since the first of these international symposia.

Let me recall with what anxiety, and how daunting, a young physician entering the wards of the Mount Sinai Hospital in 1939 found the problems of treating patients with the non-specific inflammatory bowel diseases. Ulcerative colitis was clearly distinguishable from regional ileitis. Occult bleeding could be separated from gross blood by the guaiac test. Radiographs of the small bowel, barium enemas of the colon and the rigid sigmoidoscope were the only imaging techniques. Intravenous fluids and blood transfusions were the main therapeutic supportive measures. An abscess, intra-abdominal or perineal, could be drained, and portions of the small or large bowel could be resected, or the colon extirpated leaving behind a difficult to manage ileostomy. Not a single effective anti-inflammatory drug was in sight, and instilling acquaflavin or gentian violet through a cecostomy had been recently abandoned for the treatment of ulcerative colitis. No wonder the trepidation of this nervous intern.

What are the secure advances in the present situation?

(1) The list of idiopathic IBD's has grown smaller: Yersinia, compylobacter, and C. difficile associated colitis, ischemic colitis and diversionary colitis have been separated off and out.

(2) Much has been learned regarding the "natural history" of the idiopathic groups. Whatever dogmas we hold to, the variations of the courses of ulcerative colitis and Crohn's disease have been charted in amazing detail.

(2) Our store of information regarding the potentiality of a whole host of microorganisms: viral (herpetic, cytomagalic), and bacterial (mycobacterial) for causing inflammatory bowel processes has exploded, especially in the patients with drug or HIV induced immunosuppression.

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(4) We can now study with a host of techniques the earliest stages and progression of recurrent Crohn's disease after resection; and the inflammatory changes in ileal pouches of patients who have had ulcerative colitis. The human models we have longed for are under our eyes and in our hands. The cotton top tamarin, with its neonatal ulcerative colitis and almost invariable carcinoma of the colon, offers an intriguing and exciting animal model of ulcerative colitis.

(5) We have begun to understand, as well as study, the biochemical changes in colonic tissues associated with the inflammatory pathologic and immunologic changes, and the future will include more than the leukotrienes.

(6) The brilliant and elegantly simple studies of Truelove and his associates on the role of the 5-ASA component of our oldest standby drug (sulfasalazine) has opened the way for further biochemically targeted anti-inflammatory therapy in IBD. The prompt response of the inflamed rectal mucosa in ulcerative colitis to large doses of mesolazine must lead us further along the line.

(7) The flood of newer variants of 5-ASA ha made every general practitioner of gastroenterology demand as a common-place the publication of controlled trials for all our medicines and modalities in IBD, especially as the role of the placebo becomes clarified.

(8) The richness of our immunological information no longer seems such a trackless welter as defects at the intestinal mucosal cellular level are being investigated with clues for therapeutic intervention. At the same time our empirical use of our standard conventional medications has become rationalized with the information regarding their role in the immunological and biochemical chain of inflammation.

(9) We certainly can help our patients survive the catastrophes of IBD, and have improved the quality of their lives by two major advances:

(1) Our general supportive measures including the judicious use of hyperalimentation (total parenteral alimentation) and (2) really important imaginative surgical advances which have included: a) Brooke's ileostomy which changed for the better the daily life of my patients during my lifetime b) the concept of the continent ileostomy of Kock c) the ileo anal pull through, mucosal stripping and pelvic pouch despite its complications d) the development of more and more bowel saving operations in stenotic Crohn's disease e) the complete turn around (in my clinical experiences) with perianal disease by the use of Park's concept of the intersphincteric abscess which can be successfully drained.

(10) The daily management of inflammatory bowel disease activity in both C.U.C. and Crohn's has been made easier for us and better for our patients by a greater list of anti-inflammatory medications:

1) the less toxic 5-ASA and its oral or topical use.

2) the long term use of less toxic steroids which are cleared rapidly by the liver including beclamethasone dipropionate and others on the horizon.

3) use of antibiotics including metronidazole in place of steroids in Crohn's disease.

4) greater recognition of the effacicy and safety of such immunosuppressants as azathioprine and 6-mercaptopurine, with cyclosporine still being judged.

5) such drugs as chloroquine and hydroxychloraquin and omega-3 fatty acids wait in the wings while their use in lupus and rheumatoid arthritis is explored and extended.

We certainly have the feeling that we have more ammunition to fire than ever before, yet wonder if our current medications are not simply old cures in new bottles.

(11) The beginnings of the attempt to define more clearly the risk of neoplasm of the gut and elsewhere in IBD which must lead to a more rational program of cancer surveillance without alarming our patients.

(12) The development in many countries of the partnership between the lay public, clinical and research teams and practitioners in the form of National Foundations for Crohn's Disease and Ulcerative Colitis whose growth and development have given me great personal pleasure, and especially the patients self help groups.

(13) No insignificant development of our concentrated interest in IBD has been the concomitant increase of our knowledge of the physiology of the colon (especially the role of muscular activity, electrolyte movements, and the recent studies of the biochemical requirements of the mucosal cell for nutritional survival which already has its by-products in the focus on the volatile fatty acids and "diversionary colitis"), as well as the increasing knowledge of the colonic mucosal glycoproteins.

I am sure the material to be presented at this 3rd International Symposium will bring us closer to the frontier. We shall have a clearer view from Mount Pisgah of the Promised Land, and some in this audience will cross the border and lead us on in.

IS IBD A GENETIC DISEASE?

J.I. ROTTER, T. SHOHAT, C.M. VADHEIM
Division of Medical Genetics
Departments of Medicine and Pediatrics
Cedars-Sinai Medical Center
8700 Beverly Boulevard
Los Angeles, California 90048

ABSTRACT. There is substantial evidence that genetic factors play a role, possibly even the preeminent role, in the predisposition to the inflammatory bowel diseases (IBD) - Crohn's disease (CD) and ulcerative colitis (UC). The lines of evidence include ethnic differences in disease frequency, familial aggregation, spouse and twin studies, and the existence of genetic syndromes that feature IBD. Indeed, some of the responsible genes are being identified, by a combination of genetic marker and family based physiologic studies. The best evidence exists for the HLA and complement systems. Important physiologic abnormalities being examined autoantibodies, permeability, and colonic mucins. To further these advances, and to utilize the power of modern linkage technology and human gene mapping, an international registry of mapping cell lines from IBD families is being established. The existence of a substantial genetic component to IBD susceptibility means that etiologic studies must include a consideration of the genetic components. Genetic studies will aid in the delineation of the basic etiologies of IBD, which should lead to new therapies, and will eventually provide the means to identify those at highest risk for disease prevention.

1. IBD IS A GENETIC DISEASE!

1.1. Ethnic and familial aggregation.

Epidemiologic data regarding IBD demonstrate dramatic differences in disease frequency between geographic areas and ethnic groups. Familial aggregation, i.e. an increased occurrence of disease in relatives is also well documented. These data suggest, but by themselves do not prove, that genetic factors may play a role in the etiology of IBD. From a genetic point of view, perhaps the most interesting epidemiologic observations are the reports of comparatively higher prevalence rates for the Jewish populations in the USA, Europe, and South Africa, in comparison with those of the general population in these areas (1-3). However, the frequency of IBD among Jews, although usually considerably higher than in the general population in which they reside, varies as well among the different historical ethnic subgroups within the Jewish population.

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The data from Israel show that IBD tends to occur significantly more often in Ashkenazi Jews of American or European origin than in Sephardic or Oriental Jews of North African and Asian origin (3). To further explore this issue, the authors have investigated the country of origin of U.S. Ashkenazi Jewish patients with IBD. A significant excess of patients of middle European origin relative to those of Polish/Russian origin was observed when compared to similar data from the general Jewish population (4). These data suggest that Jewish patients with IBD probably represent a non-random genetically predisposed subset of the Jewish population, and thus provide further evidence for the genetic contribution to IBD.

Familial aggregation is clearly increased in IBD, although the data do not fit a simple Mendelian pattern of inheritance. The proportion of IBD patients with a positive family history varies considerably between case series, but it is usually in the range of 10-20 percent (1,5-7). More important data are the actual observed empiric risks (i.e. recurrence risks) for IBD in different classes of first-degree relative of IBD patients. For siblings, these estimates range from 1 to 5% (1,7).

However, a great deal more data is needed to provide accurate familial risks for both CD and UC, and for the various classes of relatives. Accurate estimates of such risks are very much needed, both for the purposes of genetic counseling and of genetic modeling. For example, it is likely that many offspring of patients have not reached the age at which they would manifest symptoms, and the risk to offspring is therefore likely underestimated by the majority of studies. In such a case, a more meaningful result is obtained when an age corrected analysis is performed, as was recently described in a study by the authors (7). The use of age-specific incidence data allowed the calculation of corrected empiric risk estimates to offspring for IBD 8.9%, to siblings of 8.8%, and 3.5% to parents (7). As they are constructed so as to provide lifetime estimates of risk, these estimates are the most appropriate both for genetic counseling and genetic modeling. Unfortunately, such corrected rates have only been reported for the U.S. Ashkenazi Jewish population, and thus similar studies and analyses are needed both for different ethnic groups, and from multiple countries.

1.2. Familial aggregation is due in large part to genetic factors.

While familial aggregation can be due to environmental factors alone, the increased monozygotic twin concordance rates, the rarity of IBD concordance in spouses, and the numerous instances of family members with onset separated greatly in time, argue for a major genetic component to disease susceptibility. The available twin data report a high concordance (i.e. both twins affected) for CD, and a lesser concordance for UC among monozygotic (MZ) twins (1,8). Among the dizygotic (DZ) twins, none of the reported UC pairs are concordant, and only 8% of dizygotic twins with CD are concordant. Interestingly, there has never been reported a "mixed" MZ twin pair, that is where one twin was affected with UC and the other with CD. Most early twin studies are actually case reports, which tend to be biased toward the reporting of concordant pairs. However a more recent study by Tysk et al (8) represents an unselected set of twins with IBD from the Swedish twin registry. This study confirms that

there is no increased concordance for either CD or UC in DZ twins over that expected from sibling risks. In addition, the MZ concordance rate is higher for both diseases than comparable rates for DZ twins or sibs, strengthening the argument that genetic factors account for much of the familial aggregation.

Spouse studies can provide important clues regarding the contributions of genetic susceptibility and environmental exposure. If genetic predisposition is not important in the etiology of a disease, then spouses, who theoretically should be exposed to similar foods and infectious agents as the cases, should have an increased risk for IBD. If the risk to spouses is less than the risk to sibs, this suggests either that genetic predisposition is important, or that the necessary environmental exposure occurs prior to adult life. The incidence of reported cases of spouse concordance does not appear to be increased over population risks, and is dramatically less than the risk to sibs (1,9). These data thus also support the concept that genetic factors are required for IBD susceptibility, and are responsible in large part for the familial aggregation.

Finally, the clear association of inflammatory bowel disease with two well defined genetic syndromes - Turner syndrome and the Hermansky-Pudlak syndrome - also support the importance of genetic factors (1). The several reports of inflammatory bowel disease in patients with Turner syndrome - that is, individuals who lack all or a part of one of the X chromosomes - leave little doubt that the incidence of IBD in Turner syndrome is many times higher than that seen in the general population (1,10). Turner patients are known to have an increased risk for several diseases thought to have an autoimmune etiology, and thus it is not surprising that IBD, also a potential autoimmune disease, is increased in these patients. Both CD and UC have been reported in Turner patients, in about equal numbers.

The Hermansky-Pudlak Syndrome (HPS) is a tyrosinase-positive form of oculocutaneous albinism with widespread accumulation of a ceroid-like pigment in tissues, and with a defect in the second phase of platelet aggregation leading to a bleeding diathesis (11). The pattern of inheritance is autosomal recessive, although the responsible gene is as yet unknown. Interstitial pulmonary fibrosis with pulmonary insufficiency has been reported as the most frequent and serious complication in HPS. In addition, a form of granulomatous colitis has been noted in a number of HPS patients, particularly those from Puerto Rico (11,12). No defect in peripheral blood lymphocyte or neutrophil function has yet been identified (13). Although the etiology of HPS is unclear, there is a suggestion that the hereditary defect in HPS may be an abnormality of lysosomal function. If this speculation is correct, it would imply that the pulmonary fibrosis and granulomatous colitis may also be related to this central defect.

2. GENES RESPONSIBLE FOR IBD ARE BEING IDENTIFIED!

2.1 Genetic marker studies.

The early genetic marker studies using polymorphic blood group markers found no evidence for either linkage or association with a variety of general polymorphic markers such as ABO (1). More recent

studies have focused on markers known to be related to immunologic function; specifically the HLA complex on chromosome 6, the complement components on chromosomes 6 and 19, GM (immunoglobulin heavy chain determinants) on chromosome 14, Km (immunoglobulin light chain marker) on chromosome 2, and the T-cell receptor alpha and beta chains on chromosomes 14 and 7.

HLA studies in IBD have been confusing. A large part of the problem lies in the studies themselves, many of which had a small sample size and were done at a time when typing was readily available only for HLA class I loci, i.e. HLA A and B antigens. Thus there has been a relative lack of studies of the HLA class II (D/DR) region, that region most often implicated in autoimmune diseases. Despite this, some interesting clues emerge when the data are reviewed in aggregate.

Briefly, there have been six association studies of HLA DR antigens and UC (1). Four of them have observed an increased frequency of HLA DR2. The differences did not reach statistical significance in all studies, and was most prominent in, but not limited to, the Japanese population (14). In CD, there have also been six studies, and the only prominent finding was a positive DR4 association in the Japanese (1,15). The latter observation is of interest because if there is genetic etiologic heterogeneity within CD, then one would expect that heterogeneity would be minimized in a more homogeneous population such as the Japanese. Such a relation may more apparent as more genes of the HLA D region are examined by combined serologic and molecular methods . Thus the authors have presented preliminary data that a particular HLA DR - DQ haplotype was associated with CD (16).

In population studies such as those described above, cases and controls are compared with regard to a certain marker (e.g. an HLA antigen). These association studies should be contrasted and compared with family linkage studies. Linkage studies are designed to examine whether a certain allele of a genetic marker locus is transmitted within a family with the disease of interest. Existence of linkage between a certain marker and the disease indicates that this marker is either the gene causing the disease or that it is located in close physical proximity to that gene. Linkage is important for two reasons. One, it may be observed even when an association does not exist. Two , if linkage is found along with association for a particular locus, then this indicates that the association has identified a major gene for that disease, rather than a small polygenic contribution.

Linkage studies are conducted in families with multiple affected members. In the case of classic genetic diseases that are inherited in a Mendelian mode, extensive parametric linkage analysis methods and programs have been developed (these are called parametric because certain parameters, i.e. the mode of inheritance, the gene frequency, the penetrance, are known). In diseases that are not inherited in Mendelian fashion and the mode of inheritance is unknown, such as IBD, other analytical methods have been developed. These methods are termed nonparametric, and basically utilize for linkage assessment the information obtained from the affected individuals in the pedigree. The most common method is the sibpair method and its various extensions. This method has been applies most extensively for HLA associated diseases, as the approach is most powerful when a

marker system is highly polymorphic, as is true for the HLA gene complex. More recently, new methods of nonparametric linkage analysis methods are being developed where data derived from information on marker concordance in more distant pairs of blood relative affected with the disease can be utilized (17,18).

Several HLA haplotype linkage studies have been conducted in families with multiple-affected members with IBD. Of seven studies of HLA linkage (i.e. testing co-segregation of entire HLA haplotypes and IBD together within sibships), four observed increased haplotype sharing. The difficulty with these prior studies is that methods using sibpair data alone are not sensitive to the problem of disease heterogeneity (19). If there are forms of IBD linked to the HLA region, and other which are not, then nonparametric linkage methods which depend on sibpairs alone may not be powerful enough to identify linkage. To resolve this conflicting issue, the authors have undertaken a family haplotype study, applying a nonparametric linkage method which does not use sibpairs alone, but other more distant relatives as well (the Affected Relative Pair method) (17-19). The results do demonstrate evidence for linkage of HLA with IBD (20). In the light of these latter analyses, it appears that the prior inconclusive results with sibpair data alone reflect heterogeneity of the genetic susceptibility. As it is likely that IBD is not one disease, these combined association and linkage data indicate that there is a subset of patients, likely to be defined by a combination of serologic and molecular methods, in which the disease is linked to the HLA complex.

The complement system plays a major role in the immune response and in the inflammatory process, thus making it a potential candidate in the etiology of IBD. IBD can be associated with rare complement deficiencies, as well as with other immunodeficiency states (1). However, of more general interest was a study of functional and immunologic assays in CD patients and their clinically unaffected first degree relatives (21). This study reported that 38% of cases and 18% of their relatives demonstrated subnormal generation of chemotactic activity and decreased utilization of C3 by the alternative complement pathway. All of the relatives with C3 abnormalities were related to probands with similar abnormalities suggesting that the abnormalities were not simply secondary to the CD, and that the abnormalities are familial.

A complementary approach to studying the role of the complement system is that of looking for disease association with inherited polymorphisms. The same investigators reported a study of the known polymorphism of the third component (C3) in a series of Danish patients with CD (22). In this series, the 'F' and 'FS' phenotypes occurred significantly more often in the CD patients than in either UC patients or normal controls. Interestingly, when the CD patients were divided into those with and without small bowel involvement, the association was only seen in those with small bowel involvement. The authors have preliminary (unpublished) data of a similar nature in an entirely separate Caucasian population. These data not only suggest that there may be etiologic differences between UC and CD, but also between CD with and without colonic involvement.

Two other attractive candidate gene systems that have been examined are those of the immunoglobulins and the T cell receptors alpha and beta chains. The available data can be summarized

succinctly. Despite initial reports, the majority of available studies have not found association with the immunoglobulin genes determined serologically, nor with T cell alpha and beta chain alleles determined by molecular methods (23-25). Linkage has also not been observed with the immunoglobulin genes (23). However, these regions cannot be firmly rejected until the appropriate nonparametric linkage studies have been conducted.

2.2 Subclinical markers.

Genetic studies utilizing clinical techniques alone have their limits, since clinically unaffected individuals with the variant genotype will not be recognized. Such studies can be greatly aided by the use of subclinical markers that are closer to the basic defect and thus likely to detect more individuals with the abnormal genotype. Subclinical markers (predictors) are parameters used to detect the abnormal genotype in the absence of the full phenotype; e.g., abnormal glucose tolerance in diabetes, and serum pepsinogen I in duodenal ulcer. These markers represent abnormalities having a direct role in the pathogenesis of the disease. The detection of subclinical abnormalities in unaffected family members similar to those found in the probands can distinguish between an inherited predisposition and a secondary abnormality due to the disease process. Therefore, finding such abnormalities in clinically inaffected family members helps establish an etiological role for certain abnormality in a disease. Such an abnormality may either indicate the genetic abnormality predisposing to a disease, or identify those in whom an earlier, subclinical phase of disease process is occurring that may or may not eventuate in clinical disease.

Although several abnormalities have been described in IBD, only a few have yet been extended beyond the patients to include family members. The subclinical markers that have thus far been utilized in genetic studies include serum antibodies, measures of intestinal permeability, and certain complement functions (the latter were reviewed above).

Autoantibodies to lymphocyte surface membrane antigens (lymphocytotoxic antibodies) have been found in increased frequency in patients with IBD and their relatives including spouses (26). However, these antibodies are not specific to IBD and have been found in a variety of other diseases such as systemic lupus erythematosus, rheumatoid arthritis, malaria and others, all involving active immune response.

More specific are antibodies to colonic epithelial cells that have been repeatedly reported in both CD and UC patients (26). Of interest is the recent study of the immune reactivity to gut epithelial cell antigens in healthy family members of patients with IBD (27). Specific lysis against epithelial cell associated component antigens (colon-derived) (ECAC-C) was observed to be significantly higher among patients with IBD and among their unaffected first degree relatives than in control groups. If confirmed, the high frequency of immune sensitization to epithelial antigens compared to controls, suggests that it may represent a primary subclinical marker that either predisposes to intestinal injury, or is an earlier subclinical marker of an ongoing pathologic

process. Another attractive antibody to examine in family studies is the antineutrophil cytoplasmic antigen antibody. This antibody has recently shown to be highly specific for UC, and to occur in the majority of patients with this disorder (28).

Several studies have shown an increased intestinal permeability in CD patients (29). Such evidence is based on measurements of urinary excretion of poorly absorbed, water-soluble compounds that are unable to be metabolised, such as polyethylene glycol (PEG), or large sugars. One might logically attribute these abnormalities to the chronic inflammation of the gut in these patients. However, when intestinal permeability to PEG was examined among first degree healthy relatives of CD patients, it was found to be increased compared to that observed in healthy controls (30). These findings suggest that the permeability defect in CD patients is not secondary to clinically evident intestinal inflammation, but serves as a subclinical and possible genetic marker for CD. Further studies indicate that the abnormality in relatives appears limited to PEG, and is not detected by the use of large sugars (31). These observations certainly need confirmation, but raise the possibility that defects in permeability could enhance exposure to certain antigens that would then trigger the body's immune response.

The gastrointestinal tract is lined with a mucus layer that forms a barrier against exotoxins and microorganisms. The mucin glycoproteins can be fractioned by chromatography to at least six different species. An attractive hypothesis is the inborn abnormalities in colonic mucin species may be related to the pathogenesis of UC. It has been reported that tissue from UC patients have a selective reduction of mucin species IV, whereas other specimens had a normal appearing mucin profile (32). In addition, a comparable abnormality has been observed in the Cotton-top tamarin, a new world monkey which develops a spontaneous chronic colitis very similar to human ulcerative colitis. The deficiency of mucin species IV in this primate has been found to precede the onset of the inflammatory process (33). Thus, analysis of the intestinal mucin may serve as a potential subclinical marker for UC. Further investigation will require similar studies in healthy human family members, looking for such abnormalities in individuals without clinical disease. Furthermore, with the cloning of the mucin genes, it will be important to determine whether genetic differences in a specific mucin gene are associated with UC.

3. POSSIBLE MODES OF INHERITANCE

There are current several models of the genetic susceptibility to any disease: the simple Mendelian models, the polygenic/multifactorial model, the multilocus/oligogenic models, and the genetic heterogeneity models (34).

Any such genetic models for IBD must take into account the following observations. One, from the MZ twin data, these are diseases of reduced penetrance, i.e. genetic susceptibility does not appear to be the only determinant of disease. Two, based on the stronger family history of IBD and greater MZ concordance for CD, CD appears to be the more penetrant genotype. Three, CD and UC are clearly genetically related, since they are found together with increased frequency in families (7); they are both increased in the

Jewish population compared to the surrounding Caucasian populations; and the distinct distribution of countries of origin of U.S. Ashkenazi Jewish patients with IBD is true both for CD and UC (4). Fourth, the evidence for involvement of the HLA and complement genetic markers and genes involved in permeability and/or mucin structure (Table).

TENTATIVE CANDIDATE GENES FOR IBD

<u>Defined by genetic marker studies</u>	
Crohn's	- HLA (HLA DR4 related)
	- C3 (C3F - related)
UC	- HLA (HLA DR2 related)
IBD	- HLA region (by linkage)
<u>Defined by subclinical markers, in family studies</u>	
Crohn's	- C3 dysfunction
	- Intestinal permeability
IBD	- ECAC antibodies
<u>Possible subclinical markers, family studies needed</u>	
UC	- Colonic mucins
	- Antineutrophil cytoplasmic antibodies

3.1 Simple Mendelian Models

The susceptibility to IBD, at least based on current available data, does not appear to be inherited in any Mendelian mode of inheritance (1,5,6). The empiric risks to offspring and to siblings are much lower than expected frequencies for either autosomal dominant or recessive inheritance, and father-son cases are found in most case series, precluding X-linked inheritance.

While the weight of evidence is against simple Mendelian inheritance, several factors should be considered: there might be a very low penetrance of disease in those who are susceptible, or a proportion of those affected might have subclinical disease. The former might then require exposure to a specific combination of environmental agents, perhaps at a specific time in life, resulting in a low disease penetrance. It has been suggested that Crohn's disease might be due to a recessive gene with reduced penetrance (35). This seems highly unlikely given similar empiric recurrence risks for siblings and offspring (7), since for a recessive disorder the recurrence risks should be much higher for siblings. Alternatively, the "diseases" may have a wide variability in severity, ranging from sub-clinical intestinal disease to clinical IBD. The only way to determine if this were the case would be to do intensive studies of "unaffected" relatives of IBD cases, looking for evidence of mild chronic inflammation. Such studies have yet to be performed, but are very much needed.

3.2 Multifactorial/Polygenic Models

A common explanation for diseases that demonstrate familial aggregation, but whose aggregation does not follow a Mendelian pattern of inheritance, is that they are due to multiple genes each of small effect (hence the term polygenic), acting together to provide the susceptibility to disease. Only when one has a

sufficient number of these genes would an individual pass beyond a threshhold and clinical disease result. If environmental factors were required as well, then the term multifactorial is applied. Since IBD does not fit a Mendelian pattern, the polygenic model was suggested. When the strong and significant familial association of UC with CD was recognized, the theoretical explanation was advanced that the two diseases had certain genes in common (5,6). To account for the difference empiric risks it was proposed that if a person has only a few of these genes, they are liable to develop UC, if they have many of these genes (a more complete genotype), the clinical and pathological picture that develops is more likely to be CD.

There are practical and theoretical problems with the polygenic/multifactorial model that apply to almost any disease, but certainly to IBD in particular. One is that it gives no direction as to how to identify the disease-promoting genes. A second is the underlying premise of this model is that all of IBD is one disease. This no longer seems a likely hypothesis, as there is increasing evidence that IBD is more than one disease, i.e. that it is a genetically heterogeneous group of disorders.

One issue as regards genetically mediated etiology is the role of environmental factors. The two principal lines of evidence for the involvement of environmental factors are geographic differences and temporal changes in IBD frequency. Even if environmental factors are involved, they may be so ubiquitous that in any one population it is the only the genetically susceptible individuals that develop clinical disease. A further argument for the importance of environmental factors is often inferred from the lack of complete concordance in MZ twins. It is important to realize that this data by no means proves the importance of environmental factors. Another potential cause for reduced penetrance is that expression involves a random stochastic process, such as might occur in development, and certainly occurs in the recombination of genes in the development of the immune system. Such an explanation, for example, has been offered to explain the reduced concordance in MZ twins with insulin dependent diabetes (36).

3.3 Two locus (multilocus) models

There is increasing evidence that the genetic predisposition to a number of diseases is due to the interaction of two or more major genes, a form of inheritance termed two locus (if two major genes are involved), multilocus or oligogenic if more than two are involved (37). This concept is important for IBD for several reasons. First it is an etiologically attractive hypothesis that could explain more than one pathophysiologic defect being found in IBD patients. For example, in order to develop clinical Crohn's disease, one may need both a permeability defect that leads to increased exposure of the body's immune system to antigenic substances that ordinarily do not cross the gut mucosal barrier and a simultaneously genetically determined particular immune response. An analogous hypothesis might include abnormal mucins and certain autoantibodies as the etiologic factors in ulcerative colitis. Second, the recurrence risks for two locus disorders are very different from Mendelian disorders (34,37). Third, a multilocus model could explain the relationship of UC and CD in families. Thus, one gene may be insufficient by itself to lead to

IS IBD A GENETIC DISEASE?

J.I. ROTTER, T. SHOHAT, C.M. VADHEIM
Division of Medical Genetics
Departments of Medicine and Pediatrics
Cedars-Sinai Medical Center
8700 Beverly Boulevard
Los Angeles, California 90048

ABSTRACT. There is substantial evidence that genetic factors play a role, possibly even the preeminent role, in the predisposition to the inflammatory bowel diseases (IBD) - Crohn's disease (CD) and ulcerative colitis (UC). The lines of evidence include ethnic differences in disease frequency, familial aggregation, spouse and twin studies, and the existence of genetic syndromes that feature IBD. Indeed, some of the responsible genes are being identified, by a combination of genetic marker and family based physiologic studies. The best evidence exists for the HLA and complement systems. Important physiologic abnormalities being examined autoantibodies, permeability, and colonic mucins. To further these advances, and to utilize the power of modern linkage technology and human gene mapping, an international registry of mapping cell lines from IBD families is being established. The existence of a substantial genetic component to IBD susceptibility means that etiologic studies must include a consideration of the genetic components. Genetic studies will aid in the delineation of the basic etiologies of IBD, which should lead to new therapies, and will eventually provide the means to identify those at highest risk for disease prevention.

1. IBD IS A GENETIC DISEASE!

1.1. Ethnic and familial aggregation.

Epidemiologic data regarding IBD demonstrate dramatic differences in disease frequency between geographic areas and ethnic groups. Familial aggregation, i.e. an increased occurrence of disease in relatives is also well documented. These data suggest, but by themselves do not prove, that genetic factors may play a role in the etiology of IBD. From a genetic point of view, perhaps the most interesting epidemiologic observations are the reports of comparatively higher prevalence rates for the Jewish populations in the USA, Europe, and South Africa, in comparison with those of the general population in these areas (1-3). However, the frequency of IBD among Jews, although usually considerably higher than in the general population in which they reside, varies as well among the different historical ethnic subgroups within the Jewish population.

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diseases with a common clinical endpoint. Given the consequent complexities, these are several paradigms that the investigative community should be undertaking.

One paradigm is to greatly expand the study of proposed pathophysiologic abnormalities in individuals at greatest risk for disease, i.e. the study of subclinical markers. At the moment, this means that such studies should be extended to the relatives of IBD patients. As the available genetic markers become better defined, and new ones become identified, this will enable the refinement as to which relatives are at a high and low risk respectively for comparison in such studies.

A second paradigm is to continue to aggressively explore specific candidate genes in association and linkage studies. However, because of genetic and etiologic heterogeneity, caution must be exercised before deciding a candidate gene should be eliminated from further consideration based on a few negative studies of small sample size. Given the possible extent of genetic heterogeneity, before a candidate locus can be excluded, it is likely that a nonparametric linkage analysis will be needed, and thus will need to be done on a sufficiently large sample of families with multiple affected members. As to establishing (rather than refuting) the importance of a specific genetic locus, association studies should be considered as initial probes, but the locus must then be examined by familial linkage studies.

It should be apparent that given these complexities, that a large number of families will be needed for many of these studies. To that end, the Medical Genetics Birth Defects Center at Cedars-Sinai, in collaboration with the UCLA IBD Center, has established, for the purpose of molecular based linkage analyses, an international repository of long term cell lines from patients and family members with IBD, and the appropriate ethnically marked controls. These now number over 400, and several times that number are contemplated. These will be made available on a collaborative/consultative basis to investigators who wish to test specific genetic loci by association and linkage methodologies.

Third, as genetic markers for IBD become delineated and refined, they should be utilized to identify individuals at risk for studies of disease natural history. This will, for the first time, provide the investigative community the tools to understand the development of disease from susceptible genotype to clinical phenotype, and thereby suggest new methods of intervention for therapy and prevention.

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GLYCOPROTEIN STRUCTURE AND ULCERATIVE COLITIS

DANIEL K. PODOLSKY, M.D.
Gastrointestinal Unit
Department of Medicine
Massachusetts General Hospital and Harvard Medical School
Boston, MA 02114

ABSTRACT. Glycoproteins are abundant and markedly heterogeneous constituents of normal colonic mucosa. The large molecular weight mucin glycoproteins predominate and appear to include several distinctive components. Studies using a variety of techniques have indicated that the spectrum of colonic mucin glycoproteins is altered in ulcerative colitis. One class of mucin glycoprotein, species IV, appears to be selectively reduced. In addition, a variety of glycoconjugate determinants recognized by a panel of anti-human colonic mucin glycoproteins has been found to be altered in the colonic mucosa in association with active inflammatory bowel disease. Alterations include the reduced presence of some structures and enhanced expression of others. These findings suggest that inflammatory mediators modulate glycoprotein expression. In addition, isolation of monoclonal antibodies which specifically recognize glycoproteins from patients with ulcerative colitis suggest that distinctive glycoconjugate structures emerge in this disorder. Two monoclonal antibodies, designated MAb UC 7 and UC 11 recognize separate structures which are each specifically found in ulcerative colitis mucosa. Preliminary characterization of the antigenic determinant recognized by one of these antibodies has demonstrated an unusual carbohydrate composition.

A complex array of glycoproteins is present in the colonic mucosa. These are found within the theca of the extensive goblet cell population and in the form of a viscoelastic gel overlying the mucosal luminal surface. (1-4). The large, highly glycosylated mucin glycoproteins that are the predominant constituents of this mixture are thought to make an important contribution to mucosal integrity, but the mechanism of protection conferred by this host defense factor is not well understood. Among other functions, these glycoproteins may interfere with potentially pathogenic luminal microbes or toxic compounds to prevent direct injury to the mucosa.

Several approaches confirm the existence of extensive heterogeneity of glycoconjugate structures, particularly mucin glycoproteins, within colonic mucosa. These include direct biochemical analysis which has demonstrated subpopulations of mucin glycoproteins distinguishable on the basis of their carbohydrate composition and chromatographic behavior. Many observations have indicated particular variability in the content of substituents at the nonreducing termini of oligosaccharide side chains in mucin fractions, notably sialic acid and sulfate. The latter have been detected by specialized histochemical stains as well as through direct chemical analysis (5-7). Our

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laboratory has further separated several compositionally distinct mucin fractions or species (designated mucin species I-V) by chromatography on the ion exchange resin DEAE-cellulose (8-10). In addition to biochemical analysis, heterogeneity in colonic glycoproteins has also been demonstrated by fluorescent staining with lectins which recognize a variety of carbohydrate structures (11-13).

Monoclonal antibodies developed in our laboratory which recognize defined constituents among several colonic mucin glycoproteins have made it possible to assess the distribution of these substances within colonic mucosa (14,15). In situ localization of human colonic mucin species accomplished through use of a library of anti-human colonic mucin monoclonal antibodies and indirect immunofluorescent staining suggests that the complex mixture of colonic glycoprotein may represent the products of distinct subpopulations of goblet cells. Vecchi et al. (16) have also reported the development of a monoclonal antibody that specifically recognizes gastrointestinal goblet cells.

The concept that mucin glycoproteins contribute to normal mucosal function is supported by findings that suggest that alterations in colonic mucin glycoproteins are associated with a variety of disorders. Thus, alterations of lectin binding and histochemical staining characteristics presumably related to changes in these substances have been observed in both benign and malignant neoplasia (7,17-20). Most importantly, observations from a number of laboratories suggest that glycoconjugates may be altered in the colonic mucosa of patients with inflammatory bowel disease (5,6,13,21-24). Findings consistent with this conclusion include the observation of increased staining with specialized histochemical techniques, reflecting increased sialic acid content of mucin glycoproteins. In addition, the binding of fluorescent lectin probes to colonic mucosa has been found to be altered in samples from patients with ulcerative colitis. Furthermore, biochemical analysis has suggested that a relatively selective reduction in the content of a mucin glycoprotein species designated species IV may be specifically associated with ulcerative colitis (8,25).

In view of the observations summarized above, the content and distribution of glycoproteins within colonic mucosa of patients with inflammatory bowel disease was assessed through indirect immunofluorescent staining using a collection of 23 monoclonal antibodies directed against human colonic mucin glycoproteins (26). Intensity and distribution of staining by three anti-human colonic mucin monoclonal antibodies were significantly altered in mucosa from patients with ulcerative colitis (n = 14) when compared with normal tissue (n = 15) and with Crohn's disease as well as other inflammatory disorders (n = 15). Staining by anti-HCM MAb 17, which binds to colonic mucin glycoprotein species IV and V, was absent or diminished in 88% of samples from patients with active ulcerative colitis in contrast to 14% of normal and disease control specimens. Reduction in anti-human colonic mucin MAb 17 staining was less marked in mucosal biopsy specimens from patients with ulcerative colitis lacking acute inflammatory activity (n = 8). In contrast to the apparent loss of the MAb 17-defined epitopes, staining with anti-HCM MAbs 10 and 22 was enhanced in ulcerative colitis tissue compared with normal and disease controls. Increased staining with MAb 10 was present in 93% of samples from ulcerative colitis patients demonstrating active inflammation. Increased MAb 10 staining was not apparent in noninvolved mucosa from ulcerative colitis patients, indicating that increased expression of the specified epitope is related to the acute inflammatory process. In contrast, indirect immunofluorescent staining with MAb 22 was apparent in both involved (78%) and uninvolved (67%) ulcerative colitis mucosa in contrast to normal and disease controls (<12%). In addition, staining with several other anti-HCM MAbs (MAbs 3, 11, 15) was modestly and variably diminished (14%-28%) in ulcerative colitis, Crohn's disease, and other inflammatory disorders.

These findings demonstrate the presence of alterations in mucosal content of specific glycoconjugate structures in association with ulcerative colitis. It is also clear that inflammatory processes may result in broad changes in glycoconjugate determinants generally. The mechanism of the altered expression of these glycoproteins is unknown. Current understanding of factors which modulate glycoconjugate production is rudimentary. It is possible that inflammatory mediators regulate both production and secretion of goblet cell glycoproteins.

Many of the alterations in the expression of several glycoprotein determinants found in these studies reflect mucosal inflammation or injury in a relatively non-specific manner. This conclusion is supported by the observation that comparable alterations in the extent of goblet cell staining of several monoclonal antibodies are present in tissues from patients with either ulcerative colitis or Crohn's disease as well as a small number of samples from patients with a variety of unrelated disorders involving colonic mucosal injury. Interestingly, despite the relatively nonspecific reduction in the expression of some glycoprotein determinants, alterations in expression of other anti-human colonic mucin monoclonal antibody-defined determinants appear to be more specifically related to ulcerative colitis. As noted above, alterations in anti-human colonic mucin monoclonal antibodies in association with ulcerative colitis include both reduction of some determinants and enhancement of other epitopes.

The finding of enhanced expression of glycoprotein determinants is especially interesting in view of past studies in which selective reductions in colonic mucin glycoproteins have been observed in patients with ulcerative colitis (8,25). More recent studies have suggested that diminished content of the species (IV) may result from an alteration in cellular processing, reflecting production of an altered form or a functional defect in a particular goblet cell subpopulation (27). Whether the enhanced expression of a determinant recognized by a single monoclonal antibody reflects the presence of an altered form of this glycoprotein or some other constituent remains unknown at this time. Nonetheless, findings with the human colonic mucin monoclonal antibodies lend further support to the impression that alterations in colonic mucosal glycoconjugates may be significant in mucosal injury in general and the pathogenesis of ulcerative colitis in particular.

While the approaches described above including use of monoclonal antibodies raised against normal human colonic mucin may be helpful in examining changes in the mucosa of patients with inflammatory bowel disease, the ability of these techniques to identify aberrant structures may be inherently limited, as these techniques largely assess the representation of defined glycoconjugate constituents. Specifically, these approaches are not likely to detect disease-related structures that are not present in normal mucosa. Haviland and co-workers have indeed found aberrant expression in inflammatory bowel disease of a number of monoclonal antibody defined colonic mucosal antigens which were initially detected in malignant tissue (28).

In an attempt to define whether ulcerative colitis mucosa exhibits abnormal structural features, we have also taken an approach in which hybridomas were prepared from mice immunized with colonic mucin glycoproteins purified from mucosa of patients with ulcerative colitis. Fusion products were screened to identify hybridomas producing antibodies which bound the ulcerative colitis derived glycoprotein but not normal colonic material. After initial screening of many hybridomas, two monoclonal antibodies designated UC 7 and UC 11 were isolated which demonstrated marked differential binding to ulcerative colitis-derived glycoprotein relative to pooled glycoproteins from normal colon (29).

The specificities of monoclonal antibodies UC 7 and UC 11 were examined in greater detail by assessing their binding to individual preparations of purified colonic

mucin glycoproteins. Mab UC 7 has demonstrated significantly more binding to 21 of 27 preparations of mucin glycoprotein derived from individual patients with ulcerative colitis when compared with 29 samples prepared from normal human colon. Binding to ulcerative colitis-derived glycoprotein has resulted in mean binding of 11,380 ± 2910 cpm per ~5 ng glycoprotein compared with 2040 ± 1120 cpm per ~5 ng glycoprotein from normal tissue.

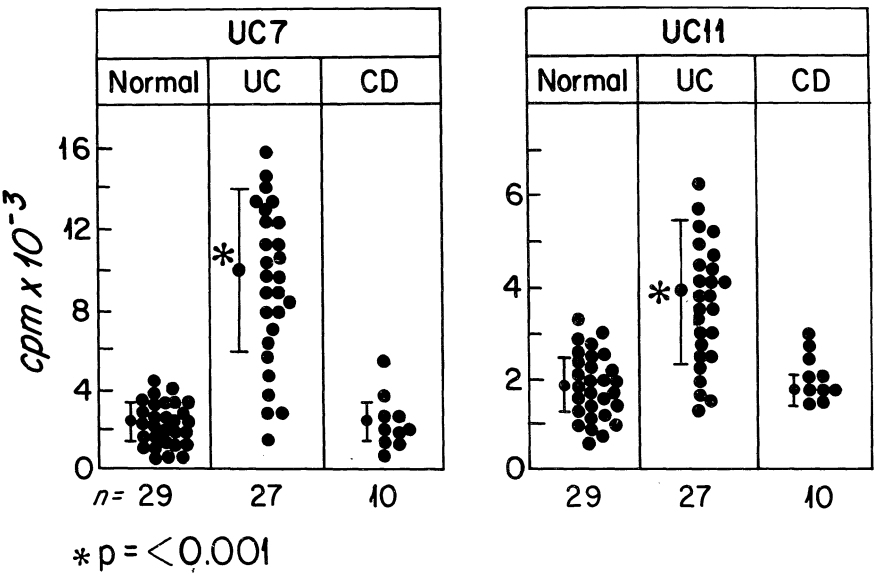

Figure 1. Binding of MAbs UC 7 and UC 11 to HCM. Polystyrene beads were coated with individual preparations of HCM purified from surgical specimens of patients with diverticulosis (normal), ulcerative colitis (UC), and Crohn's disease (CD). Solid-phase sandwich radioimmunoassays were performed by addition of spent hybridoma media to beads precoated with the antigen followed by incubation with ^{125}I-labeled sheep-antimouse Fab (29).

The structural determinant recognized by monoclonal antibody UC 7 does not appear to be related to mucosal injury in a nonspecific fashion. Binding of Mab UC 7 to mucin glycoproteins prepared from colonic mucosa of patients with Crohn's disease (with colonic involvement) was indistinguishable from normal controls. Monoclonal antibody UC 11 also bound ulcerative colitis-derived glycoprotein to a greater extent than normal colonic mucin glycoprotein or Crohn's disease colonic mucin glycoprotein when analyzed on beads coated with purified mucin glycoproteins in pooled preparations and in individual mucin glycoprotein samples (4150 cpm ulcerative colitis vs. 1890 cpm normal) (Figure 1).

Both Mab UC 7 and Mab UC 11 have been found to stain colonic mucosa from patients with ulcerative colitis using indirect immunofluorescent staining techniques. However, these two antibodies stain mucosa in easily distinguishable patterns, consistent with the presumption that they recognize discrete structural determinants. Monoclonal antibody UC 11 appears to recognize a determinant present on the colonocyte surface and within colonic goblet cells. Although staining was found in colonic mucosal samples from several patients with ulcerative colitis, indirect immunofluorescent staining was not invariable and was not observed in 5 of 17 biopsy specimens. Staining appeared relatively specific insofar as mucosal staining was observed in only five of twenty-five biopsy specimens from normal and disease controls (Figure 2).

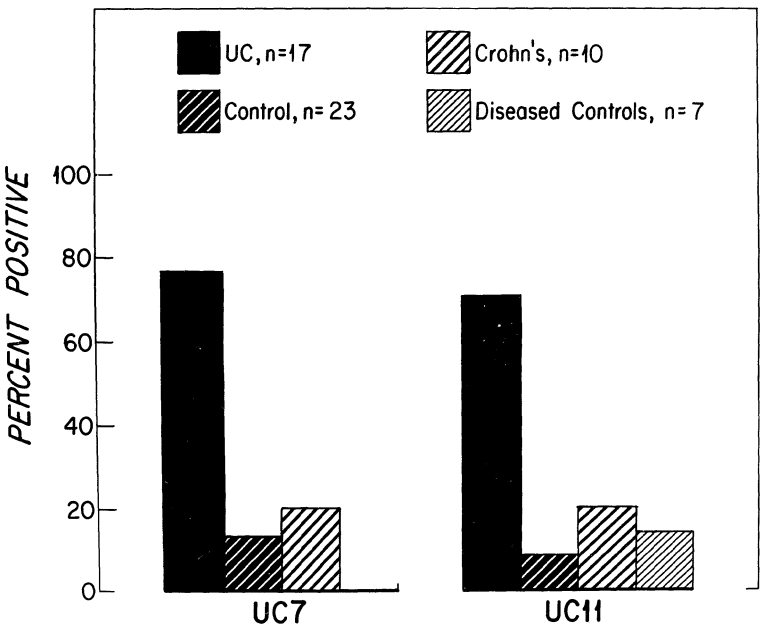

Figure 2. Indirect immunofluorescent staining of colonic mucosa with monoclonal antibodies UC 7 and UC 11. Indirect immunofluorescent staining was assessed in 2-μm frozen sections using fluorescein isothiocynate-conjugated sheep-antimouse immunoglobulin. All samples were from sigmoid and descending colon except ulcerative colitis uninvolved colon (transverse). Specimens showing staining >5% goblet cell staining were scored as positive.

Mab UC 7 also stained colonic mucosa in a distinctive fashion. Mab UC 7 stained structures on the apical surface of colonic epithelia in a discontinuous manner. In addition, Mab UC 7 consistently stained lamina propria cells (LPCs) of biopsy specimens from patients with ulcerative colitis. The cytoplasm or cell surface, or both, of these LPCs were strongly stained by indirect immunofluorescent techniques. Staining was not affected by prior incubation of tissue with mouse immunoglobulin, indicating that LPC staining was not related to nonspecific adherence to Fc receptor-bearing cells.

The nature of these cells is unknown but their distribution and appearance suggest that they may include both neutrophils and a subpopulation of lymphocytes. The ability of this monoclonal reagent to stain these LPCs indicates that they contain the same determinant present in colonic epithelial cells and goblet cells. This finding suggests that the determinant recognized by MAb UC 7 that appears to be specifically related to ulcerative colitis may be recognized by some component of the mucosal immune system. Alternatively, the structural determinant specified by MAb UC 7 may be a normal intrinsic structure common to both a subpopulation of LPCs and colonic mucosal epithelial cells.

The nature of the determinants recognized by MAbs UC 7 and UC 11 remains unknown. Although the initial immunogen was comprised of a mixture of mucin glycoproteins, indirect immunofluorescent staining of colonic mucosa with these monoclonal antibodies does not show characteristic exclusive staining of goblet cell structures. It is possible that these monoclonal antibodies recognize oligosaccharides or peptide structures that are present both in mucin itself and epithelial surfaces. Indeed, these structures must be limited in their representation within mucin, given the failure to observe diffuse or uniform staining of goblet cells. Alternatively, the determinants might exist in nonmucin constituents present in the original immunogen despite the purity of the latter as judged by standard criteria.

Preliminary efforts have been undertaken to purify the structural determinant recognized by Mab UC 7. Crude solubilized glycoproteins prepared from colonic mucosa of patients with ulcerative colitis have been applied to an affinity resin bearing the monoclonal reagent. After initial washing, glycoconjugate specifically bound to the resin was eluted. Initial compositional analysis of this relatively high molecular weight glycoprotein reveals an unusual carbohydrate composition with apparent inclusion of glucose, a sugar not normally present in mature mammalian glycoproteins. Whether Mab UC 7 is directed toward an unusual oligosaccharide structure or whether this structure is present on a single "backbone" remain unclear pending further structural characterization of this substance. If indeed the presence of the structural determinant recognized by UC 7 is uniformly associated with ulcerative colitis, it will be of interest to determine the functional characteristics of this structure and whether these anomalous structural features, if present, are antigenic in vivo.

These observations lend further support to the concept that alterations in colonic mucosa of patients with this disease may be present throughout the colonic mucosa despite limitation of active inflammatory disease to distal segments. More generally, these findings indicate that colonic mucosa of patients with ulcerative colitis may contain structural features not found in normal mucosa. Furthermore, these studies indicate the potential usefulness of monoclonal antibody technologies to identify novel structures related to colonic mucosal disease processes.

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BARRIER FUNCTION OF INTESTINAL EPITHELIAL TIGHT JUNCTIONS (TJ)

JAMES L. MADARA, SHIRIN NASH, RONDA MOORE, MICHAEL SHAPIRO, SUSAN CARLSON, CHARLENE DELP
Brigham and Women's Hospital and Harvard Medical School
Department of Pathology
75 Francis Street
Boston, MA 02115

ABSTRACT. Intestinal epithelial tight junctions are the rate limiting barriers to passive transepithelial movement of hydrophilic solutes. We have studied these important barriers in Ussing chambers using isolated sheets of mammalian intestinal epithelia and monolayers of the T84 human intestinal epithelial cell line. Studies have included both electrophysiologic and morphologic techniques. These studies show tight junctions to be highly dynamic structures which may be influenced pharmacologically or by physiologic challenges. Additionally, elements of inflammatory responses, such as the presence of the cytokine gamma-interferon, or the transepithelial migration by polymorphonuclear leukocytes, lead to deterioration in TJ barrier function. Such events may contribute to the epithelial barrier defects seen in patients with IBD.

INTRODUCTION

The epithelial lining of the intestinal tract serves as a complex barrier which restricts free transepithelial diffusion of potentially noxious compounds from the lumen. Such epithelial "barrier" function is not absolute - finite transepithelial diffusion of small molecules is known to occur. There exist two potential routes for diffusion across this epithelium: transcellular (directly across cells) and paracellular (around cells through the paracellular space). It is now known that the majority of passive permeation in this epithelium occurs via the paracellular pathway, and that the intercellular tight junction (TJ) is the rate limiting barrier to passive permeation in the paracellular pathway (see ref. 1,2 for reviews). Thus, the TJ is an exceedingly crucial barrier in this epithelium. Obviously, epithelial barrier function will be grossly abnormal in disease states characterized by epithelial discontinuities (erosions and ulcers) such as occur in active IBD. However, recently it has been suggested by others that TJ permeability may be abnormal in IBD even when the epithelium is confluent (3). Here we consider the potential for altered intestinal epithelial permeability on the basis of dynamic changes in TJ structure and function.

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MATERIAL AND METHODS

The detailed methods utilized for these studies are contained in the original referenced reports and will be referred to briefly here. For studies of native epithelium, mucosal sheets were isolated from guinea pig and hamster small intestine and studied in Ussing chambers using electrophysiological techniques (4,5). For cell culture studies, the human intestinal epithelial cell line - T84 - was used. Monolayers of T84 cells were grown on collagen coated permeable filters and were examined, using electrophysiological techniques, in modified Ussing chambers (6,10).

Light, electron, fluorescent microscopy and freeze fracture were performed using standard approaches (4-10).

RESULTS

A) TJ HAVE FUNCTIONAL LINKS TO THE CYTOSKELETON

Intestinal absorptive cells contain a cytoplasmic perijunctional ring of actomyosin (11). Using the actin binding agent cytochalasin D (10 µg/ml) in mammalian small intestine, this ring can be induced to segment and condense. Since such cytoskeletal condensation does not occur in cells depleted of ATP (4), we term this a contractile response. With perijunctional actomyosin ring contraction, tight junction structure, as assessed, by freeze fracture, is perturbed (4). Epithelial permeability is enhanced in parallel to these morphological changes (4). Transepithelial resistance to passive ion flow decreased following cytochalasin exposure as shown in Figure 1.

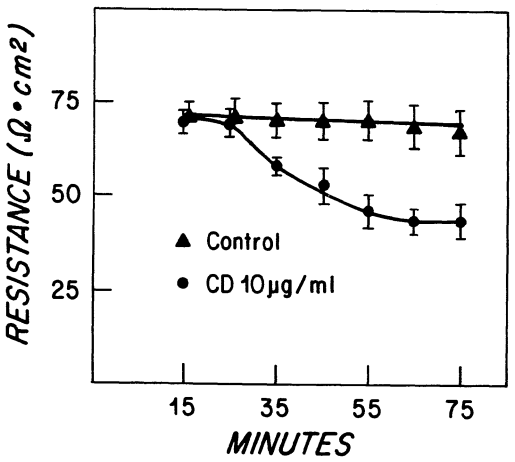

Figure 1. Time course of resistance fall after cytochalasin D exposure

Dual Na^+-mannitol fluxes (12) indicated that the decrease in resistance

accompanying cytochalasin induced segmentation and contraction of the perijunctional ring was due to altered tight junction permeability. Results similar to those described above were also found in T84 monolayers (9) indicating that comparable cytoskeletal-TJ links may be present in this model system.

B) TJ MAY BE PHYSIOLOGICALLY REGULATED

Using an electrical technique termed impedence analysis we have shown that intestinal absorptive cells may be physiologically regulated. Mammalian small intestine, when exposed to 25 mM luminal glucose, displays a reduction in transepithelial impedance. Analysis of these data show that TJ resistance is reduced from 32 ohm to 14 ohm per cm length of intestine by glucose. As shown in Figure 2, the glucose-induced change in TJ resistance is accompanied by altered TJ structure. Such physiologically regulated changes in TJ structure and function are accompanied by alterations in the perijunctional actomyosin ring (5) suggesting these alterations may also be mediated by the cytoskeleton.

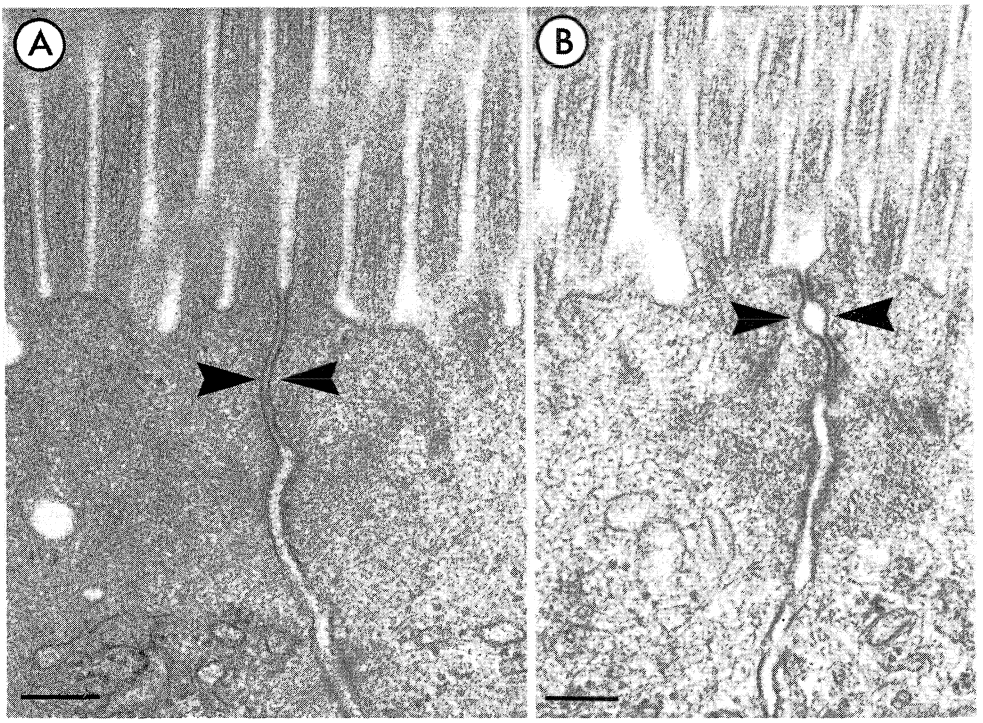

Figure 2. Electron micrograph showing control (left) and glucose exposed (right) TJ (arrowheads). Glucose elicits dilatations in TJ (from ref. 5, with permission)

C) A PRODUCT OF INFLAMMATION CAN ALTER TJ FUNCTION

Not only can TJ be altered by pharmacologic and physiologic stimuli, but analysis of T84 monolayers suggests products of inflammation may also modulate this crucial barrier. As shown in Table 1 (10) the cytokine gamma-interferon (a secretory product of activated T lymphocytes) increases the permeability of T84 monolayers. The concentration and time of exposure required to elicit this response are similar to those required for many of the immunoregulatory effects of this cytokine.

Table 1. Effect of gamma-interferon on permeability of T84 intestinal epithelial monolayers (10).

	Resistance	Mannitol Flux	Inulin Flux
	ohm cm^2	nmol/hr/cm^2	nmol/hr/cm^2
Control	417±53	9.1±1.3	1.4±0.2
IFN 1000 u/ml, 72 hr	52±48	64.0±40.0	7.3±2.7

Dual flux analysis showed that the interferon-induced alteration in monolayer permeability was entirely attributable to enhanced tight-junction permeability (10). Additionally, no biochemical evidence of cytotoxicity was found and cells were not detached from their neighbors (10). Such data, in aggregate, suggest that gamma-interferon is capable of inducing substantially altered TJ permeability in intestinal epithelia as modeled by T84 cells.

D) NEUTROPHILS TRANSMIGRATE ACROSS TJ AND ALTER TJ FUNCTION

Since active IBD is histologically characterized by transepithelial migration of polymorphonuclear leukocytes (PMN) across intestinal epithelia (crypt abscess), we have studied transmigration using the T84 monolayer model (7,8). Isolated purified (7) human peripheral blood PMN are applied to one side of T84 intestinal epithelial monolayers and are coaxed to cross the monolayers by constructing a transepithelial gradient of the chemoattractant N-Formyl-Met-Leu-Phe (7,8). As shown in Figure 3, PMN cross T84 monolayers by migrating across TJ. As shown in Figure 4, this chemotactic response is paralleled by impaired TJ barrier function as indicated by a falling resistance. Other experiments (7) showed a) these functional effects to be due specifically to chemotaxis rather than chemokinesis, b) the fall in resistance was accompanied by enhanced trans-TJ solute flow, and c) the functional effects of PMN transmigration across TJ were reversible.

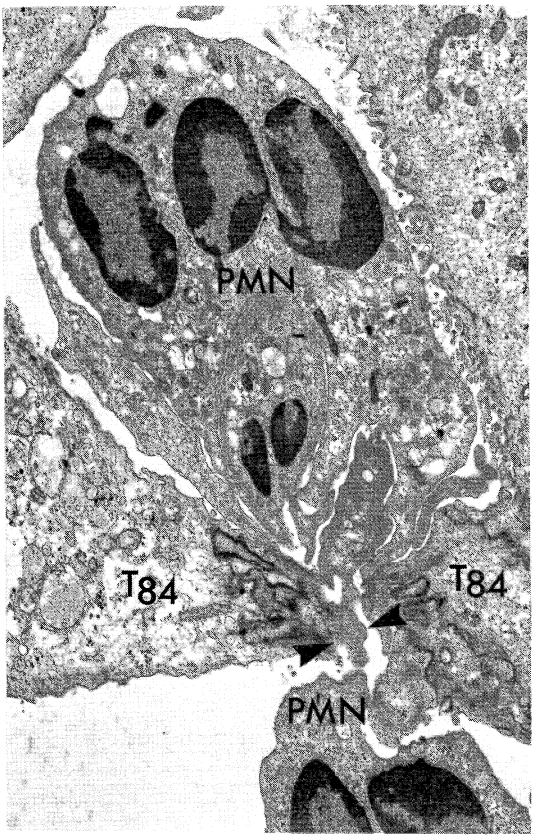

Figure 3. Electron micrograph of PMN migrating across a TJ separating T84 cells (from ref. 7, with permission).

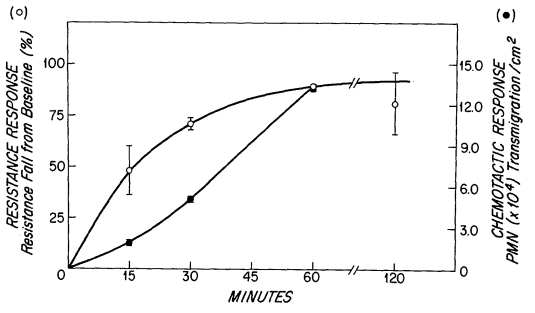

Figure 4. Time course of chemotactic and resistance responses across T84 monolayers in the presence of a 10^{-7} M gradient of N-Foryml-Met-Leu-Phe. (from ref. 7, with permission)

DISCUSSION

These data suggest that intestinal epithelial TJ are highly dynamic in structure and function (2). Not only do pharmacologic and physiologic challenges result in altered TJ structure and function, but events occurring in inflammatory states can also significantly effect TJ barrier function. Activation of T cells (and thus putative release of gamma interferon into the subepithelial space) and transepithelial migration of PMN clearly occur in IBD. Since these events substantially influence TJ barrier function in model intestinal epithelia, we speculate they may play a role in the deterioration of intestinal barrier function seen in IBD.

It has also been recently suggested that an intrinsic abnormality in TJ barrier function might be of basic importance in the development of Crohn's disease (3). If this theory is correct, the data reviewed here may be of further importance. N-formylated peptides are highly chemotactic and undoubtedly are present within the intestine given that bacteria (their source) are in the lumen in high numbers. It is possible that an intrinsic defect in TJ permeability would permit substantial diffusion of such enodgenous chemotactic compounds across the epithelium where they could be detected by circulating PMN. An inflammatory process characterized by PMN transmigration across intestinal epithelia, and ultimately stimulation of the PMN respiratory burst would logically ensue. While speculative, such a sequence of events would not be surprising, on the basis of the data presented here, if an intrinsic abnormality in TJ permeability can be confirmed to occur in these patients.

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ARE MYCOBACTERIA THE CAUSE OF CROHN'S DISEASE?

W.R. THAYER, JR., M.D.
Brown University and Rhode Island Hospital
593 Eddy St., APC 421
Providence, Rhode Island USA 02903

Abstract

The cause of Crohn's disease (CD) has remained an enigma for many years. However, in 1913 Dalziel proposed a mycobacterial origin for CD, comparing its' likeness to Johne's disease----an ileocolonic inflammation of ruminants caused by Mycobacterium paratuberculosis. Recently very slow growing, fastidious mycobacteria have been isolated from CD cases in various parts of the world. These isolates were found identical to one another and to M. paratuberculosis by random gene sequencing and restriction polymorphism of the ribosomal 5S gene. Immunologic studies and specific stains, to show the organism in infected tissues, have not been helpful. Preliminary studies with antimycobacterial antibiotics are encouraging, however. Although further studies need to be performed, atypical mycobacteria still remain a potential pathogenic organism for CD.

Introduction

Immunologists have tried in vain to find an immunologic cause for CD; unfortunately, any observed differences between patients and controls are minor leaving the pathogenesis unexplained. It is logical, therefore, that an infectious agent be considered because, although incriminating data is meager, it is consistent. There is an increased prevalence of lymphocytotoxic antibodies in patients with inflammatory bowel disease (IBD), their spouses, and other household family contacts, but not in age and sex-matched controls, spouses of controls, or in family members residing out of the household (53). Although the frequency of CD concurrence in spouses was initially thought to be low (43), a recent Mount Sinai Hospital study suggests the rate may be higher than first indicated (4). Clusters of CD have been reported (2); Reilly and Robinson described four cases developing years later in four females who were in close contact during their "teens" (48). The well-known familial association of CD has been used to suggest a genetically linked increased susceptibility, but such data could plausibly be ascribed to exposure to a common infectious agent.

It is also logical to consider a granulomagenic microorganism as

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the cause of CD, since granulomas are one of the pathologic hallmarks of the illness. Mycobacteria are the classic granuloma-producing organisms. Seventy-five years ago a Scottish surgeon, Dalziel, provided an excellent description of what was later called Crohn's disease, and noted the pathologic similarity to both intestinal tuberculosis and Johne's disease; both are caused by a mycobacteria, and involve the distal ileum or ileocecal region (19). Johne's disease, a wasting diarrheal disease of cattle, is caused by a slow growing, fastidious mycobactin-dependent mycobacteria (M. paratuberculosis), and is usually characterized by many acid fast mycobacteria within the gut lesions. Conversely, intestinal tuberculosis often has an absence of stainable and culturable mycobacteria (1, 20, 50, 54).

Attempts to isolate mycobacteria from CD date back to 1932 (18) but only recently have there been positive reports. Burnham et al. (7) isolated a strain of M. kansasii from the lymph node of a CD patient; cultures from 22 of 27 other CD specimens grew pleomorphic, probably cell wall defective organisms. Since most patients had positive skin test reactivity to an M. kansasii antigen, but not to such reagents prepared from other mycobacteria, the authors suggested the cell wall defective organism might be an M. kansasii. Others reported the isolation of slow growing, pleomorphic, unidentifiable, acid fast or variable acid fast organisms from 55% CD tissue, but in only 7% controls (52, 64). Although antisera to M. kansasii binds to the pleomorphic organisms, mycobacterial genetic probes have failed to identify a mycobacterial species (41).

Chiodini et al. (13) isolated a previously unrecognized mycobacteria from two CD patients. Subsequently recovered were two further isolates (12) all pathogenic for mice by intravenous or intraperitoneal inoculation, but not pathogenic for chickens, rats, rabbits, or guinea pigs. Feeding the isolate to infant goats produced a granulomatous ileocolitis three to ten months later (13, 60). The earliest lesions appear in Peyer's patches, and consist of non-caseous, granulomatous clusters of epithelial cells often occurring in a mantle of lymphocytes between the germinal center and muscularis mucosa. Other features include noncaseating tuberculoid granulomas with Langhan-type giant cells, confluence of granulomas, mucosal ulcerations, and lymphangitis. Lesions were seen in both the large and small intestine; the histologic features closely resembled CD. Organisms, although difficult to find with acid fast stains, were cultured from the involved areas.

Detailed biochemical studies (11) suggested the organism was closely related to M. paratuberculosis. This was confirmed by DNA:DNA hybridization (68), restriction polymorphism of the ribosomal 5S gene (9), and random gene sequencing (39, 40). Identical organisms have been isolated from CD patients, but not from controls, in other areas of the world (17, 24, 59). Identification of these organisms as M. paratuberculosis has also been confirmed by restriction polymorphism of the ribosomal 5S gene (9), and random gene sequencing (40).

The isolation rate of M. paratuberculosis remains discouragingly low (8), and some investigators are unable to isolate the organism at

all (25, 27). However, all actively involved groups have isolated pleomorphic, probably cell wall deficient organisms, similar to the findings of Burnham et al. (7) and Stanford et al. (52). Although cultured from ulcerative colitis (UC) patients, cell wall defectives are rare in controls (24, 25), but their identity remains unsettled. Chiodini witnessed the transformation of some of these organisms into the bacillary form, and showed that antibodies to the bacillary form seroagglutinate the cell wall defective organisms (12). An earlier report stated that an antibody to M. kansasii also bound to pleomorphic organisms (41). Such studies indicate the presence of a common mycobacterial antigen. Does the slow rate of reversion to bacillary forms with subsequent local hypersensitivity type immunologic response account for pathogenicity? Hawley injected cell wall deficient forms of Streptococcus faecalis into rabbit intestinal mucosa producing a granulomatous ileocolitis not seen with cell wall intact forms (30). Beaman and Scates reported cell wall defective Nocardia, closely related to the mycobacteria, exist in a cell wall deficient state in infected mice, are intimately involved in disease pathogenesis, and bacterial persistence within the host (3).

If CD is caused by a mycobacterium is there immunologic evidence for infection? It is unlikely intestinal damage is due to cytotoxicity by mycobacteria; rather it would appear the disease is a local hypersensitivity reaction to the organism. Skin tests with tuberculin (Mantoux) reveal a normal or decreased responsiveness in CD (5, 23, 57, 66); results of similar testing with atypical mycobacteria antigens (42), or those derived from M. kansasii (7, 22) were variable. CD lymphocytes respond normally when exposed to PPD (6), but a migratory inhibitory assay using atypical mycobacterial antigens evidenced white cell sensitization (63). Matthews et al. found a high percent of CD sera had agglutinins to M. paratuberculosis and M. avium but results were not different from controls (37). Grange et al., using an enzyme linked immunosorbent assay, showed increased frequency of antituberculosis antibodies (BCG) in CD patients (26). Using a similar technique but with an M. paratuberculosis antigen, Thayer et al found elevated titers in CD sera (56). However, a number of investigators cannot confirm these results (14, 28, 34). Antibodies to arabinomanan, a common mycobacterial antigen, and to A60, a membrane glycolipid present in most mycobacteria, were not found. Cho et al. (14) sought antibodies to a glycolipid reputedly specific for M. paratuberculosis and, although antibodies to this glycolipid were not found, antibodies do not develop in animals infected with the organism. Furthermore, the antigen is not found in wild type strains of M. paratuberculosis. Jiwa et al. elicited high IgG antibody levels to five mycobacterial PPD's in CD, including antibodies to a crude M. paratuberculosis antigen (32); like Matthews et al. (37) the results were not significantly different from controls.

Since M. paratuberculosis is closely related to the environmentally widespread M. avium-intracellulare complex, it is unlikely that present day serology would detect significant differences. Perhaps if, as in leprosy (15), a more specific antigen is found, serology would prove more fruitful. Cattle infected with Johne's

disease often have low antibody titers to M. paratuberculosis antigens (10). Antibody titers to M. paratuberculosis in a colony of naturally infected stumptail macaques (Macaca arctoides) were significantly higher than in non-infected controls. Surprisingly, however, clinically ill animals had undetectable titers (38).

Whorwell et al. (65) were unable to find M. kansasii antigens via immunofluorescence, and Haga (27) was unable to find M. paratuberculosis antigens in CD tissue histochemically. On the other hand, Yoshimura et al. (68), employing a liquid genomic DNA:DNA hybridization method, detected mycobacterial related sequences in over half their CD patients, but in a much lower incidence in those with UC or controls; no sequences were identical to M. paratuberculosis. VanKruiningen et al. (61) found positive staining in three patients using a peroxidase-anti-peroxidase immunohistochemical technique although two specimens were probably artifactual. Organisms were detected in positive control tissue, but no organisms were identified in the culturally positive but acid-fast stain negative orally infected goat. Immunohistochemically Kobayashi et al. (35) were unable to demonstrate mycobacteria in CD tissue using several anti-mycobacterial antibodies. Conversely, Colement et al., using a simple acid fast stain, identified mycobacteria in one-third of CD samples (16).

The failure to conclusively demonstrate mycobacteria in CD tissue is certainly damaging evidence against their role as etiologic agents. However, the sensitivity of the new immunohistochemical techniques is unknown. In the infant goat model, although mycobacteria could be cultured from the infected tissue, the immunohistochemical method gave negative results (61). If the organism resides in a cell wall deficient state, it is unlikely conventional acid fast or immunohistochemical techniques would detect them. Mycobacteria thrive inside the macrophage where, in contact with lysozyme, a cell wall deficient state is induced (36); protection is afforded by increased osmolarity within the phagosome.

Case reports suggest antimycobacterial drug therapy results in remission of CD (46, 47, 49, 62), but controlled trials have been negative (21, 31, 51). The trial drugs, randomly selected for their effectiveness in tuberculosis, were not proven effective in in vitro activity against the M. paratuberculosis isolate of CD. Thayer et al. reported clinical improvement (some marked) using a combination of streptomycin and rifabutin, a new semi-synthetic, spiropiperidyl derivative of rifamycin-S, in patients with severe refractory CD (55); all patients have been completely withdrawn from steroids. Hampson et al. (29) treated 17 patients with quadruple antimycobacterial chemotherapy using rifampin, ethambutol, isoniazid, and pyrazinamide or clofazamine. Seventy-one percent showed significant improvement in the Crohn's Disease Activity Index, and 90% were withdrawn from steroids. French investigators report encouraging results using rifampin in the treatment of CD (44, 45, 58). More recently ophthalmologists, using rifampin in the treatment of occular CD, noted coincidental improvement in gut symptomatology (33, 67).

The similarity of CD to other known mycobacterial diseases favors

a mycobacterial etiology; the M. paratuberculosis with its unique ability to replicate within the gastrointestinal tract is a viable candidate. The organism has been isolated from CD cases in a number of different centers, and it clearly causes granulomatous ileocolitis in ruminants and subhuman primates. If this organism ultimately proves responsible for some cases of CD, we have come full circle to Dalziel's original suggestion that the disease is, perhaps, caused by the same organism that causes Johne's disease in cattle.

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SMOKING AND INFLAMMATORY BOWEL DISEASE

M.J.S. Langman
Department of Medicine
Queen Elizabeth Hospital
Birmingham
England

When Rhodes and his colleagues (1) described the tendency for patients with ulcerative colitis to be non-smokers it would have been natural to assume that medical advice as a consequence of developing chronic illness had led those who had colitis and who were smokers to stop smoking. The other possibility was that the fracture clinic controls chosen were unrepresentative of the ordinary population and contained an unduly large proportion of smokers. This latter explanation was unlikely, however, because only 8% of the colitic patients were smokers and it, therefore, became necessary to confirm the original observation and to determine if the smoking habits of the patients were habits which antedated illness onset.

Subsequent studies have confirmed the association of non-smoking with colitis (2-10) and have shown that the association held for habits at, or prior to, symptom onset or diagnosis. Though risks as measured have varied, the trend has been uniform and, therefore, it has remained to ensure that data collected have neither been uniformly biased (for instance, by recall bias) nor subject to some overriding confounding influence.

If bias had been the reason for detecting a spurious association, then the same association should not be detectable in prospectively collected data. Furthermore, the same trend might be detected for Crohn's disease. Sets of data have become available (12,13) from women receiving the oral contraceptive pill and where smoking habits were determined before the onset of inflammatory bowel disease. An excess of non-smokers was detected. Secondly, an association of Crohn's disease with smoking habit has been detected but, on this occasion, with smoking rather than with non-smoking. Taken overall, therefore, it seems likely that smoking habits themselves are important and smoking would appear to protect against colitis, although it still remains possible, if likely, that some other habit of non-smokers predisposes to ulcerative colitis.

If data concerning ulcerative colitis suggest, as is likely, that non-smoking confers liability, then it becomes important to compare risks with those for Crohn's disease. Data sets again show a uniform pattern with more smokers in patients than in matched controls. Again, prospectively collected data have detected the same trend, making it

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likely that biased collection methods do not explain what has been found (12,13).

Given the uniformity of patterns it becomes almost inescapable that smoking habits do determine the occurrence of inflammatory bowel disease. If this is so, then an hypothesis is needed which allows smoking habits to be inserted into the epidemiological pattern.

Both Crohn's disease and ulcerative colitis frequency are modulated by genetic and environmental factors. It is possible, therefore, to construct some different hypotheses. Given the apparently divergent associations for Crohn's disease and colitis it is difficult to see how smoking can act as a uniform predisposing factor and, therefore, it has to be seen as likely to act against the background of other influences.

One possibility is that smoking habits do not affect the occurrence of inflammatory bowel disease, but they determine the site once genetic and other environmental factors have acted and made inflammatory bowel disease develop. This hypothesis is simple and persuasive but there is difficulty in accounting for the risks in ex-smokers since ex-smokers appear to be more likely to develop both colitis and Crohn's disease. There is no convincing way to account for this common pattern. Smokers might stop smoking between disease onset and diagnosis and so become ex-smokers for Crohn's disease and ex-smokers for ulcerative colitis, giving a common pattern of raised apparent risk. Retrospectively collected data cannot be used to determine if this is true or not. Another possibility is that ex-smokers are indeed prone to colitis and that trends are, to some extent, exaggerated by recall bias. For Crohn's disease, any association of disease with ex-smoking would be postulated as entirely representing recall bias. If these propositions were true, then one might expect a consistently stronger association between ex-smoking and colitis than Crohn's disease.

Another possibility is that smoking causes Crohn's disease and that non-smokers are neither particularly prone, nor especially protected from inflammatory bowel disease, whether Crohn's disease or ulcerative colitis. However, in both cases there is a basis of genetic and other environmental predisposing factors. If this were so then the association of Crohn's disease would be simply accounted for. Non-smoking would be associated with colitis simply through the attenuation of a pool of susceptible individuals.

Examination of the relative risks of, respectively, Crohn's disease in smokers, and ulcerative colitis in non-smokers, shows that where risks are high for one disease then they also seem to be high for the other disease when data from the same area are considered. This trend could arise because smoking exerts a variable modulating effect from place to place, or it could simply be a measure of the tendency of different sets of investigations to have greater or lesser biases built into their studies.

A third possibility is that smoking has no special effects, that it is non-smoking that predisposes to ulcerative colitis, and that smoking appears associated with Crohn's disease because the non-smoking population of susceptibles has been attenuated as they develop ulcerative colitis. This is, in effect, the mirror image of hypothesis

B. Currently, we have no way of determining if this is a reasonable hypothesis or not.

Smoking habits are measurable quantitatively and it should, therefore, be possible to determine if heavier or lighter smokers have differing risks. Our own data suggest a reasonable dose response curve for colitis with progressively diminished risk with heavier smoking. However, they show no particular relationship with Crohn's disease.

If smoking modulates disease occurrence it would be reasonable to ask if it influences disease behaviour. There have been isolated case reports in patients with colitis to suggest that smoking ameliorated their disease, but no coherent body of data. In Crohn's disease, by contrast, stopping smoking might be expected, perhaps, to bring benefit. A single data set so far suggests that those who stop smoking may be at reduced risk of recurrence (14).

Interaction with other risk factors: Smoking and sugar consumption seem to be separate interactive risk factors for Crohn's disease (15), suggesting that they operate through a common mechanism.

We conclude, therefore, that the association between non-smoking and colitis and smoking and Crohn's disease are best explained by modulation of the site of disease in individuals who already have the combination of genetic and environmental factors to cause one or the other to occur. In effect, this argues for a common group of predisposing influences.

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ROLE OF PLATELET ACTIVATING FACTOR AND INTERLEUKIN I IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

D. Rachmilewitz,
R. Eliakim,
P. Simon,
M. Ligumsky,
F. Karmeli,
Department of Gastroenterology,
Hadassah University Hospital,
Jerusalem,
Israel, and
Department of Immunology,
Smith Kline and French Laboratories,
Philadelphia,
U.S.A.

ABSTRACT. Colonic biopsy specimens from patients with active ulcerative colitis and controls were incubated for four hours in the presence or absence of calcium ionophore or anti-human IgE. Platelet-activating factor was determined in the tissue by aggregation assay after extraction with 80% ethanol. Platelet-activating factor was not detected in normal mucosa. A23187 and anti-human IgE stimulated its activity: mean $\pm$ S.E., 43.2 $\pm$ 8.6 and 33.0 $\pm$ 6.1 pg/10 mg wet weight, respectively. In active ulcerative colitis, A23187 and antihuman IgE induced significantly higher stimulation of platelet-activating factor synthesis when compared with their effects on normal mucosa. The enhanced stimulation induced by A23187 was dose-dependently inhibited by salazopyrine, 5-aminosalicylic acid and prednisolone, but not by sulfapyridine. Colonic IL-1 content and release during 24 hours of culture were significantly higher in patients with active ulcerative colitis and Crohn's disease when compared with normal subjects. Prednisolone and a dual lipocyclo-oxygenase inhibitor - 86002, significantly and dose-dependently inhibited IL-1 release. These results suggest that colonic generation of PAF and IL-1 are elevated in patients with inflammatory bowel disease and, thus, may have a role in its pathogenesis. Pharmacological suppression of colonic PAF an IL-1 production may have beneficial therapeutic effects.

INTRODUCTION

Platelet-activating factor (PAF) is an endogenous phospholipid, originally found to be released by immunoglobulin E (IgE)-antigen sensitized basophils (1,2). The cells capable of synthesizing and

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releasing PAF include basophils, eosinophils, neutrophils, platelets, monocytes, macrophages and endothelial cells (3-9). Platelet-activating factor exhibits a variety of pharmacologic actions, namely stimulation of platelet and neutrophil aggregation, vasodilatation, induction of vascular permeability and bronchoconstriction (10-15). These effects are accompanied by release of prostaglandins and leukotrienes and have, therefore, implicated PAF as a mediator of inflammation and anaphylaxis (16). In rats, administration of synthetic PAF into the abdominal aorta induced ischemic bowel necrosis (17) as well as extensive gastric mucosal hemorrhagic erosions (18). The mechanism responsible for the deleterious effects of PAF is probably stasis caused by dose-dependent slowing of mucosal capillary blood flow (19).

Interleukin-1 (IL-1) is a key mediator, released by monocyte macrophages in inflammatory and immunological responses (20-21). It acts locally by releasing prostanoids and platelet-activating factor from inflammatory cells and systemically, as a circulating hormone, it induces fever and liver production of acute phase reactants (20-22). Recently, peripheral blood mononuclear cells obtained from patients with Crohn's disease were shown to produce in-vitro high quantities of IL-1 as compared with normal control cells (23).

In the present study, colonic generation of PAF and IL-1 was assessed in patients with inflammatory bowel disease (IBD) as well as in controls. The effect of drugs conventionally used for the treatment of IBD on colonic PAF and IL-1 generation was also evaluated. The study thus elucidates the possible role of PAF and IL-1 in the pathogenesis of IBD.

MATERIALS AND METHODS

Organ culture

Rectal mucosal biopsies were obtained during colonoscopy performed in patients with untreated active ulcerative colitis (UC) and Crohn's colitis, as well as from normal control subjects without any pathology in their colon. The major reasons for colonoscopy in the control group were non-specific abdominal complaints, bleeding hemorrhoids and occult blood in the stool. The diagnosis of ulcerative and Crohn's colitis was established according to clinical, endoscopic, pathologic and radiological criteria. The study protocol was approved by the Hadassah University Hospital Helsinki Committee. Biopsy specimens were organ cultured (37°C; 5%; CO2; 95% air) for 4-24 hours as described earlier (24).

Platelet-activating factor activation was carried out by the addition to the medium of 0.2 uM calcium ionophore A23187 and 50 ul of antihuman IgE or anti-IgG. After four hours of incubation, specimens and media were transferred to separate tubes and frozen (-20°C) until assayed for PAF activity.

For IL-1 determination, fresh and cultured specimens were homogenized with a polytron homogenizer (Kinematic, CH-6010 Kriens-Lu, Switzerland) for 20 seconds at speed grade of 6 in 0.5 mL 50 mM Tris HCl buffer pH 7.4 containing 100 mM NaCl, 1 mM CaCl2 and dextrose (1 mg/l

mL). These samples, as well as the samples of the cultured medium, were kept at -70°C until assayed for their IL-1 level.

In several experiments with ulcerative colitis mucosa, 4-5 tissue samples obtained from the same individual were incubated in the absence or presence of prednisolone, salazopyrine, 5-ASA, sulfapyridine or SKF 86002 (SK&F Labs., Philadelphia, PA, U.S.A.), a dual cyclo- and lipoxygenase inhibitor.

Determination of PAF

Platelet-activating factor activity was determined by the aggregation assay using a Chrono-Log Corporation aggregometer on 80% ethanol extracts of the fresh or cultured colonic mucosa. Platelets were stirred in 400 ul buffer containing 2.6 mM KCl, 1 mM MgCl2, 137 mM NaCl, 12 mM NaHCO3, 1.3 mM CaCl2, 5.5 mM glucose, 0.25% gelatine, 1 mM creatine phosphate and 10 u/ml creatine phosphokinase (pH 7.4) (25).

IL-1 Determination

IL-1 activity was determined by its induction of IL-2 production by murine EL-4 cells, as described previously (26). Briefly, 0.25 ml cultures of $2x10^5$ EL-4 cells in a 96 well flat bottom plate are co-cultured with the sample and $2x10^{-7}$ M calcium ionophore A23187 for 24 hours. The culture fluids are then tested for IL-2 activity using the CTLL-20 IL-2-dependent cell line. IL-2 activity is directly proportional to the input of IL-1. Units of IL-1 activity were calculated relative to a standard of pure recombinant human IL-1 beta, prepared as described previously (27), by a computer program (28). All tissue extracts were centrifuged at 10,000 x g for three minutes and filter sterilized prior to assay. Statistical evaluaton was performed according to the unpaired student t-test.

RESULTS

PAF activity could not be detected in organ cultured colonic mucosa obtained from normal subjects. Minute quantities of PAF were detected in colonic mucosa obtained from patients with active ulcerative colitis (Table 1). After stimulation with calcium ionophore, PAF activity was detected in colonic mucosa of normal subjects. However, its quantity was only 20% of the amount detected in stimulated biopsies of patients with active ulcerative colitis. The same pattern, though with lesser quantities of PAF, was observed after stimulation with antihuman IgE.

TABLE 1. Basal and stimulated synthesis and secretion of PAF by human colonic mucosa

Stimulation	Normal Subjects (pg/10 mg wet wt/x ± S.E.)	Active UC (pg/10 mg wet wt/x ± S.E.)
None	Not detected (12)*	8.9 ± 3.5 (14)**
Ca ionophore	43 ± 9 (13)	200 ± 28 (23)***
Anti-human IgE	33 ± 6 (5)	70 ± 8 (6)****

PAF activity in colonic mucosa organ cultured for 4 h in fresh medium or in medium containing calcium ionophore 0.2 uM or 50 uL of anti-human IgE.
* - number of subjects.
Significantly different from normal subjects: ** $p<0.05$; *** $p<0.01$; **** $p<0.02$.

Prednisolone, when added to the culture medium in doses ranging from 25 to 100 ug/ml dose-dependently, inhibited PAF activity by calcium ionophore stimulated biopsies. The same pattern was seen when colonic biopsies of ulcerative colitis patients were incubated with salazopyrine (25-100 ug/ml) and 5-aminosalicylic acid (5-ASA) (25-100 ug/ml), whereas sulfapyridine had no effect (Table 2).

TABLE 2. Percent inhibition of calcium ionophore stimulated colonic PAF synthesis induced by drugs

Concentration (ug/ml)	25	50	100
Prednisolone	10 ± 8	78 ± 6	100
Salazopyrine	50 ± 10	75 ± 9	100
5-ASA	10 ± 12	70 ± 4	98 ± 2
Sulfapyridine	3 ± 2	2 ± 1	None

Colonic biopsies obtained from patients with active ulcerative colitis were inoculated with calcium ionophore 0.2 uM in the presence and absence of drugs. Each subject served as his own control. Platelet activating factor activity in drug free medium was 219 ± 97 pg/10 mg wet wt/4 h. Results are mean ± S.E. of three experiments performed with each drug.

Fresh colonic mucosa obtained from patients with active ulcerative

colitis contained significantly higher levels of IL-1 by comparison with mucosa obtained from normal subjects.

Colonic mucosa of patients with Crohn's colitis contained even higher levels than in ulcerative colitis (Table 3). Following 24 hours of culture, IL-1 content of the normal mucosa increased by 94 times by comparison with its levels in the fresh, uncultured mucosa. IL-1 content in the cultured mucosa of ulcerative colitis and Crohn's colitis patients also increased and reached significantly higher levels by comparison with the cultured normal mucosa (Table 3).

TABLE 3. IL-1 content and release of cultured colonic mucosa

	Normal Subjects	Ulcerative Colitis	Crohn's Colitis
	(units/mg wet wt)		
Fresh mucosa	0.20 ± 0.04 (16)	2.89 ± 0.80**	12.9 ± 4.7**
Cultured mucosa	17.1 ± 2.3	55.3 ± 6.6**	58.4 ± 5.9**
Medium	1.13 ± 0.30	20.2 ± 5.9**	67.0 ± 27.5**

Fresh and organ cultured colonic mucosa and the culture medium were processed for IL-1 determination. Results are mean ± S.E. * Number of subjects. Significantly differed from normal subjects, ** $p<0.01$.

Release of IL-1 into the medium by mucosa obtained from ulcerative colitis patients during 24 hours increased significantly as compared with its release by the normal mucosa. IL-1 release by Crohn's mucosa was also significantly increased and was even higher than the release by the ulcerative colitis mucosa (p 0.01). Prednisolone significantly and dose-dependently decreased IL-1 content and release during 24 hours of culture (Table 4). The inhibitory effect of prednisolone on IL-1 release was more pronounced than its effect on tissue content. SKF 86002 also decreased dose-dependently 24 hour IL-1 content and release.

TABLE 4. Effect of drugs and colonic IL-1 content and release

	Tissue (% inhibition)	Medium (% inhibition)
Prednisolone (ug/ml)		
1.5	75 ± 29	27 ± 18
25	42 ± 12	4 ± 1
100	35 ± 11	4 ± 1
SKF 86002 (uM)		
1	49 ± 4	56 ± 9
10	34 ± 7	27 ± 11
50	10 ± 4	10 ± 2

Prednisolone or SKF 86002 were added to the culture medium of mucosal biopsies obtained from patients with active ulcerative colitis. Tissue content and release by biopsies cultured in the absence of drugs was regarded as 100%. Results are mean ± S.E. of experiments performed with tissues obtained from three patients.

DISCUSSION

The results obtained in the present study clearly indicate that in active ulcerative colitis both basal and stimulated colonic PAF synthesis are enhanced when compared with their respective synthesis by normal colonic mucosa. Basal PAF synthesis by normal colonic mucosa was beyond detection. The quantities of PAF synthesized by unstimulated colonic mucosa of patients with ulcerative colitis, although measurable, were minute. This difference between patients and controls, although statistically significant, became clearer when PAF synthesis was stimulated either by calcium ionophore or anti-IgE. It is, therefore, suggested that PAF may serve as one of the mediators of the inflammatory response in active ulcerative colitis.

All inflammatory cells present in the inflamed mucosa are stimulated by calcium ionophore and, thus, can be the source of the enhanced colonic PAF activity observed in patients with active ulcerative colitis. The observation that anti-human IgE also stimulated PAF generation suggests that mucosal mast cells are one of the major sources of colonic PAF, though one cannot exclude that other cells expressing IgE Fc fragment receptors contribute to colonic PAF generation stimulated by anti-human IgE.

In this study, prednisolone, salazopyrine and 5-ASA were found to dose-dependently inhibit A23187-stimulated colonic PAF synthesis.

Sulfapyridine, on the other hand, was found to have no effect. Steroids probably inhibit colonic PAF synthesis by interfering with phospholipase A2 activity (29). The mechanism whereby 5-ASA and salazopyrine inhibit PAF synthesis may be related to their inhibition of lipoxygenase product synthesis, but this needs further evaluation.

In view of the accumulating evidence concerning the role of PAF in the pathogenesis of mucosal damage and inflammation and, in view of the data reported herewith, indicating its possible role in the pathogenesis of active ulcerative colitis, the role of specific PAF antagonists in the treatment of ulcerative colitis deserves investigation.

Colonic mucosa of patients with inflammatory bowel disease was found to produce and to release significantly higher amounts of IL-1 when compared with its production by normal colonic mucosa. Mucosal IL-1 was found to be associated with colonic inflammatory response in two models of experimental colitis (30-31). In the trinitrobenzene, sulfonic acid induced chronic colitis in rats and in acute colitis induced in rabbits by enteropathogenic E-coli, mucosal IL-1 was found to be the most sensitive marker of colonic inflammation, much more than myeloperoxidase activity or mucosal eicosanoids. In these two models, an excellent correlation was found between mucosal IL-1 and myeloperoxidase activity (31), indicating its possible origin in the polymorphonuclear cell infiltrates. Corticosteroids inhibit IL-1 production by macrophages (32), probably by decreasing the availability of arachidonic acid and its metabolites. Inhibitors of lipoxygenase activity were also shown to inhibit IL-1 production (33), suggesting a role for leukotrienes in its production. On the other hand, it was shown that PGE2 inhibits IL-1 production (33) and may have a role in a negative feedback control of IL-1 production or release.

In the present study, prednisolone and SKF 86002, a dual cyclolipoxygenase inhibitor, were found to significantly inhibit IL-1 release from inflamed colonic mucosa. Interestingly, prednisolone more effectively inhibited IL-1 release than reducing its tissue content, implying that steroids may have a dual inhibitory effect on IL-1 activity in the inflamed tissue. SKF 86002 was previously reported to inhibit the inflammatory activity in models, similarly to the effect of indomethacin, a cyclo-oxygenase inhibitor, and also in inflammatory models non-responsive to cyclo-oxygenase inhibitors (34). Since PGE inhibits IL-1 production, the inhibitory action of SKF 86002 on IL-1 production, as shown here, may be mainly due to its action on the lipoxygenase system.

The results of the present study imply that IL-1 may have an important role in the pathogenesis and propagation of the inflammatory response in inflammatory bowel disease and that its inhibition by specific agents may bear a potential therapeutic benefit.

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IS THERE A PRIMARY DEFECT IN THE HOST DEFENSE MECHANISM IN IBD?

Charles O. Elson, M.D.
Division of Gastroenterology, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294 USA

There have been many theories over the years as to the etiology of inflammatory bowel disease, but the main theories revolve around an infectious versus immune etiology. The two are not entirely mutually exclusive however, because even the proponents of an infectious etiology acknowledge that the immune system must be involved in the pathogenesis. However, they see the immune system as responding appropriately to rid the body of whatever the infectious agent might be and causing tissue destruction only secondarily. The immune hypothesis holds that there is no single infectious agent responsible for either ulcerative colitis or Crohn's disease, although immune reactions toward microorganisms commonly present in the lumen of the bowel may well play a role in the disease. The immune reaction in this hypothesis is seen as inappropriate and excessive. I believe the weight of evidence greatly favors an immune etiology over an infectious one. This does not imply that genetic and environmental factors do not play a role because epidemiologic data indicates that they do. However, these factors most likely exert their effects through the immune system.

It is undeniable that the immune system is intimately involved in the disease process. The lesions themselves, after all, consist of large number of immune cells infiltrating the bowel mucosa and, in Crohn's disease, the bowel wall. This infiltration is accompanied by general immune activation that is evident systemically as well as locally. There are numerous alterations in various immune parameters in patients which are beyond the scope of this talk, but which have recently been reviewed (1). One worth highlighting is the immune reactivity to colon epithelial antigens, a reactivity that is present not only in patients but also in some of their relatives. The chronic inflammation seen in IBD is quite similar to that found in diseases of immune origin involving other organs, such as sarcoidosis, or rheumatoid arthritis. The lesions contain T cells, B cells and antigen presenting cells in large numbers and there are some characteristic

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abnormalities, particularly a marked increase in plasma cells producing IgG. It is now recognized that many of the disease symptoms and manifestations can be explained by the known effects of cytokines produced by lymphoid cells. For example, IL1 can cause fever and stimulate fibroblast and smooth muscle cell growth, tumor necrosis factor produces anorexia and weight loss, IL1 and IL6 are instrumental in generating the acute phase response measured as increase in the sedimentation rate and so on. In addition, newly described interleukin 8 is a potent attractant of polymorphonuclear leukocytes. Some recent molecular biologic studies on T cell receptor gene rearrangements of lymphocytes isolated from the lesions indicate that the infiltrate is polyclonal in nature and not mono- or oligoclonal as would be expected if a single agent was responsible.

This very large literature on immune abnormalities in inflammatory bowel disease contrasts strikingly with the results of studies looking for an infectious agent. Despite years of effort and some false trails, no specific agent has ever been directly associated with these diseases. This has not been for lack of effort, because the effort has been substantial. The current candidate as an agent causing Crohn's disease is Mycobacteria paratuberculosis. However, DNA hybridization studies have been essentially negative as have been studies looking for any immune response to paratuberculosis antigens, a response that must be present to explain the strong reaction occurring in the intestine. Again, the preponderance of evidence between the two theories of etiology greatly favors a primary immune defect in IBD.

Do we need to invoke a specific infectious agent in order to explain the disease? The answer to that is no. The immune system is perfectly capable of enormous tissue destruction if misdirected, particularly via the effects of the non-specific effector cells that are involved in most immune reactions, namely the activated macrophage and the neutrophil. In the intestine, one need not look far for antigenic stimuli because the antigenic load represented by the lumenal content is enormous. It has been estimated that there are ten times more microorganism cells in the body than there are mammalian cells. A central point that is often overlooked is that the "normal" intestine is chronically inflamed, albeit mildly so. The gut is infiltrated in all of us with lymphoid cells including B cells, T cells, macrophages and large numbers of plasma cells. This point is made even more dramatically by comparisons of germ-free animals with their conventional counterparts. Germ-free animals do not have large numbers of mononuclear cells or plasma cells in their intestine, their gut-associated lymphoid tissue is negligible, and their spleen is roughly one-fifth the size of a conventional animal. When one contaminates

the germ-free animal with a bacterial flora, dramatic changes are seen in the immune system including the appearance of mononuclear cells in the intestine, to the "normal" level. However, this infiltrate remains within fairly circumscribed limits and is generally not accompanied by the appearance of neutrophils in the mucosa or by ulceration. This implies that there are mechanisms in place to limit the degree of inflammation in the bowel, even though we do not quite understand what those mechanisms are. Inflammatory bowel disease may well be a defect in those immunoregulatory mechanisms. This would explain the inability to demonstrate infectious agents, the polyclonal nature of the infiltrate, etc. In this view, inflammatory bowel disease just represents a qualitatively more severe inflammation rather than a rare and unusual process that demands an explanation by invoking a specific pathogen.

Could defects in the permeability of the mucosa and stimulation of non-specific effector cells in the lamina propria explain IBD without invoking direct involvement of the immune system? An increased uptake of ingested polyethyleneglycol of low molecular weight (400 Daltons) has been reported in patients with Crohn's disease and has been used to promote such a notion. This explanation is unlikely for a number of reasons. One must keep in mind that the barrier function of the mucosa is relative and not absolute. Lumenal materials, including macromolecules, cross the intact mucosa regularly. Moreover, breaks in the epithelial layer due to infections are not uncommon, particularly in regions of the world with poor hygeine; yet IBD is rare in these same regions of the world where intestinal infections and thus chronic breakage of the mucosal barrier are common. Moreover, uptake and transport of antigenic material from the lumen into contact with immune cells is a normal event that occurs continuously in the gut associated lymphoid tissue. Lymphoid follicles dispersed throughout the gut are covered by a specialized epithelium that actively pinocytoses lumenal antigens, mitogens, etc. and delivers them into the underlying follicles which contain macrophages, B cells and T cells. This follicle associated epithelium has been shown to take up proteins, viruses, and even whole bacteria. Thus this epithelial component of the gut is not just "permeable", it is actively taking up lumenal material. An interesting point is that the aphthoid ulcer, thought to be the earliest lesion of Crohn's disease, is an ulcer of this specialized epithelium overlying lymphoid follicles. Thus, intestinal 'permeability' and delivery of lumenal antigens to phagocytes and lymphoid cells is a normal event in the follicles and also occurs frequently across the damaged epithelium of infected intestine and cannot explain IBD.

Just what might the primary immune defect be? The most likely one is a defect in local immunoregulation in the intestine as alluded to above and very likely involving the intestinal T cells. We now recognize that the T lymphocytes within the gut are unique in many ways. First, they have surface markers consistent with memory cells; second, they are clearly more activated than cells in other lymphoid compartments and third, they appear to release cytokines upon stimulation rather than proliferate as do lymphocytes in other sites. One can visualize these sensitized lymphocytes sitting in the mucosa ready and waiting to secrete a variety of cytokines when stimulated by re-exposure to specific antigen. The potent effects of such T cell cytokines and the limited inflammation present in the normal intestine indicates that regulatory mechanisms are present that normally limits their effects. Defects in these mechanisms result in excessive release of cytokines which in turn result in further activation of resident macrophages, recruitment of others, and recruitment and activation of polymorphonuclear leukocytes, all resulting in further tissue damage. Such damage plus induction of expression of class II MHC molecules on colon epithelial cells, which may allow them to present antigen to T cells, results in further T cell activation, release of cytokines and a repeat of this sequence. The cycle tends to keep repeating until drug intervention or the immune system itself down-regulates or breaks the cycle, resolving the inflammation. However, the memory cells remain in the mucosa, able to trigger the whole process again when stimulated appropriately.

A central role for the immune system in IBD is further supported by the well recognized therapeutic efficacy of immunosuppressive therapy in IBD patients. Multiple studies have shown azathioprine and 6-mercaptopurine to be efficacious in these diseases, although their use is restricted to the most refractory cases. More recently other immunosuppressive drugs and regimens such as methotrexate, cyclosporine, and lymphocyte apheresis have shown efficacy as well. There is even a case report of a patient with chronically active Crohn's disease who went into remission after acquiring AIDS, a form of immunosuppression which is not recommended. This efficacy of immunosuppressives is difficult to reconcile and is probably incompatible with an infectious pathogen as a cause of IBD. It is quite compatible with a primary immune defect resulting in immune hyperresponsiveness in the intestine and, considering the effects of cyhclosporine and of HIV infection which are T cell specific, with a defect involving regulatory T cells in the intestine.

In summary, the absence of an infectious pathogen despite decades of searching, the immune cell composition of the lesions, the immune

activation evident in patients, the multiple immune abnormalities which have been demonstrated, including cellular and humoral autoreactivity to intestinal epithelial antigens, the ability to explain most of the disease manifestations by the known effects of immune cytokines, the involvement of intestinal lymphoid follicles at the earliest stages of Crohn's disease, and the beneficial effects of immunosuppressives are, taken together, strong evidence supporting a primary immune defect as the etiology of IBD. That defect is likely to reside in the immunoregulatory mechanisms that normally limit the chronic inflammatory infiltrate in the intestine, and will likely involve intestinal T cells, the major regulatory cell of the immune system.

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EVIDENCE AGAINST A DEFECT IN IMMUNE HOST DEFENSES AS A PRIMARY PROCESS IN IBD

Lloyd Mayer, M.D.,
Mount Sinai Medical Center,
Division of Clinical Immunology,
Box 1089,
New York,
New York 10029,
U.S.A.

Since the description of ulcerative colitis more than 100 years ago and Crohn's disease over 50 years ago, numerous hypotheses have been put forth to explain the etio-pathogenesis of IBD. Up to now, no true etiologic agent or defect has been defined, leaving the door open for wide and disparate speculations. We have moved forward from the time when investigators thought that UC was a milk allergy and that Crohn's disease was caused by an overeating of corn flakes. Still, there is no clear cut evidence that the investigators proposing these theories were incorrect. We have all assumed that the improvement seen in Crohn's colitis following diversion of the fecal stream, which has been described by many groups (1), is related to the reduction of antigenic load, allowing mucosal defense mechanisms to re-regulate themselves. However, it is just as plausible to postulate that pathogenic dietary or infectious agents, or both, are diverted from the inflamed site. After all, the layman's outlook on these diseases, that is that bowel disease is caused by something you eat, is not so far-fetched. We all accept that dietary fats and low fiber diets predispose to colon cancer. Just because we cannot identify a compound or an agent does not mean that it is not there, a point that should be kept in mind for immunologic processes as well. It does mean that our technology is such that we are unable to detect specific compounds or infectious agents. Now it is becoming increasingly clear that cell wall deficient organisms or mycobacteria do not cause Crohn's disease. But the evidence here is based upon the repeated inability to reproduce previously published studies (2) (again, a point well taken for immunologic studies reported to date), the non-specificity of the findings, the lack of hybridization in tissues with DNA probes specific for M. linda, and recent studies from our laboratory where, in collaboration with Dr. David Graham, we have been unable to demonstrate any cell mediated immune response to M. linda isolates from patients with Crohn's disease. However, again a word of caution. Who knew scrapie was caused by a prion until improved technology allowed it to be identified? To prejudge too quickly might kill an avenue of investigation that could eventually be profitable.

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In turning to mucosal defense we have an inherent problem. The question is whether there is a primary defect in host defense mechanisms. Host defense is a broad term including immune and non-immune mechanisms. The data to date seems to point towards some defect in mucosal defense but a primary immunologic defect is far from proven. Non-immunologic defense mechanisms include physical barriers such as epithelial cell integrity and overlying mucins, as well as a series of chemical barriers such as lysozyme, gastric acid, etc. These barriers are present in the oral and intestinal tract and serve to prevent organisms and toxins from entering the mucosa or to neutralize their potency before contact occurs.

There is good reason to suspect that the integrity of the GI tract is not all that sound in IBD. Hollander and his co-workers (3) clearly demonstrated that there was an increase in intestinal permeability in CD but that this persisted in disease remission and could be found in first degree relatives as well. Not only did these findings suggest a primary defect in host defense but also laid the groundwork for genetic susceptibility associated with exposure to a series of disease initiating agents. Podolsky's studies have consistently demonstrated abnormalities in mucin glycoproteins in UC (4), again, potentially allowing for increased permeability. With greater antigenic load and the potential for exposure to agents which could initiate disease, an immune response in this setting would be secondary, not primary - a naturally active immune response to foreign antigens. This does not lessen the importance of mucosal immunity in its role in IBD, but does lessen its status somewhat.

Associated with enhanced permeability is another component of the host defense system, the phagocytic or scavenger cell. In this setting one is referring to the polymorphonuclear leucocyte (PMN) and the monocyte/macrophage. While monocytes are an integral component of what has been termed an adaptive immune response, processing and presenting antigen to the T cell antigen receptor, these cells originated before adaptive immunity evolved. These phagocytic cells are considered key players in innate defense mechanisms. Both cell types, PMNs and macrophages, have the ability to phagocytose organisms and, through lysosomal pathways or release of superoxides, peroxides, etc., are capable of destroying invaders. This has been well characterized in macrophages for a number of organisms, including Listeria which, during phagocytosis, is associated with cell activation and secretion of a large number of inflammatory mediators. Now, what is the evidence that these cells play a role in IBD? For starters, histology. Inflammatory infiltrates in early IBD have significant numbers of PMNs and macrophages which, in large part have been ignored. A recent study by Saverymuttu et al. (5) documented a large influx of indium labelled PMNs into areas of active inflammation in CD. Bacterial products are excellent chemo-attractants and may reflect an increased permeability/chemotaxis axis. Studies by Tanner et al. (6), as well as histologic studies by several groups, have provided ample evidence of tissue macrophage activation, as evidenced by increased endogenous peroxides and peroxidases. A macrophage attracted by the bacterial

product FMLP present in the lamina propria through enhanced permeability can engulf organisms with subsequent activation and secretion of prostaglandins, superoxides, etc., resulting in tissue injury, fibroblast proliferation (IL-1 mediated), smooth muscle proliferation and collagen deposition (IL-1 and IL-6 mediated) and vascular congestion (procoagulant activity). In such scenario, one need not invoke immune mechanisms at all, although it is clear that T cell derived cytokines such as gamma-IFN can accelerate the process by attracting and activating phagocytic cells. Still, in any of the scenarios described, one need not implicate T cells or antibodies in the primary process. Immune responses are then relegated to a secondary phenomenon.

Just because immunologic defects have been described in IBD does not translate into their being of primary pathogenetic importance. After all, is the profound anergy seen in lepromatous leprosy a primary immunologic event? Better yet, are the absence of specific antigen or mitogen responses seen in AIDS due to a primary immune defect in these patients? Obviously not, and this relates back to the initial comments on an, as yet, unidentified micro-organism which could initiate the disease process and not stick around while resulting in immunologic deficits. The permeability/macrophage/PMN activation model proposed earlier could also result in secondary immunologic activation. But for argument's sake, let us take a look at the immunologic studies to date. It has become increasingly clear that studies performed on peripheral blood lymphocytes are not truly representative of the disease process itself. Still, studes by Auer (7), Selby and Jewell (8), Bird and Britton (9) documented that lymphopenia, differences in T cell subsets, and anergy were related more to therapy and nutritional status than the disease itself.

The studies of anti-epithelial cell antibodies by Perlmann and Broberger (10) and others have always been intriguing, but what are these antibodies doing? There has only been evidence against them being cytotoxic, both in human and animal models of inflammation. More importantly, they appear to be totally non-specific, being found in a variety of inflammatory diseases but also in unrelated disorders such as urinary tract infections (11).

What about cytotoxic cells? Again, with the exception of some recent studies by Shanahan, Targan and co-workers (12), CTLs or any cytotoxic cells have not been identified in greater numbers or with enhanced function in IBD. In fact, several groups, including MacDermott's and Fiocchi's (13,14) have reported decreased cytotoxicity. These data are certainly difficult to reconcile with a cytotoxic mediated event in a potentially "autoimmune process".

So we are left with what most investigators feel is the true immunologic defect in IBD: mucosal (i.e. lamina propria and intraepithelial lymphocytes) immunoregulation. Thus far no one has documented a difference in LPL or IEL function in IBD when compared with normal. If one postulates a defect in the control of local immune responses, where is the defect? Comparable T helper activity has been demonstrated repeatedly (15) and there has been a failure to identify a contrasuppressor cell which had been identified in the peripheral blood

of early Crohn's disease patients (16). The only finding of a difference in the lamina propria to date has been the studies of MacDermott et al. (17), where selective increases in the spontaneous secretion of IgG and IgG1 subclass in UC LPL and IgG and IgG2 in CD LPL were detected. This has not been proposed as a primary process, however, and would more likely represent a tisue immune response to enhanced antigenic load. Thus, when all the arguments are taken together, it is clear that a primary immunologic event is not crucial, but still, these processes may play a role in the chronicity of the disease.

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ANIMAL MODELS OF INFLAMMATORY BOWEL DISEASE

William F. Stenson, M.D.

Jewish Hospital of St. Louis
Division of Gastroenterology, Box 8124
Washington University School of Medicine
St. Louis, MO 63110 U.S.A.

ABSTRACT. Over the years a large number of animal models of IBD have been put forth. The stimuli used to promote inflammation in the models include infectious agents, immune manipulation, toxic compounds and tissue homogenates from IBD patients. Although all of the models are successful models of intestinal inflammation it is hard to single out one as being a more successful model of IBD because we have no specific markers of IBD for the model to mimic. Progress in the development of animal models awaits the better definition of characteristics specific to IBD.

In 1985 Warren Strober described an ideal animal model of inflammatory bowel disease (1) (Table 1). In this ideal he calls for an animal model identical to human inflammatory bowel disease having the same causal factors, pathology, pathophysiology, and clinical spectrum.

Table 1. Ideal Animal Model of IBD

A.	A disease in an animal identical to human IBD having the:
	1. Same causal factors.
	2. Same pathology and pathophysiology.
	3. Same clinical spectrum.
B.	A disease occurring in an animal that:
	1. Is accessible and reasonable inexpensive.
	2. Has a defined genetic background.
	3. Has a similar immune system to that in humans.
	4. Can be manipulated as to its:
	a) Dietary intake.
	b) Immunologic status.
	c) Exposure to infectious agents.
C.	A disease occurring in an animal that is susceptible to various forms of treatment.

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There are two problems that arise when we attempt to develop such an ideal model. The first problem is that we do not know enough about inflammatory bowel disease to define the requirements of a good model. We do not know the cause of inflammatory bowel disease. The pathology of inflammatory bowel disease is fairly non-specific, that is, there are no pathologic findings in inflammatory bowel disease that are not also seen in a number of other human diseases. There are no functional changes in the gastrointestinal tract that are specific to inflammatory bowel disease. Finally, there are no serologic or biochemical changes that are unique to inflammatory bowel disease. On a functional and histological basis, inflammatory bowel disease resembles other inflammatory diseases of the intestine that have mixed acute and chronic components. Thus, any model of inflammatory bowel disease could just as easily be a model for other diseases marked by intestinal inflammation.

The second problem is that all inflammatory intestinal diseases in man look more or less the same. The clinical manifestations of inflammatory intestinal diseases are primarily abdominal pain and diarrhea which in some diseases is bloody. The endoscopic changes associated with inflammatory diseases of the intestine are mucosal edema, erythema, ulceration, and friability. Histologically, intestinal inflammation is marked by an infiltrate with lymphocytes, macrophages, neutrophils, mast cells, and eosinophils. The distribution of cells in the inflammatory infiltrate is largely a function of the acuteness or chronicity of the process rather than a function of the inciting agent. Most inflammatory diseases of the intestine are marked by damage to the epithelial cells, although in most diseases the exact mechanism causing that damage is undefined. The characteristics described here are common to almost all chronic inflammatory diseases of the intestine irrespective of their etiology. Many of these characteristics are seen in diseases of bacterial (shigellosis), protozoal (amebiasis), mycobacterial (tuberculosis), ischemic, immunologic (dinitrochlorobenzene induced colitis), and toxic (acetic acid induced colitis) origin. The reason for the striking similarities in the histologic and functional appearance of these diseases despite their widely varying etiologies is that the cells and inflammatory mediators involved in the inflammatory response are similar in all of these diseases even though the initiating events may be different (2). That is to say, there are many different agents that can initiate an inflammatory response in the intestine; however, once the inflammatory response is initiated the characteristics of that response are largely similar irrespective of the agent that initiated the response. As a result it is relatively easy to develop models of intestinal inflammation; in fact, all of the models which we will discuss are reasonably good models of intestinal inflammation. None of them, however, appears to have attributes that make it resemble inflammatory bowel disease more than other varieties of intestinal inflammation. However, if we knew better how inflammatory bowel

disease was distinct from other intestinal inflammatory processes we would be better able to define the characteristics of an animal model of inflammation that would make it more useful in the study of inflammatory bowel disease. The usefulness of an animal model of inflammation for inflammatory bowel disease is determined by what aspect of inflammatory bowel disease one wants to study. For example, if one wanted to use an animal model to study abnormalities of mucin secretion in inflammatory bowel disease it would be important to demonstrate that the animal model of inflammation had the same pattern of mucin production as inflammatory bowel disease tissue. The obvious consequence in this is that if you are studying an aspect of inflammatory bowel disease that it holds in common with other varieties of intestinal inflammation then any one of a large number of animal models is likely to be useful. However, if one wants to study a point in the development of inflammatory bowel disease that is closer to the initiating event, then the changes in inflammatory bowel disease are likely to be more specific and few if any animal models are likely to be useful.

COLITIS THAT OCCURS SPONTANEOUSLY IN NATURE

The most interesting model in this category is the cotton-top marmoset, an endangered species living in the jungles of Colombia (3). All studies are done on animals raised in captivity, importation of additional animals is forbidden. These animals develop a colonic inflammation that resembles in many respects human ulcerative colitis. The histology of the disease is characterized by mononuclear cell and neutrophil infiltration and the formation of ulcers, there are no granulomas. In contrast to human ulcerative colitis the inflammatory process in cotton top marmosets also occurs in the jejunum and ileum in addition to the colon. Although colitis occurs in more than 50% of cotton-top marmosets maintained in captivity there have been no reports of colitis in these animals in the wild. This raises the possibility that some environmental or dietary factor induces colitis in cotton-top marmosets in captivity. Definition of the factors responsible for the development of colitis in marmosets could give an important insight into the pathogenesis of ulcerative colitis. An alternative explanation for the absence of colitis in feral marmosets is that the development of colitis may impair the ability of the animal to function in the wild and thus leads to an early death.

Cotton-top marmosets also develop colon cancer. Cancer occurs only in the animals that have already developed colitis. As in the colon cancer that develops in human ulcerative colitis, colon cancer in cotton-top marmosets appears to develop in the absence of prior adenomatous polyp formation and is frequently multicentric. Both colitis and colon cancer had been reported from captive colonies of cotton-top marmosets all around the world. There are other similarities between the spontaneously occurring colitis in cotton-top marmosets and human ulcerative colitis. The disease improves when

treated with sulfasalazine but recurs when treatment is stopped. There also appears to be similarities in the abnormalities of mucin formation between cotton-top tamarins and human ulcerative colitis.

INFECTIOUS DISEASES OF ANIMALS THAT RESEMBLE HUMAN INFLAMMATORY BOWEL DISEASE

Many animal species develop infectious diseases that have histologic similarities to inflammatory bowel disease. One of the more interesting of these infections is Johne's disease, a disease of cattle, sheep, goats, swine, and horses marked by granulomatous inflammation of the ileum (4). Johne's disease is caused by Mycobacterium paratuberculosis. Clinically the disease is marked by diarrhea, wasting, and death. The pathologic picture of Johne's disease very closely resembles that of Crohn's disease of the human ileum.

USE OF MATERIALS DERIVED FROM IBD PATIENTS TO INDUCE INTESTINAL INFLAMMATION IN ANIMALS

A number of attempts have been made to induce intestinal inflammation in animals by injecting them with material from patients with inflammatory bowel disease. Mitchell and Rees injected homogenized and filtered Crohn's disease tissue into the footpads of mice (5). Examination of the injected mice revealed granulomas at the sites of the injections and in the ileum. The investigators suggested that this experiment supported the concept that an infectious agent, perhaps a virus, was the etiologic factor in inflammatory bowel disease. However, later studies by other groups did not support this suggestion. Although others were able to produce footpad granulomas in mice by injecting Crohn's disease tissue the histologic examination of the granulomas suggested that they were foreign body reactions rather than an infectious process. There have been a number of other studies attempting to infect animals with a transmissible agent from inflammatory bowel disease tissue and these studies have been largely negative.

An especially interesting attempt to define the presence of a transmissible agent by transfer to animals was performed by Das (6). Homogenates of Crohn's disease tissue were injected into athymic (nude) mice. Some of the animals developed lymphoid hyperplasia or lymphomas. Injection of tissue from patients without Crohn's disease did not induce lymphoid hypertrophy or lymphomas in the mice. In addition, sera from patients with Crohn's disease was found to contain antibodies that reacted with the hyperplastic and neoplastic lymphoid tissue from the mice. The serum reactivity was specific for the Crohn's disease patients and was not seen in sera from healthy controls or patients with ulcerative colitis. One potential interpretation of these experiments is that Crohn's disease tissue contained a virus or other transmissible agent that induced lymphoid hyperplasia and lymphoma in

the mice. However, no virus was ever cultured from either the Crohn's disease tissue or the affected mice. An alternative explanation is that the lymphoid hyperplasia and lymphoma represent an immune response in the athymic mice to an antigen peculiar to Crohn's disease tissue. The antigen may derive either from the Crohn's disease tissue itself or from lumenal antigens that have crossed the disrupted epithelial barrier of the Crohn's disease affected intestine.

The most controversial attempt to induce intestinal inflammation in animals using material derived from human inflammatory bowel disease comes from the laboratory of Chiodini and colleagues (7). These investigators have been able to isolate mycobacteria from surgical specimens resected from patients with Crohn's disease. Many of their positive isolates were culturable only as spheroplasts and all of the isolates were found only after months to years of incubation. These results were appealing in the sense that the stringent incubation conditions and the long periods of incubation required for isolation of the organism might explain why numerous previous attempts at isolating an etiologic infectious agent from Crohn's disease tissue had been unsuccessful. A young goat was orally inoculated with the mycobacteria isolated from a Crohn's disease surgical specimen. The goat did not become clinically ill, but did develop an IgM response to the mycobacterium. At autopsy approximately 20 cm. of the terminal ileum was thickened, contained numerous transverse corrugations and demonstrated focal hyperemia. Regional lymph nodes were enlarged and contained non-caseating granulomas, acid fast organisms were identified in the granulomas and lymph nodes. Although this study demonstrates that mycobacteria can be isolated from Crohn's disease surgical specimens and that those mycobacteria can induce intestinal disease in goats it does not demonstrate that the mycobacterium is the etiologic agent in Crohn's disease. Mycobacteria appear as part of the normal non-pathogenic flora of the small intestine. The finding that these mycobacteria are pathogenic for goats does not necessarily mean that they are pathogenic for man. Graham et al. have also grown mycobacteria from Crohn's disease tissue but they were able to isolate several different types of mycobacteria from different specimens (8). Moreover, they were also able to culture mycobacteria from some specimens from ulcerative colitis patients and from healthy individuals.

IMMUNE MEDIATED ANIMAL MODELS

One of the mechanisms for the induction of intestinal inflammation is activation of the mucosal immune system. Most theories for the pathogenesis of human inflammatory bowel disease are based on the premise that inflammation in inflammatory bowel disease is induced by activation of the mucosal immune system. As a result, animal models in which inflammation is produced by manipulation of the immune system have been suggested to have greater relevance to inflammatory bowel diseases then other models. In general these models have been based on

the sensitization of the animal to a specific antigen. In one early model animals were sensitized to an antigen by systemic administration of the antigen and later were challenged by injection of the antigen into the intestinal tissue resulting in the production of intestinal inflammation (9). In a later model rabbits were immunized with ovalbumin and the animals were then given an enema with formalin which acts as a barrier breaker and enhances vascular permeability in the colon. The animals were then administered ovalbumin either parenterally or as an enema. The premise of this model is that antigen antibody complexes are formed and are deposited extravascularly in the colon because of the increased vascular permeability induced by formalin (10). This process, called the "Auer procedure", resulted in colonic inflammation marked by cellular infiltration with neutrophils and lymphocytes. There was destruction of the colonic epithelium and ulcer formation. If the procedure was repeated several times, the inflammatory infiltrate evolved from an acute inflammatory reaction to a chronic inflammatory response.

The models described above are B-cell models in which the major immune manipulation is the induction of antibodies (11). It is also possible to induce intestinal inflammation by manipulation of the T-cell arm of the immune response. The prototype for the T-cell model is the dinitrochlorobenzene (DNCB) model of colitis. DNCB is a hapten that binds to cell surface proteins and is capable of inducing delayed-type hypersensitivity if applied to the skin or intestinal mucosa. Animals, usually rabbits, are sensitized to DNCB by cutaneous injection. When the animals are challenged with DNCB administrated as an enema they develop an acute colitis. The lesion is characterized by a mononuclear cell infiltrate, vascular congestion and perivascular cuffing. In addition there is epithelial erosion, frank ulceration and mucosal hemorrhage. The sensitivity can be passively transferred by lymphocytes. The finding that an animal models of colitis initiated by B-cell manipulation (the Auer reaction) and by T-cell manipulation (the DNCB model) have very similar lesions suggests that the histologic findings in these models are the products of the activation of some final common pathway. Thus, the histologic picture in intestinal inflammation is not informative concerning the initiating event.

Sartor and his colleagues have developed a model of intestinal inflammation in rats by injecting peptidoglycans from streptococci into the intestinal wall (12). The animals develop a chronic inflammatory reaction with granulomas at the site of the injections. This model supports the concept that if increased permeability across the intestinal epithelium allows the permeation of bacterial components into the lamina propria the immune response to the bacterial components may result in a chronic inflammatory response.

TOXIC MODELS

Intestinal inflammation can also be induced by intralumenal application of toxic agents. The agents most widely used in these models are acetic acid (13) and trinitrobenzenesulfonic acid (TNBS) (14). Acetic acid appears to act by killing the colonic epithelium and allowing lumenal antigens to enter the lamina propria. It has been suggested that TNBS acts as a hapten like DNCB; however, TNBS induces colitis in animals without prior sensitization and it is possible that it acts by killing the epithelium. These models induce acute inflammation, followed by chronic inflammation followed by healing. Histologically they are very similar to IBD and to the immune based animal models described above. The patterns of eicosanoid production are very similar to those seen in IBD (13). Moreover, these models can be pharmacologically manipulated. The TNBS model responds to cytoprotective prostaglandins (15) and to a specific leukotriene synthesis inhibitor (16). The finding that toxic models of inflammation resemble immune-induced models and also resemble IBD suggests that most of what we see histologically in IBD represents the activation of a final common pathway.

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WHY THE VARIATION IN COLITIC CANCER RATES FROM DIFFERENT CENTRES

Robert H. Riddell, M.D.
Department of Pathology
Chedoke-McMaster Hospitals, McMaster Division
1200 Main Street West
Hamilton, Ontario L8N 3Z5 Canada

To answer the question, it is necessary firstly to determine whether there really are significant differences between centres and secondly, if this is the case, determine whether these differences are the result of methodological biases or variables, or whether they represent genuine differences. Let us begin by examining the risk of cancer in colitis as given in a variety of papers and compare them to determine that there really is a difference. The first thing we discover is that even the means of measuring cancer risk or rate in colitis is expressed in a variety of ways that are not always comparable. These include:

1. Risk per patient year of follow up.
   a) Crude
   b) Adjusted for length of History

2. The risk compared to a non-colitic but age-matched population.

3. The proportion of patients developing carcinoma over a specific period of time.

4. Prevalence rates - that is at a single point in time.

Examples of the first three are shown in Table 1[1]-3[2] while Figures 1[4] and 2[5] show ways of expressing the proportion developing carcinoma graphically as opposed to a tabular form. A simple comparison of these different means of expressing data do show what appear to be obvious variations at a glance. However, let us look at some of the variables at work during studies of this sort, which are well documented.[7]

1. *Inception Cohort.* This should be uniform between groups and ideally patients should be enrolled early in the course of the disease such as when symptoms are first identified or therapy first instituted. Examination of appropriate papers shows tremendous variation, some patients entering studies early in their disease, others only being referred after 20 or 30 years of disease or because of clinical symptoms of underlying carcinoma. This variation causes "starting time bias" that is it distorts calculations of the magnitude and/or timing of

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important prognostic events. This is particularly important when the prognosis of those entering late in the course of the disease differs from those entering earlier (prevalence-incidence [Neyman's] bias). For example, patients included early tend to be young, and have more extensive disease; they also have a longer time frame within which to develop carcinoma.

TABLE 1. Comparison of cancer risk/patient year by decade of disease.

Duration (yrs)	Lennard-Jones 1983 (13)	Gilat 1988 (26)	Maratka 1985 (4) (total)
	Risk/patient Year of Follow-up		
<10	0	1/3895	0
10<20	1/92(8)	1/198	1/462
>20	1/86(5)	1/100	1/315
30		1/75	

TABLE 2. Cancer risk against age-matched controls.

Age (# Cancers)	Relative Risk
20-39	x370 (3)
40-59	x 31 (7)
60-75	x 9 (3)

(Lennard-Jones 1983)

TABLE 3. Cumulative risk of colorectal cancer

	Gilat 1988 Tel Aviv-Yafo (26)		Gyde 1988 3 centres (38)	Brostrom 1986 Stockholm (25)	Hendriksen 1985 Copenhagen (7)	Maratka 1985 Prague (4)
	All	Total				
10	0.2%	0%	0.6%	0	0.8%	0
15	2.8%	9.3%	3%	1.1%	-	-
20	5.5%	13.8%	7.1%	5%	-	5%
25	-		-	13%	-	-
30	13.5%	-	24%	-	1.4%	15%
35	-		-	-	-	20%
	1970-80		1945-76	1945-79	1960-78	1945-81

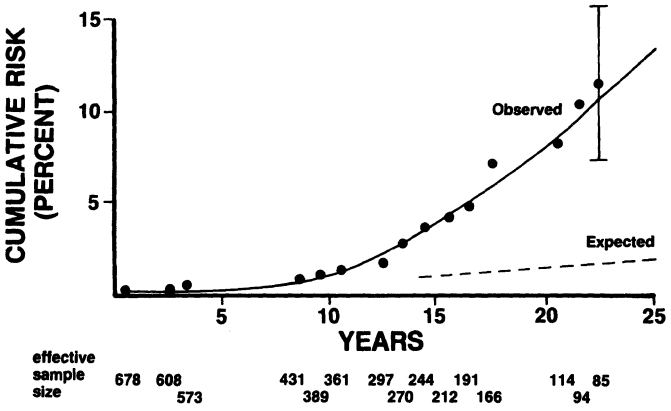

Fig. 1: Cumulative risk of developing cancer in patients with total ulcerative colitis in Stockholm County 1945-1979.

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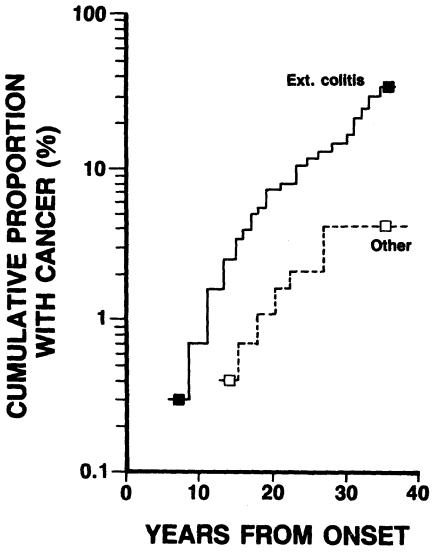

Fig. 2: Cumulative proportion of patients with colorectal cancers by extent of disease: Extensive colitis and remainder of series. Three centres combined (log scale).

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2. *Referral of Pattern Biases.* Patients are referred for a variety of reasons; this includes referral of patients because of the competence of a major centre (centripetal bias); the tendency of such centres to keep track of interesting patients (popularity bias); these together generate a patient sample that differs from that found in the general population. (Referral filter bias). In addition patients having large distances to travel to specialized centres or being fiscally unable to bear this burden may choose to be followed locally. (Diagnostic access bias)

3. *Entry Criteria.* Although carcinoma in ulcerative colitis is much more frequent in patients with total ("universal") colitis, in practice, the definitions of extent are unclear and variable, while the method of assessing the extent of disease tends to vary. With regard to extent, "extensive" colitis is variably defined as disease proximal to the hepatic flexure, although some include this under total colitis. Others use extensive for patients with proximal limit of disease between the hepatic and splenic flexures and sometimes for all disease that is not total or limited to the rectum[6]. However, the means of defining the extent of disease vary in different studies and are shown in Table 4. Some use barium enemas, which may be either double (air) contrast or sometimes single contrast. Others may use colonoscopy but the proximal limit of disease may be either a visual limit or the proximal limit on biopsies. These two may vary considerably and patients with apparent left sided disease on biopsy may prove to have involvement of the entire colon on multiple biopsies. Some studies use any or all of these criteria to define the most proximal limit of disease. The result of this is that there will be unhomogeneity even in groups such as total whites that should be easily defined.

TABLE 4. Methods of determining the extent of disease

Means of Defining "Extent"	
Barium enema	- double contrast
	- single contrast
(? active/quiescent)	
Colonoscopy	- visual
	- biopsies

It should also be recalled that colonoscopy did not really come into vogue until the early 1970's and full colonoscopy until about the mid 1970's. We currently have no idea how to handle patients presenting initially with proctosigmoiditis, but found a decade later to have

extended proximally to the right colon. Are they entered into surveillance as if they had total colitis from the beginning, and are they even at risk?

4. *Problems with the Diagnosis of "Colitis"*. It should be remembered that colitis is an actively evolving group of diseases and that new conditions continue to appear in the literature, some of which are easily confused with ulcerative colitis. These are shown in Table 5 when it can be appreciated, for instance that Crohn's colitis really did not gain clinical acceptance until, at least, the mid 1960's. Studies going back before this are therefore likely to be contaminated, and the onus is on those carrying out the study to exclude as many of these as possible. Indeterminate colitis remains an enigma. A variety of infections could not be identified until relatively recently while even now in typical acute infectious colitis no pathogen can be identified in upwards of 40% of patients. Chronic or low grade ischemic colitis remains a problem and there is frequently no good way of easily separating it from ulcerative colitis or Crohn's Disease. All of these conditions have the potential for increasing the size of the group under study, and because most do not have an increased risk of carcinoma, will have the effect of diluting the patient population under study with regards to the number of carcinomas that can be attributed to colitis.

TABLE 5. Problems with the diagnosis of "colitis"

1. CD - especially pre 1965
2. Indeterminate colitis (late 1970's)
3. Infection - C. jejuni/coli (mid 1970's)
   - C. difficile (1980)
   - Verotoxin E. coli (late 1980's)
   - 40% + no offender
4. Collagenous colitis
5. Ischemic colitis
6. Colonoscopy after 1970
7. Air contrast enemas after ? (still used)

Effect: Dilution

5. *Method of Follow-up and Endpoints*. Variations in the method of follow-up are shown in Table 6; in some of the studies quoted clinical cancer was the endpoint, in others endoscopic cancer, a dysplasia-associated mass, high grade, and sometimes low grade dysplasia or a combination of these. Variables in surveillance studies include the expertise of the colonoscopist which in turn may reflect the ability to obtain a clean colon. Some endoscopist are much more suspicious of endoscopic lesions than others. While some take perhaps 5 biopsies of

the entire colon, others will take three to four every 10 cm. Further variability comes in with the pathologist who not only needs to be accurate but needs to know and state which criteria are being employed. Hopefully both intra and interobserver variability are small but there are numerous studies to suggest that this is not the case.[8-10] During follow-up, the number of biopsies taken include a diagnostic/suspicion bias, that is a more frequent or detailed search is employed when there is an suspicion of underlying dysplasia. An expectation bias may also come into play, that is follow-up may be affected by key features such as an endoscopic lesion or knowledge that previous dysplasia was present which will engender a much more intensive search, sometimes in a particular segment of large bowel. All of these may increase the likelihood of an occult carcinoma being found. Similar expectation bias may come into play in histological interpretation; this can be overcome by "blind" interpretation, that is, no knowledge or prior biopsies.

At the time of endoscopy, the colonoscopist does need to know what is being searched for, how areas of dysplasia or carcinoma (early or late) or both appear endoscopically. It should be realized that the endoscopic criteria for all of these have never yet been properly addressed.

TABLE 6. Some variables in the method of follow-up

Time interval between colonoscopy
colonoscopies & period of follow-up
Expertise of endoscopist
? complete colonoscopy
? visualization of abnormalities and visualization criteria used
? # of biopsies
Expertise of pathologist
Accurate criteria
Which criteria?
Intra-observer variability
Inter-observer variability (confirmation)
Willingness to recommend colectomy

6. *Completeness of Follow-up of Cohort.* This is a major problem in several series. It is generally accepted that a loss of 10% of patients presents a serious problem and that if this exceeds 20% serious doubt must be cast on the validity of the entire study.[7] Yet a proportion of patients in any series inevitably come to colectomy for fulminant disease, incapacitating disease, steroid resistance and a variety of other reasons.

7. *Should Dysplasia be Found, What is the Method of Histological Confirmation?* Is this referral to a second pathologist and if so does it matter who this is? Or does the endoscopist choose to repeat the colonoscopy despite the potential problems of sampling artifact and the reliance on the expertise of the endoscopist? How should one interpret a dysplastic biopsy followed by further negative biopsies? Does this mean that other dysplasia "disappeared".

8. *The Criteria for Colectomy Vary Markedly Between Centres (Table 7).* In some centres it is clear that a clinical carcinoma is the endpoint of the study. In others it is low grade dysplasia, particularly if a endoscopic mass is present, or in others high grade dysplasia whether an endoscopic lesions is or is not present. Some demand dysplasia on repeated biopsies, some multifocal dysplasia. There is a common but possibly misplaced reliance on the fact that a negative pathology report means that no dysplasia is present. Clearly false negative reports can occur for a variety of reasons.

TABLE 7. Endpoint of Study

1.	Low grade dysplasia ± DALM
2.	High grade dysplasia ± DALM
3.	Clinical carcinoma
4.	Repeated dysplasia
5.	Multifocal dysplasia

9. *Factors Affecting the Decision for Surgery.* Some of these are shown in Table 8. Perhaps the most noteworthy feature is that dysplasia by itself, or the risk of possible underlying carcinoma is rarely the major reason for colectomy. Frequently the clinical activity of disease, the patients suitability and attitude towards reception and the attitude of the physical overwhelm. This may also be affected on the clinical competence of the available surgeon.

TABLE 8. Some factors affecting the decision for surgery

1.	Activity & persistence of disease
2.	Cancer (or risk of)/Dysplasia
3.	Age & suitability for resection
4.	Experience of surgeon (esp. pouch)
5.	Underlying disease not clearly U.C.
6.	Attitude of patient
7.	Attitude of physician

Application of Biases to "Outlying" Papers

Although Gilat et al consider their incidence to be low, the question is compared with which other series.[2] Some of these have a notoriously high referral rate of patients with carcinoma, or very small numbers of patients with carcinoma. Their figures are actually in line with many other series such as those at St. Mark's (Table 1) and at face value considerably higher than other series[3-6]. In Tables 1 - 3 above it is clear that of those selected two seem to have rates of carcinoma that are much less than those expected and appear to be similar to the general population at large (Maratka 1985 and Hendriksen 1985). It may, however, be worth a slightly closer look at these. If we look at the entry criteria for the Maratka paper, it is worthwhile noting the entry dates which range from 1942 to 1981. All of the diagnostic problems shown in Table 5 come into play and these may be particularly relevant in that the paper states that it was a referral centre for most of Czechoslovakia, "especially up until 1960". If one bears this in mind and looks at the entry criteria shown in Table 9, notice particularly that the history refers to blood per rectum, tenesmus and/or diarrhea. One can run through virtually all of these entry criteria and infections, particularly those with a post infective diarrhea and Crohn's disease can fit as easily as ulcerative colitis. It therefore seems likely that the number of patients in this study may have been diluted by patients not having ulcerative colitis. In addition, given the relative frequency of infections in the population, it is not inconceivable that patients having ulcerative colitis and later developing carcinoma in the remainder of the country may well never have been referred in the first instance. Yet despite this, the cumulative risk of colorectal cancer in this study as shown in Figure 3 is not too dissimilar to other studies.

TABLE 9. Maratka 85 - Entry Criteria 1942-81

History:	Blood p.r. tenesmus and/or diarrhea
Procto/sigm:	Hemorrhage and/or ulceration
Biopsy:	Inflammation and ulceration
XR:	Air 1971-81
Microbiology:	Bacteriology & parasitology -ive for sp. agents

The second study at marked variance is that by Hendriksen et al. from Copenhagen in 1985 (Table 3). The dates of this study are between 1960 and 1978 which again means that some of the criteria shown in Table 5 also come into play. This paper is of interest in that of the 783 patients included, 318 (41%) had disease apparently limited to the rectum, 124 (16%) were total and the remainder were designated extensive (319-41%). This study is remarkable for two major features. If we take

the fact that the patients with proctitis are unlikely to have a risk of carcinoma that is greater than the general population, then the number of patients with total or extensive colitis is 443. The first major factor that comes into play in this study is the colectomy rate - 149 patients have colectomy, mostly in the first two years. Presumably this will be made up almost entirely of the extensive and total colitic group; indeed it is conceivable that the entire total colitic population could have had their colon removed and this would still mean a colectomy rate of 25% in the extensive group. However, if we remove the 149 patients who underwent colectomy from the extensive plus total group of 443, then this leaves 294 patients at risk.

The second important feature here is the high proportion of patients that seem to have either been lost to follow-up or died, 198 of the 783 patients - or approximately 25%. This in itself represents a huge number and caused serious doubts on the validity of the study.[1] If those lost to follow-up and those that died were equally distributed between the three major groups of extent, then about 115 patients will have been lost from the extensive plus total group and 139 will have died. This leave only 140 patients in this group who between them developed 6 cancers over a 20 year follow-up period. This makes a huge difference in that the rate will be pushed up to approximately times 5.5 that reported or about 8%. Further, this paper includes 'extensive' disease as disease extending beyond the rectum but not total radiologically; some of these cancers likely occurred in this group rather than total disease.

Interestingly enough, although Gilat et al. claim that their rate of carcinoma is low compared with some studies, compared to those shown in Table 3 is actually quite respectable and possibly the highest in this group, particularly when patients with just total colitis are considered. The final outcome was actually clinical cancer, that is, there was not attempt to conduct surveillance within this patient population.

Summary

Given the huge number of biases to which reports of incidence/prevalence of cancer in colitis are subject, it is perhaps surprising that they agree as well as they do. It is possible that this reflects similar bias which may come into play in large referral centres irrespective of the country in which they operate. The figure for carcinoma of 0.5 - 1% p.a. after the first decade is probably fairly accurate".

The list of biases provided is by no means complete. For instance, no account is taken of the fact that it is much more likely that carcinoma will complicate ulcerative colitis in a population in which there is already a high indigenous incidence of colorectal carcinoma, perhaps analogous to post gastrectomy carcinomas in the stomach, which seem now to be much more of a problem in those countries with a high instance rate of gastric carcinoma than in other parts of the world where it is now almost a curiosity.

Most studies seem to point to an incidence of 0.5 - 1.0% p.a. after the first decade of disease, a figure that probably continues to rise

but which applies primarily to patients with "extensive" or total colitis determined radiologically. These studies raise as many questions as they attempt to answer, and even fundamental questions, such as whether patients with distal disease by radiologic criteria but total disease endoscopically or on biopsy, are at increased risk of developing carcinoma is currently unknown.

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IS THERE ANY BENEFIT FROM CANCER SURVEILLANCE IN ULCERATIVE COLITIS?

J. E. LENNARD-JONES
St. Mark's Hospital
City Road
London EC1V 2PS
England

ABSTRACT. The success or failure of a surveillance programme in colitis must be judged by its effect on mortality from colorectal carcinoma. The object of surveillance is to reduce the mortality among those patients for whom surgical treatment does not appear indicated for other reasons. Published evidence suggests that the cumulative mortality among patients with extensive colitis who survive with an intact colon 25 years from onset of their colitis is about 8%. This mortality appears great enough to justify the possible dangers, discomfort and cost of a surveillance programme with a reasonable expectation of success. The techniques of surveillance aim to detect an undoubted pre-cancerous phase or, failing that, carcinoma which has not spread outside the bowel wall. Evidence for benefit of surveillance is at present indirect and based on the mortality among patients who cease follow-up and the pathological stage of carcinoma at the time of colectomy.

1. CRITERIA FOR ASSESSMENT OF A SURVEILLANCE PROGRAMME

The ultimate criterion for success or failure of a cancer surveillance programme in ulcerative colitis is its effect on cancer mortality.

The situation in ulcerative colitis is complicated because surgical treatment removes the large intestine and this can eliminate the cancer risk. To take the extreme situation, if every patient were to be treated surgically early in the disease course, death from colorectal carcinoma would not occur. The reason why every patient does not accept, or is not advised to accept, surgery is that the outcome of operation is uncertain. Post-operative death is uncommon but does occur, complications requiring further hospital admission, sometimes with further surgery, may occur in the short or long-term (1,2). The symptomatic consequences of surgical treatment, such as bowel frequency or management of a stoma, are also appreciable. Patients therefore wish to avoid surgical treatment unless the outcome is likely to give a better quality of life than they experience with their colitis or the operation preserves them from a dangerous complication of the disease.

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The outcome of a surveillance programme is therefore judged by its success or failure in preventing death from colorectal carcinoma among patients who wish to avoid surgical treatment unless driven to it by disability or as a life-saving measure.

2. CONDITIONS FOR THE SUCCESS OF ANY CANCER SURVEILLANCE PROGRAMME

2.1. The incidence of carcinoma should be great enough to give a reasonable expectation of a positive result.

2.2. The risk of death from carcinoma, and its possible reduction by surveillance, should be sufficient to justify the hazard of invasive investigation; the time and effort spent by the patient and doctors; the unpleasant features of surveillance experienced by the patient; the financial cost; and the use of limited resources for this purpose rather than any other such as cancer surveillance in another high risk group.

2.3. The sensitivity and specificity of the techniques employed should be sufficient to detect pre-cancer, or cancer at a curable stage, in a high proportion of the cases in which these changes are present, yet without an unacceptable proportion of false positive results.

2.4. Effective treatment should be available for the prevention of carcinoma if pre-cancerous change is recognised or cure if a symptomless carcinoma is discovered.

3. EXPECTATION OF A POSITIVE RESULT

Life table analyses calculate the cumulative cancer risk among living patients with an intact colon. Some patients, about one third of those with extensive colitis, accept removal of the colon and rectum because of dangerous acute inflammation or disabling symptoms, a few patients die of their colitis and more of unrelated causes. Since some patients are removed each year from lifetable analysis for these reasons, the proportion of patients from an inception cohort who actually develop carcinoma is less that the estimated cumulative probability among survivors untreated surgically. The proportion of patients treated surgically depends on local policy; the proportion of patients who die of unrelated causes depends on the age distribution of the inception cohort since survival is high among young people but begins to fall with increasing rapidity in each successive decade over the age of 50 years as cardiovascular and other diseases become more common.

In a study of 308 patients with extensive colitis over a minimum period of 17 years with 97% completeness of follow-up, the estimated cumulative probability of carcinoma was 7.2% (95% C.I. 3.6-10.8) at 20 years from onset of symptoms and 11.6% (C.I. 6.4-16.8) at 25 years (3). These findings are similar to those in three other series (4,5,6). An incidence of one in eight patients over 15 years (15 not 25 years

because carcinoma is very rare during the first 10 years of illness) appears great enough to give a surveillance programme a reasonable chance of detecting pre-cancer or cancer. Our own series (6) shows that one of these positive findings occurs in about one out of every 80 patients each year after the disease has been present for 10 years.

Why the emphasis on extensive colitis? Carcinoma does complicate ulcerative colitis shown on barium enema to involve only the left colon, but the risk is many times greater in patients shown radiologically to have more extensive or total disease ((3,11,13). A surveillance programme for patients with left-sided colitis thus has a smaller chance of success and it is doubtful if the use of medical resources, or the discomfort and inconvenience to patients, are justifiable if the pick-up rate is likely to be many times less than in extensive disease.

At present, the carcinoma risk is not known among patients shown on colonoscopy and/or biopsy to have extensive colitis, but in whom radiological changes are absent or limited to the left or distal colon. Research is needed to establish the probability of carcinoma in this group of patients.

4. RISK OF DEATH FROM CARCINOMA IN COLITIS

A surveillance programme is not worth while if carcinoma which presents clinically is always curable. In these circumstances, it is enough to advise patients to seek early advice for any change in symptoms. This is not the case in ulcerative colitis.

In ulcerative colitis a tumour may be found because the patient develops new symptoms such as pain, anaemia or a palpable mass. Other carcinomas are found unexpectedly on investigation or during the course of surgical treatment. Several series have shown that the prognosis among such patients is similar to that among patients in the general population who develop colorectal carcinoma (7-14). The proportion of patients who survive 5 years after diagnosis of carcinoma found in one of these ways, and appropriate surgical treatment when possible, varies from 31-55% in different series (7,8,10,11,12,13,14). The development of carcinoma is thus not invariably associated with a fatal outcome in the absence of a surveillance programme but there is an appreciable mortality.

If it is assumed that one third of all carcinomas in colitis, found without a surveillance programme, are cured surgically, then the mortality from colorectal carcinoma complicating extensive ulcerative colitis is about 8% during 25 years after onset of disease. This mortality is confined to patients who do not undergo colectomy for treatment of inflammation within this time.

5. RISKS AND COST OF A SURVEILLANCE PROGRAMME

The risks, cost and success of a surveillance programme have to be judged against the mortality from carcinoma.

The risk of surveillance in colitis is that of endoscopy and biopsy. Endoscopy may introduce infection or perforate the bowel; biopsy can cause haemorrhage or perforation. Preparation of the colon for endoscopy can lead to water and electrolyte disturbance or aggravate colitis. Adverse effects are possible from drugs used for sedation or analgesia. In practice, these risks appear to be small and in our own series 3170 sigmoidoscopies with biopsy and 811 colonoscopies with multiple biopsies were performed without serious complication (6).

The demands of surveillance on the patient include time spent (with possible loss of earnings), unpleasant and possibly painful investigations, and the uncertainty and fear associated with investigation for cancer. The psychological effects of surveillance programmes of all types have been little studied and should not be discounted (15).

The financial implications of consultations and investigations over many years have not been fully assessed. All the costs must not be attributed to cancer surveillance because patients with colitis also need supervision and treatment of their disease. A calculation in England based solely on the costs of colonoscopy has yielded a figure of £6,015 per carcinoma diagnosed (one in every 48 colonoscopies) but this is likely to be an under-estimate (16). Conversely, an American estimate of $200,000 under optimal circumstances for each cancer found or prevented appears high (17).

6. SENSITIVITY AND SPECIFICITY OF INVESTIGATION

There are several possible elements in a surveillance programme which are complementary.

6.1. Clinical assessment includes a knowledge of the duration and disease course up to the time of examination, a review of symptoms, abdominal palpation, digital ano-rectal examination, and laboratory tests. The sensitivity and specificity of clinical features such as a change in symptoms or unexpected anaemia is not known.

6.2. Endoscopy includes examination of the distal colon with a rigid or flexible instrument, and colonoscopy. Sensitivity in the detection of macroscopic dysplastic lesions, stricture or carcinoma has not been assessed.

6.3. The interpretation of biopsies and/or cytological brushings taken from macroscopic lesions, strictures or flat mucosa has been studied. The clinical significance of biopsies from an elevated lesion depends on the presence or absence of dysplasia in the epithelium. Observer variation in recognising dysplasia, yes or no (regardless of grades), is low and the sensitivity and specificity of biopsy from an elevated lesion are likely to be high.

The sensitivity and specificity of biopsies taken from flat mucosa are unlikely to be as great as those from macroscopic lesions for several reasons. A carcinoma can occur in the absence of

dysplastic changes elsewhere in the large intestine. Dysplastic changes, when present, tend to be patchy. Clinical decisions are affected by the assessment of dysplasia as indefinite, low or high grade and the agreement between two observers in the grading of dysplasia in biopsies seldom exceeds 60% (18).

6.4. Findings on barium enema. Radiology has a role in surveillance when endoscopy is refused, incomplete or inconclusive. A barium enema can only demonstrate an elevated lesion or stricture, for these reasons carcinomas diagnosed radiologically tend to be at a more advanced pathological stage than those detected by endoscopy and biopsy (6). A formal comparison of colonscopy and barium enema has been only attempted once (19) and it was concluded that radiography is of limited value.

7. POSSIBILITY OF SURGICAL PREVENTION OR CURE OF CARCINOMA

Proctocolectomy can prevent the development of colorectal carcinoma but patients are naturally reluctant to undergo such a radical treatment. A neglected aspect of regular clinical assessment is that patients with symptomatic extensive colitis may be encouraged to accept surgical treatment in the absence of dysplasia or carcinoma when operation appears appropriate on grounds of disability and prognosis. The cancer risk is a factor to be considered in prognosis; particularly the potentially long life span, and thus long period at risk, of a young person, together with the more favourable results of surgery in the young than in the elderly.

The classic role of surveillance is to seek presumed pre-cancerous change (dysplasia) and advise proctocolectomy at that stage. Severe/high grade dysplasia is generally accepted as a pre-cancerous change but the frequency with which invasive cancer develops or the time scale of this transformation are not known. Information on the time course of high grade dysplasia is difficult to obtain because it is unethical to with-hold operation as an unrecognised carcinoma at the same or a different site may be present. Pooled follow-up data from the few patients who refuse operation or for whom it is contra-indicated are needed to answer the question.

The significance of low grade dysplasia as a pre-cancerous lesion is not well established, except when it is found on the surface of an elevated lesion. Most clinicians do not regard the finding of low grade dysplasia as an immediate indication for surgical treatment so details of follow-up data are available for analysis. Our own data (6) suggests that about one patient in five with low grade dysplasia develops high grade dysplasia or carcinoma within 5 years, and conversely the remaining 80% of patients do not. In some of the remainder low grade dysplasia in flat mucosa appears to be a transitory finding.

Surgical treatment can cure colorectal carcinoma complicating colitis. The success rate is similar to that in carcinoma without colitis and depends on the pathological stage of the tumour. For Dukes

A stage tumours, 5-year survival was at least 95%, for Dukes B lesions, 60-70%, and for Duke C lesions 20-56% in three series (8,10,11). Surveillance may thus reduce mortality by enabling surgery to be undertaken at an earlier stage of carcinoma than would be found if the lesion presented clinically.

8. EFFECT OF SURVEILLANCE ON CANCER MORTALITY IN COLITIS

There is no direct evidence at present that surveillance reduces the mortality from colorectal carcinoma in colitis. Indirect evidence comes from the outcome among patients lost to follow-up and the pathological stage of carcinoma at colectomy:-

8.1. In our own series, 5 of 48 patients with extensive colitis who ceased to attend developed carcinoma, and three died as a result, over 348 patient-years of follow-up. In contrast, among 344 patients followed within a surveillance programme over 3706 patient-years, there were only 2 deaths from colorectal carcinoma (6). A review of all patients with ulcerative colitis from another hospital, reported on 84 lost to follow-up: over 315 patient years, 5 developed carcinoma with 3 deaths. Among 313 patients followed over 1168 patient years there were no cancer deaths (16). There was no obvious selection bias in either of these two series to account for the difference in outcome between those who continued to attend the clinic and those who did not.

8.2. Among four representative surgical series of patients with colorectal carcinoma complicating colitis diagnosed without a surveillance programme, the pathological stage of the carcinoma was Dukes A,14%; B,23%; C,28%; and disseminated 33% (8,10,11,12). Among our own series of 344 patients followed regularly, 17 developed carcinoma and the pathological stage of the tumours was Dukes A,52%; B,17%; C,17% and disseminated 12%. In four other surveillance programmes run on similar lines which included 577 patients (16,20,21,22), three Dukes A and two Dukes B carcinomas occurred but there was no more advanced tumour and no cancer death. Such results are encouraging but do not give proof of benefit because lead-time bias may reduce the apparent benefit of early diagnosis so that a corresponding reduction in mortality is not as great as expected.

9. CONCLUSION

Formal demonstration of the success or failure of surveillance in reducing cancer mortality in colitis is not available. Such proof would entail a comparison of the outcome in at least two groups of patients (a) a group of patients who do not attend for regular supervision but seek medical advice whenever they feel the need to do so, and who are investigated according to the apparent clinical indication (b) a group of patients seen and investigated regularly, without regard to disease activity. Such a study would be difficult to

organise as it would require informed consent by patients, large numbers and prolonged observation over many years.

For the present, surveillance is undertaken because patients with long-standing extensive colitis have a clinically significant incidence of colorectal carcinoma. They are already attending for treatment of their disease, and both patient and doctor wish to minimise the cancer risk. Regular surveillance in some form offers probable benefit and appears appropriate in the absence of evidence to the contrary.

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ENDOSCOPY IN IBD - WHAT HAS IT ACCOMPLISHED?

MICHAEL O. BLACKSTONE, M.D.
Associate Professor of Medicine
Department of Medicine
Gastroenterology Section
The University of Chicago
5841 South Maryland Avenue Box 400
Chicago, Illinois 60637

For nearly 20 years, endoscopy has been widely used for diagnosis and management of patients with inflammatory bowel disease (IBD). It is performed by many physicians so unhesitatingly so that one takes its value for granted, particularly regarding management decisions, but is this really the case? Just what does endoscopy actually accomplish in the diagnosis and management of IBD? The following is an attempt to provide an 'accounting' regarding the value of endoscopy in IBD, to answer this question regarding each of the following indications:

1. Assessing extent and severity
2. Distinguishing ulcerative colitis from Crohn's disease and other colitides
3. Denoting recurrence following surgery in Crohn's disease
4. Determing cancer risk
5. Establishing an upper GI cause of symptoms
6. Evaluating patients with cholestasis
7. Endoscopic dilatation and strictures

ASSESSING EXTENT AND SEVERITY

The commonest indication for colonoscopy in IBD is to determine extent and grade severity. The clinician subjects the patient to colonoscopy often in the naive belief that "... knowing extent and location is ... important when considering therapeutic options,"[1] Yet no study has ever prospectively evaluated what importance this information has in the management of patients by withholding the results (endoscopic as well as biopsy) from the clinician unless surgery seemed imminent (and the surgeon insisted on knowing the results), or a change in management was actually going to occur which the physician felt he needed the results from colonoscopy to justify. Furthermore, no study has been published comparing the outcome for patients hospitalized for IBD who had colonoscopy compared with those who were managed without this modality.

Determining extent: While colonoscopy is more accurate in ulcerative colitis than barium enema,[2] knowing the extent or that the extent may have changed,[2] does not alter immediate management which does not depend on a precise knowledge of the extent of disease. Even for managing the long-term cancer risk in ulcerative colitis (see below), it may be that defining this 'true' (microscopic) extent does not indicate a cancer risk different from that which would be deter-

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mined on the basis of radiologic extent.[3] Indeed, most studies defining cancer risk are based on a radiologic, rather than colonoscopic determination of extent.[3]

For Crohn's colitis, the advantage of colonoscopy over radiology[4] seems less certain than for ulcerative colitis, particularly if a double contrast barium enema is performed. Even granting that there is an advantage, this would not be sufficient to indicate a different outcome, either to medical management or by a more 'tailored' approach to colonic resection where the question is usually over whether or not to leave the rectum in place. For this, proctoscopy, rather than colonoscopy is the indicated procedure.

Grading severity: Currently, there is no uniform grading system for endoscopic activity for either ulcerative colitis or Crohn's disease. In one study which systematically examined clinical activity, as assessed by Crohn's disease activity index, and a similar index for patients with ulcerative colitis, there was only poor correlation between colonoscopic findings and clinical indices of disease activity.[5] More recently, Modigliani, et al., in a careful study of patients with Crohn's disease found no correlation between severity as indicated by endoscopic findings and clinical activity, nor could endoscopic criteria predict for patients with acute attacks of colonic or ileocolonic Crohn's, disease refractoriness to steroids.[6]

Experienced clinicians have long known that a surprising degree of well-being is possible for patients with either ulcerative colitis or Crohn's disease even with markedly abnormal proctoscopic appearances, conversely, a great deal of clinical debility, particularly from abdominal pain and diarrhea in patients with unimpressive endoscopic findings. This would suggest that a functional effect (motor, secretory or absorptive) from even minimal histologic changes might be the most important variable, but one which is as yet, ill-defined, in determining clinical activity, but one which bears little relationship to endoscopic findings. Hence, in the management of ulcerative colitis or Crohn's disease, the grading of severity is much less significant than the overall clinical assessment of disease activity.

DISTINGUISHING ULCERATIVE COLITIS FROM CROHN'S DISEASE AND OTHER COLIDITIES

While colonoscopists have long held that certain visual features could distinguish ulcerative colitis from Crohn's disease, up until recently, this impression was unproven. However, in a large prospective study of 350 patients[7] with proven ulcerative colitis, Crohn's disease, or 'indeterminate colitis' (where differentiation was impossible even after surgery), the accuracy of colonoscopy was finally established to be on the order of 90%. Diagnostic errors occurred in only 7% and these were in cases where the disease was markedly active. Not unexpectedly, the endoscopic features most predictive of Crohn's disease were: (1) Discontinuous involvement, (2) anal lesions and (3) the presence of 'cobblestoning'. Findings indicative of ulcerative colitis were: (1) Granularity, (2) erosions and (3) microulcers. Somewhat surprisingly, the pattern of continuous involvement was less

useful in differentiating ulcerative colitis from Crohn's disease, being present in nearly all patients with ulcerative colitis, but in 45% of patients with Crohn's disease.[7] In this study, histologic features were not used along with endoscopic signs, so it is still unclear as to what the contribution for differentiation would be from biopsies taken at the time colonoscopy is performed, and what number of biopsies and location would be optimal.

While it is clear that colonoscopy can differentiate ulcerative colitis from Crohn's disease, it is less certain how often colonoscopy is actually necessary to do this in a clinical context, where features such as known small bowel involvement, prior radiologic evidence of skip areas or the presence of perianal disease will be decisive for the clinician without colonoscopy. Moreover, since the treatment of ulcerative colitis and Crohn's disease largely overlap, it is usually the distribution of involvement, whether distal, left-sided, subtotal or universal would determine the clinical approach, rather than whether an individual case can be correctly differentiated except where an ileal reservoir were contemplated which would be contraindicated in Crohn's disease. While clinicians may continue to insist that the differentiation is important in the management of patients, there is no prospective data bearing on this point. Colonoscopy, and multiple biopsies being as expensive as they are (in the U.S. in excess of $1,000, it seems doubtful that in the large majority of cases where colonoscopy would be requested for differentiation that this would prove to be cost effective.

Regarding the differentiation of IBD from infectious colitis, the commonest situation where differentiation might be thought important, in an acute setting, bacterial colitis may present a similar endoscopic and histologic appearance[8] to either ulcerative colitis or Crohn's disease which would argue against performing colonoscopy in this setting. Moreover, the collection and submission of specimens to the laboratory which ultimately will establish the diagnosis of an infectious colitis except in colonic amebiasis, tuberculosis of the colon, and CMV colitis. However, because these conditions are for the most part infrequent, it would not be reasonable to suggest that colonoscopy be performed in all cases, but only where, as in individuals with risk factors for AIDS, or colonic tuberculosis. In the case of colonic amebiasis, performing amebic serology coupled with flexible sigmoidoscopy with biopsies ought to be as effective as colonoscopy, but at a much lower cost.[9]

In cases where presenting as acute colitis, where an infectious origin is suspected, but none found, a diagnosis of 'acute self-limited colitis' will be considered. Here, histologic changes are useful in differentiating this type of colitis from IBD,[10] but there is no evidence that colonoscopy with biopsies taken throughout the colon would be more effective in establishing this diagnosis than those taken from the rectum and sigmoid by the less expensive flexible sigmoidoscopy.

DENOTING RECURRENCE FOLLOWING SURGERY IN CROHN'S DISEASE

Diarrhea along with abdominal pain frequently occurs following

colonic resection and anastomosis for Crohn's colitis, prompting colonoscopy because of the possibility of a recurrence. Prior to the advent of colonoscopy, because of the limitations of barium contrast studies in these patients, the frequency with which anastomotic recurrences would occur both in the presence and absence of symptoms was not well-defined. Using colonoscopy, Rutgeerts, et al.,[10] found the recurrence rate to approach 75% following surgery ('curative' resection of the terminal ileum and part of the colon) in patients examined within one year.

Recurrences are located in the neoterminal ileum or at the anastomosis in 90%, with aphthous ulcers being seen colonoscopically as the typical appearance, with biopsies showing an inflammatory infiltrate, eosinophils, and villous changes.[10a] More advanced lesions may be expected after one year as larger ulcerations, nodular thickening of folds, and ultimately, 3 to 10 years after surgery, stenoses.[10a] Yet significant endoscopic changes may be present without symptoms, so, as is true of IBD in general, the correlation between gross findings and symptoms is poor. Therefore, for an individual patient, correlation of endoscopic findings with symptoms is imprecise, demanding for the most part the physician's clinical judgment in relating a patient's symptoms to the anastomotic appearance. The findings of an anastomotic stricture with active inflammation may well explain abdominal pain, vomiting and diarrhea and could be helpful to the clinician in determining the next therapeutic step. Other findings such as aphthous ulcers or enlarged anastomotic folds would be less helpful, particularly regarding the indication for corticosteroids.

While colonoscopy may have settled the question as to the frequency of postoperative recurrence, the findings themselves are usually not decisive in determining the next therapeutic steps.

DETERMINING CANCER RISK

While there is an increased cancer risk for patients with ulcerative colitis involving the entire colon of 5 to 10% after 10 years and 20% after 20 years or more, and endoscopic surveillance can indicate patients at high risk, particularly with the histologic finding of high grade dysplasia[11] or marcroscopic dysplasia[11a] there is no general agreement as to the efficacy of currently practiced endoscopic surveillance in actually reducing cancer mortality. With the notable exception of Lennard-Jones, et al.,[11] where of 16 cancers detected in patients enrolled in an ulcerative colitis surveillance program, 11 were Dukes' A, the large majority of cancers found by other groups because of endoscopic surveillance have been Dukes' B or C lesions,[12,13] similar to both colitic and noncolitic cancers found in unscreened patients.[14] Even a high proportion of Dukes' A (7/16) has been reported in unscreened patients,[15] although this series is highly atypical from what has been reported for colitic cancer in both screened and unscreened patients with no A lesions or in less than 15%.[12,13] Given that the survival of patients with ulcerative colitis cancers found in nonsurveillance settings does not differ from that of colon cancer in the general population,[14] if the stage of cancers found by surveillance does not differ from unscreened patients, it is doubtful

that surveillance ultimately affects colon cancer mortality.

Surveillance though is expensive. In the U.S., with a cost of colonoscopy and biopsy interpretation which is often in excess of $1,000., it has been estimated that one must spend at surveillance $200,000., to find one cancer,[16] with an outcome which is not clearly different from a cancer discovered without surveillance, bringing into question just what is being accomplished at so great a cost. Also unresolved though bearing potentially importantly on cost is the issue of the interval between screening examinations to indicate the malignant potential of the colon for the ensuing interval. Whether a variable interval based on a 'patient-specific hazzard rate' detects as many cancers as surveillance done at fixed intervals requires further study.[17]

Another major problem with surveillance, although one which is underappreciated is the lack of uniformity in assessment of dysplasia by pathologists even with a special interest in IBD. It would appear that even in the best hands, the false 'negativity' rate approaches 20% where a true high-grade dysplasia (which demand colectomy) is interpreted as something less than this (either 'low-grade' or 'indefinite') and thus the opportunity for a timely operation is lost.[18] To what extent this problem can be overcome using flow-cytometric DNA analysis to determine the presence of aneuploidy, currently being investigated in a number of centers is unknown though preliminary data seems encouraging.[19] Whether either patient or surgeon would accept the need for colectomy based on flow-cytometry and not either a macroscopic lesion or high-grade epithelial dysplasia cannot be determined from these studies, though it seems unlikely because DNA aneuploidy still can be found in normal or simply inflamed tissues.[20]

At present, one would need to conclude that while determining cancer risk in ulcerative colitis patients is a laudable goal, endoscopic surveillance as it presently exists does not clearly reduce cancer mortality and cannot, therefore, be justified on a cost-effective basis.

ESTABLISHING AN UPPER GI CAUSE OF SYMPTOMS

Gross involvement in Crohn's disease of the stomach and/or duodenum when examined endoscopically may be expected in 2 to 3% of all patients with Crohn's disease,[21] while biopsy evidence is found in a higher proportion, in some series exceeding 30%, even in the absence of endoscopic abnormalities.[22] While endoscopy may find more gastroduodenal Crohn's disease, the clinical relevance of this particularly in the absence of macroscopic changes is unclear, and that symptoms which may have prompted the endoscopy are nonspecific, occurring whether or not there is any gross or histologic abnormality demonstrated. In addition to the gastroduodenal area, the esophagus is occasionally involved both in Crohn's disease[23] where this may be the only site of involvement, and in ulcerative colitis.[24] Moreover, there appears to be an increased prevalence of peptic ulcer disease in patients with Crohn's disease which is most accurately diagnosed with endoscopy. Finally, patients with Crohn's disease or ulcerative colitis who are on steroids or other immunosuppressives are at risk for Candida esophagi-

tis.

Nevertheless, despite specific abnormalities that can be demonstrated in patients with upper GI complaints and IBD, these patients are no more likely to have specific and treatable abnormalities at endoscopy than others in the general population who come to endoscopy because of symptoms where in the absence of a specific macroscopic lesion such as a peptic ulcer, there is no predictable response to any specific therapy, such as the use of H_2 blockers[25] or as has more recently been tried, single or a combination therapy for Campylobacter pylori when this is found in antral or duodenal biopsies.[26] While studies in patients with IBD and upper GI complaints are lacking, it is our impression that a specific diagnosis is made in such patients in no more than 10 to 20%, similar to others in the general population subjected to endoscopy because of nonspecific symptoms. Endoscopy in patients with IBD, for the most part fails to yield diagnostic information which would lead to specific therapy being instituted. As is true of all patients with nonspecific upper GI symptoms, more likely than not, they will be treated empirically as nonulcer dyspepsia, based on physician preference rather than scientific evidence.

EVALUATING PATIENTS WITH CHOLESTASIS

Up to 15% of patients with ulcerative colitis may have liver function abnormalities suggesting cholestasis, i.e., raised transaminase and alkaline phosphatase though with disproportionate elevations of the latter.[27] The large majority of these patients are entirely asymptomatic or have only mild puritis. Nevertheless, ERCP is requested, even for asymptomatic patients, because in as many as 50%, where the bile ducts are visualized, typical changes of sclerosing cholangitis will be present.[27]

The value of cholangiographic evidence of sclerosing cholangitis, however, can be questioned in the absence of jaundice, plain or cholangitic episodes where either biliary surgery or endoscopic dilatation and/or stent placement would be considered. In asymptomatic patients, the course even with typical radiographic changes of sclerosing cholangitis seems variable enough to preclude any definitive prognostic statement, in contrast to the same radiologic picture where in symptomatic patients where the 5 year survival may be only 50 to 60% or less especially for patients with persistent hyperbilirubinemia $\geq$ 4 mg % as well as evidence of seconary biliary cirrhosis on liver biopsy, and individuals after 10 years who were asymptomatic at presentation.[28] Given that if all patients with cholestatic liver function tests were subjected to ERCP, asymptomatic individuals might be at least twice as numerous as symptomatic patients. Individuals with asymptomatic liver function abnormalities in ulcerative colitis are likely to constitute a significant percent, if not the majority of patients who would be subjected to ERCP and would gain the least from it.

In Crohn's disease, liver function abnormalities suggesting cholestasis may be present as well, but in a smaller proportion, about 5% of patients who are otherwise asymptomatic.[29] The risk of sclerosing cholangitis appears to be substantially less in Crohn's disease as well. While in patients with small bowel involvement, there may be

concern regarding the presence of a common duct stone, in fact, this would be unlikely in an asymptomatic patient as would pancreatitis, complicating Crohn's disease producing a symptomatic biliary obstruction, or Crohn's disease itself of the duodenum producing ampullary obstruction. While the value of ERCP in symptomatic patients with cholestatic liver function tests is unquestioned, where ERCP is requested for the asymptomatic patient, it will for the most part provide no useful information.

ENDOSCOPIC DILATATION OF STRICTURES

The therapeutic potential of endoscopy has been used in IBD in a limited fashion for dilatation of colonic, anastomotic enterocolic, and gastroduodenal strictures[30] as well as for treatment of symptomatic sclerosing cholangitis.[31]

Regarding gastroduodenal and colonic strictures, there have been several reports of the use of galloon dilatation for ileal strictures, particularly at an anastomotic site.[30] In some cases, this has allowed for tapering of steroids. While these scattered reports indicate that balloon dilatation is feasible, and that a short term benefit may occur, what the intermediate and long-term benefits of such nonsurgical intervention may be is unknown at the present time, particularly as to how often surgery is prevented, and what reduction in obstructive symptoms may occur, as well as the frequency with which patients can be weaned from immunosuppressive therapy. It is conceivable that many patients with Crohn's disease and anastomotic strictures could benefit from balloon dilatation, but further experience will be necessary to determine how often this actually occurs. At present, one must reserve balloon dilatation for patients who either refuse surgery or where surgery would otherwise be problematic because of the likelihood of a short bowel syndrome following surgery.

For sclerosing cholangitis, intrabiliary balloon dilatation alone appears ineffective and a combination of endoscopic sphincterotomy, dilatation along with the placement of a stent appears necessary, but even then with variable results.[31] Whether there is a long-term benefit in patients with sclerosing cholangitis remains at present entirely unknown.

CONCLUDING VIEWPOINT

Endoscopy is on the whole better suited than radiology to answer the various questions which arise in the management of patients with IBD and as such represents a notable advance. Nevertheless, its overall clinical impact is only modest at best, one which does not, for the most part, justify its high cost when applied to patients with IBD. Studies which critically examine the impact of endoscopy on management are greatly needed. Hopefully, in the future, with the results of such studies, we may better define indications for patients with IBD when endoscopy provides a substantial benefit, as well as those instances when it can be dispensed with altogether.

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THE PROBLEM OF POSTOPERATIVE RECURRENCE OF CROHN'S DISEASE

David B. Sachar, M.D., F.A.C.P.
The Mount Sinai Medical Center, Box 1069
Division of Gastroenterology
One Gustave L. Levy Place
New York, NY 10029-6574

The single most frustrating problem in the management of Crohn's disease is the stubborn incurability of the condition. Nobody expects medical therapy to effect a permanent cure of Crohn's disease, but even among the 70% of all patients who ultimately come to surgery, the overwhelming majority will ultimately experience a recurrence of their disease. For those whose original disease was ileitis, recurrent disease almost invariably appears just proximal to the ileocolonic anastomosis; for those with initial colitis or ileocolitis, recurrence develops on either or both sides of the anastomosis (15). Although this tendency to postoperative recurrence has been recognized for more than half a century since the early description of the disease by Crohn, Ginzburg, and Oppenheimer (3), confusion and controversy persist regarding the frequencies and risk factors for this unwelcome phenomenon (9,12,26,29).

The sources of uncertainty about the problem of postoperative recurrence can be grouped into three principal categories.

Definitions of Recurrence

The first category comprises different definitions of the term, "recurrence." If, for example, the criterion of recurrence is the finding of endoscopic lesions at the anastomosis, then "recurrence" is rapid and nearly universal, affecting over 70% of patients within one year and 85% by three years (24,25). If, by contrast, recurrence is equated with reoperation, then "recurrence" will be much slower and less frequent, reaching only 25-30% by five years, and 40-50% after 20 years of postoperative followup (2,19). Most current studies have adopted a clinical definition of recurrence (11), less sensitive than the endoscopic criterion but more sensitive than the requirement for reoperation. This clinical definition refers to the return of symptoms proven radiologically, endoscopically, and/or pathologically to be attributable to the reappearance of Crohn's disease. Irrespective of theoretical arguments over whether such reappearance of disease is truly a fresh "recurrence" or merely a "re-exacerbation" of preexisting pathology, a

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surgically rehabilitated patient may once again fall ill as a result of newly demonstrable lesions of Crohn's disease. By this pragmatic definition, the cumulative rates of postoperative recurrence are approximately 20% by two years, 30% by three years, and 40-50% by four years.

Types of Operation

Besides different definitions, the second category of factors contributing to disagreements over postoperative recurrence rates pertains to the type of operation in question. For example, there are differences in the overall frequencies of postoperative recurrence following first resections as opposed to those following subsequent resections. Of all patients undergoing first resections for Crohn's disease, about 45% will ultimately require a second operation; but of those patients having a second operation, only about 25% will come to operation a third time. Those cumulative totals, however, apply to different intervals of postoperative followup, so it is necessary to consider actual rates as well as overall frequencies of postoperative recurrence. Some smaller studies have not demonstrated any differences in recurrence rates following primary or subsequent resection (23), but many larger series have suggested that both clinical recurrences and reoperations occur more rapidly after second resections than after first resections (11,17,19,30).

In any event, no two studies of postoperative recurrence rates can be compared unless they are both referring to the same type of operation, preferably first resection. By the same token, the operations must be comparable in terms of whether they are resections or bypasses (14), or whether they include or exclude operations performed primarily for perianal disease. Moreover, with the advent of strictureplasty, we can anticipate important differences in surgery-free intervals following this conservative procedure compared to the presumably longer surgery-free intervals following conventional resection (28).

Still another example of the influence of type of operation upon postoperative recurrence rate is the crucial difference between anastomosis and ileostomy. Although no one any longer believes the old assertion that Crohn's disease virtually never recurs extensively proximal to an ileostomy following total proctocolectomy (7,16), most studies still confirm the concept that recurrence rates are significantly lower after ileostomy than after anastomosis (8,22,27). It is essential, therefore, to distinguish between series that include ileostomies and those that do not (13).

Statistical Methods

Besides definitions of recurrence and types of operation, the third source of controversy is confusion over statistical methodology. As Lennard-Jones and Stalder first showed in 1967

(17), and as Greenstein et al confirmed in 1975 (11), estimations of recurrence rates from crude data are neither reliable nor comparable; actuarial analyses by life-table techniques are the preferred method.

Indeed, careful scrutiny and proper understanding of cumulative recurrence curves constructed by this method indicate that there is probably no such thing as a "vulnerable" early period postoperatively, nor a "safe" interval following which a patient is "out of the woods." On the contrary, cumulative postoperative recurrence curves tend to be exponential, so that for the population remaining at risk, the chance of recurrence remains relatively constant at roughly 10% in each and every year, no matter how much time has elapsed since the original surgery (23).

Another critical implication of careful statistics is that many of the proposed risk factors for disease recurrence are not independent variables (26,27). For example, age at time of surgery is highly dependent upon preoperative duration of disease; presence or absence of granulomas may vary with duration or anatomic location of disease; anatomic distribution is confounded by indication for surgery and by choice of operative procedure.

When an effort was made to untangle these several proposed risk factors by multivariate analysis (27), two factors in particular emerged as important determinants of clinical recurrence rates. One, as already cited above, was selection of ileostomy versus anastomosis. The other, somewhat surprisingly, was preoperative duration of disease. Among patients with preoperative duration of 10 years or more, the 5-year cumulative recurrence rate was only 20%, whereas patients with preoperative durations less than 10 years experienced a recurrence rate of 60%. This difference was statistically significant at the 98% level, and when corrected for the possible confounding effect of ileostomy, significant at the 99.5% level.

These observations, of course, are not an argument for delaying surgery; they are, rather, a possible indication of the different clinical pathways that Crohn's disease may follow.

"Aggressive" versus "Indolent" Crohn's Disease

As de Dombal et al suggested in 1971 (4), we have speculated that there might be at least two different patterns of Crohn's disease, one "inherently indolent," which tends to recur slowly, and the other "inherently aggressive," which tends to recur more quickly (27). Our data and others' suggest that this might indeed be the case.

In a recent review of surgical indications for initial and subsequent operation in 770 patients with Crohn's disease undergoing intestinal resection at The Mount Sinai Hospital, we found evidence that the disease seemed to occur in two different clinical patterns, independent of anatomic

distribution (10). A relatively aggressive "perforating" type (e.g., fistula,abscess) and a more indolent "non-perforating" type (e.g., stenotic obstruction) tended to retain their identities between repeated operations and to influence the speed with which reoperation occurred. Specifically, second operations were performed for perforating indications much more often among cases where the initial indication had been perforating than among those whose initial indication had been non-perforating (72% versus 29%, $p<0.00001$). This trend to similarities in operative indications was maintained within each anatomic category of Crohn's disease, and even between second and third operations ($p<0.001$). Moreover, operations for perforating indications were followed by reoperation approximately twice as fast as operations for non-perforating indications, whether going from first to second operation (perforating, 4.7 vs. non-perforating, 8.8 years, $p< 0.001$) or from second to third operation (perforating, 2.3 vs. non-perforating, 5.2 years, $p<0.005$).

It is important to note that these findings are only tentative and indeed still controversial. In fact, directly contradicting data have been recently reported by expert investigators at the Cleveland Clinic Foundation (20). Nonetheless, the concept of intrinsically aggressive versus indolent Crohn's disease, independent of anatomic location, is consistent not only with clinical experience but with other published observations. In 1970, for example, Baker at St. Mark's Hospital in London noted that "patients with a preoperative history of more than 10 years' disease appear to do better than the others" (1). The following year saw de Dombal et al's observation that "patients with 'early' recurrence had a shorter history of symptoms at operation, and a poorer outlook than those with 'late' recurrence" (4).

More recently, Levine et al from Johns Hopkins found that "patients requiring surgery for distal ileal Crohn's disease can be separated into two groups, those requiring early surgery (disease duration of <3 years) for seemingly aggressive illness, and those requiring late surgery (peak incidence between 8 to 11 years) for fixed ileal obstruction" (18). It would be interesting to compare the postoperative recurrence rates in these two groups. Finally, Rutgeerts et al in Leuven have identified early endoscopic markers of "aggressive postoperative evolution," associated with a preoperative course of "continuously active Crohn's disease " contrasted with a pattern of "slow" evolution of postoperative lesions that tended to lead to "late stricture formation" and ultimate obstruction (25).

If there are indeed different clinical forms of Crohn s disease, marked by different patterns of postoperative recurrence, several scientific and clinical implications should be considered. Scientifically, this concept suggests possible differences in etiologic agents, in immunoregulatory mechanisms of host defense, in biochemical profiles of

collagen metabolism, or in other pathogenetic pathways to account for the observed clinical and pathologic differences in natural history of the disease. Clinically, therapeutic trials for prophylaxis against postoperative recurrence should be targeted specifically on the higher risk population with identifiably more aggressive disease.

Conclusions

In the last analysis, the most important question is what the problem of postoperative recurrence of Crohn's disease means to our patients. After all, most patients with Crohn's disease will sooner or later require surgery no matter what the risks of postoperative recurrence may be. What can we tell them? They must be helped to understand that the overwhelming majority of all postoperative patients - even if they have at some point experienced recurrent disease - still view their quality of life as having been improved by their operations (25). Whatever the outcome of the "numbers games" in calculating recurrence rates (6), the fact remains that psychosocial rehabilitation and improved quality of life are still "the name of the game" (5,26).

Summary

Most patients with Crohn's disease require an operation sooner or later and the overwhelming majority will ultimately experience a postoperative recurrence at the anastomotic site. Endoscopic lesions can be seen at the anastomosis in 85% of patients by three years after surgery. While only 40-50% of postoperative patients will ever undergo a second operation, clinical manifestations of recurrent disease develop at a cumulative rate of about 10% per year. Postoperative recurrences of Crohn's disease are well recognized even after total proctocolectomy and ileostomy, but rates are higher following reanastomotic procedures.

Evidence accumulated from published observations over the past 20 years, reinforced by new data from The Mount Sinai Hospital, suggests that Crohn's disease may follow at least two different patterns: "aggressive" disease characterized primarily by fistulae and abscesses, early requirement for surgery, and relatively rapid fistulizing-type recurrence; versus "indolent" disease characterized mostly by fibrotic stenosis and strictures, late requirement for surgery, and relatively slower obstructive-type recurrence. Pathophysiologic investigations and clinical trials alike should take into account this duality of clinical patterns.

Regardless of the patterns of recurrence, however, surgery performed for proper indications is almost invariably rehabilitating for people disabled by the ravages and complications of Crohn's disease.

Synopsis

Most patients with Crohn's disease require an operation and the overwhelming majority will ultimately experience recurrent disease at the anastomosis. Clinical manifestations of postoperative recurrence appear at a cumulative rate of nearly 10% per year. New evidence suggests that Crohn's disease may follow at least two different patterns: "aggressive" fistulizing disease with early surgery and rapid recurrence, versus "indolent" stricturing disease with relatively later surgery and slower obstructive recurrence. Pathophysiologic and clinical studies should take into account this duality of clinical patterns.

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ENDOSCOPIC EXAMINATION OF THE SMALL BOWEL IN IDIOPATHIC INFLAMMATORY BOWEL DISEASES

G.N.J. Tytgat, S.O.P. Hofer, P. Fockens, M. v. Haastert
Department of Gastroenterology/Hepatology
University of Amsterdam
Academic Medical Center
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands

Endoscopy is now an established technique in the diagnosis and differential diagnosis of idiopathic inflammatory bowel diseases. In all probability the impact of endoscopy is superior to that of any other imaging technique, especially when the patient is examined before anti-inflammatory therapy is given. In the past most emphasis was given to the role of colonoscopy in IBD (1-9). Currently increasingly the small intestine is examined. The purpose of this manuscript is to review the usefulness of ileoscopy in idiopathic inflammatory bowel disease.

Endoscopy of the terminal ileum

Involvement of the terminal ileum in Crohn's disease is common. The contribution of endoscopy is somewhat limited because it is often impossible to intubate the terminal ileum due to narrowing and stricturing of the ileocecal valve. Even if the terminal ileum itself can not be intubated it may be possible to make a presumptive diagnosis of Crohn's disease through inspection of the colonic side of the ileocecal valve which often shows ulcerative abnormalities suggestive of Crohn's disease.

Endoscopy is not always indicated in Crohn's disease of the terminal ileum if characteristic X-ray documentation has already been obtained. Radiologically rather pathognomonic for Crohn's disease is the combination of three different adjacent patterns of abnormality in the terminal ileum. Characteristically the distal segment reveals circumferential involvement, usually with luminal narrowing and some spiking of the contours. Often there may be complete destruction of the fold pattern with creation of a rather long tubular narrowing (string-sign). In addition there may be evidence of cobblestoning. The adjacent more proximal intermediate segment almost always reveals a large saddle-like mesenteric ulceration with some retraction of the anti-mesenteric border creating a saccular appearance. Due to surrounding inflammation in the mesentery with enlargement of lymphnodes there may be fixation of the ileal loop in omega fashion. The abnormalities in the most proximal segment are usually more discrete and may consist of mild swelling and

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irregularity of the fold pattern and some patchy aphthoid erosions of scattered small ulcers. If endoscopic intubation is possible in the presence of such typical radiological abnormalities, one sees the same pattern of alterations as already suggested by the X-rays. The most distal segment reveals more or less circumferential involvement with extensive confluent ulceration, preceded by an intermediate segment usually with one long confluent ulceration along the mesenteric border and some scattered abnormalities of the anti-mesenteric border together with retraction and finally preceded by a proximal segment with spread out tiny focal aphthoid erosions or patches of inflammation with punctate erythema and/or mucopurulent exudate.

Endoscopy of the terminal ileum is of utmost importance if the diagnosis is rather uncertain or if the X-ray findings are equivocal or difficult to interpret. The endoscopic findings in such circumstances vary widely from no visible abnormalities to tiny aphthoid erosive defects and/or focal punctate erythematous spots, to somewhat larger but still superficial ulcers and perhaps necrotic Peyer's patches to occasionally even extensive ulcerative abnormalities compatible with full blown Crohn's disease.

Especially in the younger patient population, Peyer's patches may be quite pronounced in the terminal ileum and may fool the radiologist. In such circumstances the endoscopy can readily differentiate between Peyer's patches and genuine inflammatory changes suspicious of Crohn's disease.

Ileoscopy is also of importance in monitoring the effects of therapy. If anti-inflammatory therapy is successful there should be regression of the endoscopic abnormalities and healing of ulcers.

Role of ileoscopy after ileocecal resection

An important indication for endoscopy of the small intestine is the monitoring of the neoterminal ileum after ileocolonic resection (10-12). In a surprisingly high percentage of patients one may see tiny remaining abnormalities in the neoterminal ileum soon after surgery especially if a rather limited disease-free segment of some 5-10 cm is removed at surgery. In all probability such tiny lesions are left behind at the time of resection. We presume that these remaining lesions are the starting point for later full-blown recurrence. Such recurrent disease is nearly always limited to the distal 20 cm proximal to the anastomotic line, although not necessarily involving the anastomosis. Recrudescent Crohn's disease does not seem to depend upon the type of anastomosis (side-to-end versus end-to-end) nor upon the suturing technique (one- versus two-layer technique). Often there is also evidence of slow healing of the anastomotic line itself with persisting linear defects around the anastomosis.

The follow-up of such endoscopic abnormalities is most interesting. Some lesions such as circumferential ulceration of the anastomosis or

the presence of pre-anastomotic erosions and ulcers may remain stationary for several years without any evidence of progression nor any evidence of healing. In other patients there is evidence of quite rapid progression of the small early lesions towards larger ulcers and finally stricturing. Surprisingly many of such patients remain asymptomatic and have virtually no biochemical abnormalities despite the presence of sometimes quite impressive endoscopic abnormalities. Whether early anti-inflammatory therapy especially with the 5-aminosalicylic acid preparations is capable of slowing down the progression of these early persisting abnormalities in the neoterminal ileum remains to be determined.

Endoscopy is also important in case of anastomotic stricturing because of the current possibility for through-the-scope balloon dilatation. In our experience dilation of anastomotic strictures in Crohn's disease has been quite rewarding, leading to long lasting relief of pain and cramps.
For endoscopic follow-up studies, a more objective scoring system is obligatory.

An attempt to quantify the endoscopic abnormalities after ileocecal resection for Crohn's disease is given in table 1. Other investigators have also attempted to develop and validate an endoscopic index of severity (13).

The overall evolution of the endoscopic abnormalities in a substantial consecutive group of patients with Crohn's disease is summarized in figure 1. It is readily obvious that there is a steady increase in patients with recrudescent-recurrent disease. Suggestive evidence has been presented that the presence of fecal flow is an essential factor in full blown recurrence of Crohn-like lesions in the neoterminal ileum (14).

Endoscopy in pouch-monitoring and pouchitis
Patients with pancolitis are increasingly referred for colectomy and ileoanal pouching. Endoscopy has an important role in pouch monitoring and in the detection of pouchitis.

Initially the ileo-anal anastomosis is severely inflamed and friable. After 2 to 3 months, both the ileoanal anastomotic line and the suture lines within the pouch have healed, allowing take-down of the protective ileostomy. Reanastomosis may be delayed in case of development of small defects or fistulas among the suture lines, dehiscence of the anastomotic line or evidence of ischemic damage of the pouch mucosa.

The endoscopic aspect of the pouch always changes as soon as faecaloid material enters the pouch. There is almost always evidence of some minor inflammatory changes within the pouch itself as well at the anastomosis with some mild swelling and patchy erythema. In some patients the Kerckring folds gradually flatten and disappear.

Table 1. Endoscopic assessment of disease activity after ileocecal resection for Crohn's disease

NEOTERMINAL ILEUM	SCORE		
	0	1	2
Color	normal	patchy abnormal	widespread abnormal
Friability	no	mild	severe
Aphthoid lesions	no	< 10	> 10
Ulcer	no	< 10	> 10
Ulcer linear	no	1-2	> 2
Abnormal segment	< 5 cm	5-10 cm	> 10 cm
Subtotal maximum	0	6	12

ANASTOMOTIC LINE			
	0	1	2
Friability	no	mild	severe
Aphthoid lesions	no	< 2	> 3
Ulcerated circumference	no	< 50%	> 50%
Distensibility	normal	rigid	stenotic
Subtotal maximum	0	4	8
Total maximum	0	10	20

Pouchitis remains a significant source of postoperative morbidity. Pouchitis may be seen in 20 or more percent of the patients, especially in those operated for chronic ulcerative colitis and in those exhibiting extrainterstinal manifestations of their disease (15,16). The pathogenesis of pouchitis, despite all recent hypotheses is still poorly understood. Pouchitis may be diagnosed in the presence of swelling, erythema, friability and punctate haemorrhagic spots or/and mucopurulent exudates together with superficial erosive defects or larger ulcerative lesions. Occasionally, in the more severe forms, extensive ulceration may be seen, not only in the pouch but also in the prepouch ileum.

The endoscopist should be aware that the appearance of the mucosa in pouchitis may readily mimic the abnormality seen in Crohn's disease (16,17). Occasionally it may be difficult to distinguish pouchitis from ischemic damage.

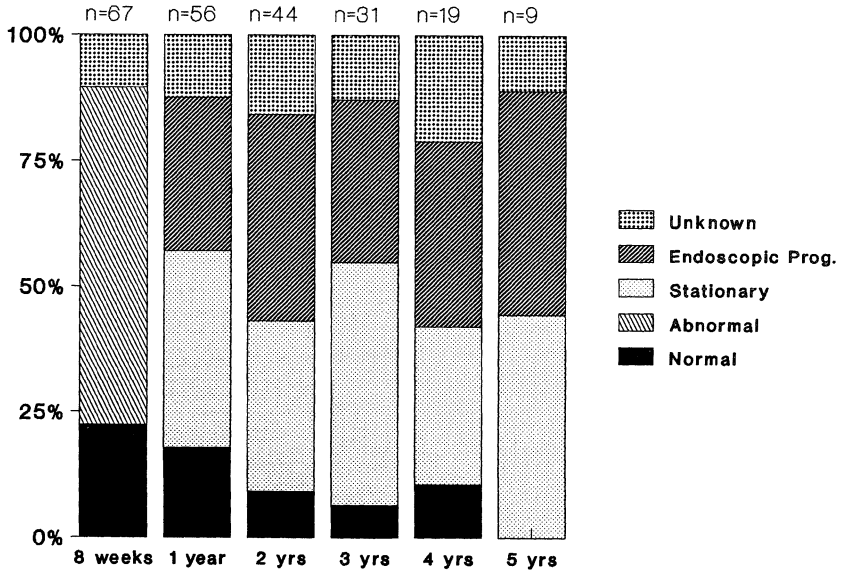

Figure 1. Evolution of the endoscopic abnormalities in the neoterminal ileum in a consecutive group of patients who underwent ileocecal resection.

Endoscopy is necessary to monitor the effects of therapy. Medical therapy includes metronidazol, drainage, if necessary irrigation and occasionally even steroids, either systemically or in enema form, together with 5-aminosalicylic acid. Some patients with severe pouchitis do not improve with metronidazol monotherapy. Only after switching to corticosteroids and 5-aminosalicylic acid does gradual improvement in the endoscopic appearance occur.

Conclusion

Increasingly endoscopic inspection of the small bowel is applied in the diagnosis and differential diagnosis of Crohn's disease both before but especially after resection and in pouch-monitoring in patients with ulcerative colitis. The visual endoscopic inspection with attention for detail is of paramount importance to obtain a high degree of accuracy. Although endoscopy allows taking biopsies of both normal and abnormal mucosa, the contribution of histology is often limited as in the majority of the biopsies non-specific abnormalities are seen. It should be stressed at this point that infectious diseases both bacterial and viral may closely mimic the abnormalities seen in IBD (17). Therefore infectious entities must always be ruled out before a diagnosis of idiopathic inflammatory bowel disease is made.

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CROHN'S DISEASE IN CHILDREN AND ADOLESCENTS: DIMINISHED GROWTH VELOCITY

Theodore M. Bayless, M.D.
Johns Hopkins University School of Medicine
Baltimore, Maryland U.S.A.
Marjorie Kanof, M.D.
Massachusetts General Hospital
Boston, Massachusetts U.S.A.

Crohn's disease is a chronic, relapsing inflammatory illness that may affect any portion of the gastrointestinal system. At least 12% of patients have evidence that the illness started before age 15 (1). Of this group of children and prepubescent adolescents, 20 to 30% demonstrate severe growth retardation. This is usually defined by height less than the 3rd percentile for age, or by height being two standard deviations below the average height for a certain age, or by bone age two years less than chronological age (2-4).

Growth Velocity

We have asked the question: How often does decreased height velocity occur? How often does this decrease precede the diagnosis? In healthy children it is known that the expected linear growth from age 3 until puberty will follow a predictable height velocity curve. This velocity of growth can be affected by overt metabolic, endocrine, or systemic disease, or as in phases of Crohn's disease, by prolonged subtle illness. Children with a sustained period of subnormal growth velocity will progressively fall below their usual height percentiles. As will be stressed in this chapter, reversal of this growth (and of an accompanying developmental) delay will depend upon early diagnosis and proper and effective treatment of the underlying disorder. Avoiding steroid suppression of growth will be vital.

Frequency of Diminished Height Velocity

We determined both frequency of changes in linear growth velocity, and the temporal relationship between the onset of symptoms referable to Crohn's disease and abbreviated linear growth in 50 consecutive children and prepubescent adolescents (5). We also focused on the correlation (or lack of correlation) between changes in velocity of weight gain and linear growth velocity.

Decreased height velocity antedated the diagnosis of Crohn's disease in 44 of 50 (88%). Twenty-one (42%) had a reduction in height velocity before any intestinal symptoms were noted.

Relationship to Weight Gain Velocity

In terms of weight gain, 17 of 32 patients with attenuated linear growth had a reduction in height velocity before any weight loss, seven of the 32 (22%) maintained normal weight gain velocity while their growth rate had already diminished (5).

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There was no difference in the site of involvement between patients with attenuated linear growth and patients with normal growth. Symptoms were also similar.

Severe Growth Retardation

Patients who were less than the 5th percentile at the outset of available data (pre-morbid) were excluded. At the time of diagnosis 10 of 44 patients with delayed linear growth (20% of the original 50), had heights less than the 5th percentile for age. The interval from the onset of decreased height velocity to the diagnosis was significantly longer in the ten patients with pronounced growth retardation then in the others. Mean duration was 42 months, with a range of 18 to 78 months, compared to a mean of 19.5 months in the 34 patients who were at or above the 5th percentile at the time of diagnosis. The range was 3 to 33 months ($p < 0.05$).

Other Factors in Diminished Growth

Multiple factors could be involved in this diminished growth velocity and the eventual stunting of those with prolonged unrecognized or inadequately treated disease. (**Table 1**).

TABLE I
CROHNS DISEASE:
FACTORS IN DIMINISHED GROWTH VELOCITY

ACTIVE DISEASE
INFLAMMATORY MEDIATORS
INTERFERE WITH LINEAR GROWTH
DECREASED NUTRIENT INTAKE
ANOREXIA, ALTERED TASTE, EARLY SATIETY
AVOIDING PAIN OR DIARRHEA
RESTRICTED DIETS
INCREASED GUT LOSSES
PROTEIN LOSING ENTEROPATHY
ELECTROLYTES, MINERAL, TRACE METALS
CARBOHYDRATES
BLEEDING
INCREASED REQUIREMENTS
FEVER, SEPSIS
INCREASED CELL TURNOVER
REPLACE LOSSES
CATCH UP GROWTH
ENDOCRINE ALTERATIONS
DECREASED SOMATOMEDIN ACTIVITY
INCREASED SOMATOMEDIN INHIBITORS
DRUG-CELL-NUTRIENT INTERACTIONS
CORTICOSTEROIDS
DECREASED CELL GROWTH
CALCIUM, PROTEIN
SULFASALAZINE
FOLATE
CHOLESTYRAMINE
FAT, VITAMINS

Disease Activity

Disease activity, even subtle or subclinical as in the 21 prepubescent adolescents who had a reduction in height velocity before (often years before) any abdominal or gastrointestinal symptoms, can diminish growth velocity.

Since 22% of those with diminished growth still had normal weight gain velocity, one can invoke the role of one or more inflammatory mediators which could be produced by active (although subtle) intestinal inflammation which could in turn impair growth. This hypotheses can be supported by the demonstration of regulation of osteoclast function by lymphokines, including tumor necrosis factors alpha and beta (6) and by interleukin 1 and lymphotoxin (7). It is also possible that serum proteins, such as the somatomedin inhibitors, limit energy expenditure for growth (8,9). Transforming growth factor Beta, which seems to regulate replication and differentiation of mesenchymal pabenchymal cells, chondrocytes and osteoblasts and osteoclasts, can probably be contracted at multiple levels by other local and systemic agents (10). Thus, there are multiple factors which could be involved at a molecular and at a cellular level.

Continued disease activity in prepubescent adolescents who after diagnosis are inadequately treated will also delay growth velocity and sexual development (3). This occurs, even in youngsters on alternate day prednisone or in some who are receiving other medications. Some with extensive areas of disease involvement may be rendered asymptomatic with medical therapy but still do not grow at a normal velocity despite hyperalimentation and provision of excessive calories and protein.

Decreased Nutrient Intake

Delayed linear growth in Crohn's disease is most often attributed to chronic undernutrition secondary to a combination of decreased nutrient intake, increased nutritional requirements and increased nutrient losses (11-14). Attention has been focused on increased energy needs for growth, highlighted by reports of acceleration in growth velocity in response to increased caloric supply provided by either intravenous hyperalimentation or by enteral supplements (15-18). Dietary intake is also chronically insufficient in the majority of severely growth-retarded patients (13-16). Although the exact mechanisms by which malnutrition causes growth retardation are not known, it is clear that impaired nutritional status is a second important factor contributing to linear growth retardation in children with Crohn's disease. We had focused on disease activity as another factor, earlier.

Increased Gastrointestinal Losses

Protein losing enteropathy, as currently measured by alpha-1-antitrypsin loss, is a sensitive indication of active Crohn's disease (12). This nutrient loss along with carbohydrate, electrolyte, mineral, trace metal and blood losses (19,20) also may contribute to diminished growth in Crohn's disease.

Increased Nutrient Requirements

Factors such as fever, sepsis and increased cell turnover contribute to increased energy-nutrient needs. Also repair processes, replacing loss as well as

"catch up growth" also increases the needs of the young patients with Crohn's disease. If puberty is superimposed on active Crohn's disease, nutrient requirements would be further increased.

Endocrine Alterations

Although no primary endocrine abnormality has as yet been identified in patients with severe growth retardation and Crohn's disease (21), somatomedin C levels are decreased in severely growth retarded children with Crohn's disease (22). When nutritional status is improved somatomedin C levels rise quickly along with a concomitant increase in growth velocity. It is not yet clear whether decreased somatomedin C levels contribute directly to growth failure or, instead, reflect metabolic adaptation to a suboptimal nutritional status. Decreased bone density, a not uncommon finding, probably involves an interplay between metabolic and nutrient factors as well as adrenocortical steroid medications.

DRUG-CELL-NUTRIENT INTERACTIONS

Adrenocortical Steroids

It is well established that long-term use of daily adrenocortical steroids suppresses growth in many prepubescent children with inflammatory bowel disease (or with any other chronic illness). Occasionally a child with very active disease may show an increased growth rate on corticosteroids. Perhaps this provides further evidence that disease activity can be a major suppressant of growth. As will be discussed in the section on therapy, efforts should be made to wean patients on to other anti-inflammatory agents or on to an alternate day steroid regimen. If disease activity can be suppressed on alternate day steroids (often in combination with other medications), normal growth velocity and sexual development can be achieved (3).

Corticosteroids and Malnutrition May Influence Endogenous Somatomedin

Corticosteroids and malnutrition may influence endogenous production of somatomedin inhibitors. It is also possible that corticosteroids can interfere with the activity of several enzyme networks involved in cartilage production. Hyams and colleagues have shown significantly lower serum concentrations of markers of type 1 collagen production in children with inflammatory bowel disease receiving daily corticosteroid therapy compared to those not receiving steroids, or interestingly to those patients receiving corticosteroids on an alternate day basis. This provides supporting evidence for the concept of excellent growth on alternate day steroid therapy (23).

Sulfasalazine. Although interference with folate absorption has been demonstrated, it is rare to encounter folate deficiency on long-term sulfasalazine. Some physicians will provide folic acid to everyone on sulfasalazine. Alternatively, we follow red blood cell folate levels as well as mean corpuscular volumes (MCV's).

Goals of Therapy

Resumption of adequate growth and development is an important management goal in the child or prepubescent adolescent with Crohn's disease. We also use achievement of this goal as a measure of the adequacy of our therapy. The other goals, including minimizing drug side effects are listed in **Table 2.**

TABLE II
CROHN'S DISEASE IN PREPUBESCENT ADOLESCENTS
GOALS OF THERAPY

A. SUPPRESS DISEASE ACTIVITY
B. RESUMPTION OF ADEQUATE GROWTH AND DEVELOPMENT
   1. IF POSSIBLE
   2. AS MEASURE OF ADEQUACY OF THERAPY
   3. MEET NUTRITIONAL NEEDS
C. DECREASE MORBIDITY, HOSPITALIZATION, LOSS OF SCHOOL TIME
D. MINIMIZE DRUG SIDE EFFECTS
E. PERMIT NORMAL TEENAGE APPEARANCE AND ACTIVITY
F. TRY TO RESERVE SURGERY FOR ABSCESS DRAINAGE, FULMINANT COLITIS, LIFE-THREATENING, PERSISTENT OR RECURRENT HEMORRHAGE

Management

Suppression of Disease Activity

In patients with disease limited to the ileum we have been able to suppress clinical and laboratory evidence of disease activity. There is little control trial evidence that multiple therapy is better than single agent. Nonetheless, we have made use of multiple medications in an effort to lessen steroid use. Also it can be argued that sulfasalazine and prednisone inhibit different phases of arachidonic acid metabolism. In addition, sulfasalazine and 5-ASA bind oxygen free radicals.

Avoiding Daily Steroid Use

Although most patients who require prednisone therapy are started on daily doses (1 to 2 mgm/Kg), we try to taper over to alternate day therapy after a few weeks. Sulfasalazine is usually added, hopefully for some degree of steroid sparing. If there is either a component of obstruction, deep fissuring or fistula formation, a broad spectrum antibiotic, such as tetracycline, was used instead of sulfasalazine. In the past few years metronidazole has been utilized, sometimes in addition to sulfasalazine and prednisone. With this multi-drug approach, sometimes combined with bowel rest in the form of elemental diet or TPN, most patients can be weaned over to alternate day steroid therapy. If we are unable to sustain an acceptable velocity of growth despite all of these measures including alternate day prednisone, it usually means there is extensive disease, such as pancolitis or diffuse jejuno-ileitis.

In adults, azathioprine or 6-mercaptopurine (6-MP) will permit "steroid-sparing" in about 70% of patients with refractory but uncomplicated Crohn's disease.

Similarly about 70% of patients who seem to require daily prednisone to have adequate control of symptoms, can be weaned either off prednisone or at least to lower, alternate day doses (24). We have had little experience with azathioprine or 6-MP in adolescents but it is our understanding that some patients with diffuse disease have responded well. Obviously, the long-term concern will be of neoplastic transformation.

In our experience with Crohn's disease, linear growth suppression seems to occur with as little as 5 mgm of prednisone given on a daily basis. Prednisone, at a daily dose of 4 to 6 mgm/m2 caused growth suppression in asthmatic children (25). Prednisone may have an even greater growth retarding effect then hydrocortisone. This is presumably due to the longer half life of prednisone. **(Table 3)**

TABLE III
CORTICOSTEROIDS AND GROWTH

DIMINISHED GROWTH RATE AND SKELETAL MATURATION
- CORTISONE: AS LITTLE AS 45 MGM/M2/D
- PREDNISONE: AS LITTLE AS 4 TO 6 MGM/M2/D (ASTHMA)
  - (EQUIVALENT TO 20-30 MGM/M2 OF HYDROCORTISONE)
  - GREATER GROWTH SUPPRESSION WITH PREDNISONE

PRESUMABLY BECAUSE OF LONGER T 1/2 AND OCCUPYING GC RECEPTORS

ALTERNATE DAY ADMINISTRATION: NORMAL GROWTH VELOCITY
- (ASTHMA, NEPHROTIC SYNDROME, UC, CROHN'S AND CHRONIC HEPATITIS
- 30 TO 60 MGM ON ALTERNATE DAY (ASTHMA)
- 300 TO 400 MGM CORTISONE FOR 3 DAYS OF EACH WEEK (NEPHROTIC SYNDROME)
- ONE REPORT OF LESS GROWTH INHIBITION WITH ACTH

DELAYED SKELETAL MATURATION
- LONG-TERM STEROID THERAPY
- GREATER SUPPRESSION OF BONE AGE THAT HEIGHT
- ? MORE PRONOUNCED IN MALES ?

OSTEOPENA IN AREAS OF TRABECULAR BONE
- VERTEBRAE
- STIMULATION OF BONE RESORPTION
- CORTICOSTEROID INDUCED INHIBITION OF INTESTINAL CALCIUM TRANSPORT
- DECREASED OSTEOBLAST METABOLIC ACTIVITY
- DIRECT CORRELATION BETWEEN DEGREE OF BONE DEMINERALIZATION AND GROWTH RETARDATION (GLOMERULAR DISEASE)

As discussed above, alternate day administration has been associated with normal growth velocities in children with asthma, nephrotic syndrome, inflammatory bowel disease and chronic hepatitis (26).

We have usually added calcium supplements and at times, Vitamin D for patients who continue long-term prednisone.

Encouraging High Caloric Intake

Most children and adolescents will require at least 80 Kcal/Kg daily to achieve adequate weight gain and growth. As discussed earlier, adequate growth will occur if nutritious supplementing is adequate, if the underlying disease is reasonably well controlled and alternate day or no adrenocortical steroid therapy is utilized.

The provision of at least 70% of the recommended daily allowance (RDA) is essential. This is most acceptable as a high calorie, high protein diet. Lactose intake is curtailed or lactose hydrolyzed milk or yogurt is recommended if the child is lactose intolerant. If caloric and protein intake is inadequate, defined formula supplements such as Ensure or Sustacal are recommended. Most of the available supplements are also lactose free. Elemental diets given as a major source of calories can be useful if concomitant bowel rest is needed. Intermittent courses of elemental diets seemed to be helpful in terms of accelerating growth in at least one Canadian study (27). Total parental nutrition was the original route that provided evidence that enhanced caloric protein intake might enhance growth even in some patients with persistent disease activity.

Summary

Our studies indicate that decreased linear growth may be the earliest sign of Crohn's disease in children and prepubescent adolescents. There was also a direct correlation between the duration of suppressed linear growth before the diagnosis (and institution of therapy) and the development of severe retardation of growth.

There is some potential for catch-up growth if active disease (inflammation) is suppressed, daily adrenocorticosteroid use is minimized, and adequate energy intake is provided. Prompt diagnosis and institution of multi-faceted therapy is important if one is to minimize growth impairment. We have utilized correction of the attenuated linear growth velocity as a useful marker of the adequacy of treatment of children and prepubescent adolescent with inflammatory bowel disease.

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SKELETAL COMPLICATIONS OF INFLAMMATORY BOWEL DISEASE

Michael D. Sitrin, M.D.
Clinical Nutrition Research Unit
University of Chicago
5841 S. Maryland, Box 223
Chicago, Illinois 60637

Abstract

Skeletal complications of inflammatory bowel disease are important causes of morbidity and disability. Osteopenia is common and may reflect singly or in combination osteoporosis, osteomalacia, and osteitis fibrosa cystica. Patients with inflammatory bowel disease, particularly those with Crohn's disease and ileal resection, are frequently vitamin D deficient. Poor dietary intake and malabsorption of vitamin D, and increased metabolism and excretion of vitamin D metabolitis all likely contribute to the deficit. Calcium deficiency is also common, due to inadequate intake and malabsorption. Corticosteroid therapy is a major cause of osteopenia. Glucocorticoids impair calcium absorption, increase urinary calcium loss, promote bone resorption and inhibit bone formation. Osteonecrosis occurs in steroid-treated inflammatory bowel disease patients, and frequently necessitates hemiarthroplasties or total joint replacement. Increased marrow pressure limiting blood flow, vascular occlusion, and cytotoxic effects on bone cells, are thought to be responsible for osteonecrosis.

Introduction

Skeletal complications of inflammatory bowel disease are important causes of morbidity and disability. Bone may be altered as a direct consequence of the inflammatory bowel disease, particularly in patients with significant nutritional deficiencies, or may be damaged by medications and other therapy. In this review, the major skeletal manifestations of inflammatory bowels disease, including metabolic bone disease and osteonecrosis, will be discussed.

Metabolic Bone Disease

Several types of metabolic bone disease, singly or in combination,

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occur in patients with inflammatory bowel disease. Osteoporosis, in which bone mass is reduced, but bone mineralization is normal, is most common. Some patients demonstrate rickets or osteomalacia, in which a defect in bone mineralization occurs. In others, osteitis fibrosa cystica, reflecting marked secondary hyperparathyroidism and bone resorption, is a prominent feature. It is important to recognize that bone x-rays and measurements of bone density by photon absorptiometry or computerized tomography only demonstrate osteopenia. Differentiation of the type of metabolic bone disease requires bone biopsy and quantitative histologic analysis. Factors which have been demonstrated to contribute to metabolic bone disease in inflammatory bowel disease include vitamin D and calcium deficits and treatment with corticosteroids or total parenteral nutrition.

VITAMIN D DEFICIENCY

Vitamin D deficiency is one of the most common nutritional deficits observed in patients with Crohn's disease. In various series, as many as 68% of patients with Crohn's disease have had low serum levels of 25 (OH) vitamin D, the major circulating form of the vitamin [1-3]. A number of pathogenetic mechanisms contribute to vitamin D deficiency in patients with inflammatory bowel disease. Dietary intake of vitamin D may be inadequate due to generalized anorexia or to avoidance of vitamin D fortified dairy products because of lactose intolerance. Malabsorption of dietary vitamin D occurs in patients with regional enteritis, particularly those who have had ileal resections [4,5]. Efficient absorption of vitamin D is dependent on an adequate intraluminal bile salt concentration, as the vitamin is solubilized in mixed micelles in the luminal fluid [6]. The bile salt binding resin cholestyramine is often used in patients with ileal disease or resection to diminish watery diarrhea, and can accelerate vitamin D depletion by both decreasing luminal bile salt concentration and by directly binding the vitamin [7]. Steatorrhea will diminish vitamin D absorption by retaining the vitamin in the lipid phase of intestinal fluid. Absorbed dietary vitamin D is delivered from the intestine predominantly as a component of chylomicrons, and thus transport may be affected by dietary triglyceride absorption [8].

Studies have indicated, however, that most of the circulating 25 (OH) vitamin D originates from cutaneous production of vitamin D, and it has, therefore, been somewhat difficult to explain the high prevalence of vitamin D deficiency solely on the basis of dietary lack and malabsorption. Patients with inflammatory bowel disease demonstrate the usual seasonal variation of serum 25 (OH) vitamin D levels, and limitation of outdoor activities because of disease could reduce cutaneous vitamin D production [9]. A number of mechanisms have been suggested whereby vitamin D excretion or degradation could be accelerated in patients with inflammatory bowel disease. An enterohepatic circulation of vitamin D metabolites has been demonstrated [10]. Intravenously injected ^{3}[H]-vitamin D, 25 (OH) vitamin D, 1,25 $(OH)_2$ vitamin D, and 24,25 $(OH)_2$ vitamin D appear in

bile, and a significant fraction of biliary radioactivity is reabsorbed by the intestine. Malabsorption of enterohepatically circulating vitamin D could, therefore, potentially contribute to vitamin D depletion. It has been demonstrated, however, that little of the biliary vitamin D is present as unchanged vitamin, but instead that extensive metabolism and conjugation occurs prior to biliary excretion. To date, there is little evidence that much of the biliary vitamin D re-enters the circulating serum pool of vitamin D metabolites, and it appears, therefore, that loss of enterohepatically circulating forms plays a minor role in depletion of 25 (OH) vitamin D [11]. 25 (OH) vitamin D circulates in the plasma bound to a specific vitamin D binding protein with a molecular weight of about 58,000 daltons. Excessive loss of 25 (OH) vitamin D and other metabolites bound to vitamin D binding protein could occur as part of protein-losing enteropathy, a common feature of active inflammatory bowel disease. A similar mechanism of vitamin D depletion has been demonstrated in patients with the nephrotic syndrome. More recently, a new mechanism of vitamin D depletion has been suggested [12,13]. Several investigations in rat and man have suggested that calcium deficiency accelerates the metabolic clearance of 25 (OH) vitamin D. Clements et al. have proposed that calcium deficiency increases hepatic metabolism and biliary excretion of 25 (OH) vitamin D through as yet unidentified metabolic pathways [13]. Potentially, a vicious cycle could exist, where vitamin D deficiency leads to calcium malabsorption which in turn accelerates 25 (OH) vitamin D catabolism and accentuates the vitamin deficit.

Patients with severe cholestatic liver disorders (complicating inflammatory bowel disease), such as sclerosing cholangitis, often demonstrate marked vitamin D deficiency and bone disease. In these patients, vitamin D malabsorption appears to be the major factor, as hepatic production of 25 (OH) vitamin D becomes impaired only with far-advanced cirrhosis [14].

A small number of patients with Crohn's disease and vitamin D deficiency (about 5%) will present with clinically apparent osteomalacia or rickets. These individuals will complain of bone pain, deformities, pathologic fractures, muscle weakness, or even tetany and other manifestations of neuromuscular irritability from hypocalcemia. Many asymptomatic patients with low serum 25 (OH) vitamin D levels, however, have significant metabolic bone disease. Screening laboratory studies such as serum calcium, phosphorus, alkaline phosphatase, and bone x-rays will usually be normal [3]. Vogelsang et al. have recently studied 31 patients with Crohn's disease and low winter-time 25 (OH) vitamin D levels, measuring bone mineral content of the distal radius by single photon absorptiometry, the cortical area ratio calculating from hand radiographs, and assessing lumbar spine x-rays. 45% of patients showed signs of metabolic bone disease, a higher prevalence than was observed in Crohn's disease patients with normal serum 25 (OH) vitamin D levels. Furthermore, bone mineral content and cortical area ratio correlated with serum 25 (OH) vitamin D levels, especially in men. Patients with vitamin D deficiency and osteomalacia on bone biopsy consistently

demonstrate histologic improvement with adequate vitamin D therapy [3].

Vitamin D deficiency can generally be treated by oral vitamin D supplementation (typically 4000 - 25,000 I.U. daily), monitoring the adequacy of vitamin D treatment by periodic measurement of the serum 25 (OH) vitamin D level. Some patients with severe malabsorption respond poorly to large oral vitamin D doses and may require parenteral treatment. Studies in experimental animals and man have demonstrated that absorption of 25 (OH) vitamin D is greater than of vitamin D, and is less affected by luminal bile salt deficiency and steatorrhea [8]. In some cases, treatment with 25 (OH) vitamin D orally can be used instead of vitamin D injections.

CALCIUM DEFICIENCY

Calcium deficiency also plays an important role in the metabolic bone disorders of inflammatory bowel disease. Dietary calcium intake is often inadequate, particularly in those who avoid dairy products. Several factors may lead to calcium malabsorption. Vitamin D deficiency causes a marked reduction in active transport of calcium, particularly in the duodenum and ileum. Steatorrhea decreases intestinal calcium absorption as unabsorbed fatty acids bind calcium, forming poorly-soluble calcium soaps. Hylander et al. reported that calcium malabsorption occurred in 53% of patients with small bowel resection, mainly for inflammatory bowel disease, and that calcium absorption was inversely correlated with the length of resected small bowel [15, 16]. Calcium absorption tended to improve with time after resection as intestinal adaptation occurred [17, 18]. Controversy exists concerning the importance of colonic calcium absorption in patients with the short bowel syndrome [15-18]. Treatment with corticosteroids results in a major decline in intestinal calcium absorption (see below).

CORTICOSTEROIDS AND BONE

Treatment with corticosteroids is a major factor contributing to the osteopenia of inflammatory bowel disease. Compston et al. studied bone mineral content in 75 unselected patients with inflammatory bowel disease [19]. Severe osteopenia, more than 2 standard deviations below age and sex matched normals, was noted in 30.6% of patients. Bone mineral content in spinal trabecular bone was negatively correlated with lifetime steroid use.

Corticosteroids have multiple effects on calcium and bone metabolism. Steroids decrease intestinal calcium absorption by unclear mechanisms [20]. Some studies have found that high doses of steroids can decrease serum levels of 25 (OH) vitamin D and 1,25 $(OH)_2$ vitamin D, but other investigators report no significant effect of glucocorticoids on vitamin D metabolism. Corticosteroids clearly also decrease the 1,25 $(OH)_2$ vitamin D-dependent active transport of

calcium across the proximal small intestine [20]. Less well appreciated is that high doses of steroids also increase urinary calcium loss, probably by interfering with renal tubular calcium reabsorption [21]. Malabsorption of calcium and increased urinary loss both tend to decrease serum ionized calcium concentration and, therefore, stimulate parathyroid hormone secretion. Serum parathyroid hormone levels tend to be elevated in steroid-treated patients, and secondary hyperparathyroidism contributes to the increased bone resorption noted on bone biopsy. A direct stimulation of bone resorbing cells by glucocorticoids has also been noted.

In addition to increasing bone resorption, corticosteroids also depress bone formation. Canalis has demonstrated effects of glucocorticoids on cellular proliferation, type 1 collagen synthesis, and alkaline phosphatase activity in cultured rat calvariae [22]. The combined effect of increased bone resorption and decreased bone formation accounts for the dramatic reduction in bone mass sometimes noted with steroid therapy.

A number of therapies singly and in combination have been tried for steroid-induced osteoporosis. Obviously, one should try to treat the inflammatory bowel disease patient with the lowest steroid dose for the shortest duration possible. Alternate day-steroid treatment has not been clearly shown in man to result in better preservation of bone mass [23]. Vitamin D metabolites and calcium supplementation have been utilized to augment intestinal calcium absorption and prevent secondary hyperparathyroidism [24]. Although some promising results have been obtained, other studies have not demonstrated a beneficial effect on bone mass [25]. Thiazide diuretics reduce urinary calcium loss and could benefit those with hypercalciuria from high dose steroids. In a double-blind placebo-controlled trial, Reid et al. reported that (3-amino-1-hydroxypropylidene)-1,1-biphosphonate, a potent inhibitor of bone resorption, prevented bone loss in glucocorticoid-treated patients [26]. Fluoride supplementation stimulates osteoblastic activity and bone formation, and when combined with calcium and vitamin D treatment has been reported in some, but not all, studies to preserve bone mass [25,27,28]. The high incidence of gastrointestinal side effects from fluoride may limit its usefulness in inflammatory bowel disease.

No clinical trials of these therapies have been performed in inflammatory bowel disease patients and are clearly needed before definitive treatment regimens can be recommended. As a preliminary recommendation, it is reasonable to be certain that patients with inflammatory bowel disease on steroids have a generous calcium intake of 1000 mg/d or greater and are not vitamin D deficient. If hypercalciuria is demonstrated, thiazide diuretics can be tried to decrease renal calcium losses. Measurements of spinal bone density by dual photon absorptiometry or quantitative computer tomography should be performed, and if bone mass is low or if serial studies demonstrate rapid bone loss [29], additional treatment with higher doses of vitamin D metabolites, fluoride, or biphosphonates should be considered.

BONE DISEASE ASSOCIATED WITH TOTAL PARENTERAL NUTRITION

Metabolic bone disease is a frequent complication in patients on long-term total parenteral nutrition (TPN). Early studies reported patients who developed severe symptomatic bone disease, and were found to have osteomalacia on bone biopsy. This syndrome was apparently caused by aluminum contamination of protein hydrolysates used in TPN [30]. Excess aluminum has been demonstrated to have multiple effects on vitamin D metabolism and parathyroid gland and bone function. Switching patients from protein hydrolysates to crystalline amino acid preparations containing little aluminum resulted in marked improvement. Some aluminum is still present in TPN components, particularly intravenous phosphate preparations, and could potentially accumulate in patients with impaired renal function. Some have suggested that an abnormal response to intravenous ergocalciferol also played a role in TPN-associated osteomalacia [31]. More recently, severe osteoporosis has been noted in home TPN patients, sometimes associated with a low bone turnover rate [32, 33]. Hypercalciuria is frequently noted with TPN, and urinary calcium losses are affected by the amino acid, phosphorus, and acetate content of TPN solution [34-35]. Because of long-standing malnutrition, drug therapy, etc. many patients have a reduced bone mass upon initiation of TPN.

OTHER FACTORS

Undoubtedly, many other factors play important roles in the metabolic bone diseases associated with inflammatory bowel disease [37]. Some studies have found an association between bone density and body mass index in inflammatory bowel disease patients, indicating that protein-calorie malnutrition has profound skeletal effects. Phosphate malabsorption from intestinal disease or antacid use can cause chronic phosphate depletion and osteomalacia. Severe hypomagnesemia interferes with parathyroid hormone secretion and action, and could also affect vitamin D hydroxylating enzymes. Other trace elements are known to be important in bone structure and function. Chronic metabolic acidosis from diarrheal fluid bicarbonate loss or renal dysfunction as occurs with amyloidosis, can decrease bone mineral content. Women with inflammatory bowel disease frequently have secondary amenorrhea. Estrogen lack is well-known to diminish intestinal calcium absorption and to decrease bone formation. Serious consideration must be given to estrogen supplementation of post-menopausal women with inflammatory bowel disease.

OSTEONECROSIS

Osteonecrosis or aseptic necrosis is a bone disorder characterized by death of all the cellular elements of bone, including osteocytes, fat cells, and hematopoetic elements [38]. This may ultimately lead to fractures, collapse, and deformity, resulting in secondary osteoarthritis. Hips, knees and shoulders are most commonly affected,

and involvement of multiple bilateral sites is typical. Osteonecrosis presents as pain with weight bearing and motion, which may progress to rest and nocturnal pain. On physical examination, there is pain with movement and often limitation in range of motion.

Vakil and Sparberg recently reported that 4.3% of their patients with inflammatory bowel disease over a 10 year period developed osteonecrosis [39]. All of these patients and all previous cases of osteonecrosis in inflammatory bowel disease had received corticosteroid therapy, which appears to be the major causative factor.

The pathogenesis of steroid-induced osteonecrosis is uncertain and may well be multi-factorial. Some data suggest that raised pressure within the marrow space may be important [40]. The vascular supply of bone is such that with increased marrow pressure there will be decreased blood flow to bone. It has been postulated that glucocorticoids increase marrow pressure by inducing hypertrophy and hyperplasia of marrow fat cells. In addition, infiltration of the marrow space by inflammatory cells could raise pressure. Vascular occlusion has also been suggested to play a role in steroid-induced osteonecrosis [38, 40]. Experimental animal studies have indicated that steroids may cause fat emboli that occlude bone marrow vessels. Hypercoagulable states seen in inflammatory bowel disease could also predispose to thrombosis.

Most studies have suggested that it is high dose, intensive corticosteroid treatment that promotes osteonecrosis. There appears to be great individual variability in sensitivity to steroids, however, with osteonecrosis reported with as little as replacement doses. The patients described by Vakil and Sparberg were younger and received lower doses and duration of steroids than reported for steroid-induced osteonecrosis in other disease states, suggesting special sensitivity to glucocorticoids in inflammatory bowel disease [39]. Shapiro et al. reported 3 children who developed osteonecrosis after becoming hyperlipdemic while on steroids and parenteral nutrition [41].

Several radiologic tests are useful in the detection of osteonecrosis. Bone x-rays may be negative early after symptom onset. Later, a combination of porotic and sclerotic lesions will be seen, representing attempts at repair and collapse. Ultimately, osteoarthritis develops in the affected joints. Bone scans may show decreased uptake secondary to bone necrosis or increased uptake reflecting attempts at repair. Computer tomography and especially magnetic resonance imaging are sensitive methods for detecting osteonecrosis [42].

Bone marrow pressure can be measured through a large needle inserted into the marrow space, and contrast injected to evaluate venous flow. Another approach used by some is to obtain a diagnostic core biopsy. This may also be therapeutic, since removal of the core will decrease marrow pressure [40]. In early stages, conservative treatment with rest and analgesics is recommended. In late stages, after collapse has occurred, orthopedic procedures such as hemiarthroplasty or total joint replacement are often needed [43].

Other Bone Disorders

Periosteal new bone formation is a rare complication of inflammatory bowel disease. Most cases demonstrate bilateral linear periosteal reduplication and clubbing in the form of hypertrophic osteoarthropathy. Bookman et al. recently described a 20 year old man with a proliferative periosteal new bone growth over the left forearm that demonstrated granuloma formation on bone biopsy [44].

Osteomyelitis of pelvic bones can occur in Crohn's disease patients with fistulae or pelvic abscesses.

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ENTERAL NUTRITION IN INFLAMMATORY BOWEL DISEASE

Ernest G. Seidman, M.D., Philippe Atlan, M.D. and Claude C. Roy, M.D. Departments of Pediatrics and Nutrition, Université de Montréal. Gastroenterology Division, Hopital Ste-Justine, 3175 Cote Ste-Catherine Rd., Montreal, Que., Canada H3T 1C5.

Abstract. Nutrition has gained a more prominent role in the management of inflammatory bowel disease, but remains ever controversial. Malnutrition, complicated by growth failure in the pediatric age group, represents a common, serious problem for many patients. Although the etiology of malnutrition is multifactorial, inadequate nutrient intake is the primary cause. Clinical studies suggest that nutritional supplementation through the enteral route restores body composition and reverses growth failure. Elemental diet therapy has also been shown to be an effective method of inducing remission in acute Crohn's disease. How dietary therapy improves disease activity remains conjectural, but possible mechanisms include the gut adaptive response to "bowel rest", and local immunological or nutritional alterations fundamental to healing of the intestinal inflammation.

Enteral Nutrition As An Adjunctive Treatment In IBD

ETIOLOGY AND ASSESSMENT OF MALNUTRITION IN IBD

Malnutrition is a serious problem that complicates IBD in a significant proportion of both adult (Driscoll and Rosenberg (1978)) and pediatric patients (Seidman et al. (1989)). The malnutrition and its potential associated problems may become more debilitating than the underlying disease process.

The mechanisms contributing to the malnutrition are numerous (Table I). Inadequate caloric intake is the most important cause in the majority of affected patients (Belli et al. (1988), Motil and Grand (1985)). Eating may bring on painful symptoms or diarrhea, resulting in decreased intake. Iatrogenic dietary restrictions often further compromise nutrient intake. Anorexia may also be associated with the presence of chronic inflammation, depression, or result from the administration of various drugs.

In addition to deficits in protein and energy, malabsorption and excessive gut losses may result in additional specific micronutrient deficiencies (electrolytes, metals, trace elements and vitamins). In

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order to appropriately determine the need for nutritional support, an assessment of the patient's nutritional status must be made (Table II). A carefully performed subjective nutritional assessment at the bedside, based on a detailed history and through physical examination is probably as useful as sophisticated anthropometric measures and diverse laboratory testing (Baker et al. (1982)).

TABLE I. Causes of Malnutrition in Patients with Inflammatory Bowel Disease.

Inadequate Nutrient Intake
Disease-induced
Iatrogenic
Malabsorption
Diminished absorptive surface (inflammation, fistulae, resection)
Bacterial overgrowth, Blind loop
Bile salt deficiency
Altered motility
Increased Gut Losses
Protein-losing enteropathy
Electrolytes, minerals, trace metals
Bleeding
Drug-Nutrient Interactions
Corticosteroids (calcium, protein)
Sulfasalazine (folate)
Cholestyramine (fat, vitamins)
Increased Requirements
Sepsis, fever
Increased cell turnover
Replenish stores
Promote catchup growth

In the pediatric patient, growth retardation complicates Crohn's disease in approximately one-third of patients, often despite minimal disease activity (Seidman (1989)). The nutritional impact of IBD is particularly severe in the prepubertal patient, in whom the protein and energy costs for growth are unlikely to be met. The clinician must devote special attention to the growth of such patients, serially documenting height and weight on standard curves for age. Simple calculations, such as height for age and weight for height deficits will permit the classification of the degree of chronic or acute malnutrition, respectively (Suskind and Varma (1984), Atlan and Seidman (1989)).

In the prepubertal adolescent with IBD and growth failure, the potential for catchup growth is limited in time by progressive bone maturation and eventual epiphyseal fusion. These changes may be documented simply by bone age X-rays, and can be estimated by sexual development stage. The aim of therapy is to assure adequate nutritional support, avoiding or reversing any deceleration in growth velocity. The

essentials of the nutritional assessment of IBD patients are summarized in Table II, and described elsewhere (Atlan and Seidman (1989)).

TABLE II. Basic Nutritional Assessment of the IBD Patient

1. Subjective nutritional assessment
   - detailed history and physical exam
2. Anthropometry
   - height, weight (percentiles)*
   - growth velocity*
   - height for age, weight for height deficits*
3. Dietary history/Estimation of Requirements
   - assisted by an experienced dietician
4. Laboratory evaluation
   - visceral protein status (Albumin, retinol binding protein, pre-albumin, etc.)
   - hematologic profile
   - electrolyte, metal trace element and vitamin status
   - bone age*

*for pediatric age group (see Atlan and Seidman (1989)).

ENTERAL NUTRITION IN THE TREATMENT OF MALNUTRITION

The simplest method to combat dietary inadequacy is to increase the oral intake of nutrients. Despite the best of intentions by both the patient and the medical team, this is often not feasible, as anorexia, pain, diarrhea, nausea or vomiting preclude these recommendations. In this situation, the provision of nutritional supplements by offering cans of chemically defined formulas will not always succeed. One controlled study by Harries et al (1983) demonstrated that supplementary caloric intake improved not only patients' nutritional status, but also laboratory parameters of disease activity. Kirschner et al. (1981) showed that, despite the presence of inflammatory disease, the enteral route may be used to achieve nutritional rehabilitation, and reverse growth failure.

A major disadvantage to using these supplements orally is that the patient often complains of early satiety, resulting in inadequate total caloric intake. Our experience utilizing polymeric oral nutritional supplements in pediatric Crohn's patients revealed that, over the long term, disappointing growth ensued in a high proportion of cases (Seidman et al. (1989)). A controlled study by Imes et al. (1986) on the effect of oral supplements on Crohn's disease showed that long term compliance was poor in adult patients. These unsatisfactory results were attributed to unpalatability, and to the abdominal cramps and diarrhea that ensued.

When the clinical situation is such that the patient cannot voluntarily increase the oral intake of nutrients or supplements, other means of providing nutritional support must be considered. The choice is bet-

ween enteral nutrition by gavage infusion or parenteral nutrition. Total parenteral nutrition (TPN) is widely available, allowing the option to use "bowel rest" without compromising the patient's nutritional status. However, the high cost and potential risks associated with TPN (sepsis, mechanical and metabolic complications) relegate its use for patients in whom the enteral route has failed, or cannot be used effectively. Contraindications to enteral nutrition are listed below.

TABLE III. Contraindications To Enteral Nutrition

1. Intractable vomiting or severe gastric stasis (consider nasojejunal tube)
2. Intestinal obstruction or perforation
3. Severe short bowel (< 40 cm)
4. End-jejunostomy syndrome with inability to concentrate intestinal contents
5. Patient non-compliance (rare)

A variety of enteral nutrition preparations are currently available for use in IBD patients (Seidman (1989)). Our preference is to administer a defined formula diet (elemental or semi-elemental) via nasogastric tube as a continuous infusion. These preparations are readily absorbed in the proximal small bowel and are generally well-tolerated despite intestinal inflammation, strictures or short bowel. After an initial brief hospitalization, during which the rate of administration and caloric density of the formula are increased progressively (Sabbah and Seidman (1989)), the patient is discharged home on a nocturnal nasogastric infusion. This regimen allows the patient to resume usual daytime activities (school, work, play, etc.), and avoids the potential for additional family stress encountered with forcing daytime feedings.

In adult patients, basal energy requirements can be accurately predicted by the Harris and Benedict formula (1919):

Basal Metabolic Requirements (kcal/24 hr):
Males
= 66.5 + (13.75 X weight (kg)) + (5 X height (cm)) - (6.75 X age (yr))
Females
= 655 + (9.56 X weight) + (1.8 X height) - (4.67 X age)

Recent studies by Chan et al. (1986) found that resting energy expenditure in Crohn's disease patients, measured using indirect calorimetry, were very similar to that predicted by the Harris-Benedict equation. Total energy requirements depend upon the level of physical activity of the individual. In general, most hospitalized patients would require an addition 20-30% above predicted basal requirements. It must be noted that superimposed infection, fever (13%/^{o}C > 37), or surgery further increase requirements. In addition to meeting energy needs, specific micronutrient deficiencies (Sabbah and Seidman (1989)) must be identified and corrected (common examples include iron, folic acid,

Vitamins B12, A and D, zinc, magnesium and calcium).

In the pediatric age group, chronic undernutrition is the primary cause of growth retardation, which is diagnosed in about one third of Crohn's disease and 10% of Ulcerative Colitis patients (Seidman et al. (1987, 1989)). A prerequisite for reinitiating normal growth velocity in these patients is that body weight be appropriate for height. Therefore, the caloric intake required to permit catchup growth should be estimated according to the child's ideal weight for age, rather than the actual weight.

Our current recommendation is to use intermittent courses of enteral elemental diet, administered by nocturnal gavage. In our recently published controlled trial (Belli et al. (1988)), adolescent Crohn's disease patients who received elemental diet therapy by nocturnal gavage grew significantly better than the control group (126 vs 29% of ideal height velocity, $p < 0.01$). This improvement was accomplished by administering 60-80 kcal/kg body weight per day using Vivonex (Norwich Eaton Pharmaceuticals), administered over a 10-14 hour period overnight. Each treatment period lasts one month, and is repeated every four months, for a total of 3 months per year. Appropriate vitamin, mineral and trace element deficits are supplemented according to individual requirements (Sabbah and Seidman (1989)).

Not uncommonly, an adolescent with IBD is refered for nutritional therapy of growth failure, in whom both pubertal development and bone maturation are already well advanced. In such cases, growth retardation may have been overlooked for a prolonged period of time, as the patient may be relatively asymptomatic, with minimal disease activity. Short stature is a common and unfortunate long term complication of pediatric Crohn's disease, whether medically or surgically treated (Castille et al. (1980), Seidman et al. (1989)). Therefore, surgery should be considered for growth failure in the prepubertal Crohn's disease patient only if optimal medical and nutritional therapy have failed.

Enteral Nutrition As A Primary Therapy in IBD

Traditionally, nutritional therapy had been considered as an adjunctive treatment in the management of IBD patients. More recently, there has been considerable interest in diet as a primary therapy (Seidman et al. (1987), Seidman (1989)). This has largely evolved from the favorable results reported using TPN and bowel rest to control the disease activity and complications of IBD (Muller et al. (1983), Ostro et al. (1985)). However, the literature concerning the use of TPN and bowel rest in IBD remains controversial, as many studies are either retrospective, or clouded by the selection of patients unresponsive to maximal medical management, and often maintained on steroids.

ELEMENTAL DIET THERAPY TO INDUCE REMISSION IN IBD

The interest in elemental diets as primary therapy in Crohn's disease evolved from the concept that modified bowel rest could be achieved without necessitating the use of TPN. Early uncontrolled studies demon-

strated clinical and radiological improvements of Crohn's disease using elemental diets are reviewed elsewhere (Seidman et al. (1987), Whittaker (1989)). Several prospective, randomized controlled trials have compared corticosteroids (O'Morain et al. (1984), Sanderson et al. (1987), Saverymuttu et al. (1985), Seidman et al. (1986)) or TPN (Alun Jones (1987)) with elemental diets in the management of acute Crohn's disease. The results (Table IV) suggest that elemental diet can induce remission with comparable efficacy and rapidity to that achieved with standard medical therapy. Not only have disease activity indices and nutritional status improved, but objective markers of inflammation (sedimentation rate, fecal protein and granulocyte losses) have improved significantly (Bjarnason et al. (1988), Logan et al. (1981)).

One larger series, in which a semi-elemental diet was used, suggested that steroids were more efficacious than diet therapy (Lochs et al. (1988)). These differences illustrate the importance of specifying the nature of the nutritional therapy (i.e., elemental versus semi-elemental or defined formula diet) used to treat the disease activity in IBD. Unfortunately, no study reported to date has adequately compared elemental (amino acid) versus semi-elemental (peptide) formulas as primary therapy for Crohn's disease. In addition, factors such as the severity, duration, and particularly the localization of Crohn's disease may largely influence response to any given therapy. In general, distal disease (colon, perianal) responds less favorably to nutritional treatment, whether by enteral or parenteral route (Lochs et al. (1984), Teahon and Levi (1989), Whittaker (1989)). There is no evidence that nutritional therapy has a significant impact on the course of patients with isolated colitis, whether due to Crohn's disease or ulcerative colitis (Seidman et al. (1987), Whittaker (1989)). Malnourished colitis patients can, however, benefit from nutritional support.

Currently, few centres recommend the routine use of elemental diets for acute Crohn's disease. Teahon and Levi (1989) recommend an elemental diet (Vivonex) as the sole dietary intake for 4 weeks, and report a success rate of at least 80 per cent. We agree with this group's report that remissions are site dependent, with distal disease (Crohn's colitis) faring less well.

The advantages of using an ED to induce remission of Crohn's disease (Table V) include the virtual absence of side effects, the avoidance of drugs that stunt growth, and nutritional repletion with improved growth in young patients. ED is also simpler, safer, and less expensive than TPN. It also affords the potential to manipulate the diet after the initial bowel rest period, using an elimination diet to attempt to prolong remission (Alun Junes (1987), Teahon and Levi (1989)). Its major disadvantage is its undesirable taste, a problem that, in our experience, is easily overcome by nasogastric infusion. Finally, ED can be administered nocturnally, at home, without necessitating lengthy hospitalization, and allows for rapid return to school and full daytime activities. Other disadvantages include the high early relapse rate when discontinued (Navarro et al. (1982), Seidman et al. (1986)), and the lower efficacy in distal (colonic/perianal) disease. At the present time, we utilize elemental diet therapy for selected cases of active

TABLE IV. Controlled Trials: Elemental Diet as Primary Therapy in Crohn's Disease

Study	Patients Randomized (N)	Treatment Period (Weeks)	% Remission		Statistical Difference
			Diet group*	Control group**	
O'Morain et al. (1984)	21	4	(E) 81.8	(P) 80	None
Saverymuttu et al. (1985)	32	1.5	(E) 93.7	(P) 100	None
Seidman et al. (1986)	18	3	(E) 77.8	(P) 66.7	None
Sanderson et al. (1987)	17	6	(S-E) 87.5	(P) 85.7	None
Alun Jones (1987)	36	2	(E) 84.6	(TPN) 87.5	None
Lochs et al. (1988)	107	6	(S-E) 52.7	(P) 78.8	$p < 0.001$

* E = elemental diet; S-E = semi-elemental
** P = prednisone or prednisolone; TPN = total parenteral nutrition

Crohn's disease in the pediatric age group, particularly those with severe growth failure in whom steroids may impair catchup growth.

TABLE V. Pros and Cons of Elemental Diet As Primary Therapy in Crohn's Disease

Advantages:
Improved growth (vs. Prednisone)
Nocturnal administration (vs. Supplements)
Excellent compliance
Few complications (vs. TPN)
Steroid sparing
Less costly (vs. TPN)
Short hospitalization (vs. TPN)
Potential for elimination diet, food intolerance identification
Disadvantages:
Unpalatable
Cost (vs. Prednisone)
Less effective in colitis (vs. Prednisone)
Significant early relapse rate when discontinued
Fistula may reopen when discontinued

ENTERAL NUTRITION IN THE MANAGEMENT OF SPECIFIC PROBLEMS IN CROHN'S DISEASE

Many questions remain concerning the optimal management of Crohn's disease and its diverse complications. The potential uses of enteral nutrition in various subsets of patients are summarized in Table VI, and reviewed below.

Strictures. The rationale for the use TPN or an elemental diet in Crohn's disease complicated by stricture or fistulae is the opportunity to decrease intestinal secretions, intraluminal flow and motility. It is difficult to make specific therapeutic recommendations, as the literature is devoid of randomized trials comparing nutritional therapy (TPN or enteral) with standard medical management. In an uncontrolled series, Teahon and Levi (1989) were able to avoid initial surgery in 21/28 patients with strictures treated with an elemental diet (Vivonex). Of these 21 patients, 9 subsequently relapsed and required surgery, for an overall success rate of 43%. These results are similar to our experience with pediatric Crohn's patients. Even for those cases who eventually require surgery, preoperative enteral nutrition with Vivonex improves nutritional status and usually allows for the reduction or eventual withdrawal of steroids (Blair et al. (1986)).

Fistulas. As noted above, no randomized trials have compared nutritional with conventional medical management of fistulas. In addition, studies concerning Crohn's disease management do not specify whether

the fistula occured post-operatively or spontaneously. Teahon and Levi (1989) attempted to treat 7 Crohn's disease patients with fistulae using elemental diet alone (5) or elemental diet followed by surgery (2). All 5 patients treated with Vivonex alone relapsed, while those who received Vivonex followed by surgery did well. Studies using TPN and bowel rest report an overall success rate of 35% (Elson et al. (1980), Muller et al. (1983), Ostro et al. (1985)). Thus, nutritional therapy should generally be considered as an adjunct to surgery in such cases. The benefits of an initial trial of elemental diet therapy include the avoidance of the costs and risks of prolonged TPN; improved nutritional status, thereby theoretically reducing the complications related to surgery in a debilitated patient; and avoidance of the potential risks of prolonged high-dose steroids.

Short Bowel Syndrome. Severe Crohn's disease involving the small bowel may result in anatomically (multiple resections) or functionally insufficient bowel. Such patients are unable to maintain adequate nutrition on a normal diet orally. It should be noted that a partially functional bowel of between 40 and 60 cm is all that may be required to avoid TPN-dependency. Elemental diets require little digestion or pancreatico-biliary function, and are well suited for the patient with a short gut. Experience with pediatric patients suggests that continuous infusion of an elemental diet enhances collaboration in comparison with bolus naso-gastric feedings (Seidman (1990)).

TABLE VI. Potential Uses of Elemental Diet in Crohn's Disease

Induction of remission
Reversing growth failure and malnutrition
Stricture and fistula management
Steroid dependent/resistant patients
Short bowel syndrome
Preoperative preparation
? Improving prognosis: Maintenance of remission

Steroid Dependent/Resistant Patients. Le Quintrec et al. (1987) noted in an uncontrolled study that seven of nine steroid-dependent adult patients with Crohn's disease achieved remission with an elemental diet, five of whom remained in remission without steroids for a follow-up of 6 to 16 months. In the same report, only four of ten steroid-resistant patients entered into sustained remission with nutritional therapy. In two steroid-resistant patients in whom ED failed initially, TPN did not improve symptoms, and surgery was required. An uncontrolled trial of TPN in severe, steroid-resistant Crohn's disease demonstrated a rapid and significant improvement in 90 per cent of cases (Lerebours et al. (1986)).

Our experience in pediatric Crohn's disease has been that ED therapy is of substantial benefit in steroid-dependent patients, particularly if growth failure or malnutrition is present. However, the efficacy of

nutritional therapy, whether enteral or parenteral, is less effective in those steroid-dependent cases principally involving the colon and/or perineum (Teahon and Levi (1989)). A trial of ED therapy in cortico-dependent patients is definitely worthwhile before considering additional immunosuppression or surgery. For those patients who are corticoresistant, nutritional therapy (TPN or elemental diet) should also be considered.

Maintenance of Remission. A variety of diets have been proposed in an attempt to maintain remission in IBD, usually without proven benefit (Levi (1985)). Controlled studies have not supported a role for a "low residue" diet, nor for a "high fiber-low refined sugar" diet (Alun Jones et al. (1985), Heaton et al. (1979), Levenstein et al. (1985), Ritchie et al. (1987)). Although nutritional therapy is an effective method of inducing remission in Crohn's disease, relatively little information is available regarding its use for the maintenance of long-term remission. Most reports have suggested that the majority of patients on TPN relapse promptly when they return to a normal diet (Muller et al. (1983)). Our randomized trial of elemental diet versus prednisone as primary treatment of Crohn's disease in children revealed similar rates of induction of remission by 3 weeks (Seidman et al. (1986)). However, the relapse rate over the next 6 weeks was higher for those patients who had completed the dietary therapy as compared to those still on steroids. Long-term remission of pediatric CD patients utilizing an oligopeptide solution chronically has been reported by Navarro et al. (1982). However, relapse promptly occurred once the elemental diet was discontinued. More recently, we examined the effect of chronic intermittent elemental diet and bowel rest (4 months/year) on growth and disease activity index in adolescents with Crohn's disease (Belli et al. (1988)). Patients treated with Vivonex had a significantly lower Crohn's disease activity index and required less prednisone compared to controls. Too few patients were studied to draw conclusions regarding relapse rates. A multicentered Canadian trial is now underway to evaluate the effect of chronic intermittent elemental diet therapy on long term maintenance of remission.

Hunter and colleagues (1985) have provided provocative evidence that the exclusion of specific foods on the basis of clinical intolerance improves the clinical course of Crohn's disease dramatically. An elimination diet was used subsequent to the induction of remission of acute Crohn's disease using an elemental diet (Alun Jones et al. (1985), (1987)). An oligo-antigenic diet was then initiated, supplemented initially by Vivonex, while foods were introduced in a planned sequence every few days. The adverse reactions to foods encountered apparently resembled the symptoms of the underlying IBD. One other group (Teahon and Levi (1989)) has reported success with this regimen, and also noted that grains, meat, and dairy products head the list of offending foods. Although these results are certainly very encouraging, double-blind food challenges and controlled trials are needed before this regimen can be recommended. The success of any exclusion diet also depends upon the assistance of a dietician to evaluate the adequacy of the diet.

A Scientific Basis For The Nutritional Management of IBD

Encouraging results using enteral nutrition as primary therapy for acute Crohn's disease (Table IV) have stirred the controversy regarding the role of diet in the management of IBD. Irregardless of one's position for or against, the very fact that TPN and elemental diets are effective in selected cases is of considerable interest in terms of theories on the etiology of IBD.

The mechanisms by which an elemental diet improves disease activity in Crohn's disease are unknown. The beneficial effects have been generally ascribed to "bowel rest" and/or improved nutrition. Simply stated, the rationale for the use of "bowel rest" in the management of Crohn's disease is to allow the inflammatory lesions to heal while the bowel is rested. In fact, clinical and experimental studies have shown that bowel rest using TPN or elemental diets results in mucosal hypoplasia and loss of brush border enzymes (Dowling (1967), Guedon et al. (1986), Levine et al. (1985), Morin et al. (1980), Nelson (1981)). A large number of factors (Table VII) contribute to the adaptive response associated with bowel rest. Probable mechanisms include the fact that elemental diets are absorbed in the proximal small bowel, contain very little fat, alter gut hormone and pancreatico-biliary secretions (normally trophic for the small bowel mucosa), and influence gut mucosal metabolism, blood flow and motility (Seidman (1989)).

TABLE VII. Hypothetical Mechanisms of Action of TPN or Elemental Diet in the Management of Crohn's Disease.

Gut Adaptive Response to Bowel Rest
- Decreased gut metabolic activity
- Altered motility, blood flow
- Induction of distal bowel atrophy
- Decreased pancreatico-biliary secretion
- Altered gut hormones/trophic factors
- Essential fatty acid deficiency

Nutritional Effects
- Improved nitrogen/caloric intake
- Correction of micronutrient deficiencies (vitamins, trace elements)
- Decreased enteric losses (protein, trace elements)
- Altered fat and fibre intake

Immunologic Effects
- Decreased antigen (dietary, bacterial) permeability
- Altered fecal flora
- Improved cell-mediated immunity
- Decreased gut lymphocyte recirculation owing to diminished lymphatic flow
- Decreased lymphocyte losses via gut
- Altered local synthesis of inflammatory mediators (↓ linoleic acid)

The presence of fat in the diet also has important trophic effects on intestinal adaptation, and may abrogate the atrophy normally associated with "bowel rest" (Levine et al. (1985), Morin et al. (1980, 1982)). Essential fatty acid defiency has recently been shown experimentally to induce reversible intestinal atrophy (Hart et al. (1988)).

Whatever the mechanisms involved in the adaptive response to bowel rest, it remains controversial as to whether Crohn's disease patients respond to the bowel rest or to improved nutrition. Although bowel rest appears to benefit certain patients, no studies have directly compared isocaloric but different diets (elemental vs complete, defined formula diet) head on, without steroids. Greenberg et al (1988) recently reported the results of a controlled trial in which patients with steroid-resistant Crohn's disease were randomly assigned to TPN, enteral nutrition with a non-elemental formula, or parenteral nutrition with an oral diet. Remission rates were similar in the 3 groups, suggesting that bowel rest was not essential to inducing remission in refractory Crohn's disease. Duration of remissions was not reported.

Equally controversial is whether the improved clinical course of Crohn's disease treated by nutritional means is merely due to the enhanced provision of calories and specific nutrients. To resolve this point, the long-term course of nutritional support alone versus isocalorically fed, but conventionally treated (steroids, salazopyrine) IBD patients will have to be compared. No such randomized, controlled trial has been carried out. The hypothetical role of various dietary components in altering bowel inflammation are summarized in Table VII, and reviewed in detail elsewhere (Seidman (1989)).

Another potential mechanism of action of nutritional therapy is that both TPN and elemental diets remove dietary antigens from the gut lumen. Excessive permeability to luminal antigens (bacterial or dietary) resulting from chronic inflammation (Seidman et al. (1986b)) could play a role in the perpetuation of the immune mediated lesions (Seidman and Walker (1988)).

Improvement of abnormal intestinal permeability in active Crohn's disease has been demonstrated in patients treated with an elemental diet (Sanderson et al. (1987)). Restoration of an intact mucosal barrier, thus preventing excessive macromolecular antigen uptake, appears to be another beneficial effect of ED therapy. Abnormal antigen uptake, along with a local immunoregulatory defect, may act in concert to fuel the chronic mucosal inflammation in Crohn's disease (O'Morain et al. (1981) (1987)).

The question remains as to which luminal antigen, if any, can induce or maintain the chronic inflammation characteristic of IBD. Increased IgG and IgA antibodies to cow's milk antigens have been reported in patients with IBD (Falchuk and Isselbacher (1976), Jewell and Truelove (1972), Wright and Truelove (1965)). Our recent studies have failed to demonstrate altered peripheral T-cell activation to casein or β-lactoglobulin (β-Lg) in young Crohn's disease patients (Gurbindo et al. (1988)). However, Biancone et al. (1987) demonstrated preferential responses of lamina propria lymphocytes to β-Lg as compared to autologous peripheral mononuclear cells, supporting the concept that modulation of cell-mediated responses to luminal antigens occurs locally in gut-

associated lymphoid tissues, leading to a preferential, intestinal response. It remains to be established whether local mucosal lymphocytes, reactive to specific common dietary antigens, contribute to the induction or maintenance of the chronic intestinal inflammation in IBD.

Perhaps the most provocative evidence to date suggesting that dietary factors play a role in the exacerbations of Crohn's disease is the report of successful maintenance of long-term remission in the large group of patients treated only with a specific food exclusion diet (Alun Jones et al. (1985), (1987)).

Other potential immune mechanisms of action of elemental diet or TPN in active Crohn's disease include alterations in fecal flora, reduced gut lymphocyte losses and improved cell-mediated immunity (Table VII). An attractive, but untested hypothesis concerning the effect of elemental diets in IBD is that the restricted lipid intake might alter the local synthesis of inflammatory mediators such as ecosanoids (Donowitz (1985), Rask-Madsen et al. (1984)), as reviewed recently (Seidman (1989)).

Eicosapentanoic acid (EPA), a polyunsaturated fat found in large quantities in fish oil, competes with arachidonic acid, thereby reducing the production of inflammatory mediators. Experimental studies have demonstrated that dietary lipids - particularly polyunsaturated fatty acids - modulate leukotriene synthesis (Lee et al. (1985), Lokesh et al (1988)). One pilot study suggests that EPA supplementation resulted in improved clinical course and histology of patients with ulcerative colitis (O'Morain (1987)). A reduction in dietary fat intake has also been shown to dramatically improve the expression of autoimmune disease in animal models (Morrow et al. (1986)). Transplanted animals maintained on an essential fatty- acid-deficient diet have been shown to prevent renal allograft rejection (Schreiner et al. (1988)). This treatment appears to result in marked depletion of activated local macrophages, possibly resulting from a relative lack of arachidonate metabolites.

These exciting new approaches to the nutritional therapy of immune-mediated disorders may assist us in developing new treatments for IBD, as well as shedding some light on the etiology and pathogenesis of these disorders.

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TOTAL PARENTERAL NUTRITION IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE: AN UPDATE

JOEL B. MASON, M.D. AND IRWIN H. ROSENBERG, M.D.
USDA Human Nutrition Research Center on Aging
at Tufts University
711 Washington Street
Boston, Massachusetts 02111, USA

ABSTRACT. Malnutrition is a common feature of inflammatory bowel disease especially in hospitalized patients. Numerous studies emphasize the critical importance of nutritional restoration in achieving clinical remission. In some patients nutritional repletion and maintenance cannot be accomplished by oral or enteral routes of administration and parenteral nutrition support is required. In selected patients with malnutrition, a 7-10 day period of preoperative intravenous nutrition can be expected to decrease surgical morbidity. When parenteral nutrition is used as primary therapy in patients with acute Crohn's disease in exacerbation, in-hospital remission rates between 40 and 80% can be expected. Clinical responses are most likely in patients with small bowel disease or a combination of small and large bowel disease; total parenteral nutrition has a minor and only supportive role in the management of patients with colitis in the absence of small intestinal disease. Temporary closure of enterocutaneous fistulae in Crohn's disease can be expected in about 30% of patients. Favorable responses and restoration of growth are observed in growth-retarded children who are treated with total parenteral nutrition. Increasingly, home parenteral nutrition has been employed, especially in patients with extensive and unresectable disease and in patients with previous extensive small bowel resections. The experience indicates that such home parenteral nutrition can be carried out with reasonable social rehabilitation although complications and re-hospitalization are common. Total parenteral nutrition is an important element in the armamentarium of management of inflammatory bowel disease but its costs and complications demand that this treatment modality be used when nutritional restitution and maintenance cannot be accomplished more safely and reliably by enteral means.

Introduction

Early descriptions of inflammatory bowel disease (IBD) cite malnutrition as a prominent feature. Protein and calorie deficits are among the most commonly seen nutritional complications of inflammatory bowel disease. Caloric deficit usually presents as weight loss in an adult. In children with IBD it frequently presents as growth retardation in the form of stunted growth (low height for age), wasted

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growth (low weight for height) or delayed puberty (Kirschner et al, 1978). Protein deficits are reflected by anthropometric and biochemical data demonstrating contraction of the major protein-containing compartments in the body (eg: skeletal muscle, visceral organs, serum) with accompanying impairments in the functions associated with those structures. Hypoalbuminemia, as well as decreased body weight have been shown to be associated with increased morbidity and mortality among inpatients (Braga et al, 1987).

Energy and Protein Needs

Protein and energy malnutrition are among the most commonly seen forms of malnutrition in inflammatory bowel disease and various parameters which reflect protein-energy nutriture such as body weight, serum albumin, total lymphocyte count and delayed skin hypersensitivity have all been shown to serve as predictors of in-hospital morbidity (Braga et al, 1987; Smale et al, 1981). Caloric requirements, as a general rule, increase in the setting of fever and sepsis. Each centigrade degree elevation in temperature over normal increases the basal metabolic expenditure by approximately 13%. Sepsis will typically increase the BMR by 1.5-2.0 times (Long et al, 1979). However, in the absence of fever or sepsis, patients with chronic inflammatory bowel disease do not have a remarkable increase in caloric expenditure (Barot et al 1982; Chan et al, 1986).

Protein requirements are frequently increased in active inflammatory bowel disease. There is an increase in the loss of protein through the inflamed bowel mucosa. This has been demonstrated by recovery of $^{51}CrCl_3$ in the stool after intravenous injection of the radiodligand as well as by intestinal clearance of alpha-1-antitrypsin (Florent et al, 1981). The clearance of antitrypsin is proportional to the Crohn's disease activity index (Meyers et al, 1985). At least one study showed that as many as 76% of Crohn's patients have excessive losses of protein in the stool (Beeken, 1975). An increase in protein turnover proportional to the increase in the erythrocyte sedimentation rate also occurs in patients with active inflammatory bowel disease (Powell-Tuck et al, 1984), contributing to the increased nitrogen losses incurred through protein-losing enteropathy and gastrointestinal bleeding.

The Rationale for Nutritional Management

The importance of correcting nutritional deficiencies in patients with inflammatory bowel disease cannot be overemphasized. In addition to the primary benefits of correcting nutritional deficits in regard to growth, strength, and sense of well-being, there are major benefits to be achieved by correcting secondary manifestations of nutritional deficiencies on other systems: the anemia related to iron and folate deficiency, for example, is common and often debilitating.

The functional integrity of the immune system is clearly impaired in protein-calorie malnutrition (Bistrian et al, 1975). Furthermore, the rate of collagen deposition at the site of experimentally-induced cutaneous wounds is impaired in malnourished subjects (Haydock et al, 1986). Protein-calorie malnutrition and deficiency of micronutrients also have documented effects on gastrointestinal function and structure.

The patient with inflammatory bowel disease who becomes significantly malnourished, therefore, may enter a vicious cycle where the secondary effects of malnutrition on gastrointestinal function and structure may lead to a further increase in gastrointestinal symptoms and malabsorption, which further worsens nutrient balance.

Total Parenteral Nutrition

Total parenteral alimentation has been an important advance in the management of patients with severe inflammatory bowel disease. Some patients with significant nutritional defects, who require surgery, are treated with total parenteral alimentation prior to operation. Several studies in patients with inflammatory bowel disease and other gastrointestinal disorders emphasize that a period of preoperative total parenteral nutrition may be useful in reversing some of the immunologic and other abnormalities associated with malnutrition, and may be capable of reducing postoperative morbidity and mortality (Mullen et al 1978; Rombeau et al, 1982). Further work needs to be carried out, however, to determine more accurately which patients will benefit from perioperative TPN, and to investigate the nutritional parameters that should be followed to indicate adequate nutritional repletion prior to surgery. At present, we recommend preoperative total parenteral alimentation for approximately seven to ten days in patients with significant nutritional depletion. We are unaware of evidence that longer periods of preoperative nutrition support are justified.

Studies from a number of centers stress the role of total parenteral alimentation and bowel rest in the management of patients with inflammatory bowel disease that has not responded to conventional medical treatment with corticosteroids, sulfasalazine, and other measures (Sales et al, 1983). Various series indicate that 40-80% of patients with serious Crohn's disease who are poorly responsive to medical treatment will experience a decrease in symptoms during a three-to four-week period of total parenteral alimentation and bowel rest (Rosenberg et al, 1988). The retrospective experience with TPN and bowel rest in the treatment of severe exacerbations of ulcerative colitis is far less encouraging than that with Crohn's disease (Elson et al, 1980; Fischer et al 1973; Sales et al, 1983).

The question of whether parenteral nutrition and bowel rest offers a therapeutic advantage over the provision of nutrients via an enteral route continues to be a management issue in the treatment of acute exacerbations of inflammatory bowel disease. Controlled trials of individuals with colitis alone (Dickinson et al, 1980; McIntyre et al, 1986), or with small bowel involvement (Lochs et al, 1983), have failed to show significant advantages of bowel rest over continued enteral nutrition. Greenberg et al (1988) were particularly interested in examining this issue among patients with Crohn's disease who were refractory to conventional outpatient medical therapy. Patients in three medical centers were randomized in a prospective fashion to three groups which received either TPN alone, a defined enteral supplement via a nasogastric tube that was isocaloric and isonitrogenous to the TPN group, or an ad lib hospital diet supplemented with a modest amount of nutrients delivered by peripheral parenteral nutrition. After three weeks of medical and nutritional therapy the substantial declines that

were observed in disease activity were not significantly different in three groups. These studies suggest that the provision of TPN and bowel rest during acute exacerbations of inflammatory bowel disease does not provide a therapeutic advantage over the administration of nutrition support by an enteral route. The study might also be interpreted as demonstrating that the salutory affects of providing adequate amounts of nutrition are more critical in determining the clinical outcome of treatment than whether or not bowel rest acompanies the nutrition. It remains unclear which subpopulations of such patients, if any, would receive additional benefit from the parenteral route. The judgment of whether to proceed with parenteral nutrition and bowel rest in a particular patient should therefore include thoughtful consideration whether such a therapeutic route will indeed provide advantages over the enteral route, particularly in view of the additional costs and complications associated with parenteral therapy. One should also consider that glutamine, which is not present in commercially available TPN, is a preferred energy source for the intestine and, when provided as a supplement to animals with intestinal injury, facilitates the healing process (Jacobs et al, 1988).

TPN for Crohn's Fistulae

Enterocutaneous fistulae are a common and debilitating complication of Crohn's disease and do not respond well to conventional medical treatment. Initial reports of total parenteral alimentation and bowel rest were optimistic; some patients experienced a permanent closure of these fistulae (Greenberg et al, 1981; MacFadyen et al, 1974; Mullen et al, 1978). More recent studies, however, show that total parenteral alimentation is less effective in causing permanent closure of fistula, with such closure occurring in only 30% of patients (Bos et al, 1981; Elson et al, 1980). Some patients with Crohn's disease who have been treated surgically may develop postoperative enterocutaneous fistulae that tend to heal better with total parenteral alimentation and bowel rest; the more optimistic reports may have been describing patients with this type of fistula rather than those caused primarily by transmural inflammation due to Crohn's disease. Although fistulae due to Crohn's disease do not regularly close with total parenteral alimentation, it should be emphasized that patients with fistulae are often severely nutritionally depleted because of inability to eat and because of nutrient losses through the fistula track. A period of preoperative nutritional support prior to resection of the affected bowel is often useful.

The small intestinal mucosa undergoes both structural and functional atrophy during a course of TPN and bowel rest (Guedon et al, 1986): the activity of brush border saccharidases and aminopeptidases as well as the length of microvilli decrease significantly after as little as 3 weeks of TPN. The reinstitution of enteral feeding in a patient who has been on a course of TPN and bowel rest should be done gradually in deference to this atrophy. Small meals, occasionally requiring the use of defined formulas which contain oligomeric and monomeric forms of sugars and proteins, are appropriate transitional feedings which will minimize symptoms while the patient recovers the functional integrity of his mucosa. Most of the enzyme activities recover within 10 days after

resumption of an enteral diet (Guedon et al, 1986).

Home Parenteral Nutrition (HPN)

Long-term home parenteral alimentation has been used to meet nutrient requirements of patients with Crohn's disease who have had extensive intestinal resection resulting in the short bowel syndrome (Fleming et al, 1980). Such patients can be safely and effectively maintained on home total parenteral alimentation, allowing nutritional and social rehabilitation in some of these patients. Such patients can do well for extended periods of time at home (Kushner et al, 1986) although preliminary data suggests that up to one-quarter may require rehospitalization during the first year because of TPN-associated complications (Howard et al, 1989). Study of such individuals on long-term home total parenteral nutrition has provided examples of micronutrient deficiency syndromes, such as vitamin E, biotin, selenium, and molybdenum deficiency (Abumrad et al, 1981; Howard et al, 1982; Johnson et al, 1981; Mock et al, 1981). In addition, metabolic bone disease consisting of both osteoporosis and osteomalacia appears in this patient group, although the cause of these disturbances in bone and mineral metabolism remains controversial (Klein et al, 1980; Shike et al, 1980).

It was recently emphasized that such patients are susceptible to formation of gallstones, presumably because the lack of stimulation by food results in stasis in the gall bladder, and because many of these patients have had ileal resections with depletion of bile salts and the related tendency toward lithogenic bile (Messing et al, 1982; Rosensweig et al, 1969; Cano et al, 1986). An occasional small meal in such long-term TPN patients might decrease biliary complications by promoting occasional contractions of the gallbladder although this has not yet been demonstrated. Inflammatory bowel disease patients frequently develop minor, and occasionally marked, elevations of serum aminotransferases, alkaline phosphatase and bilirubin over the initial six weeks of TPN therapy (Bengoa et al, 1985). These abnormalities usually resolve promptly once the TPN has been discontinued and frequently even if the TPN is continued (Baker et al, 1987). Of considerable concern, however, is the chronic liver disease that occasionally develops in patients on long-term TPN. Recent reports describe steatonecrosis in a rare patient on long-term total parenteral nutrition (Craig et al, 1980); children on long-term TPN often develop severe cholestasis, which may lead to portal hypertension and cirrhosis (Dahms et al, 1980).

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5-ASA IN ULCERATIVE COLITIS

Stephen B. Hanauer, M.D.
University of Chicago Medical Center
Department of Medicine
Section of Gastroenterology
5841 So. Maryland Avenue
Chicago, IL 60637

Abstract

5-ASA, the active moiety of sulfasalazine, offers the advantages of "targeted" delivery of a mucosal anti-inflammatory agent with equal or enhanced therapeutic potency and a markedly reduced side-effect profile in IBD. Although the mechanism(s) of action remain uncertain, the compound can be used as a model to study both anti-inflammatory mediators and intestinal delivery systems for alternative non-systemic therapies.

Introduction

Historically, and to the present, sulfasalazine has been a first-line agent for the treatment of inflammatory bowel disease (1). Originally developed to provide a sulfa and salicylate conjugate to the connective tissue of the colon in patients with ulcerative colitis (2), it has recently been demonstrated that sulfasalazine acts as a carrier molecule for the delivery of 5-aminosalicylic acid (5-ASA, mesalazine, mesalamine) into the colon after bacterial azo reductase activity frees 5-ASA from the sulfapyridine moiety (3).

While both sulfasalazine and 5-ASA have anti-inflammatory properties in both animal models and in human inflammatory bowel disease, the independent action of 5-ASA has implied that the salicylate component is the active portion of sulfasalazine (4). Certainly, it has been demonstrated that the sulfa component contributes to the majority of the adverse effects attributed to sulfasalazine (3), however, aside from rectal instillation of 5-ASA, there has never been evidence that, on an eqimolar basis, 5-ASA has superior therapeutic effects compared to sulfasalazine. Furthermore, while sulfasalazine has been shown to be effective in a dose-dependent manner for the treatment of mild to moderate acute ulcerative colitis and in maintenance of remission in quiescent ulcerative colitis (5), similar, satisfactory or compelling dose-response studies have not, as yet, been completed for oral 5-ASA preparations.

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Pharmacology

5-ASA is a zwitter ion which, in an unprotected form, is rapidly absorbed from the proximal gastrointestinal tract (6). Hence, in order to deliver 5-ASA to distant sites along the digestive tract it is necessary to provide delivery systems which either conjugate 5-ASA to a carrier molecule (similar to sulfasalzine) or coat the molecule to delay luminal release and absorption.

5-ASA is metabolized by N-acetylation primarily within the gut epithelium (7), but secondarily by luminal bacteria or the liver. Once acetylated, 5-ASA is rapidly excreted into the urine. 5-ASA is found within the serum primarily in the acetylated form with a ratio of acetylated to non-acetylated 5-ASA approximately 5 to 1.

5-ASA is poorly soluble and unstable in the presence of water and is rapidly oxidized (6). Therefore, in order to provide a stable enema preparation, 5-ASA must be suspended with preservatives and anti-oxidants (8).

Mechanisms of Action

5-ASA exhib its anti-inflammatory activity in the gastrointestinal tract, although the exact mechanisms have not been fully elucidated. 5-ASA is the 5-amino derivative of salicylic acid and is structurally related to other salicylates. However, whereas other salicylate derivatives with potent cyclooxygenase-inhibiting properties have been recognized to aggravate the inflammation in inflammatory bowel disease (4, 9), both the 5-amino (mesalamine) and 4-amino (PAS) derivatives have demonstrated anti-inflammatory activities suggesting that the amino group alters the determinant of GI anti-inflammatory activity (8).

5-ASA inhibits both the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism (reviewed in 4, 6, 8). It has been suggested that the more potent lipoxygenase inhibition shifts arachidonic metabolism into the "cytoprotective" prostaglandin system (9-11). In addition, 5-ASA has the ability to scavenge oxygen-free radicals (12), inhibits the production of platelet activating factor (13) and other mediators of inflammation (8), and inhibits lymphocyte function (14). The exact mechanism of action in inflammatory bowel disease has not been identified.

Preparations

5-ASA is available in a variety of delivery systems throughout the world. Pharmaceutical companies and national regulatory agencies differ in the marketing and approval of specific products such that there is a variety of preparations according to individual countries.

TOPICAL

5-ASA is stable in a wax matrix making suppository preparations a stable and effective preparation for rectal application. Doses range from 250 mg to 1000 mg. Suppositories of 5-ASA have been demonstrated to migrate to approximately the recto-sigmoid junction, approximately 15 or 20 cm (15).

Rectal suspensions (retention enemas) of 5-ASA are available in doses of 1000 to 4000 mg in volumes of 60 to 100 ml (Table 1). These volumes have provided adequate delivery to the splenic flexure in the majority of patients with active ulcerative colitis (16, 17). The absorption from rectally administered 5-ASA has been small, approximately 10% for the suppositories (18) and 20% of the administered dose for the retention enemas (6, 19). Absorption is increased in patients who retain the enemas for longer periods of time and in patients with less active disease (6). Absorption also is reduced at acetic pH in both the rectum and in intestine (6). Therefore, most commercially available enemas are slightly acetified (pH 4-6) (8).

ORAL

Oral delivery systems of 5-ASA may be divided into carrier systems or delayed-release formulations.

Azo-Prodrugs. After the recognition that 5-ASA was an effective moiety of sulfasalazine, Sidney Truelove from Oxford and the Pharmacia drughouse envisioned a double-molecule of two 5-ASA components linked by the same azo bond in sulfasalazine (20). Olsalazine (formerly azodisalicylate) undergoes successful transit through the stomach and small intestine with only minimal absorption of the parent molecule allowing bacterial azo-reductase activity to liberate 5-ASA molecules into the colon (21). The parent molecule has minimal pharmacologic properties (22), although olsalazine has been shown to produce concentration-dependent small intestinal secretion (23).

Other prodrugs have 5-ASA coupled via an azo-bond to p-amino-benzoic acid, p-aminobenzoylglycine and p-aminobenzoyl-ß-alanine. These compounds have undergone limited clinical testing, but appear to be effective when similar concentrations of 5-ASA are released into the large bowel (24).

Delayed-Release Preparations. Asacol^{R}, 5-ASA coated with Eudragit-S, provides 400 mg of 5-ASA (similar to the molar quantity in 1 gm of sulfasalazine) within an acrylic resin shell designed to breakdown at approximately pH 7 (25). This was initially developed to provide colonic release of 5-ASA in a manner similar to sulfasalazine, however, absorption studies have demonstrated up to 40% absorption, primarily from the small intestine (24, 26).

Claversal^{R} (Mesasal^{R}/Salofalk^{R}) provides 250 mg (and eventually 500 mg) of 5-ASA in a buffered, delayed-release tablet coated with Eudragit-L, a polymer which dissolves at pH 6 correlating with the

distal small bowel (27). Again, absorption studies have demonstrated a higher proportion of small intestinal absorption compared to the azo-bond compounds (26), however, gamma-scintigraphy studies demonstrate that the majority of the 5-ASA is delivered throughout the colon (28).

Pentasa® is a sustained-release preparation of 5-ASA encapsulated into microgranules of ethylcellulose. This preparation releases 5-ASA in time- and pH-dependent manner throughout the gastrointestinal tract (29). Originally formulated to release 50% of 5-ASA into the small intestine, absorption studies have revealed approximately 50 to 80% of the 5-ASA excreted in the feces (24, 26).

Clinical Trials

TOPICAL THERAPY

Azad Khan (30), Klotz (31), and Van Hees (32) demonstrated the topical effectiveness of 5-ASA in enema and suppository form comparable to oral or rectal sulfasalazine and superior to sulfapyridine. Subsequent, placebo-controlled studies have demonstrated the efficacy of 500 mg suppositories administered b.i.d. (33) or t.i.d. for acute ulcerative proctitis and 500 mg suppositories nightly for the maintenance of remission in ulcerative proctitis (24).

Large, multi-center, placebo-controlled studies of 5-ASA enemas reveal the effectiveness of 4 gm 5-ASA enemas in 60 ml suspensions for acute ulcerative colitis (19) and, a recent dose-ranging study suggests that there is no significant dose-response between 1 and 4 gm 5-ASA suspended in 100 ml volumes (34).

In addition to the efficacy of 5-ASA enemas as single agents for active left-sided colitis, the high dose (4 gm) 5-ASA enemas provide superior efficacy to hydrocortisone enemas (35) and are useful in refractory patients who have not responded to sulfasalazine, topical steroids, or systemic steroids (17). As might be expected from the experience with oral delivery of 5-ASA via sulfasalazine, maintenance therapy is necessary. It remains uncertain whether patients who respond to topical 5-ASA will remain in remission after substitution of an oral 5-ASA preparation.

There is some evidence that topical 4-ASA may also be effective in acute ulcerative colitis, although the dose-effect needs to be clarified because of some evidence of superiority of a 2 gm dose compared to 4 gm enemas (36, 37).

AZO-LINKED PREPARATIONS

Olsalazine (Dipentum®, Pharmacia) has been tested, most extensively, as a maintenance agent in quiescent ulcerative colitis (38, 39). Here the drug appears to be as effective as sulfasalazine with a reduction in overall adverse effects. A small, placebo-controlled, dose-ranging study in acute ulcerative colitis has demonstrated efficacy in mild to moderate ulcerative colitis in doses between 1.5 and 3 gm daily (40). Up to 15% of patients who initiate therapy with olsalazine (38) may

notice a transient increase in diarrhea, hence, a gradual dose-titration will probably be advisable when initiating therapy in patients with active disease. Further dose-ranging studies are needed in active ulcerative colitis.

MESALAMINE (MESALAZINE)

Asacol®, 800 mg or 2.4 gm, has been tested against sulfasalazine, 2 gm daily, in a small, four week trial of active, mild to moderate ulcerative colitis. Although the trial was too small to confirm a statistical dose-response, there was a numerical advantage to the higher dose with 43% of those taking 2.4 gm daily achieving "symptomatic remission" (41). In a placebo-controlled U.S. study at the Mayo Clinic, Asacol at a dose of 1.6 gm daily (comparable to 4 gm of sulfaslaazine) was not statistically superior to placebo, however, a 4.8 gm dose did demonstrate statistical improvement in these patients referred to the tertiary center (42). Maintenance studies with Asacol have confirmed comparable results to sulfasalazine in doses between 800 mg and 1.6 gm daily (43, 44).

Claversal®/Mesasal®/Salofalk®, in clinical trials with doses of 1.5 gm daily in active ulcerative colitis and 750 mg daily in quiescent disease compared to sulfasalazine 3 and 1.5 gm daily, have demonstrated comparable efficacy with a marked reduction in the side effect profile (45, 46). Even patients who were tolerant of sulfasalazine had fewer reports on adverse effects when randomized to this 5-ASA preparation.

A large, multi-center study compared Claversal to placebo in patients with "inactive" Crohn's disease (CDAI < 150) by reducing the number of patients who relapsed over a one year period of time (47). This very exciting maintenance study needs to be confirmed with stratified analyses for patients with different disease locations and post-operative status.

Pentasa®, at a dose of 1.5 gm daily, has been effective in maintaining remission in ulcerative colitis compared to 3 gm of sulfasalazine (48). A large, U.S. multi-center, placebo-controlled, dose-ranging study compared Pentasa at doses of 1, 2, and 4 gm daily to placebo over eight weeks (49). Both the 2 gm and 4 gm daily doses were superior to placebo with numerical (but not statistical) superiority of the 4 gm dose in the time to response and in histologic improvement.

Open-label studies of Pentasa have been optimistic (50), if not convincing, as treatment for mild to moderate Crohn's disease and the results of controlled studies in active and quiescent disease are anxiously awaited.

Adverse Effects

While it has been difficult to demonstrate improved efficacy of 5-ASA products (aside from topical therapy) compared to sulfasalazine, there is a definite advantage in the side effect profile (24). Less than half as many patients treated with oral 5-ASA products complain of side effects compared to sulfasalazine, and 80% of patients who are

intolerant of sulfasalazine can tolerate oral 5-ASA in either coated or azo-linked preparations (51). Nevertheless, a small percentage of patients (20%) may have identical side effects from 5-ASA that occurred with sulfasalazine. Sperm abnormalities are reversed by substitution of oral or topical 5-ASA for sulfasalazine (52) as are most "allergic" phenomena (24). Worsening of colitis may be salicylate-related and is one adverse effect that is not overcome by 5-ASA substitution in either topical or oral preparations. Up to 15% of patients who are treated with olsalazine may develop a transient worsening of diarrhea that is usually overcome as the colitis heals and the colon adapts to increased fluid loads (24) where reports of pancreatitis (53) and pericarditis (54) have been noted with both topical and oral 5-ASA therapy. Although there is a potential for salicylate-induced nephrotoxicity, to date, there have been no confirmed reports of this complication.

Future Considerations

The recognition that 5-ASA is an active moiety of sulfasalazine has opened the door for additional basic and clinical research initiatives. The mechanism(s) of 5-ASA activity in ulcerative colitis and (potentially) in Crohn's disease need to be clarified. The concept of "targeted" delivery of a topically (mucosal) active agent needs to be tested in patients with specific disease locations (e.g., ileitis, ileo-colitis, left-sided colitis). Optimal dose-ranging studies need to be performed to justify dosage recommendations for both acute and quiescent ulcerative colitis. It is also uncertain whether patients with left-sided colitis who respond to topical therapy can be maintained with oral delivery of 5-ASA. The adjuvant role in acute and refractory ulcerative colitis (and Crohn's disease) in conjunction with steroids and immunosuppressives needs to be studied and, finally, the role of 5-ASA in Crohn's disease needs much greater clarification.

Ultimately, the concept of "targeted delivery" may be applied to other agents such as non-systemic corticosteroids and even other immunomodulators. Thus, we expect the risk/benefit ratio for the treatment of inflammatory bowel disease to be favorably improved.

NEW SALICYLATES - ORAL

Product	Preparation	Dose	Delivery
Pentasa (Marion - US) (Ferring - Abroad)	Mesalamine encapsulated in ethylcellulose microgranules	250 mg	Time/pH release 30-55% urinary recovery
Asacol (Norwich-Eaton - US) (Tillots - UK)	Mesalamine coated with Eudragit-S	400 mg	Release at pH > 7 20-35% urinary recovery
Claversal/Salofalk (Smith Kline/Falk)	Mesalamine in sodium/glycine buffer coated with Eudragit-L	250, 500 mg	Release at pH > 6 25-45% urinary recovery
ROW-ASA (Reid-Rowell)	I. Mesalamine in enteric-coated compressed, coated with coteric opadry	250, 500 mg	Release at pH > 4.5 ~ 60% urinary recovery
	II. Mesalamine in enteric-coated tablet coated with Eudragit L100	250, 500 mg	Release at pH > 5 ~ 30% urinary recovery
4-ASA (Reed & Carnrick)	Enteric coated with Eudragit compound	500 mg	Time/pH release
Dipentum (Pharmacia)	Olsalazine (azodisalicylate)	250 mg	Two molecules of 5-ASA released into colon ~ 25% 5-ASA urinary recovery
Balsalazide (Brorek)	4-aminobenzoyl-B-alanine-5-ASA	500 mg	Inert carrier delivers 5-ASA into colon

RECTAL PREPARATIONS

Product	Preparation
ROW-ASA/Salofalk/Claversal	Enemas - 4gm/60ml buffered suspension pH 4.5
(Reid-Rowell - US) (Interfalk - Canada) (Smith Kline - International)	Suppository - 0.5gm/1gm
Pentasa (Marion - US) (Ferring - Abroad)	Enema - 1,2,4gm/100ml Buffered suspension pH 4.8
4-ASA	Enema - 2gm Na-4-ASA requires reconstitution

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5-ASA PREPARATIONS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

A.B.R. Thomson, M.D., PhD., F.R.C.P.(C), F.A.C.P.
Division of Gastroenterology
519 Robert Newton Research Building
University of Alberta
Edmonton, Alberta, Canada
T6G 2C2

ABSTRACT. The 'new salicylates' - topical and oral formulations of 5-ASA (5-aminosalicylic acid) - offer the potential advantage over sulfasalazine of targeted release of drug and a lower profile of adverse effects. These encapsulated or non-sulfa azo compounds have been shown to be superior to placebo and equivalent to sulfasalazine in the treatment of active ulcerative colitis and the maintenance of remission. Early evidence suggests that Claversal may also be beneficial for the maintenance of patients with Crohn's disease of the small intestine or colon, with even fewer side effects than in patients treated with placebo.

1. INTRODUCTION

1.1. Steroids

Glucocorticosteroids are useful for the treatment of acute ulcerative colitis (UC) and Crohn's disease (CD) [1,2]. For example, controlled randomized trials have demonstrated the clinical usefulness of adrenocorticoids ('steroids') in patients with active UC, including cortisone or prednisone taken orally [1,3-5], intramuscular ACTH (corticotropin) [5-15], or systemic steroids [3,8]. Combined systemic and local therapy is superior to systemic therapy alone, and systemic therapy does not increase the risk of perforation of the colon [16]. The superiority of alternate-day steroids is unproven for either efficacy or adverse effects (suppression of pituitary-adrenal axis) [17], except in overcoming growth retardation in children [18]. Corticotropin may be more effective than hydrocortisone in active UC, but adverse effects may also be more common [5].

Prednisone is also useful to treat CD of the ileum or ileum/colon [19]. In the American National Cooperative Crohn's Disease Study (NCCDS), prednisone was given in a dose of 0.25 to 0.75 mg/kg body weight up to a maximum of 60 mg daily over 4 months, with the dose adjusted to the clinical index of disease activity. Benefit was observed in patients with involvement of the ileum (ileum alone or ileum plus colon), but there were insufficient numbers of patients with Crohn's colitis to exclude steroids as a potentially useful form of therapy [19].

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Whereas rectal and oral steroids are remission-inducing agents, they are generally considered to be ineffective in maintaining remission in either UC or in CD, or to reduce recurrences after resection [19-23]. There appears to be no added benefit of combining sulfasalazine (SASP) with steroids in patients with active or inactive CD, and SASP has no steroid-sparing effect [23,24]. While it is generally considered that steroids have no role in maintenance therapy in CD or UC, recent evidence suggests that methylprednisone may be effective in the prevention of relapses for selected patients with CD in clinical remission who have altered laboratory tests [25].

It is well appreciated that major adverse effects may develop with steroid therapy. These effects are generally dose- and time-dependent [26-28]. For example, osteonecrosis ('avascular necrosis') is a serious complication of steroid therapy characterized by death of all of the cellular elements of bone [29].

1.2 6-MP, Azathioprine

Immunosuppressive agents such as 6-mercaptopurine (6-MP) and azothioprine may be useful to reduce the dose of steroids and to heal fistulae or perianal disease in patients with CD. However, bone marrow suppression, pancreatitis and the possibility of hematologic malignancies has limited its widespread use in patients who do not respond to other forms of therapy [30-36]. 6-MP may have some use as a remission-maintaining medication in CD [37,38].

1.3 Metronidazole

There are four controlled trials of metronidazole (MTZ) in UC: when MTZ suppositories are compared with placebo in chronic proctitis there was no benefit [39]. In severe active UC in hospitalized patients, MTZ is not useful as an adjunct to IV steroids [40]. In moderately acute UC, MTZ was inferior to SASP [41] but in a double-blind randomized trial of MTZ 0.6 g/day versus SASP 2 g/day, MTZ was superior to SASP in maintaining remission of UC for up to 1 year [42]. Furthermore, preliminary data suggests that MTZ may prove to play some role in the treatment of UC resistant to steroids [43].

MTZ is effective in the treatment of perianal CD [44]. If MTZ is successfully used for perianal disease and then is discontinued, the relapse rate is 72% as compared with 13% if the drug is maintained [45,46]. However, if MTZ was reintroduced after exacerbation, all patients once again improved. When MTZ 800 mg daily was compared with SASP 3 g in an 8-month double-blind crossover Swedish trial in CD [47], MTZ was clinically equivalent to SASP and superior in raising the hemoglobin concentration and lowering plasma orosomucoid. Patients with colonic CD may have done better than those with small bowel involvement, and no comment was made of the response of perianal disease. A major North American study of MTZ in CD has been reported in abstract form and confirms the superiority of MTZ over placebo in CD [48]. However, two other double-blind studies have not

reported a benefit of MTZ as compared with placebo [49,50] or cotrimoxazole [51].

Adverse effects of metallic taste, furred tongue, nausea and dark urine occur in 5-10% of patients treated with MTZ [52], and peripheral neuropathy is common [46,53,54] unless low doses are used [44]. A disulfiram-like reaction may occur when taken with ethanol, and MTZ may potentiate the effect of oral anticoagulants on the prothrombin time.

1.4 Cyclosporin

Cyclosporin A may be useful for the treatment of resistant CD and a response rate of approximately one patient in two has been reported in uncontrolled studies [55-58].

Brynskov et al [59] reported the effect of a 3-month treatment with low-dose cyclosporin (5 - 7.5 $mg.kg^{-1}.day^{-1}$) in 11 chronically active, therapy-resistant CD patients: clinical improvement occurred in approximately 3 patients in 4, depending upon which index of clinical activity was used. Nephrotoxicity was not a problem but 7 patients developed paresthesias.

In 12 patients with active CD and 12 with UC, Baker and Jewell [60] reported no adjunctive benefit of cyclosporin (initially 15 $mg.kg^{-1}.day^{-1}$ reducing to 7.5 $mg.kg^{-1}.day^{-1}$) to an intravenous regimen of corticosteroids. However, the finding of a rapid reversal of expression of Class II molecules on the inflammed epithelium raised the possibility of 'a therapeutic benefit over longer periods of time'. Such a long-term maintenance study is currently in progress in Canada in patients with CD.

1.5 Methotrexate

A randomized, open-label preliminary trial of methotrexate plus standard medications (corticosteroids, SASP, MTZ or previous 6-MP) used in patients with refractory UC or CD suggested that this folic acid antagonist with antimetabolite and anti-inflammatory properties may play a role in some patients not responsive to standard therapy [61].

2. SULFASALAZINE (SASP)

2.1 Pharmacology

The components of sulfasalazine (SASP, salicylazosulfapyridine, Azulfidine, Salazopyrin), sulfapyridine (SP)and 5-ASA (5-aminosalicylic acid) (Figure 1), are split at the diazo bond by enteric bacteria, with sulfapyridine acting simply as a carrier for 5-ASA to reach the colon (Figure 2). About 25% of SASP is absorbed from the upper gastrointestinal tract, with blood levels detectable in 1-2 hours, peaking in 3-4 hours and reaching a steady state within 24 hours [62-64]. The remaining SASP reaches the colon unchanged.

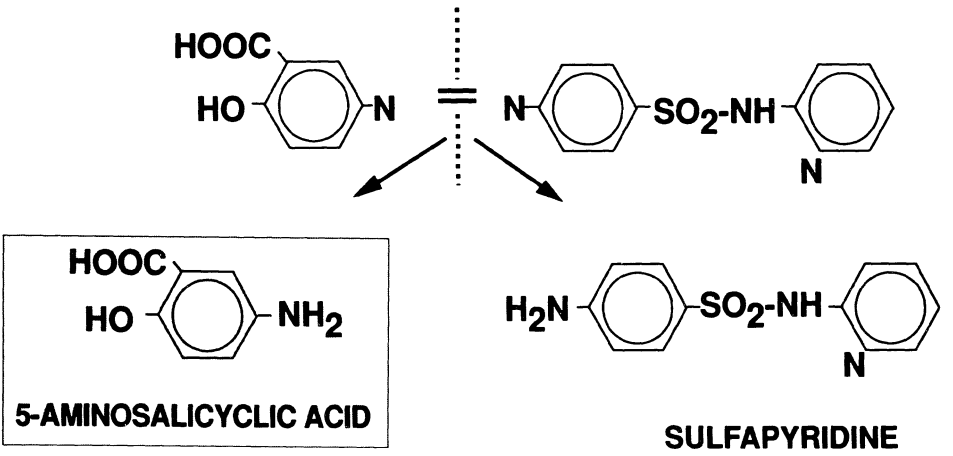
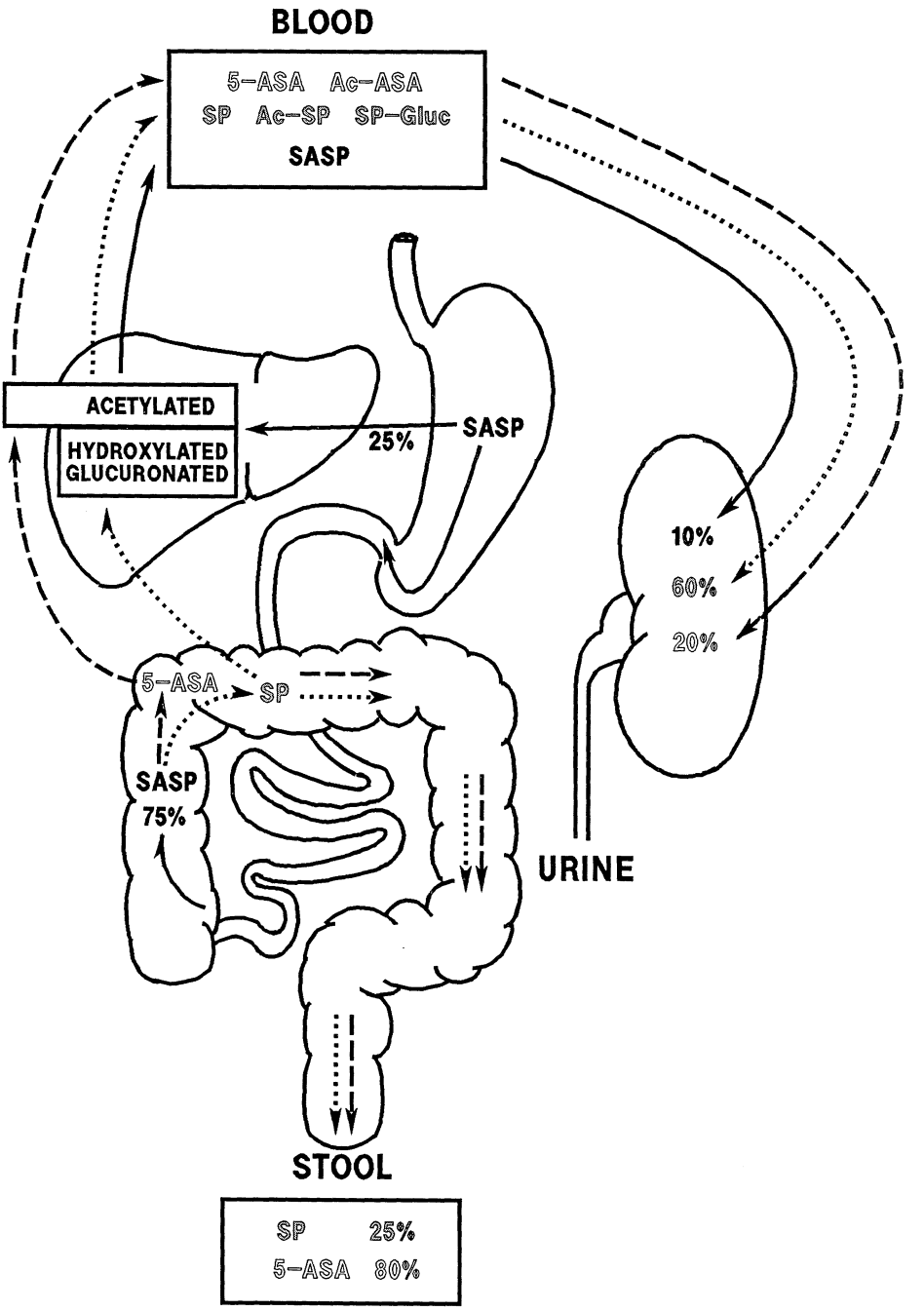


Figure 1. The components of sulfasalazine.

About one-quarter of orally administered SASP is absorbed intact in the small intestine and is either excreted unchanged in the urine, or undergoes an enterohepatic circulation. Were 5-ASA to be available for absorption in the upper intestine (which of course it normally is not), such absorption would proceed rapidly [65]. The SASP which passes down along the intestine enters the colon where it is broken down by intestinal bacteria which split the azo bond that joins the sulfapyridine (SP) and the 5-ASA moiety. The bacterially-released SP is absorbed from the colon, metabolized and excreted in the urine. About 75% of the 5-ASA remains within the lumen of the colon but the remaining 25% is absorbed, acetylated and inactivated in the wall of the colon and in the liver [64,66-70]. It remains uncertain whether the acetylated form of 5-ASA (Ac-5-ASA) or 5-ASA itself is active in the treatment of inflammatory bowel disease [71-73]. Thus, in order for this topically active agent to be effective in the treatment of inflammatory bowel disease, it must be protected from absorption and allowed to be delivered to the site of inflammation in the small or large intestine. This 'protection' is provided by slow- or delayed-release formulations of 5-ASA or by sulfa-free azo compounds of 5-ASA.


BLOOD
5-ASA Ac-ASA
SP Ac-SP SP-Gluc
SASP
ACETYLATED
HYDROXYLATED
GLUCURONATED
25%
SASP
10%
60%
20%
5-ASA
SP
SASP
75%
URINE
STOOL
SP 25%
5-ASA 80%

2.2 Clinical Efficacy

SASP is useful to treat mildly or moderately severe attacks of UC when used in doses of 1-1.5 gm qid [74,75]. About 70% of patients with mild/moderate UC respond favorably to SASP, as compared with an approximate 35% response rate with placebo [74,76]. SASP is more effective than salicylazosulfadimidine [75] or sulfonamides not bound to salicylates [76], but steroids remain superior for treating severe attacks of UC [3,4]. Patients with UC should be maintained for years on SASP to reduce the frequency and severity of attacks when taken in a dose of 2 gm/day [63,77-82], although occasionally higher doses of SASP may be necessary [63,81].

In the National Co-operative Crohn's Disease Study (NCCDS), SASP in a dose of 1 gm/15 kg body weight up to a maximum of 5 gm/day given over 4 months was effective in CD when the colon (colon or ileum plus colon, but not the ileum alone) was involved [19]. One previous study [83] but not a subsequent trial [84] confirmed the use of SASP in the treatment of active CD involving the colon.

Although the NCCDS [19] and a European cooperative study [21] failed to demonstrate a benefit of SASP in Crohn's ileitis (in contrast to colitis or ileocolitis), two more recent clinical trials have suggested that SASP in fact may be useful in the treatment of ileitis [84,85]. Although the American study demonstrated no added benefit for the combination of SASP plus steroids [24], the European cooperative study suggested that the combination was more effective than either alone in Crohn's colitis [21]. Because the presence of colonic involvement may not always be known (depending in part on the manner of establishing the presence of colitis, e.g. single or double contrast barium enema, colonoscopy or biopsy), and because of the data obtained in the carefully-performed Dutch and American studies suggesting that SASP may be useful to treat patients with Crohn's ileitis [84,85], it would appear to be acceptable to use SASP as a first choice in all patients with active CD of whatever site of involvement.

Unfortunately, there is no evidence that SASP is useful maintenance therapy in CD, and SASP does not reduce the high relapse rate after intestinal resection [19,21,23,86-88].

2.3 Adverse Effects of Sulfasalazine

Some 5% to 55% of patients taking SASP develop adverse effects and approximately 20 - 30% of patients cannot tolerate the drug [69,89-93] (Table 1). Most of the adverse effects of SASP correlated with serum SP levels, which in turn may be related to the patient's acetylator phenotype or can be explained as allergic reactions similar to those observed with sulfonamides [89]. Persons who are genetically slow acetylators of sulfonamides more commonly have adverse effects with SASP than do rapid acetylators [94,95]. SP is subjected to polymorphic acetylation - fast acetylators have high levels of acetylated SP but low levels of SP, whereas the acetylation of 5-ASA differs from SP and is not genetically controlled.

Table 1. Side effects of SASP in patients with IBD

1)	General	fever
2)	GI	pain, diarrhea, nausea, vomiting, acute pancreatitis, exacerbation of IBD
3)	Skin	rash, hair loss
4)	Blood	WBC - agranulocytosis, leukopenia, pancytopenia platelets - thrombocytopenia RBC - hemolytic anemia, Heinz bodies with or without anemia, methemaglobinemia, sulfhemoglobinemia, folate deficiency
5)	CNS	headache, peripheral neuropathy, giddiness
6)	Rheumatological	myalgia, arthralgia, aching limbs, Raynaud's phenomenon, systemic lupus erythematosis
7)	Lung	fibrosing alveolitis, pulmonary infiltration and eosinophilia, pneumonitis
8)	GU	toxic seminal changes
9)	Liver	hepatitis, cholestasis, granulomatous hepatitis
10)	Heart	pericarditis

The frequency of adverse effects varies with the symptom and with the vigor of the search: for example, subtle abnormalities of the red blood cells (contraction, hemolysis and Heinz body formation) are uncommon in patients taking 1 - 1.5 gm/day, but the incidence of these changes rises to 35% of those patients taking 2 gm/day and to 80% of those taking 4 gm/day [94]. While desensitization is possible for some patients who are intolerant to SASP [92], patients are still at potential risk of developing serious allergy side effects such as agranulocytosis, hemolysis, and dose-related side effects such as headache and nausea. Indeed, SASP may itself induce an exacerbation of UC [96] and may result in folate deficiency [97] and male infertility [98]. Hair loss during SASP therapy has been reported [99,100]. Late onset hepatotoxicity [101], pneumonitis [102,103] and systemic lupus erythematosus [104,105] have been reported in patients on doses as low as 1.5 g/day after more than 1 year.

It was partially because of the need to target the release of 5-ASA to the area of inflammation, as well as the need to reduce the prevalent adverse effects from SASP, that the new 5-ASA compounds were developed. Some of the adverse effects observed with SASP are not observed with 5-ASA. For example, a significant improvement in semen quality may be obtained in male patients with IBD after replacing SASP with 5-ASA [106-110]. At least ten cross-over studies have demonstrated that 5-ASA has about a 10-fold lower potential than SASP for inducing allergic reactions or causing intolerance [111].

3. THE NEW SALICYLATES

3.1 Background

We owe much to the development of the new oral and topical salicylates for the therapy of chronic idiopathic inflammatory bowel disease to the early work of Dr. Nana Svartz of Sweden [112]. Yet, it was only 12 years ago that Dr. Sidney Truelove's group in Oxford demonstrated that the active therapeutic moiety of sulfasalazine (SASP) in enema preparations was 5-ASA [113]. Other workers have confirmed that 5-ASA represents the active agent for the treatment of inflammatory bowel disease [114-118]. The development of these new compounds has been reviewed in detail [119-122].

Several formulations of 5-ASA have been developed to avoid the minor and major adverse effects of SASP (Table 2). Because 5-ASA is rapidly absorbed from the upper intestine, alternate carrier molecules have been developed to deliver this topically-active therapeutic agent to the target inflammatory tissue in the terminal ileum and/or colon. The 5-ASA compounds are generally efficacious in the treatment and maintenance of patients with UC, both when given as enemas or in tablet form. More than 80% of patients who are intolerant of SASP will do well with 5-ASA. The 5-ASA compounds may also prove to be useful for the treatment and effective maintenance of remission in patients with CD.

3.2 It's All In the Name

The generic nomenclature for 5-ASA is mesalazine, which is also known as mesalamine in the U.S.A. The encapsulation of mesalazine with ethylcellulose (Marion, Pentasa), Eudragit-S (Norwich Eaton and Tilots, Asacol) or Eudragit-L 100 (Smith Kline & French/Falk, Claversal/Salofalk) allows for the release of 5-ASA at various pH values between 4.5 and 7, so that 5-ASA is delivered to the small intestine or colon.

These new oral salicylates are summarized in Table 2. Two general approaches have been used to deliver 5-ASA to the target tissue, and these approaches include non-sulpha conjugated azo-bond preparations (olsalazine, balsalazide and ipsalazide) as well as the development of coated forms of 5-ASA such as Asacol, Claversal/Salofalk, Pentasa, or Rowasa. Olsalazine (Pharmacia, Dipentum) consists of two molecules of 5-ASA linked by an azo-bond, with most of the 5-ASA released in the colon [124-126], in analogy with SASP.

Asacol (Tillot) is a tablet of mesalazine covered with an 80-130 um cover of an acrylic polymer Eudragit-S which is soluble at a pH of 7 and delivers 5-ASA to the colon [67]. Some 5-ASA in Asacol may be excreted unaltered in the feces [127,128]. The current formulation of Salofalk appears to be similar to Claversal or Mesasal, marketed by Falk and Smith, Kline & French, respectively. This medication is coated with the methacrylic acid copolymer Eudragit-L 100 which is dispersed at a pH of 6 and above, allowing 5-ASA to be released in the distal ileum as well as in the colon for

Table 2. New Oral Salicylates

Generic name	Trade name	Company	Formulation	Sites of Release
COATED				
Mesalazine/ Mesalamine	ASACOL	Norwich-Eaton - US & Canada; Tillots, U.K.	Eudragit-S cover	colon
	CLAVERSAL SALOFALK	Smith, Kline & French	Eudragit-L 100	distal ileum
	PENTASA	Marion-US, Ferring - abroad	Ethylcellulose cover	sm. intestine and colon
	ROWASA	Reid-Rowell	Coateris-Opadry cover	-
4-ASA	-	Reed & Carnrick	Eudragit cover	-
CONJUGATED				
Olsalazine	DIPENTUM	Pharmacia	Azo compound, gelatin cover	colon
Balsalazine	-	Brorek	Azo compound	colon

Adapted from: Hanauer, S. (#128); and from Jarnerot, (#121); and Klotz, (#111) with permission. The Asacol tablet is 400 mg, and all the other preparations are 250 or 500 mg. The 5-ASA in the azo-compounds olsalazine and balsalazine is released in the colon after bacterial splitting of the azo bond, in analogy with sulfasalazine. The delivery of Pentasa and 4-ASA is time/pH-dependent whereas the release of Claversal/Salofalk, Asacol and Rowasa are pH-dependent (pH>6, pH>7, pH>4.5, respectively).

treatment of IBD at these sites [129].

The biopharmaceutical and pharmacokinetic properties of oral 5-ASA compounds has been reviewed [111] (Table 3).

The different release patterns of these agents is accomplished by variations in the coating and buffering system; varying amounts of 5-ASA can be recovered from feces, indicating that the 5-ASA is available for local action. The assessment of the amount of 5-ASA

Table 3. Biopharmaceutical and pharmacokinetic properties of oral 5-ASA compounds

(Reference #)	Salofalk (#114)	Pentasa (#130)	Asacol (#131)	Olsalazine (#125, #132)
Galenic formulation	Cellulose ether Eudragit L, Na_2CO_3 buffering	Coating with ethylcellulose	Coating with Eudragit S	Azocompound
Release mechanism	pH dependent	pH dependent	pH sensitive	Bacterial cleavage
C_{max} (μg/ml)	0.3 to 1.5	1.1 to 2.9	0.1 to 9.7	0.1 to 0.8
Urinary recovery	44% (11% 5-ASA/ 33% Ac-5-ASA)	53% (12% 5-ASA/ 41% Ac-5-ASA)	20%	16%
Fecal recovery	35% (16% 5-ASA/ 19% Ac-5-ASA)	40% (14% 5-ASA/ 26% Ac-5-ASA)	-	28% (21% 5-ASA/ 7% Ac-5-ASA
Fecal recovery (volunteers)	5% 5-ASA/ 32% Ac-5-ASA	9% 5-ASA/ 38% Ac-5-ASA	7% 5-ASA/ 33% Ac-5-ASA	13% 5-ASA 39% Ac-5-ASA

The excretion of 5-ASA, olsalazine and sulfapyridine in urine and feces has also been reviewed and summarized by Jarnerot (#121).

reaching the colon can be made from examination of the urinary recovery of 5-ASA, fecal excretion of 5-ASA including fecal dialysate, and the early plasma 5-ASA peak. The more 5-ASA absorbed in the small intestine and lost in the urine, the more that is unavailable for the treatment of distal small intestinal or colonic inflammation.

3.3 Possible Mechanisms of Action

The mechanism of action of the 5-ASA compounds has not been established but may relate to its topical effects on inflammed colonic mucosa with inhibition of the colonic formation of prostanoids [133], leucotriene B_4 [134-136], leucotriene C_4 [137,138], inhibition of generation of reactive oxygen species released from neutrophils migrating to the site of inflammation [139-141], or inhibition of formation of platelet-activating factor (PAF) [142]. PAF is released

from inflammatory cells, activates neutrophils, releases secondary messengers and mediates mucosal ulceration. PAF activity is present in the mucosa of active UC and is inhibited by SASP, 5-ASA and prednisolone but not by sulfapyridine [143].

3.4 Therapeutic Trials

The new salicylates have been prepared for enema or for oral formulations for the treatment of patients with active disease and for the maintenance of remission of UC (including proctitis) and CD.

3.4.1 Topical Therapy: Acute and Maintenance Therapy

There are many trials which attest to the usefulness of topical 5-ASA enemas to treat active distal UC [144] (Table 4), but there is less data to support a role for topical therapy to maintain disease remission in UC. For example, Sutherland and Martin [145] reported on the use of 5-ASA enemas in the maintenance of remission in distal UC and proctitis: 29 patients who achieved remission using 4 g/day 5-ASA (Rowasa, Reid-Rowell) enemas for 6 weeks were then randomly allocated to receive either 4- or 2-g enemas for 6 months. There were no significant differences between the two treatment groups in clinical or endoscopic endpoints.

Biddle et al [146] also reported that 5-ASA enemas were effective in maintaining remission in left-sided UC: 9 of 12 patients on 5-ASA enemas remained in remission at one year, compared with only 2 of 12 on placebo. Thus, one gram of 5-ASA as maintenance retention enema may be useful to prevent clinical relapse for periods of up to one year [146]. In some patients enemas may be administered as maintenance therapy used less frequently than once daily. It is unknown how long topical therapy should be extended but recurrence rates are high when enema therapy is discontinued, even when oral sulfasalazine is used as maintenance therapy [146-150]. These relapse rates observed upon discontinuation of enema therapy range from 0 to 85%, with an interval between discontinuation of topical aminosalicylates and symptomatic relapse varying from three months to one year. If sigmoidoscopic and histological remission has been achieved, remission may last longer [149].

5-ASA enemas (4g 5-ASA, Rowasa, Reid-Rowell) are of no proven benefit in the treatment of radiation proctitis [151].

Aminosalicylate sodium USP, para-aminosalicylic acid or 4-ASA is a safe drug which has been used for years for the treatment of tuberculosis. 4-ASA has been reported to be useful as topical therapy of left-sided UC [148,152,154]. 4-ASA differs from 5-ASA in the amino group in the para- instead of the meta-position. 4-ASA enemas are superior to placebo and equivalent to 5-ASA enemas in the treatment of distal colitis (Table 4). The mechanism of action of 4-ASA is also unknown: it does not inhibit lipoxygenation of arachidonic acid and is not a scavenger of free radicals [155].

Table 4. Topical treatment of active ulcerative colitis with newer 5-aminosalicylic acid-based drugs

1 5-ASA			
5-ASA (Rowasa) vs placebo	Sutherland et al (#118)	1987	S
5-ASA (olsalazine) 1 gm vs placebo	Selby et al (#156)	1985	
5-ASA (mesalamine) 1-4 gm vs placebo	Hanauer (#157)	1989a	S
5-ASA 4 gm vs topical hydrocortisone 100 mg	Campieri et al (#116)	1981	S
5-ASA 1 gm (Pentasa) vs 25 mg prednisolone	Danish 5-ASA group (#158)	1987	NS
5-ASA 2 or 4 gm SASP-intolerant	Campieri et al (#159)	1984	OS
▪ REFRACTORY UC			
5-ASA 4 gm vs 100 mg hydrocortisone	Friedman et al (#160)	1986	S
5-ASA 4 gm (Rowasa)	Guarino et al (#147)	1987	OS
	Barber et al (#161)	1985	OS
5-ASA 0.7 gm vs SASP or SP	Azad-Khan et al (#113)	1977	S
	Willoughby et al (#162)	1986	S
5-ASA 1 gm vs 2 gm	Powell-Tuck et al (#163)	1986	NS
▪ MAINTENANCE			
5-ASA 2 gm (Rowasa) vs 4 gm	Sutherland & Martin (#145)	1987	NS
5-ASA (Olsalazine) vs placebo	Selby et al (#156)	1985	NS
2. 4-ASA			
4-ASA 1gm, 2 gm vs placebo	Selby et al (#152)	1984	S
4-ASA 1 gm vs placebo	Gandolfo et al (#153)	1987	S
4-ASA 2 gm vs 5-ASA 2 gm	Campieri et al (#154)	1984	NS
4-ASA 2 gm vs placebo	Ginsburg et al (#164)	1987	S

S - significant difference in clinical, sigmoidoscopic and/or histological improvement
NS - no significant difference (i.e. equivalent)
OS - open study

It is unknown what is the effect of topical treatment of CD of the rectum or sigmoid colon. 5-ASA suppositories have been used to treat active distal UC (proctitis) and CD when the rectum is involved [165-169].

In some of the above studies in patients with active left-sided UC, the benefit of the 4-ASA or 5-ASA enemas was added to SASP therapy. In fact, when patients on oral SASP therapy stop this medication and are treated just with topical agents, there may be clinical deterioration [170]. Presumably, oral SASP works best in the right and transverse colon; in patients with left-sided disease, topical therapy is necessary to provide optimum management of this location of disease. Even low doses are effective; for example, mesalamine enemas are significantly more effective than placebo for mild to moderately active proctosigmoiditis with no significant difference between 1 and 4 gm enemas [157].

In summary, clinical response to topical therapy may occur quickly. Longer durations of treatment may be required to achieve sigmoidoscopic and histological improvement. Thus, 5-ASA enemas are superior to placebo, equivalent to topical corticosteroids, and useful in the treatment of refractory UC (Table 4). It has been suggested that the direct topical application of 5-ASA or 4-ASA to the distal colon by means of retention enemas is 'the treatment of choice for patients with less than 60 cm of active disease' [120].

3.4.2 ORAL THERAPY

3.4.2.1 Ulcerative Colitis (UC): Acute Therapy

Clinical improvement or remission of mild to moderate exacerbations of UC was achieved in 85% [171], 81% [172] and 72% [173] of patients after 4-7 weeks' treatment with 2.4 g daily of mesalazine coated with Eudragit S (Asacol) (Table 5). When a higher dose (4.8 g/day) regimen of Asacol was compared with placebo, good efficacy and tolerance were noted in patients with mild to moderately active disease [126]. Pentasa in doses of 2-4 gm/day has also been shown to be superior to placebo as a single agent in the treatment of active ulcerative colitis regardless of steroid therapy or extent of disease [174].

Olsalazine (Dipentum) was shown to be valuable in mildly active UC [156,175], but this was not confirmed [176]. However, a recent study of 37 patients with their first attack of mild or moderately severe distal UC showed that 2 g/day olsalazine was at least as effective as SASP 3 g/day and was better tolerated [177]. Indeed, about 80% of patients intolerant of SASP can tolerate olsalazine [123,175,178].

In an important international study, Mesasal/Claversal was found to be equivalent to SASP in the treatment of active UC [179]: mesalazine 1.5 g/day coated with Eudragit-L (Claversal), was compared with SASP 3 g/day in 220 patients with active mild to moderate UC in an 8 week randomised double-blind parallel group study in 46 gastroenterology outpatient clinics in 7 countries. After 4 weeks 50

Table 5. Oral treatment of active ulcerative colitis with newer 5-aminosalicylic acid-based drugs

1.	**ASACOL**		
	Asacol 4.8 g/day vs placebo	Schroeder et al (#126)	1987
	1.6 g/day vs placebo	"	
	0.8 g/day vs SASP 2 g/day	Riley et al (#172)	1988
	2.4 g/day vs SASP		
	5-ASA 0.8 g tid vs SASP		
	1 gm tid	Mihas et al GE (#171)	1988
	5-ASA 1.5 g vs SASP 3 g/day	Barbara et al (#173)	1988
	5-ASA, 3.2 g/day		
	some SASP-intolerant	Habel et al (#180)	1988
2.	**PENTASA**		
	2 or 4 gm vs placebo	Hanauer et al (#174)	1989b
3.	**OLSALAZINE (DIPENTUM)**		
	Olsalazine SASP-intolerant	Gabel et al (#181)	1985
	Olsalazine 2 g/day vs placebo	Selby et al (#156)	1985
	Olsalazine 1 g bid vs placebo	Hetzel et al (#176)	1986
	SASP-intolerant, olsalazine 0.75, 1.5 or 3 g vs placebo	Meyers et al (#175)	1987
	Olsalazine vs SASP 3 g/day	Rao et al (#177)	1989
4.	**MESASAL**		
	5-ASA 1.5 g/day vs SASP 3 g/day	Maier et al (#182)	1985
	Mesasal 1.5 g/day vs SASP 3 g/day	Rachmilewitz (#179)	1989

S - significant difference
NS - no significant difference (i.e. equivalent)

of 70 patients (71%) taking mesalazine and 38 of 58 (66%) taking SASP had achieved clinical remission of their disease; 8 week clinical remission rates were 74% (37/50 patients) and 81% (35/43) in the two treatment groups, respectively. Endoscopic remission at 8 weeks was present in 20 of 41 patients (49%) taking mesalazine and 18 of 38 (47%) taking SASP. There was a higher incidence of adverse events among patients taking SASP (25/105, 24%) than among those taking mesalazine (16/115, 14%). Thus, the therapeutic efficacy of 1.5 g coated mesalazine daily was similar to that of SASP 3.0 g daily. Higher doses of mesalazine coated with Eudragit L may prove to be even more efficacious, and clinical trials with doses up to 4.0 g daily are warranted.

3.4.2.2 Ulcerative Colitis (UC): Maintenance Therapy

Asacol, balsalazine, Dipentum, Pentasa and Claversal are equivalent to SASP for maintenance therapy of UC (Table 6).

Table 6. Oral treatment of inactive ulcerative colitis (maintenance therapy) with newer 5-aminosalicylic acid-based drugs

1.	**Asacol 2.7 g/day**			
	vs 2.3 g/day SASP	Dew et al (#183)	1982	NS
		Riley et al (#184)	1988b	NS
	SASP-intolerant	Habel & Greenberg (#180)	1988	OS
	"	+Donald & Wilkinson (#185)	1985	OS
2.	**Balsalazine vs SASP**	McIntyre (#186)	1984	NS
3.	**Olsalazine (Dipentum)**			
	Olsalazine vs placebo	Sandberg-Gertzen et al (#123)	1986b	
	Olsalazine 500 mg bid vs SASP 1 g bid	Ireland et al (#187)	1988	NS
	SASP-intolerant	Sandberg-Gertzen et al (#188)	1988	OS
4.	**Pentasa**			
	Pentasa 1.5 g/day vs SASP 3 g/day	Mulder et al (#100)	1988	NS
5.	**Claversal**			
	Claversal 0.75 g/day vs SASP 1.5 - 2 g/day	Rutgeerts et al (#189)	1989	NS
	5-ASA (Salofalk), 0.5-1 g/day	Maier et al (#190)	1988	
	vs SASP 1-2 g/day	Maier et al (#182)	1985	
6.	**5-ASA 1 g/day vs placebo enemas**	Biddle et al (#146)	1988	S

S - significant difference
NS – no significant difference (i.e., equivalent)
OS - open study
+ - 7 patients had Crohn's colitis and were intolerant of SASP; 4 or 7 had poor disease control when starting 5-ASA and achieved a remission during the first 6 months of treatment. All 3 with Crohn's colitis in remission when starting on Asacol remained in remission during the first year of the maintenance study. * 5-ASA suppositories and 5-ASA tablets and/or 5-ASA suppositories were also used in the study

For example, a recent major international study has demonstrated that or Claversal 750 mg/day is equivalent to SASP 1.5 - 2.0 g/day in the maintenance of UC in a 1-year double-blind trial [189]. Three hundred and thirty-four patients whose disease was controlled on a stable dose of SASP (1.5 - 2.0 g/day) for a 1-month pre-trial, entered the study; 131 patients in the coated 5-ASA group and 142 on SASP were analysed for efficacy: no significant difference was observed between treatments with respect to the cumulative rate of annual relapse, 28% of the 5-ASA patients versus 23% of those treated with SASP had an exacerbation of their disease. The incidence of drug-related adverse events and subsequent withdrawals was also similar. These results are consistent with previous comparative trials of 5-ASA against SASP [100,183,191,192]. Thus, mesalazine is useful for the treatment of mild to moderately active UC and in the maintenance of remission [77]. Overall, about two patients in three with active UC will respond to 5-ASA tablets, whereas almost all patients with active left-sided disease will respond to topical therapy [193].

Asacol in low or high doses (2.7 g) may be equivalent to SASP in inactive UC [183,194]. Balsalazine 2 g/day may be equivalent to SASP 2 g/day in maintaining remission in inactive UC [186]. Dipentum is superior to placebo for maintenance therapy for patients with extensive UC but not in those with ulcerative proctitis or with distal UC [123]. Also, Dipentum is equivalent to SASP for maintenance therapy in UC [187,188]. Pentasa 1.5 g/day is equivalent to SASP 3 g/day for maintenance therapy in UC [100].

3.4.2.3 Crohn's Disease (CD)

Studies on the therapeutic effectiveness of oral 5-ASA in CD have been reviewed [195] and are shown in Table 7 [196-201]. The most comprehensive study is that by Rasmussen and co-workers [202] involving 67 patients with mild or moderate active CD who took 1500 mg daily of Pentasa or placebo for 16 weeks. About one-half of the patients had disease restricted to the ileum, whereas the remainder had ileo-colonic CD. While the clinical improvement was numerically higher in patients treated with Pentasa (57%) as compared with placebo (33%), these differences were not statistically significant [201-203].

In a retrospective study from Queen's University, Beck and colleagues [195] reported that 67% of 39 CD patients treated with an average daily dose of 2174 mg of Asacol improved as compared with 80% of 106 patients treated with an average daily dose of 3200 mg of SASP. Thus, some 5-ASA compounds may be superior to placebo but possibly inferior to SASP in the treatment of active CD, and not all 5-ASA preparations are alike and further double-blind placebo-controlled studies are in progress. Of course, SASP may also be useful for the treatment of acute CD of the colon [19,21].

Preliminary studies have suggested that mesalazine may be useful in maintaining remission in Crohn's ileocolitis [204] and this finding has been confirmed [205]. A randomized, double-blind, placebo-controlled, multi-centre international study was undertaken to

Table 7. Studies on the therapeutic effectiveness of oral 5-ASA in Crohn's disease

Author (yr/ref #)	Type of study	Drug	Dose per day (mg)	Duration of study	Number of patients	Improvement	
Rasmussen (1983) (#203)	Open	Pentasa	1500	6 weeks	18	72%	-
Saverymuttu (1986) (#196)	Placebo Controlled	Pentasa	1500	10 days	6	-24%	NS
		Placebo	-	10 days	6	-10%	
Klotz et al (1985) (#197)	Sulfasalazine Controlled	Salofalk	1500	8 weeks	15	87%	NS
		Sulfasalazine	3000	8 weeks	15	80%	
Donald & Wilkinson (1985) (#198)	Open	Asacol	800*	3-24 months	7	57%	-
Barbara et al (1987) (#199)	Open	Asacol	2400	7 weeks	32	72%	-
Hanauer (1987) (#200)	Open	Claversal	1500	6 weeks	25	94%	-
Rasmussen (1987) (#202)	Placebo Controlled	Pentasa	1500	16 weeks	30	57%	NS
		Placebo	-	16 weeks	37	33%	
Beck et al (1989) (#195)	Retrospective	Asacol	2174**	Variable	39+	67%	NS
		Sulfasalazine	3200	Variable	106	80%	

(I) = ileum; (IC) = ileum plus colon; (C) = colon; Im = improved; Un = unchanged; De = deteriorated *Later in the study the dose was increased (exact dose not available); ** Mean dose; four patients had Salofalk (mean dose 1928 mg/day); + Eight additional patients were treated with 5-ASA because they were nonresponders to sulfasalazine. They are included with the sulfasalazine analysis, but not in the analysis of response to 5-ASA. Four of these patients improved on 5-ASA and four did not; ++ includes three patients with gastroduodenal plus ileocolic disease.

evaluate the safety and efficacy of 5-ASA (Mesasal/Claversal) in maintaining remission over 6-12 months in patients with inactive CD. A total of 248 patients were entered from eight countries, and 206 of these were evaluable. The patients had had their CD for an average of 5 years, with their disease in remission for at least one month prior to entry into the study, and for an average of over 12 months previously. Thirty percent of patients had had a previous resection, 16% of patients had been treated with salazopyrin while none of the evaluable patients received glucocorticosteroids. Treatment consisted of 5-ASA 500 mg tid or placebo (P). 'Relapse' was defined as the first occurrence of Best's Crohn's Disease Activty Index (CDAI) ≥150, which had increased 60 points from the pre-trial index. The cumulative life-table relapse estimate for efficacy patients was lower in 5-ASA compared to P (22.4% versus 36.2%, respectively, Logrank test $p = 0.0395$). The 12-month relapse estimate in the 5-ASA group was also lower in patients with ileal disease (8.3% for 5-ASA and 31.0% for P, $p = 0.0535$) and in patients with previous bowel resections (14.2% versus 47.0%, $p = 0.0436$). The incidence of side effects was similar in both treatment groups. It is concluded that 5-ASA was significantly superior to placebo in preventing relapse of Crohn's disease; this effect was most apparent in patients with disease restricted to the ileum and in patients with previous bowel resection. 5-ASA was well tolerated as demonstrated by a low incidence of adverse events.

3.4.3 CONTRAINDICATIONS AND ADVERSE EFFECTS OF THE NEW SALICYLATES

Contraindications to 5-ASA therapy include severe renal or liver disease, active peptic ulceration and coagulopathies. Hypersensitivity reactions have been rarely described, such as drug rash, fever, bronchospasm and a lupus-like syndrome. Pericarditis has been reported with SASP and with Asacol [180,188]. There is one previous report of a patient who developed nephrotic syndrome after five months' treatment with 2.4 gm daily of mesalazine [206]; 2-fold rises in plasma creatinine concentrations have been reported in 2 of 21 patients treated with 2.4 gm daily of Asacol for four weeks [172,184]. Aside from these rare hypersensitivity reactions, 5-ASA can cause nausea, vomiting, headache, rash and gastrointestinal disturbances in 1 to 5% of patients [111].

SASP and the newer 5-ASA compounds may cause diarrhea in patients with UC [96,207-212]. In the presence of diarrhea, the cleavage of the azo-bond in Dipentum may be incomplete [213]. In fact, diarrhea is a frequent adverse event with olsalazine [123,214]. Olsalazine may increase ileostomy output [215] and 5-ASA may stimulate fluid secretion in the ileum and colon [216,217]. Olsalazine may also accelerate intestinal transit [218]. Olsalazine-induced diarrhea may affect in excess of 18% of patients and may require discontinuation of the drug [123], although the diarrhea may lessen in time with continuation of administration of olsalazine [219,220].

In SASP-intolerant individuals, the 5-ASA compounds are well tolerated. The quoted prevalence figures vary: the frequency of side

effects with the 5-ASA compounds is variable: 15% with Asacol, 13% with olsalazine [221], 14% with Asacol [222], or 11% with olsalazine [223]. It should be stressed that this signifies that about 85% of patients who are unable to tolerate SASP will be able to do well with one of the 'new salicylates'. Indeed, with Claversal, the prevalence of reported adverse events was less than that observed in patients taking placebo [205].

The sulfapyridine (SP)-induced side effects of SASP can be avoided by switching to mesalazine [193,224,225]. Some patients intolerant of one form of 5-ASA may occasionally be treated successfully with another form of 5-ASA: some patients may tolerate olsalazine but not mesalazine and some tolerate mesalazine but not olsalazine [178]. Two patients with a past history of allergic reactions to SASP have been reported who subsequently experienced allergic reactions to Asacol, suggesting that at least in some patients the adverse effects of SASP are due to 5-ASA rather than sulfapyridine [226]. Thus, patients allergic to sulfasalazine 'should be treated very cautiously with 5-ASA preparations' [122,223].

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4-AMINO SALICYLIC ACID IN THE TREATMENT OF ULCERATIVE COLITIS: PRELIMINARY REPORT OF A RANDOMIZED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF ORAL 4-ASA.

A.L. GINSBERG, M.D.
Professor of Medicine
George Washington University School of Medicine
2150 Pennsylvania Avenue, N.W.
Washington, D.C. 20037
U.S.A.

ABSTRACT. 4-Aminosalicylic acid (4-ASA), a drug which has been used to treat millions of persons with tuberculosis has been demonstrated to be highly effective and safe in the treatment of left sided ulcerative colitis when administered as a retention enema. A three month placebo controlled double blind trial utililizing 4-ASA (4 g/day), enterically coated with Eudragit S & L which dissolves at pH 6.8 (Reed & Carnrick Pharmaceuticals) is in progress. Of the first 32 patients studied, 7 of 15 receiving active drug were judged to have improved whereas only 1 of 17 receiving placebo improved ($p < .05$). Patients allergic or intolerant to sulfasalazine with extensive disease were more likely to respond to 4-ASA. Although a few patients who had active disease despite taking full doses of sulfasalazine responded when 4-ASA was added to their treatment regime, most did not. Oral 4-ASA is effective in the treatment of ulcerative colitis and is particularly helpful in patients with severe extensive colitis who are allergic or intolerant to sulfasalazine.

4-ASA (aminosalicylate sodium U.S.P., para-aminosalicylic acid), has been used orally for many years in the treatment of tuberculosis and is established as a relatively safe, well tried drug. It is structurally similar to mesalamine (5-ASA), the active moiety of sulfasalazine, differing only in the position of the amino group. The sodium salt of 4-ASA is more stable than 5-ASA (1,2), and animal studies suggest that 4-ASA may have more anti-inflammatory activity (2). Furthermore, there are no reports of any nephrotoxicity with 4-ASA. For these reasons it was felt that 4-ASA should be tried in patients with ulcerative colitis.

Five independent studies from different parts of the world have clearly documented the effectiveness of topical 4-ASA administered as a retention enema in patients with proctitis and left sided colitis (1, 3-6). Selby, Bennett and Jewell (3) from the John Radcliffe Hospital in Oxford, England in a placebo controlled trial demonstrated that 80%

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of patients treated with 4-ASA enemas (either 1g or 2g) had clinical improvement and 72% had sigmoidoscopic improvement. These results were significantly better than the results in patients treated with placebo.

CLINICAL RESPONSE TO 4-ASA OR PLACEBO ENEMAS (Selby et al.)

	Improved	Unchanged or Worse	
4-ASA	20	5	
Placebo	11	16	p <.005

SIGMOIDOSCOPIC RESPONSE TO 4-ASA OR PLACEBO ENEMAS

	Improved	Unchanged or Worse	
4-ASA	18	7	
Placebo	8	19	p <.005

Gandolfo et al.(4) from Boston in a 2 week placebo controlled trial found 4-ASA enemas (2g) to be significantly more effective than placebo in improving symptoms. Two weeks was not long enough to achieve statistically significant sigmoidoscopic improvement. In a longer open label trial 46% of patients had complete resolution of all signs and symptoms of disease and an additional 31% were significantly better but still had some residual sigmoidoscopic evidence of disease for a total response rate of 77%.

Ginsberg (5) and coworkers from Washington D.C. performed a randomized double-blind placebo controlled trial of 2g 4-ASA in a 60ml volume as a nightly retention enema in patients with left sided ulcerative colitis. Disease activity was assessed by grading clinical symptoms of blood, mucus, urgency, disease extent, sigmoidoscopic findings and degree of histologic inflammation in rectal biopsies. All posttreatment disease variables in the treatment group showed improvement at 4 weeks with further improvement at 8 weeks. In contrast, no significant improvement in any variable was seen in the placebo group at either 4 or 8 weeks.

PLACEBO CONTROLLED TRIAL OF 4-ASA ENEMAS (Ginsberg et al.)

	Improvement*	Unchanged or Worse
4-ASA	10	2
Placebo	2	11

*Clinical, sigmoidoscopic and histologic (p<.005)

The 11 treatment failures who had received placebo were subsequently treated with 4-ASA, and nine of them have had clinical, sigmoidoscopic and histologic improvement. Overall, 19 of 23 patients (84%) treated with 4-ASA enemas had significant improvement in disease activity. Fifteen of these patients had normal sigmoidoscopic examinations, and eleven had an absence of histologic inflammation after therapy. Clinical benefit was often obvious within the first week, although some patients required 2 to 3 weeks before they could be certain of improvement. No adverse effects were seen.

Nagy et al.(6) from Hungary demonstrated that 1.4g of 4-ASA taken as a nightly retention enema resulted in clinical and sigmoidoscopic improvement in 10 patients with ulcerative colitis. In a further study

they found 4-ASA and salazopyrin enemas to be equally effective.

Campieri et al.(1) from Bologna, Italy have performed the only controlled comparison of 4-ASA and 5-ASA enemas and found them to be equally effective in producing clinical, sigmoidoscopic and histologic improvement.

COMPARISON OF 4-ASA AND 5-ASA ENEMA (Campieri et al.)

Improvement	4-ASA	5-ASA
Clinical	24/31 (77%)	26/32 (81%)
Sigmoidoscopic	24/31 (77%)	25/32 (78%)
Histologic	13/31 (41%)	15/32 (46%)

The mechanism by which the aminosalicylates reduce inflammation in colitis is unknown. 5-ASA is known to inhibit prostaglandin and leukotriene synthesis and is a scavenger of free radicals. In contrast, 4-ASA does not appear to have an inhibitory effect on the lipoxygenation of arachidonic acid and is ineffective as a radical scavenger (7). These observations suggest that these postulated mechanisms of drug action in inflammatory bowel disease are probably not correct. It makes little sense to assume that 4-ASA and 5-ASA which are structurally so similar, would have different mechanisms of action.

On the basis of the above results utilizing 4-ASA in enema form, it seemed reasonable to evaluate the efficacy of an oral preparation of 4-ASA designed to release 4-ASA in the colon. A preparation of 4-ASA enterically coated with Eudragit S & L which dissolves at pH 6.8 was studied, and a dose of 4g (one gm q.i.d) was chosen. Patients were randomized to receive either active drug or placebo.

STUDY DESIGN:

Patients were stratified into 3 groups prior to randomization.

Group A: Patients with active extensive disease (>60 cm) who were taking sulfasalazine.

Group B: Patients with active extensive disease (>60 cm) not taking sulfasalazine because of allergy or intolerance.

Group C: Patients with active limited left sided disease (<60 cm).

It was felt that it would be unethical to discontinue either sulfasalazine or corticosteroids in patients with active extensive ulcerative colitis and randomize patients to receive either placebo or a drug not yet shown to be effective. For this reason, patients that had been on a stable dose for at least one month of sulfasalazine or corticosteroids or both, who still had active disease, were eligible for study. Patients taking these medications were continued on them at the same dose for at least the first month of the study. Patients were randomized to receive in addition either 4-ASA or placebo. If at the 4 or 8 week visit clinical remission was attained, corticosteroids were tapered 5 mg every 2 weeks until discontinued, and ultimately sulfasalazine was also tapered and discontinued. If patients did not improve and corticosteroids could not be tapered, the patients were declared treatment failures. At this point, the code was broken. If the patient had been receiving placebo, they were then eligible to receive open label 4-ASA.

The following criteria were required of all patients to enter the study: granular friable rectal mucosa with at least a grade of 2 on a modified Baron scale (0= normal vascular pattern; 1= loss of vascular pattern, mucosal edema, and no bleeding; 2= granularity and friability; and 3= discrete ulceration and spontaneous bleeding); rectal biopsies showing inflammation compatible with active ulcerative colitis; the presence of blood in the stool at least once a day; three or more bowel movements per day; the absence of enteric pathogens and parasites in the stool. Patients were required to either not be taking sulfasalazine or to have been maintained on a stable dosage for at least one month. Patients were also required to either not be taking oral corticosteroids or to have been maintained on a stable dose for at least one month. Patients were not allowed to have taken either steroid enemas or 5-ASA or 4-ASA enemas for at least one week prior to entry into the study. Patients with less than 20 cm of active disease were excluded as were patients who had previously been unsuccessfully treated with investigational oral 5-ASA compounds. All patients signed an informed consent form that had been approved by the Committee on Human Research of the George Washington University Medical Center.

At the completion of the controlled trial, a physicians overall assessment of markedly improved, improved, unchanged, or worse was made on the basis of clinical symptoms and sigmoidoscopic findings. After classification as treatment success or failure, the code was broken. Patients who were treatment failures and had received placebo were then entered into an open label study of oral 4-ASA.

PRELIMINARY RESULTS:

12 patients in group A with extensive active colitis refractory to sulfasalazine have been studied. 5 patients were randomized to receive 4-ASA and one of them with severe disease had clinical and sigmoidoscopic improvement allowing tapering and ultimate discontinuation of corticosteroids and sulfasalazine. 7 patients received placebo. 6 of the seven were declared treatment failures at 1 month and the seventh was declared a treatment failure at 3 months. When these 7 were treated with open label 4-ASA, 2 achieved complete clinical, sigmoidoscopic and histologic remissions with discontinuation of corticosteroids and sulfasalazine and a third had enough clinical and sigmoidoscopic improvement to also permit discontinuation of corticosteroids and sulfasalazine. Of the treatment failures in this group, 3 subsequently underwent total proctocolectomy.

8 patients in group B with extensive active colitis who were intolerant or allergic to sulfasalzine have been studied. 4 patients were randomized to receive 4-ASA. Two of the 4 had complete clinical, sigmoidoscopic and histologic remissions and a third had some clinical and sigmoidoscopic improvement. The fourth patient failed to respond to 4-ASA and large doses of corticosteroids and had a total proctocolectomy. Of the 4 patients who received placebo, all four were declared treatment failures at the end of 3-4 weeks. Two of these had prompt and complete clinical, sigmoidoscopic and histologic remissions allowing discontinuation of any corticosteroids, when treated with open

label 4-ASA. The other 2 patients were unresponsive.

12 patients in group C (left-sided ulcerative colitis) with >20 cm of active disease but <60 cm of active disease have been studied. Of 6 patients randomized to 4-ASA, three improved. In contrast, 1 of 6 patients randomized to placebo improved.

Overall, 7 of 15 patients randomized to 4-ASA improved whereas only 1 of 17 patients receiving placebo improved ($p < .05$).

PRELIMINARY RESULTS OF PLACEBO CONTROLLED TRIAL OF ORAL 4-ASA

	IMPROVED	UNCHANGED OR WORSE
GROUP A		
4-ASA	1	4
Placebo	0	7
GROUP B		
4-ASA	3	1
Placebo	0	4
GROUP C		
4-ASA	3	3
Placebo	1	5
TOTAL		
4-ASA	7	8
Placebo	1	16

These preliminary results are encouraging and suggest that oral 4-ASA is an effective treatment for patients with ulcerative colitis. The fact that less than 50% of patients had definite improvement is not at all discouraging. Many of our patients had severe colitis. They were referred for our study as a last attempt at medical control before performance of colectomy, only after all other therapies including sulfasalazine and corticosteroids in high doses had failed.

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OLSALAZINE (DIPENTUM®) - THE FIRST CHOICE IN THE TREATMENT OF ULCERATIVE COLITIS

GUNNAR JÄRNEROT
Department of Medicine
Division of Gastroenteorlogy
Örebro Medical Center Hospital
S-701 85 Örebro
Sweden

ABSTRACT

When considering pharmacology, bioavailability and toxicology everything points to the fact that in ulcerative colitis olsalazine, Dipentum®, is the first choice of the new sulpha-free 5-ASA based drugs. It has the same frequency of side effects as mesalazine, but delivers the pharmacologically active drug 5-ASA to the colon in a more reliable way than the mesalazine preparations.

INTRODUCTION

Sulphasalazine, although originally developed by Nanna Svartz for the treatment of rheumatoid arthritis (1), is now used more often for inflammatory bowel disease. Sulphasalazine consists of a salicylate radical linked to sulphapyridine by an azo bond. The azo bond is split by the colonic bacteria, with a liberation of 5-aminosalicylic acid (5-ASA) and sulphapyridine. The sulphapyridine is almost completely absorbed from the colon, metabolized and excreted in the urine (2-4). Most of the side effects of sulphasalazine have been ascribed to the sulphapyridine moiety and correlate with its serum concentration (5).

When given orally, 5-ASA is rapidly absorbed from the small intestine (6, 7), acetylated and excreted in the urine. From the colon 5-ASA is poorly absorbed.

For a long time it was not known whether the pharmacological effect of sulphasalazine resided in the complete molecule or in one of its two metabolites, but in 1977 Azad Khan et al demonstrated that in ulcerative colitis (UC) 5-ASA was the active moiety (8). This discovery has resulted in the development of new 5-ASA based sulpha-free alternatives to sulphasalazine for the treatment of inflammatory bowel disease. To overcome the rapid absorption of 5-ASA from the small intestine, several slow- or delayed-release preparations have been manufactured. 5-ASA has been given the generic name mesalazine. Other azo compounds

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have also been synthesized using a carrier other than sulphapyridine. The most extensively studied new azo compound is Dipentum® (Pharmacia) which has been given the generic name olsalazine. this chapter will mainly deal with this new drug.

CHEMISTRY, PHARMACOLOGY AND TOXICOLOGY

Olsalazine sodium is a sulpha-free 5-ASA based drug consisting of two 5-ASA molecules linked together by an azo bond. Olsalazine is absorbed to less than 3% before reaching the colon. The absorbed olsalazine is sulphated in the liver and most of the absorbed amount is excreted again in the bile. The remainder is eliminated very slowly by routes which are incompletely known, but probably renal excretion is the most important.

Thus, almost all orally ingested olsalazine reaches the colon, where its azo bond is split by the colonic bacteria delivering two molecules of 5-ASA (9). This is acetylated in the colonic mucosa and by the colonic bacteria. Of the 5-ASA released in the colon about 20% is absorbed as 5-ASA or acetyl-5-ASA and excreted in the urine. The remaining part is eliminated in the faeces.

Olsalazine does not appear to have mutagenic potential, and toxicological testing in animals (rat, rabbits) failed to demonstrate any results of clinical relevance. There was no evidence of carcinogenicity in tests lasting up to 24 months in mice and rabbits, and no evidence of teratological effects in rats and rabbits. Bacterial mutagenicity tests did not show any mutagenic activity. That olsalazine gives such a low systemic load of 5-ASA is toxicologically important. In rats 5-ASA can have nephrotoxic effects (10), especially in Gunn rats (11). In contrast to olsalazine some of the new mesalazine preparations set free considerable amounts of 5-ASA already in the small bowel where it is rapidly absorbed and excreted in the urine. This may affect renal function and although the new mesalazine drugs have been available only for a fairly short period of time reports on renal damage have already appeared in the literature (12-16). To my knowledge no such side effects have been reported during olsalazine treatment. Thus, from a toxicological point of view 5-ASA should be regarded as a different drug than 5-ASA based azo compounds.

This could also explain why the side effects during 5-ASA and olsalazine treatment differ. The dominating side effect with olsalazine is diarrhoea which occurred in 6.3% of 804 olsalazine treated patients (17). The possible mechanisms behind the olsalazine induced diarrhoea have recently been discussed elsewhere (18) and will not be repeated here. This type of side effect has also been reported using mesalazine (19, 20). However, the side effects necessitating withdrawal of mesalazine were more vague like tiredness, headache, nausea etc which possibly could be a systemic 5-ASA effect. In spite of the varying type of side effects the essential thing is that both mesalazine and

olsalazine are tolerated equally well. In sulphasalazine intolerant patients about 15% had to be withdrawn both in mesalazine and olsalazine treated patients (21). However, some patients who could not tolerate mesalazine tolerated olsalazine, and vice versa (22).

CLINICAL CONSIDERATIONS

Olsalazine has been developed for treatment of colonic disease, especially ulcerative colitis. When chosing a drug for treatment of colitis it is desirable that the active moiety is delivered to the colon with as little systemic 5-ASA load as possible for renal safety. It is also desirable that the tolerance of the drug is good. As said earlier the tolerance for olsalazine and mesalazine appears to be very similar and a recent study of earlier untreated patients showed that olsalazine is better tolerated than sulphasalazine (23).

The crucial point is then the colonic concentrations of 5-ASA which are reached with the different 5-ASA based drugs. Earlier studies of the faecal recovery of the administered dose of the various drugs have been difficult to evaluate as the faecal 5-ASA concentration is rapidly diminished when faecal samples are stored at room temperature as well as during the time before the samples have been frozen to -20°. Furthermore, faecal samples must be stored under anaerobic conditions to prevent the 5-ASA being further metabolized into unknown metabolites (24). Therefore, urinary excretion of 5-ASA and its acetylated metabolite gives a better estimate of how much of the orally administered 5-ASA that never reaches the colon but is absorbed already in the small intestine and excreted in the urine. Studies, summarized elsewhere (18) indicate that the mesalazine drugs Pentasa®, Salofalk® and Claversal® deliver about two thirds of the orally administered dose to the colon. Asacol® which is also mesalazine and olsalazine (Dipentum®) deliver almost all of the administered dose to the colon. A recent and very elegant study which so far has only been published in abstract form supports these assumptions. Laursen et al (25) using in vivo dialysis measured the concentration in free faecal water of the active moiety 5-ASA after administration of equimolar doses of four of the new 5-ASA based drugs. The material consisted of 14 patients with inactive ulcerative colitis who were treated for seven days with each of the four drugs and the analysis were performed during steady state. The 5-ASA concentration in free faecal water was for Pentasa® 12.6 ± 2.2 (SEM), for Salofalk® - Claversal® 15.0 ± 2.0, for Asacol® 23.3 ±3.1 and for Dipentum® 23.7 ± 1.9 mmol/lit. Thus, Dipentum® and Asacol® were superior deliverers of 5-ASA to the colon in comparison to the two other drugs.

The percentage of the administered dose excreted in the urine measured as 5-ASA + acetyl-5-ASA were for the four drugs: Pentasa® 37%, Salofalk® - Claversal® 54%, Asacol® 31% and Dipentum® 22%. The urinary excretion was significantly lower for Dipentum than for any of the three other drugs.

The reason why Dipentum® and Asacol® gave similar faecal 5-ASA concentrations but a significantly higher urinary excretion after Asacol® is probably the formulation. Dipentum® which is an azo compound does not deliver its two 5-ASA molecules until the azo bond is split by the colonic bacteria, that is it delivers the 5-ASA at the target. Asacol® is a tablet of 5-ASA covered with an 80-130 µm thick cover of the acrylic polymer Eudragit S®. It is soluble at pH 7 and above. It is thus dependent of the pH in the gastrointestinal tract. This has been found to vary considerably between individuals (26, 27). Consequently, in some patients the tablets dissolve early in the small intestine where part of the 5-ASA content is absorbed and excreted in the urine.

When these findings are taken into consideration one can only conclude that olsalazine, Dipentum® is the first choice for treatment of ulcerative colitis. It has the same frequency of side effects as the mesalazine drugs. It appears to bear less risk of renal damage although it can induce diarrhoea which, however, is not a serious side effect. Finally, it is the most reliable deliverer of 5-ASA to the colon of the new drugs.

CLINICAL RESULTS IN ULCERATIVE COLITIS (UC)

ACTIVE ULCERATIVE COLITIS

A study of olsalazine in 40 patients with active UC using Dipentum® 2 g/day for 2 weeks showed a significantly better outcome than placebo-treated patients (28). However, another study of 30 patients treated with olsalazine 2 g daily or placebo for 6 weeks showed an insignificant advantage for the olsalazine treatment (29), results which differed somewhat from those reported by Meyers et al (30). In the Meyers study, 66 patients with mildly to moderately active UC compared placebo with olsalazine 0.75, 1.5 or 3 g daily for 3 weeks. 35% of the olsalazine treated patients improved clinically, compared with 16% in the placebo group. A dose-response relationship was suggested in favour of the olsalazine 3 g group. Finally a recent 4 week study in 37 patients presenting with a first attack of distal UC showed 2 g Dipentum® daily to be as effective as 3.0 g sulphasalazine daily but Dipentum® was better tolerated (23).

In my opinion it is not so important how well any of the new 5-ASA based drugs work in active ulcerative colitis as they are all inferior to corticosteroids in this situation. However, maintenance treatment should be instituted already during this phase of the disease, so from that point of view a 5-ASA based drug as supplement to corticosteroids is motivated. When the disease becomes quiescent the steroids are tapered and maintenance treatment continued. As mentioned Dipentum® ought to be the first choice.

INACTIVE ULCERATIVE COLITIS

A group of 102 patietns with UC in remission were randomized either to Dipentum® 1 g daily or placebo for 6 months or until relapse (31). This is the only placebo controlled relapse prevention study performed so far with any of the new 5-ASA based drugs. The recurrence rates in the olsalazine and placebo groups were 23% and 49%, respectively ($p<0.01$). In patients with proctitis no difference was seen. In patients with distal UC a non-significant trend in favour of olsalazine occurred. In patients with extensive or total UC the recurrence rate in the Dipentum® group was 23.8% and in the placebo group 66.7%. This finding is important, as the more widespread UC is, the more severe the disease (32).

Another large study of 164 patients compared Dipentum® 1 g daily with sulphasalazine 2 g daily for 6 months or until relapse. No significant difference was seen between the groups (33). That Dipentum® and sulphasalazine are comparable as maintenance therapy for UC in remission has been further substantiated by a recent comparison (34).

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Immunosuppressive Drugs: Do They Have Any Role in the Treatment of IBD? (A)

Daniel H. Present, M.D.
Mount Sinai School of Medicine
New York, New York 10029
Address correspondence to:
Daniel H. Present, M.D.
12 East 86th Street
New York, NY 10028

After 20 years the question of immunosuppressives in the management of inflammatory bowel disease is no longer a subject for a debate. The scientific evidence is clear and incontrovertible that these drugs are effective in both Crohn's disease and ulcerative colitis. The lack of acceptance by the medical community is based on: 1) a failure to carefully review uncontrolled and controlled trials; 2) a lack of personal experience in treating patients with these agents; and 3) an unfounded fear of toxicity which has not been observed. The evidence of efficacy from published controlled and uncontrolled trials will be presented with emphasis on the personal series of Dr. Korelitz and myself.

I. Are Immunosuppressives Effective in IBD?

A. Type of Immunosuppressives

The first issue is that of different types of immunosuppressives. Efficacy has been seen with busulfan, chlorambucil and nitrogen mustard (1) and recently with parenteral methotrexate (2). Numerous uncontrolled reports have also shown efficacy of cyclosporin in Crohn's disease, and recently the first controlled trial using cyclosporin has shown efficacy as compared to placebo (3). These studies strongly suggest that "many" immunusuppressives can improve the clinical course of IBD. This debate, however, will center on 6-mercaptopurine (6-MP) and azathioprine, the two major anti-metabolic agents used in IBD.

B. Are 6-Mercaptopurine and Azathioprine the Same Drug?

The drugs are closely related, since azathioprine is converted, *in vivo* to 6-MP. There have been no controlled trials comparing the two in IBD patients, but in one trial using both agents in lupoid hepatitis and chronic active hepatitis (4), the authors concluded that both were equally effective. In IBD, both drugs have demonstrated similar toxicity (leukopenia, pancreatitis, allergic hypersensitivity) and if a patient is allergic to one drug and is rechallenged with the other, the same allergic reaction reoccurs. There are some differences in dosage and *in vitro* studies, but with

D. Rachmilewitz and J. Zimmerman (eds.), Inflammatory Bowel Diseases 1990, 227–234.

the currently available evidence we must regard them as "clinically" similar in IBD patients.

C. Evidence for Efficacy

Scientists tend to discount uncontrolled data and label this type of report as "anecdotal" and overenthusiastic, and will only accept statistically controlled trials showing efficacy. However, as Dr. John Lennard-Jones (5) has pointed out, controlled trials can be misleading, if they do not use the correct dose or the appropriate length of time, or in large enough numbers of patients and for a specific clinical type of disease.

1. Uncontrolled Studies in Crohn's Disease

The uncontrolled data is overwhelmingly enthusiastic as regards the efficacy of immunosuppressives in Crohn's disease, with reports of closure of fistulae, steroid sparing, and positive clinical response. One of the most significant papers is that of Drucker (6), using low doses of azathioprine for long periods of time without concurrent drugs (especially steroids). His patients showed 100% response to the drug, closure of fistulae and no relapses, and the author points out that azathioprine's efficacy is best in "chronic" as compared to acutely ill patients which is borne out by our personal experiences. His study also demonstrates that azathioprine is also effective without concurrent steroids.

2. Controlled Trials

The literature contains seven controlled trials using azathioprine and one using 6-MP in the management of Crohn's disease (7).

Willoughby in 1971 reported on 22 patients who were in remission induced by steroids. Ten of 11 patients randomized to azathioprine stayed in remission, whereas only 3 of 11 placebo patients remained in remission for the 6 month period.

Watson reported a controlled trial in abstract form, in 11 patients attempting to maintain remission. There was no definite improvement with azathioprine. Since the final report was never issued and because of the small number of patients, we should dismiss this study.

Rhodes reported only 15 patients entered into a controlled double blind study and showed no efficacy of azathioprine. The design of this study was flawed in that patients received azathioprine for only two months. Even in this poor trial, the authors noted some patients worsened when azathioprine was withdrawn, and also cited closing of an abdominal wall fistula while on azathioprine. This fistula closed, but reopened after azathioprine was stopped.

Klein, treated 27 patients for a 4 month period of time with either azathioprine or placebo. There was no "statistical" improvement in active Crohn's disease, however "only" placebo patients went to surgery and the author noted "some" dramatic responses to azathioprine. This is cited as a negative controlled trial but it does have positive responses.

Rosenberg reported on 20 patients treated for almost 6 months with either a placebo or azathioprine. Maintenance of improvement while reducing steroids was an important criteria for success in this

trial. Results showed that 7 of 10 placebo patients relapsed, whereas only 2 of 10 azathioprine patients relapsed. It must be considered a positive clinical trial.

A larger series of 51 patients was reported by O'Donoghue who studied patients in remission and taking azathioprine. Patients were randomized to either azathioprine or placebo and were monitored as to maintenance of remission. The relapse rate was 5% at one year in patients receiving azathioprine compared with 41% at one year in those receiving placebo. This "statistically significant trial" concluded that azathioprine reduced the relapse rate in Crohn's disease.

The major reluctance of clinicians to use immunosuppressives stems from the National Cooperative Crohn's Disease Study (NCCDS) (8) with negative results using azathioprine. This study also evaluated sulfasalazine and steroids, and the design was "prejudiced" against a "slow" acting drug such as azathioprine, which may take up to 3-4 months to work. Many patients exacerbated when taken off their maintenance therapy and the trial was terminated when the Crohn's Disease Activity Index rose over 450. Although 59 patients were randomized to azathioprine there were 22 withdrawals, leaving only 37 patients in the trial. Despite this design bias, the response rate of azathioprine was shown to be "better" than that of placebo, but did not reach statistical significance. With two more positives, we would have had a statistically significant study. The largest and longest controlled trial using immunosuppressives in Crohn's disease is reported by myself, Burton Korelitz and other colleagues from Mt. Sinai Hospital and Lenox Hill Hospital (9). The patients were clearly defined and included only "chronically" ill patients who had failed "all" other available therapeutic agents. Our design differed from the NCCDS in that we added either the active ingredient or placebo to medications that were controlling the patient. The results showed 67% response with 6-MP as compared to 8% with placebo ($P>0.0001$).

The study confirmed that the drug is slow in onset, with a mean time of 3.1 months to show efficacy. This slow onset accounts for failure in many of the other controlled trials. 6-MP demonstrated significant steroid sparing in that 75% of patients could either discontinue the steroids or significantly reduce the dosage and still maintain clinical improvement.

Fistulae were closed in 31% of patients with moderate improvement in another third. The study demonstrated closure of major fistulas that are considered by most physicians only amenable to operative intervention. These include gastro-colic, colovesical and ileovesical fistulae. Not only has 6-MP closed these fistulae, but it has "maintained" closure for five years or longer, a therapeutic response that has not been seen with any other medication used for Crohn's disease.

Since our initial paper, Dr. Korelitz and myself have studied over 150 more patients in an uncontrolled manner and find the response rate to continue at approximately 70%. We have demonstrated that if the patient stays on the 6-MP once response has occurred, they maintain their improvement in over 90% of cases.

Our controlled trial is bolstered by two recent reports showing

efficacy of immunosuppressives in Crohn's disease. Nyman (10) used both 6-MP and azathioprine and demonstrated improvement in 41 of 42 patients, with 1/4 obtaining complete remission. There was significant steroid sparing and no patient required an "ileostomy" following institution of 6-MP.

Goldstein (11) treated 38 patients of whom 21% went into a complete remission, with another 50% showing significant improvement. Healing of fistulae was demonstrated in 70% of patients.

Close reading of these studies provides evidence that is "clear and bold" that both 6-MP and azathioprine are effective agents in the treatment of Crohn's disease.

3. Uncontrolled studies in ulcerative colitis

The uncontrolled data show greater efficacy in ulcerative colitis as compared to Crohn's disease. "Miraculous clinical improvement", amelioration of pyoderma gangrenosum and steroid sparing was reported in approximately 80% of all ulcerative colitis patients treated with azathioprine or 6-MP. Again, some series showed efficacy when azathioprine was used without concurrent steroids.

4. Controlled trials

There are 4 controlled trials using azathioprine in ulcerative colitis in 134 patients (7). In Jewell's prevention study, 11 of 20 azathioprine treated patients remained symptom free compared to 5 of 20 placebo patients. This trial was not statistically significant.

Rosenberg's trial showed steroid sparing that was statistically significant when compared to placebo.

Caprilli's patients showed efficacy with azathioprine equal to that of sulfasalazine without concomitant use of steroids.

A final controlled trial by Kirk and Lennard-Jones demonstrated statistically significant steroid sparing as well as improvement in activity of ulcerative colitis patients treated with azathioprine. The authors concluded that azathioprine had a role in the management of ulcerative colitis.

My personal experience with 6-MP shows a 73% (40% remission, 30% moderate improvement) response rate in ulcerative colitis patients (12). Steroids can be withdrawn or significantly lowered in 68% of patients. Surgery can be avoided in 2/3 of refractory cases.

The only drawback to using these agents would be toxicity and the clinician should look objectively at the available data.

II. Does Toxicity Outweigh the Efficacy of Immunosuppressives

A. Steroids versus 6-MP/Azathioprine

It is somewhat puzzling from a scientific point of view that authors are very concerned about the potential toxicity of immunosuppressives, yet strongly advocate the chronic use of steroids in the therapy of Crohn's disease and ulcerative colitis (13). We have cited four controlled trials showing efficacy of 6-MP/azathioprine in Crohn's disease and 3 in ulcerative colitis. This is contrasted with the NCCDS controlled trial showing efficacy of steroids in active disease but no superiority of steroids over placebo in prophylaxis against recurrence. The European Cooperative Crohn's Disease Study (14) also did not definitively demonstrate efficacy in maintenance. On

the other hand, experienced clinicians such as Jones and Lennard-Jones noted that long term treatment with steroids was less encouraging, with frequent need for surgery and several deaths. Sparberg and Kirsner noted progression while on steroids and pointed out that acute responses were unpredictable.

There is "no" convincing evidence in the literature that steroids are valuable in the long term management of Crohn's disease, and I need not remind experienced clinicians that Crohn's disease is not an acute process, but rather a chronic, recurrent illness.

And what about steroid toxicity? In the European Cooperative Crohn's Disease Study 3/225 patients died of septic complications related to steroid therapy. In the National Cooperative Crohn's Disease Study 32% of patients on high dose steroids and 26% on prophylactic doses required drug reduction because of side effects. In the NCCDS 2/3 of patients could not discontinue steroids after they had been introduced. Furthermore, the NCCDS did not go long enough to demonstrate the type of toxicity that clinicians have seen after years of steroid usage: diabetes, hypertension, cataracts, bone collapse, aseptic necrosis of the hips and increased susceptibility to infection. The risk/benefit ratio is not convincing and does not justify chronic steroids in inflammatory bowel disease.

B. Toxicity of 6-MP/Azathioprine in Crohn's Disease

In the prior cited trials with 6-MP/azathioprine, short term toxicity was limited to leukopenia and reversible allergic reactions (pancreatitis, arthritis). There is only one reported death, a patient in the O'Donohue study which was secondary to pancytopenia after 11 years of azathioprine usage. Rosenberg, in his review of the literature, stated that the drug was relatively safe for short term use.

Goldstein cited all effects seen over 18 years which included only reversible leukopenia, one reversible allergic reaction, occasional skin warts, and no mortality. Nyman noted rare leukopenia and four cases of pancreatitis with no mortality. Verhave and Grand (15) reported that azathioprine is not only effective "in children" but is safe, with minimal toxicity.

C. Present, Korelitz Series

The personal series of Dr. Korelitz and myself (16) is the largest series with the longest followup in the literature looking at toxicity. We have reported on almost 400 patients seen over 18 years, with a mean followup of over 5 years. The mean treatment time was 34 months.

Pancreatitis was the most frequent acute reaction, and occurred in 3.3% of patients, occurring in the first 3-4 weeks, and disappeared when the drug was discontinued. There was no instance of chronic pancreatitis. The reaction appears to be a form of hypersensitivity.

Bone marrow toxicity was seen in 2% of patients and rapidly reversed. Other allergic reactions, including rash, fever and joint pain, were seen in 2% and rapidly reversed with discontinuation of the drug.

Our overall short term toxicity was 7.6%, with reversibility in all patients and no mortality.

Long term toxicity is more difficult to evaluate, especially since some patients have been maintained on concurrent steroids, adding to the risk of infection. We could document only 29 patients (7.4%) who experienced significant infections while taking 6-MP. In our clinical judgment only 7 (1.8%) were possibly related to 6-MP. All the infections observed in this study have been seen in inflammatory bowel disease patients "not taking" immunosuppressives, including herpes zoster, CMV infection of the bowel, liver abscess, etc. We did not have a "single" mortality related to infection in almost 400 patients taking 6-MP over an 18 year period.

Almost all articles cite great "fear" of the long term use of immunosuppressives with regard to neoplasia, which is related to an increased incidence of lymphoma occurring in transplant patients receiving azathioprine. In our series, we did see one patient who developed a diffuse histiocytic lymphoma of the brain, having taken the drug for approximately 9 months. It is difficult to evaluate the significance of a "single" lymphoma in our series. Other centers have reported an increased incidence of lymphoma and neoplasm in patients with Crohn's disease unrelated to immunosuppressives. At Mt. Sinai Hospital, Greenstein had 9 lymphomas in over 2700 IBD patients not taking immunosuppressives. Also, in Kinlen's (17) large series of 327 patients with IBD treated with immunosuppressive drugs, no cases of lymphoma were observed while taking azathioprine.

Other neoplasms were seen in our study which could "not" be definitively related to the use of immunosuppressives, including adenocarcinoma of the lung in a heavy smoker, carcinoma of the breast in a patient with a strong family history of breast cancer, islet cell carcinoma of the pancreas, etc.

III. Conclusion

The data has been presented and is clear. 6-MP and azathioprine are effective in both "controlled" and "uncontrolled" data in both Crohn's disease and ulcerative colitis, both for "chronically active" patients and for maintenance of remission. Closure of perianal fistulae is equal to or better than that seen with metronidazole. Closure of major internal fistulae and maintenance of closure has not been seen with any other therapeutic modality and can simply not be ignored.

Short term toxicity occurs in less than 10% of patients and is rapidly reversible with no mortality. Long term toxicity shows no evidence for an increased risk for super infections, and since the current literature does not document an increased risk of neoplasm with the use of 6-MP/azathioprine, there is no contraindication to their use in appropriately selected patients. In view of the inability to cure Crohn's disease with surgery, the high recurrence rate even in ileostomies after total colectomy, it is "scientifically" unsound to deny a patient a trial with these drugs prior to extirpative surgery. Since ulcerative colitis patients undergoing ileoanal anastomoses with a proximal pouch have a failure rate of 5-10%, and have significant morbidity in 20% of patients, and there is no long term followup data, ulcerative colitis patients not at risk for carcinoma should also have

a trial with immunosuppressives prior to colectomy. 6-MP and azathioprine should now be accepted as "standard therapy" for chronically ill patients with inflammatory bowel disease and the "fear" of using these drugs should only be held valid if new data arises to contradict the current literature. We should close this debate and turn to further studies of other immunosuppressives such as methotrexate and cyclosporin to see if they hold any advantage over 6-MP/azathioprine.

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IMMUNOSUPPRESSIVE DRUGS: DO THEY HAVE ANY ROLE IN THE TREATMENT OF IBD?

(B)

Charles O. Elson, M.D.
Division of Gastroenterology, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294 USA

Rationale: The immune system seems to be involved in the pathogenesis of IBD although the mechanisms are unknown. Certainly the immune system shows evidence of activation during exacerbations of disease. Based on these considerations, immunosuppressive agents have been given empirically to patients with IBD.

Ideal Agent: Before considering whether the use of immunosuppressives in IBD is wise, it is germain to consider the qualities that one would like to see in an ideal immunosuppressive agent. First, the agent would act very selectively on the immune system, targeting only those processes important in the disease pathogenesis; this, in turn would presume a thorough knowledge of the immunopathophysiology of the disease. Second, the agent should be non-toxic so that it doesn't substitute another form of suffering for that already afflicting the patient. It follows that such an agent would not require close monitoring of the patient. Third, the agent should work rapidly, quickly relieving the patient's symptoms and initiating resolution of the lesions. Fourth, it should be effective when given as a single agent and, lastly, it should not entail any long-term risks to the patient which might be worse than the original disease.

Current Agents: Such an agent does not exist today. In fact, the currently available agents, and even those on the horizon, are far from this ideal. The current agents are not selective but instead suppress the immune system globally including both detrimental and beneficial responses. Current agents represent a bludgeon rather than a scalpel. Even were we to have relatively selective agents, we have little understanding of the immunopathophysiologic mechanisms of Crohn's disease and would not really know what aspect of the immune system that we want to suppress. The toxic side effects of current agents are substantial; e.g. with 6-mercaptopurine or Azathioprine one in ten

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patients had side effects sufficient to necessitate the stopping of therapy, which represents an additional source of suffering for the patient. Currently available agents take such a long time to take effect that proponents of their use have suggested that they should be continued for a year or two before being considered a failure. this long delay is too long for many instances when they might be helpful and, in addition, puts the patient at an additional risk for complications related to inadequate control of the activity of the disease. The close monitoring required because of the toxic effects represents an additional cost and inconvenience for the patient.

Potential long-term risks are also substantial. Septic complications are already frequent in Crohn's disease and one can expect that these complications will be worse when the immune system is globally inhibited. Opportunistic infections occur at a higher rate in all patients who are immunosuppressed and represent another important potential risk. Although the initial experience with Azathioprine and 6-mercaptopurine have not shown a substantial increase in septic or opportunistic infections, a large literature exists that indicates that such will occur the longer these agents are used. Another important risk which will be discussed at more length below is that of neoplasia developing due to the immunosuppression. There is an increased risk of cancer already in inflammatory bowel disease in general. At least in ulcerative colitis the activity of the disease is not a factor in the risk of cancer developing thus reducing the activity of the disease with immunosuppressives would not reduce the cancer risk, but increasing the duration of disease will increase it.

Current immunosuppressive agents are not particularly effective, which may explain why their use has remained controversial for so many years. The data on Azathioprine as a therapy for Crohn's disease are conflicting with some studies showing efficacy and others not. Included in the latter group is the National Cooperative Crohn's Disease Study in which patients were treated for four months with Azathioprine but without any statistically significant benefit. The believed efficacy of 6-mercaptopurine in the treatment of Crohn's disease is based on a single study which has not been repeated. In addition, this study determined efficacy by measuring whether or not goals were met that were set individually for each patient. this considerably "ratchets up the gain" in sensitivity. For example, a partial response such as reduction of steroids, temporary avoidance of surgery, etc. was defined as success. The weak effect of these agents is also demonstrated by their need to be used as adjunctive therapy,

usually in association with steroids. There is no evidence that 6-mercaptopurine or Azathioprine is effective when used alone.

Risk of Neoplasia: The risk of neoplasia is of sufficient concern to warrant careful consideration. The incidence of neoplasia is increased even in patients with Crohn's disease, although not to as great an extent as it is in ulcerative colitis, a related condition. How much immunosuppressive therapy will increase this already increased risk is not well defined. However, there is a large literature on the risk of neoplasia in patients immunosuppressed during transplantation, and this literature is extremely worrisome. Renal transplant patients have a 30-100-fold increased rate of neoplasia over expected. This increase does not occur across the board for all cancers but has an unusual spectrum with the increase being particularly great in non-Hodgkins lymphoma, squamous cell carcinoma and hepatoma. There is a fairly striking increase in the incidence of lymphoma of the brain which is very rare in the general population. This experience relates mostly to renal transplant patients who have been given Azathioprine, admittedly with other agents. It does not appear to be peculiar to Azathioprine, however, because the early experience with cyclosporin A is even worse. Moreover, a similar spectrum of neoplasia occurs in non-transplant patients who are treated with immunosuppressives and although the increase is not as great as in renal transplantation, it is still substantial. For example, there is a 10-fold increase in relative risk for non-Hodgkins lymphoma in rheumatoid arthritis patients treated with immunosuppressive agents. The mechanism for the marked increase in the renal transplant recipients is unknown but three factors are thought to be important; stimulation of the immune system by the graft, the intensity of the immunosuppression, and the time over which the immunosuppressive is given. These same factors are present to varying extents in patients with IBD if one translates stimulation of the graft to stimulation of the immune system by intestinal content. Such chronic stimulation plus immunosuppression plus prolonged treatment are likely to result in significant increases in neoplasia in patients with IBD. It is ominous that a lymphoma of the brain has already been reported in a patient treated with 6-mercaptopurine.

Risk of Genetic Damage: Those immunosuppressives that are nucleic acid analogues and interfere with nucleic acid metabolism have an additional risk, that of genetic damage. Such damage would not necessarily manifest as neoplasia and could be quite subtle with effects perhaps not being evident until the next generation in the form of having children with congenital defects. This concern particularly

applies to younger patients who might be expected to be treated for prolonged periods with such drugs and who have their childbearing ahead. This risk of genetic damage is one aspect of what I would term the risk of the "not yet known". Physicians have empirically used treatments in the past only to recognize years later that these treatments had serious adverse effects which were not even imagined at the time the treatment was in vogue. Radiation treatment of the thymus causing later thyroid carcinoma and estrogen treatment during pregnancy resulting in a high incidence of vaginal carcinoma in daughters are two examples that come readily to mind. I would propose that immunosuppressive therapy in IBD represents a similar risk of the "not yet known".

Natural History of Crohn's Disease: The natural history of Crohn's disease and ulcerative colitis must be considered when one advances the use of immunosuppressives in this disease. Much of our thinking on the natural history of Crohn's disease and ulcerative colitis is generated in large referral centers which tend to see patients with more severe disease. An interesting article by Binder in 1985 reported the natural history of a regional patient group from the county of Copenhagen. The patients were treated with sulfasalazine and intermittently with corticosteroids. When these failed, surgery was performed. An interesting point of this study is that the majority of the patients did quite well and had no impairment of their capacity to work. In this study this was accomplished without the use of immunosuppressives, which makes the point that most patients with Crohn's disease and ulcerative colitis do quite well with current therapy. The promotion of more general use of immunosuppressives will undoubtedly result in many patients being treated inappropriately. I would propose that the patient populations being seen at major centers such as Mt. Sinai in New York are clearly skewed and not representative of patients with IBD as a whole. The interpretation of studies on therapy must consider this type of patient bias. A last concern raised by the natural history of IBD is the chronic nature which would seem to, in turn, require a prolonged use of immunosuppressive medication, not only for initial effect but also for maintenance of the effect once any is achieved. The relapse rate after discontinuing immunosuppressive therapy is not well defined but appears substantial. This means that years of therapy with their attendant risks will be necessary. Although never directly measured, it is reasonable to postulate that the quality of life on such longterm therapy, along with the need to take concomitant medications, and be followed on a regular basis, etc. will be poor.

An Effective Alternative Therapy is Available - Surgery: For ulcerative colitis, surgery is a cure. Surgical therapy is unquestionably effective in Crohn's disease, although not a cure. Most patients have remissions that can last for many years during which time they are taking no medication and have little need to even see their physician. The quality of life after surgery has been studied and found to be quite good. In fact, 90% of patients would undergo the surgery again. Proponents of immunosuppressive therapy point out that the disease inevitably recurs after surgical resection. This is not in question, however one needs to factor in the disease-free interval during which patients experience a very good quality of life. From the literature, 75% of Crohn's disease patients will go 5 years without recurrence and 50% will go 10 years, again with a very good quality of life. The surgical approaches are well worked out and morbidity and mortality are quite low. A second argument against surgery in Crohn's disease is that a short bowel syndrome might result if too much bowel is resected. The incidence of this complication has been reduced greatly by a widespread adoption of more conservative resections due to the recognition that the disease is present throughout the entire bowel and wide resection margins do not decrease the relapse rate.

In summary, currently available immunosuppressive agents are significantly toxic, marginally effective, and have substantial risks associated. Their use applies only to a small minority of patients and their enthusiastic promotion will thus cause inappropriate usage. Surgery represents an effective alternative with less risk and better quality of life. I believe that this assessment of the risks and benefits of immunosuppressive therapy is reflected in the lack of adoption of immunosuppressive therapy by the gastroenterology community at large, who have come to a similar conclusion that immunosuppressive therapy should not be used in the management of IBD. Instead of subjecting patients to great risks for marginal benefit, we need to search for more effective anti-inflammatory medications, which will more effectively control this disease.

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Cyclosporin in Inflammatory Bowel Disease

Daniel H. Present, M.D.
Simon Lichtiger, M.D.
Mt. Sinai School of Medicine
New York, NY 10029
Address all correspondence to:
Daniel H. Present, M.D.
12 East 86th Street, New York, NY 10028

Abstract

The purpose of this report is to review currently available information regarding the role of cyclosporin in the management of both Crohn's disease and ulcerative colitis. The uncontrolled reports in the literature and a single double blind controlled trial indicate that cyclosporin is an effective therapeutic agent in both diseases. The onset of action is rapid, within one-three weeks and relapse is seen often when the drug is stopped. Major adverse effects, including nephrotoxicity, hepatotoxicity and infection are rarely seen, especially with close monitoring of cyclosporin trough levels. The observed incidence of neoplasia is small but long term observation is required to ascertain the true risk. Future double blind controlled trials are needed before the specific indications for using cyclosporin to treat inflammatory bowel disease can be determined.

Introduction

Cyclosporin is a potent immunosuppressant polypeptide derived from the fungus tolypocadium inflatum gans. It has been used in humans since 1978. Cyclosporin is unlike prior immunosuppressive agents in that it does not cause myelosuppression but rather, reversibly inhibits the activation of primary helper T-cells (1). Since its introduction in the management of transplants it has raised the patient survival in cadaveric kidney transplants to 95% and graft survival to 80%. One year survival after liver transplant is now in excess of 80% compared to 60% prior to the use of cyclosporin. Heart and lung transplant have now become possible with the use of cyclosporin.

Ulcerative colitis and Crohn's disease are chronic illnesses in which immunologic mechanisms appear to play a role in perpetuating and/or increasing the inflammatory component (2). It would then seem rational to use cyclosporin in the treatment of inflammatory bowel disease for numerous reasons.

In these chronic illnesses there has been a limited armamentarium with few new therapeutic agents introduced in the last 10 years. Sulfasalazine and the new 5-ASA agents have shown efficacy in both

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ulcerative colitis and Crohn's disease. Corticosteroids have shown efficacy in both illnesses but when used for prolonged periods of time toxicity often outweighs the therapeutic benefit. Antibiotics such as metronidazole have shown efficacy in active Crohn's disease and in one recent report had a preventative effect in ulcerative colitis. There are no controlled trials to demonstrate efficacy of total parenteral nutrition in ulcerative colitis and in Crohn's disease the efficacy has been of limited duration.

Most important have been the studies which have shown efficacy of 6-mercaptopurine and azathioprine in the treatment of both Crohn's disease and ulcerative colitis (3). There have been numerous uncontrolled studies showing efficacy in Crohn's disease and 4 of the 8 double blind controlled trials have shown efficacy in either active disease or maintenance of remission. In ulcerative colitis 3 of the 4 controlled trials have shown either efficacy in decreasing activity or steroid sparing. Recently, in an uncontrolled study methotrexate (4) has shown efficacy in both ulcerative colitis and Crohn's disease.

Many of the above therapeutic agents such as steroids, metronidazole and sulfasalazine have show some immunosuppressive action either in vitro or in animal studies.

A major drawback in the use of 6-MP and azathioprine in the treatment of inflammatory bowel disease has been the slow onset of action, the mean response time being approximately 3 months in both diseases (5). Cyclosporin, on the other hand, has shown rapid onset of action, in several autoimmune disorders, often within a few weeks.

Pharmacokinetics of Cyclosporin

Cyclosporin is absorbed in the small intestine with a bioavailability of approximately 30% (6). The absorption half life is about 1 hour with a mean peak concentration at 4 hours. Cyclosporin is absorbed into the lymphatic system and is metabolized in the liver and excreted predominantly into the biliary system. Enterohepatic recycling is observed in approximately 25% of patients with a second peak observed about 8 hours after administration. Absorption of cyclosporin is limited by delayed gastric emptying, diarrheal states, short bowel syndrome and biliary diversion by T-tube. In the blood, 50% of cyclosporin is bound to red cells, with 10% or less binding to white cells and the remainder is in the serum. The majority of cyclosporin in plasma is bound to low density lipoproteins.

Cyclosporin concentrations may be measured by utilizing radioimmunoassay (RIA) which measures both the parent drug and active metabolites. High performance liquid chromatography (HPLC) measures only the parent compound. The radioimmunoassay is easy to use because the polyclonal antibodies measure the combined concentration of cyclosporin and its metabolites, whereas a new improved radioimmunoassay has been developed using monoclonal antibodies with more specificity for the parent drug. In evaluating transplantation and autoimmune patients receiving cyclosporin, blood is monitored for cyclosporin trough concentration on a regular basis.

In the management of inflammatory bowel disease the erratic absorption of cyclosporin may play an important role in the

therapeutic response. Erratic oral absorption with inadequate therapeutic levels have been noted with radiation enteritis, diarrhea, anemia, malabsorption, vomiting and uremic enteropathy (7). If cyclosporin is administered parenterally in a bolus form, toxic levels may be achieved quickly with a rapid drop to below therapeutic levels. This is contrasted with continuous infusion of cyclosporin where steady therapeutic levels are maintained. The therapeutic implications of these various routes of administration will be discussed later.

Also important is the interaction between corticosteroids and cyclosporin. High dose intravenous methyl prednisolone has been shown to produce a rise in blood cyclosporin concentrations, and in turn, cyclosporin may decrease the rate of elimination of corticosteroids. A synergistic action has been suggested for these two agents.

Since cyclosporin metabolism occurs within the liver and is predominantly dependent upon the mixed function oxidase enzyme system, several drugs have been shown to interfere with cyclosporin metabolism. Phenytoin, phenobarbital, rifampin and isoniazid induce the cytochrome P450 enzyme system which decreases the half life with subsequently low cyclosporin blood levels causing decreased immunosuppression. Conversely, erythromycin, ketoconazole, moxalactam and possibly cimetidine inhibit cytochrome P450 enzymes, increase the half life and blood levels and thereby increase immunosuppression. Metaclopramide increases absorption of cyclosporin and Verapamil potentiates cyclosporin. Lovastatin recently was shown to increase the occurrence of myopathy when used with cyclosporin.

Immunologic Effects of Cyclosporin

The immunosuppressive effect of cyclosporin is due to its selective action on T-lymphocytes rather than B-lymphocytes. It predominantly inhibits T-lymphocyte proliferation as well as inhibition of the activation of the primary helper T-cells, and the subsequent release of many of its lymphokines. It's inhibition of secretion of Interleukin 2 is most important after allograft transplantation and secretion of Interleukin 3, 4 and 5 and gamma Interferon are also impaired. As was noted earlier, cyclosporin is not associated with myelosuppression and has little to no effect on mature cytotoxic T-cells.

Benefit Versus Risk in Cyclosporin for Inflammatory Bowel Disease

In the early medical literature, cyclosporin was used only for transplant patients and diseases with a short term survival. In the last few years immunosuppresssion, especially that with cyclosporin is being considered for chronic nonfatal illnesses. Cyclosporin has been used and shown efficacy in rheumatic and connective tissue disorders (rheumatoid arthritis), nephrotic syndrome, chronic active hepatitis, myasthenia gravis, and multiple sclerosis. More recently, the drug has been used for psoriasis, uveitis and type I diabetes. It is important to note that the efficacy is often lost when the treatment is stopped. Since the drug does not cure the underlying illness, as shown in psoriasis and type I diabetes, a close look at toxicity is mandatory prior to initiating cyclosporin (8). The therapeutic effect of a

potent agent should persist long enough to justify the risks in using the agent. In cyclosporin the quality of the therapeutic effect has varied according to the individual disease. For example, excellent results have been observed in rheumatoid arthritis, psoriatic arthritis, nephrotic syndrome and type I diabetes, whereas lesser responses have been seen in myasthenia gravis and multiple sclerosis. An important aspect to consider is the timing of introduction of cyclosporin. In type I diabetes, approximately 1/3 of recent onset patients do not respond to cyclosporin with the explanation that too few beta cells are available and that treatment should be started as soon as possible. It may be likely that cyclosporin would be more effective in less advanced lesions, and reversibility might then be obtained. With these concepts in mind, we must now look at the benefits of cyclosporin in inflammatory bowel disease and then the toxicity which has occurred in clinical trials, and finally, the potential long term risks with this agent.

Historical Review - Cyclosporin in Crohn's Disease

The first report of cyclosporin in Crohn's disease was that of Allison and Pounder (9) in 1984. A patient with extensive ileitis, suffering from a steroid psychosis, continued to be active on sulfasalazine. The patient was treated for 8 weeks with improvement and with only minimal side effects of hirsutism and tremor. Bianchi (10) rapidly followed this report with 2 cases, one with active colitis and one with an ileocaecal stricture. The patient with the active colitis improved, whereas the latter patient failed and required surgery. No side effects were noted.

Several centers then embarked on pilot studies and a conference was held in London in 1986 to review 74 patients who had participated in 11 pilot studies. Disease activity in this group varied from acute to chronic active, and patient selection was also diverse, including resistant cases versus unselected cases. Three of the centers used concomitant steroids, some azathioprine, and the dosage and duration of cyclosporin varied. This meeting was important in that there was consensus that the onset of action of cyclosporin was rapid, often within one to 3 weeks and that both acutely ill patients and chronically ill patients responded with the latter showing greater efficacy. Rapid relapse was often seen after stopping cyclosporin and toxicity appeared to be low. The question of frequency of adequate absorption of cyclosporin was raised at this meeting.

Peltekian (11) in 1987 reported on 15 patients all suffering from active disease who were treated with cyclosporin. Ten of 15 patients improved, all within 4 weeks. Five patients had to withdraw, 3 with side effects, one because of noncompliance and one with poor absorption. Of the 10 patients who responded 7 maintained their improvement and half of those could discontinue steroids. Relapse was often noted after stopping cyclosporin.

Allam (12) contributed an important case report in the patient with ileocolitis who was suffering from a short bowel syndrome and was refractory to steroids and azathioprine. The patient was treated with total parenteral nutrition and responded but had a subsequent relapse.

Intravenous cyclosporin was initiated and the patient did well, however, efficacy was not sustained when the drug was given orally for 7 months. Reintroduction of the intravenous therapy once again resulted in efficacy. The author suggested that there might be a place for intravenous cyclosporin in patients with severe Crohn's disease who did not respond to oral therapy.

Parrott (13) in 1988 reported on 13 patients, the majority with ileal disease, who were treated with an initial high dosage of cyclosporin. Only 6 of the 13 showed a response to therapy, whereas 7 showed no response or deteriorated. The investigators prejudiced their study against cyclosporin by withdrawing steroids during the first week. Of the 7 nonresponders, 2 patients already had complications that would not have allowed the drug to be effective (abscess and stricture) and in another patient, adequate absorption was not seen and therapeutic cyclosporin levels were never achieved. One patient had severe nephrotoxicity and one hepatotoxicity, but these were reversible.

In 1989 further reports on the use of cyclosporin in Crohn's disease have been reported. Brynskov et al (14) used low dose cyclosporin (5-7.5 mg/kg) in 11 chronically active, therapy resistant Crohn's patients. Eight of 11 (72%) showed initial improvement, however only 5 of the 8 (45%) maintained their improvement at a 3 month period. Of great importance is that 4 out of 11 patients showed evidence of malabsorption. No serious toxicity was noted, and the authors concluded that there was a role for low dose cyclosporin in Crohn's disease.

Fukushima and colleagues (15) studied 7 patients with active Crohn's disease for a 16 week period using 8 mg/kg daily. Steroids and sulfasalazine were discontinued rapidly and the patients were maintained on elemental diet. Three out of 7 patients improved, and one of the 3 closed an enterocutaneous fistula. No toxicity data is given.

Stange (16) and colleagues studied 11 patients with Crohn's disease, adding cyclosporin to their current medications, which included steroid and metronidazole. Response was seen in 10 of the 11 Crohn's disease patients with relapse seen in 2 during cyclosporin therapy and 3 after the medication was discontinued. The side effects were mild and the authors concluded that cyclosporin appeared to be a relatively safe alternative drug for the treatment of IBD.

Baker and Jewell (17) have reported on the use of cyclosporin in severe Crohn's disease. Twelve hospitalized patients were treated with intravenous steroids for 5 days followed by oral steroids and oral cyclosporin, 15 mg/kg/day. There were 7 patients with ileocolitis and 5 with colitis of whom 6 showed a very good immediate response to cyclosporin. Three patients were unresponsive and required urgent surgery. Two withdrew, one because of anxiety and one who was found to have a dilated colon. One patient died of cardiac failure and peritonitis. The outcome for Crohn's disease was similar to that predicted by the group based on their historical controls, and they concluded that in severely ill patients cyclosporin was of no benefit. On a positive note, they did report that early relapse was not seen

after cyclosporin withdrawal.

The first placebo controlled double blind randomized trial using cyclosporin in chronic active Crohn's disease has been completed (18), with a statistically significant response rate of 59% as compared to 32% with placebo. Of all patients treated, approximately one third had substantial success and one third were moderately better. Response was seen in 2 weeks, and patients appeared more likely to respond if they were also taking concomitant steroids. Cyclosporin trough levels were higher at one month in responders as compared to nonresponders, but were not statistically higher at other points in the study comparing responders to nonresponders. Three patients showed complete malabsorption and 7 partial malabsorption. Of the 10 malabsorbers, half of them occurred in patients who improved and half in nonimproved patients. Minor toxicity was often seen, but no major toxicity was noted. The authors concluded that cyclosporin appears to work quickly in chronic Crohn's disease, it may be synergistic with steroids, and that in this short term trial toxicity was not significant.

In summary, in several small uncontrolled trials and in one double blind controlled trial, cyclosporin has shown efficacy in Crohn's disease, most favorably in chronic as compared to acute patients.

Historical Review - Cyclosporin in Ulcerative Colitis

There is limited data available regarding the use of cyclosporin in ulcerative colitis. The initial case report from Gupta (19) evaluated one aged patient with proctocolitis who appeared to improve within 6 weeks but relapsed on lowering the dosage of cyclosporin. The response was seen within 6 weeks. Kirschner (20) in an abstract reported two patients who improved within two weeks following the administration of intravenous cyclosporin plus intravenous steroids. In a subsequent abstract, the authors have reported 5 patients, all of whom had failed intravenous steroids, and in whom cyclosporin induced a response in 3 of 5. All responding patients experienced relapse during tapering of oral cyclosporin.

In 1988 Shelley (21) reported a 58 year old female in whom oral cyclosporin at a dose of 10 mg/kg/day healed pyoderma gangrenosum of the face and at the same time there was an associated remission of the patient's sclerosing cholangitis and ulcerative colitis. Cyclosporin was stopped after 7 months, and in a 14 month followup there has been no relapse of the pyoderma or ulcerative colitis.

Stange (16) and colleagues have also treated 2 ulcerative colitis patients with cyclosporin, both showing an initial response but one of the patients subsequently relapsed and required colectomy. The initial patient obtained a complete remission.

Baker and Jewell (17) have also reported on the use of cyclosporin for the treatment of severe active ulcerative colitis. Twelve patients, 7 with universal disease and, 4 with leftsided disease and one with proctitis were initially treated with intravenous steroids and then placed on oral sulfasalazine plus oral steroids. Six patients had a good immediate response to cyclosporin therapy whereas 3 did not improve and required urgent surgery. Three patients withdrew

from the study because of nausea and vomiting. Adverse reactions were minimal and the authors stated that there was excellent absorption of cyclosporin from the GI tract in all patients. Since 3 of 12 required surgery the conclusion was that the response was similar to those receiving steroids alone when using historical controls and that cyclosporin was of no benefit in acute severe ulcerative colitis.

It is difficult to draw conclusions regarding the currently available data in both ulcerative colitis and Crohn's disease since the reported trials are quite variable as regards patient selection. In ulcerative colitis, both acute, subacute and chronic patients had been evaluated with a variable extent of disease and the prior response to therapy not well defined. Concurrent therapy was also variable. In Crohn's disease the problem is even greater when trying to compare acute, subacute or chronic patients. The extent of disease, small and/or large bowel, and the presence of fistulae and stenosis provides great variation in response. The prior response to therapy and concurrent therapy was also not standardized. For example, in several of the studies, steroids were withdrawn rapidly when cyclosporin was introduced, whereas in others steroids were maintained.

Another major variable is that of absorption. It is clear that malabsorption may occur in many patients, especially those with Crohn's disease. In acutely active ulcerative colitis where oral intake is limited and where malfunction of the small bowel may be occurring, perhaps secondary to ileus, malabsorption may also prove to be a problem.

Personal Experience With Cyclosporin in Crohn's Disease and Ulcerative Colitis

We have now treated 21 patients (10 Crohn's disease, 11 ulcerative colitis) with cyclosporin. We have asked the questions as to whether cyclosporin is therapeutically effective in severe refractory IBD, is it a steroid sparing agent, and is there significant toxicity with its use. Our selection criteria includes both Crohn's disease and ulcerative colitis patients who have failed conventional oral and parenteral therapy or who are steroid dependent or steroid toxic or those with Crohn's disease who have refractory fistulous disease and finally, in ulcerative colitis, hospitalized patients who have failed parenteral therapy and are candidates for surgery.

Methods and Results in Crohn's Disease

Our Crohn's disease protocol called for the use of 4 mg/kg/day of intravenous cyclosporin for up to 14 days. We evaluated patients according to goal oriented criteria as used with our 6-MP study in chronic Crohn's disease patients. We then transfer patients to oral maintenance cyclosporin in a dose of 6-8 mg/kg daily with frequent evaluation of cyclosporin trough levels. Patients are maintained for 6 months with a final grading based on goals such as clinical improvement, steroid withdrawal and/or closure of fistulae. Our results show improvement in 9 out of 10 patients. The mean response

time is rapid and usually occurs in less than 10 days. In 5 fistula patients, 3 have closed and 2 have shown moderate improvement. Of 7 patients taking chronic steroids, 3 have been able to discontinue this medication, 3 have had significant lowering of the dose and one patient failed and was unable to stop the steroids. Two of the improved patients have exacerbated when the cyclosporin was discontinued, and one each is being treated with 6-mercaptopurine and methotrexate.

Our data shows a greater response compared to the literature, which may be a reflection of the initial induction phase using intravenous cyclosporin.

Methods and Results in Ulcerative Colitis

In ulcerative colitis, our inclusion criteria is that of severe ulcerative colitis as defined by Truelove and Witts. We have studied acutely hospitalized patients who required surgery, that is, having failed 7 or more days of intravenous steroids (22). Our protocol indicates two distinct phases. In the acute phase, we are administering cyclosporin in a dose of 4 mg/kg/day intravenously for a maximum of 14 days. If the patient does not respond in this time, according to our modified Truelove-Witts rating, the patient is considered a failure and undergoes a colectomy. If the patient does improve they go on to the chronic phase of their study in which cyclosporin is given in doses of 6-8 mg/kg/day for 6 months. At the end of 6 months, success is defined as a clinical remission, colonoscopic healing and total steroid withdrawal.

Of the 11 patients entered, 8 had universal disease and 3 had leftsided disease with a mean duration of disease of 4.1 years. All had failed at least 7 days of intravenous steroids except for one patient who refused intravenous steroids because of a previous episode of aseptic necrosis of the hip. Of the 11 patients entered, 2 failed and underwent colectomy within the first 14 days. Another patient who failed cyclosporin was advised but refused to have a colectomy. There were 8 patients (73%) who responded by our criteria, with a mean response time of 7.2 days. These patients then became eligible for the oral phase of the study. Of these 8 responders, 6 have remained in remission for long periods of time (4-12 months) and 5 of 6 have been able to withdraw steroids. Two of these 8 patients subsequently failed, one undergoing a colectomy and one patient transferring to 6-mercaptopurine. This latter patient has now gone into a complete remission and is currently taking 6-mercaptopurine plus sulfasalazine. The patient in the acute phase who refused colectomy continued to be active and had to undergo surgery 7 months later. Therefore, of the initial group of 11 patients, 6 (55%), have done extremely well with cyclosporin alone and one patient has improved following transfer to 6-mercaptopurine.

Toxicity is of great concern when using a potent drug such as cyclosporin. The major adverse effects reported in the transplant population are nephrotoxicity, hepatotoxicity and infection. In our combined Crohn's disease and ulcerative colitis data we saw only one

episode of moderate renal toxicity which was reversible on decreasing the dose of cyclosporin. We saw no hepatotoxicity or significant infection. Minor side effects were frequently noted and included a mild tremor, paresthesias, hirsutism, gum hyperplasia and headaches.

We conclude that intravenous cyclosporin is rapidly effective in the treatment of active ulcerative colitis that has already failed intravenous steroids. Colectomy was avoided in 73% of patients. We also note that oral cyclosporin maintained response in 6 of 8 of this group (75%) and in 6 of 11 (55%) of the original patients entered into the study. Cyclosporin appears to be steroid sparing in ulcerative colitis and adverse effects are mild.

Risks of Immunosuppressives

The data in inflammatory bowel disease and in other autoimmune disorders suggest that cyclosporin does not seem to increase the incidence of infection with the doses currently being utilized (23). This contrasts with the increased risk of infection seen with high dose steroids and with myelosuppression such as that seen with azathioprine and cyclophosphamide.

Nephrotoxicity is the most important toxicity that accompanies cyclosporin administration (24). It is divided into two major subgroups, the first being a functional toxicity without significant morphologic abnormality. At therapeutic cyclosporin doses, a decrease in renal function is observed in almost every patient with a mild decline in creatinine clearance. The serum creatinine increases, due to a lowered glomerular filtration rate, and the pathogenesis is that of selective preglomerular vasoconstriction. Careful monitoring of serum creatinine and serum trough levels of cyclosporin, with dose adjustment will rectify this functional toxicity. If the serum creatinine is not allowed to rise to greater than 50% above baseline levels significant renal toxicity is not seen. A second form of toxicity is morphological, with tubular and vascular interstitial lesions noted. Tubular toxicity is seen when cyclosporin trough levels are maintained at toxic levels. Presence of nephrotoxic agents may also worsen this complication. These include aminoglycosides, amphotericin, trimethoprim sulfamethoxasole and nonsteroidal anti-inflammatory agents. Patients with vascular interstitial nephrotoxicity have had significant higher cyclosporin A trough levels or have been exposed to additive agents. Whether these lesions can occur on lower dose cyclosporin given for prolonged periods of time is uncertain at our current state of knowledge.

The risk of tumors is worrisome with the chronic use of immunosuppressive agents (25). A definite increased incidence of certain neoplasms occurs in patients who are immunodeficient. In the transplant population there is a more than threefold increase in the numbers of neoplasms with predominance of lymphomas, Kaposi's sarcoma and carcinomas of the skin, lips and perineum. The lymphomas are unique in that they are usually the non-Hodgkin's type and show a marked predilection for the brain. Another complicating problem is the fact that different immunosuppressive agents appear to induce different types of neoplasms. For example, azathioprine has been

incriminated in epithelial carcinoma in multiple sclerosis, alkalating agents appear to increase the risk of leukemia in rheumatoid arthritis and cyclosporin may induce early lymphomas when used in high dosages. The pattern of malignancies observed with cyclosporin is different than that seen with the more conventional immunosuppressive therapy. The average time of appearance of neoplasm is shorter with cyclosporin, and there is a disproportionately higher incidence of lymphomas, Kaposi's sarcoma and carcinoma of the kidneys when compared to conventional therapy. However, many of these patients were treated with multiple immunosuppressives which again confounds the issue. Lymphomas developing in cyclosporin treated patients also appear to respond more readily to therapy than those seen with conventional therapy and in many there have been complete remission when the only therapy was reduction or cessation of cyclosporin (26).

In summary, the risk of neoplasia with cyclosporin is small, less than 0.1%, but this is still not negligible and further long term studies at lower doses must be awaited in order to determine the true risk.

Conclusion

In inflammatory bowel disease the clinician must weigh each individual case, understanding both the acute and chronic inflammatory process in the bowel as well as the risks associated with the immunosuppressive drug to be selected in management. The evidence in the literature suggests that treating cases earlier and more aggressively would probably require a less toxic dosage for longer periods of time. Numerous questions remain to be answered regarding the use of cyclosporin in inflammatory bowel disease. Is the best administration oral or intravenous? How frequently should blood levels of cyclosporin be drawn to avoid toxicity? Is there a need for renal biopsies to evaluate the effect on the kidneys when cyclosporin is used for prolonged periods of time? What is the interreaction with other medicines currently used to treat inflammatory bowel disease (steroids, 5-ASA, 6-MP)? Should patients be treated with combined therapy initially, or converted to other immunosuppressive agents after they have shown response to cyclosporin. Controlled trials will be required to answer these and many other questions before cyclosporin can be advised for use by the practicing gastroenterologist.

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USE OF METHOTREXATE FOR REFRACTORY INFLAMMATORY BOWEL DISEASE

Richard A. Kozarek, MD
Section of Gastroenterology
Virginia Mason Clinic - PO Box 900
Seattle, Washington 98111, and
Associate Clinical Professor of Medicine
University of Washington
Seattle, Washington

Abstract. Methotrexate is an antimetabolite with significant anti-inflammatory properties. As such, it has been used in a heterogeneous group of inflammatory disorders and prompted a study of its use in idiopathic inflammatory bowel disease. Eighty percent of 38 patients with refractory Crohn's disease or chronic ulcerative colitis patients had a statistically significant clinical improvement to 25 mg of parenteral methotrexate weekly within 12 weeks. This clinical improvement was associated with steroid reductions and endoscopic and histologic improvement or normalization in a subset of patients. Seventy-seven percent of 30 patients switched to a tapered oral methotrexate dose have maintained remission with oral methotrexate at mean follow-up of approximately one year. Toxicity was generally mild and related to minor liver function abnormalities, nausea and abdominal cramping, or leukopenia, although one opportunistic infection and one case of hypersensitivity pneumonitis were noted. Moreover, given methotrexate's known ability to induce hepatic fibrosis and cirrhosis, long term follow-up of our patients remains necessary. Additional studies will be required to define what place methotrexate will play in the treatment of idiopathic inflammatory bowel disease.

Introduction

Delayed clinical response and potential side effects have limited the acceptance and application of the immunosuppressive agents 6-mercaptopurine (6-MP) and azathioprine as a treatment for idiopathic inflammatory bowel disease.[1,2] Methotrexate is a folic acid antagonist which has both antimetabolite and anti-inflammatory properties.[3] As an antimetabolite it has been used primarily in treating childhood leukemias, and it has been widely applied in psoriasis and various forms of arthritis for its anti-inflammatory effects.[4-9] More recent data suggest that the drug is useful in the treatment of refractory asthma[10,11] and it is currently undergoing

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investigation as therapy for sclerosing cholangitis and primary biliary cirrhosis.[12,13] Because of its effects in a diverse group of conditions in which inflammation is a prominent feature, we used this drug in an open label study to treat patients with refractory Crohn's disease and chronic ulcerative colitis.

Materials and Methods

Thirty-eight patients (Crohn's disease 26, chronic ulcerative colitis 12) with refractory inflammatory bowel disease and in whom surgery was being contemplated were enrolled in an acute short course of parenteral methotrexate. After description of the treatment plan, definition of the investigational nature of the treatment, explanation about alternative therapies, and delineation of potential side effects, informed consent was obtained. Twenty-nine patients were on chronic corticosteroids (> 6 months), 3 on home central hyperalimentation, 31 on active sulfasalazine or metronidazole, and 13 had failed previous 6-MP or azathioprine. Twelve Crohn's patients had primary colonic disease, 11 ileocolitis, and 3 small bowel disease alone. Three patients with gut involvement also had symptomatic esophageal involvement. Ten Crohn's patients had active rectal fistulae and eight patients had previously undergone a total of 26 small bowel or colonic resections. Symptoms were primarily abdominal pain, intractable diarrhea, low grade bleeding, rectal fistulae, or a combination thereof. A single patient with four previous ileal resections had obstruction as her primary complaint. Nine of the chronic ulcerative colitis patients had pancolitis and three proctosigmoiditis. These patients primarily complained of diarrhea, bleeding, and tenesmus.

Baseline work-up included a physical examination, laboratory data (complete blood count, erythrocyte sedimentation rate, chemistry profile, and urinalysis) and either colonoscopy (Crohn's patients) or flexible sigmoidoscopy and biopsy (ulcerative colitis patients). The latter group had all had pancolonoscopy and serial biopsies showing no active dysplasia within one year of methotrexate therapy. A previously published study ranging from 0 (no symptoms or signs of disease) to 15 (severe disease) was recorded for Crohn's patients at baseline and weekly thereafter.[14] For patients with chronic ulcerative colitis a clinical activity index was defined as the sum of degree of bleeding, number of liquid stools, number of extracolonic manifestations, and feeling of well-being and was recorded weekly. This index has previously been published.[15]

The acute treatment phase consisted of 25 mg of methotrexate intramuscularly once weekly for 12 weeks during which time corticosteroid taper was attempted if clinical improvement warranted. In addition to the activity index and follow-up blood work which were obtained weekly, side-effects were recorded, and a single 24 hour methotrexate blood level obtained between week 6 and 10. All patients had repeat endoscopic and histologic studies at week 12. Those patients with significant side effects prior to week 12 or those

patients who did not experience significant improvement at 3 months were withdrawn from methotrexate therapy.

Patients who evidenced significant clinical improvement by week 12 were switched to 15 mg of oral methotrexate weekly and an attempt was made to decrease this dose by 2.5 mg/month thereafter to a minimum of 7.5 mg weekly. Follow-up office visits, symptom scoring, and blood work were done every 2 months and repeat endoscopic visualization was undertaken only if clinically warranted by symptom recrudescence. Attempts were made to discontinue corticosteroids, sulfasalazine, or metronidazole in Crohn's disease patients whereas most ulcerative colitis patients were continued on concomitant sulfasalazine therapy if previously initiated.

Results

Thirty of 38 patients (79%) had significant clinical improvement in the first 12 weeks of treatment including 21 of 26 patients with Crohn's disease (81%) and 9 of 12 patients with chronic ulcerative colitis. At week 12, the modified Crohn's disease activity index had fallen from 12.6 to 4.3, the mean prednisone dose from 21.5 to 6.2 mg, and 9 of the 17 patients on corticosteroids were off medication. Because of previous right colon resection or terminal ileal disease, all Crohn's patients had evaluable disease colonoscopically. Nine of 26 went into endoscopic remission, 5 of whom had no histologic abnormalities noted on random biopsy. In contrast, the ulcerative colitis activity index fell from 12.4 to 5.4 mg at 12 weeks. Mean prednisone dose fell from 39 to 12.7 mg, and only 3 patients could be completely withdrawn. Despite significant endoscopic improvement in 9 patients, only 1 normalized histologically. One of the three acute ulcerative colitis failures had colectomy and the other two substantial corticosteroid increase. Of the 5 treatment failures in Crohn's patients, 2 underwent colectomy, 2 were started on central parenteral hyperalimentation, and the fifth was treated with high dose steroids.

Twenty of the 21 responders with Crohn's disease went onto oral methotrexate with 16 patients (80% chronically treated patients, 62% of all treated patients) maintaining a clinical remission at a mean follow-up of 46.8 weeks. Modified CDAI was 4.5 at week 12 and 3.8 at week 47. Mean prednisone dose, in turn, was unchanged at week 47 (3.0 mg compared to 3.3 at week 12). Five of 10 rectal fistulae ultimately healed and mean methotrexate dose at 47 weeks was 12 mg weekly. Four patients were withdrawn from therapy at a mean of 36 weeks of therapy: 2 small bowel obstructions, 1 right colon obstruction, and 1 increase in ankylosing spondylitis symptoms. Three patients (two with multiple previous bowel resections) required resection and the patient with ankylosing spondylitis was switched back to 6-MP which had previously controlled her back pain.

Ten patients with ulcerative colitis (9 responders and 1 non-responder at 12 weeks who refused surgery and had severe diabetes mellitus) underwent weekly oral methotrexate therapy. Seven patients

(70%, 58% of total ulcerative colitis patients) have maintained a clinical response at a mean follow-up of 50 weeks and a range from 12-82 weeks. Mean activity index was 3.8 at 12 weeks and 3.0 at 50 weeks whereas mean steroid dose was 8.3 at 12 and 9.8 mg at 50 weeks. Mean methotrexate dose at 50 weeks was 13.9 mg weekly. Of the three patients who flared, mean flare occurred at 21 weeks and was treated with colectomy in two and corticosteroid boost in one.

Two serious side effects of therapy occurred. One patient with ulcerative colitis developed hypersensitivity pneumonitis at week 52. This was manifest as pulmonary infiltrates profound hypoxemia, and a lung biopsy demonstrating an intense T cell lymphocytic infiltrate. This pneumonitis responded to drug cessation and high dose corticosteroids. A second patient with Crohn's disease who had had a dramatic clinical response to methotrexate developed a pneumonitis at week 8. Presumed to be viral or a partially treated bacterial pneumonitis, methotrexate was discontinued because of experience with the previous patient. In addition to the above, 4 patients experienced nausea and abdominal cramping or diarrhea within 24 hours of methotrexate therapy, 4 had a mild (< 2 x normal) AST increase, 3 developed transient mild leukopenia, 1 accelerated hair loss, 1 a metallic taste, and 1 split nails. A final ulcerative colitis patient who had a significant autoimmune hemolytic anemia became more anemic with methotrexate therapy. Methotrexate was stopped and colectomy was undertaken.

Discussion

Originally used as an anti-metabolite because of ability to inhibit folic-acid, methotrexate has become increasingly utilized for its anti-inflammatory properties. In doses that have no measurable effect upon cellular or humoral immunity,[7,16,17] methotrexate has been found to inhibit both neutrophil chemotaxis and the wheal-and-flare response.[18,19,20] As such, it has been used to treat a heterogenous group of illnesses to include rheumatoid arthritis, polymyositis, Reiter's syndrome, polymyalgia rheumatica, psoriasis, and asthma.[4-11] It has also been anecdotally reported to improve liver function tests in primary biliary cirrhosis and sclerosing cholangitis [12,13] and is undergoing prospective testing in these latter diseases.

Methotrexate's efficacy in a disparate group of illnesses in which inflammation appears to play a primary role prompted this study to evaluate its effect in patients with refractory inflammatory bowel disease. There is an obvious precedent in treating refractory Crohn's disease and, to a lesser extent, chronic ulcerative colitis with immunosuppressive agents, and both azathioprine and 6-MP have utilized as such.[1,2] Methotrexate may differ, however, because in the dosage utilized measurable immunosuppression does not occur.[18] Moreover, in contrast to 6-MP and azathioprine which often take from 3-6 months to effect clinical improvement, methotrexate appears to work more quickly.[11] Responses at 8-10 weeks of parenteral therapy were usual and several patients responded within the first 4 weeks. Because we

elected to discontinue this medication in all but one patient who failed to respond to 12 weeks of parenteral therapy, it is uncertain what the results of more prolonged treatment with methotrexate would be in the initial non-responders. The patient alluded to above, in fact, had a significant clinical and sigmoidoscopic improvement by week 28 and has currently completed 70 weeks of therapy.

Our current data on the treatment of Crohn's disease [20/26 (81%) response] is comparable to our originally published data in which 11 of 14 (79%) patients went into clinical remission by week 12 and in a which a statistically significant decrease in modified CDAI and prednisone dose were noted (Table 1).[15] Moreover, we have now noted that 9 of 26 patients treated to date have undergone endoscopic remission (Fig. 1 and 2), often healing deep ulcerations and cobblestones into areas of atrophy and mild stenosis. Five of these patients had no residual Crohn's disease on mucosal biopsy, something, I believe, is a function more of sampling error and lack of transmural tissue for analysis than of histologic cure. As support, one patient who healed her ileocolonic anastomosis grossly and histologically had active Crohn's noted upon subsequent resection done for recurrent obstructive symptoms.

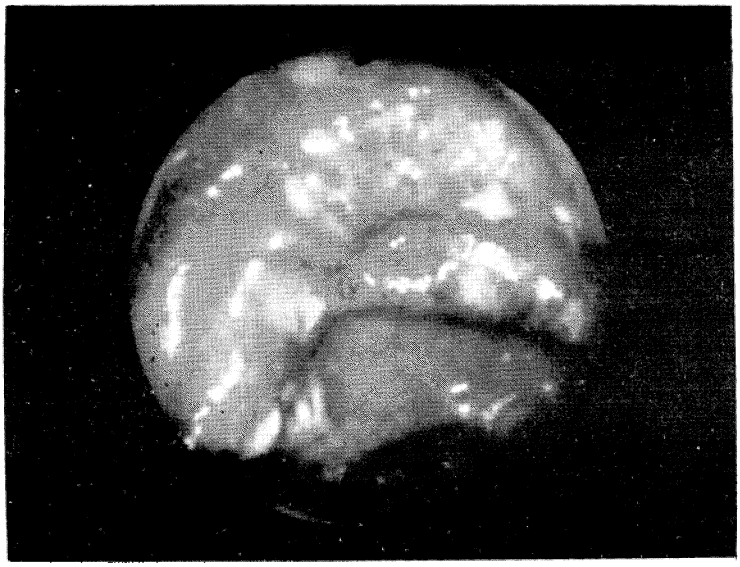

Figure 1. Punctate ulcerations at hepatic flexure in patient with Crohn's colitis.

TABLE 1. Clinical Response and Corticosteroid Dosing with Methotrexate Administration in 14 Patients with Refractory Crohn's Disease

Patient	Disease Site	Follow-up in Weeks	Response	Prednisone Dose at Onset	Prednisone Dose at 12 Weeks	Modified Crohn's Activity Index at Onset	Modified Crohn's Activity Index at 12 Weeks	Ongoing Methotrexate Therapy
1	Colon	40	Yes	20	0	15	5	Yes
2	Colon	30	Yes	0	0	10	2	Yes
3	Small bowel	36	Yes	20	0	15	6	Yes
4	Colon	22	Yes	15	10	15	2	No
5	Colon	22	Yes	10	2.5	7	2	Yes
6	Colon	12	No	40	15	14	9	No
7	Small bowel	12	No	0	0	15	15	No
8	Small bowel	9	Yes	60	0	15	7	Yes
9	Small bowel, colon	18	Yes*	0	0	15	7	Yes
10	Small bowel	12	Yes	15	15	13	6	Yes
11	Small bowel	20	Yes	60	20	15	3	Yes
12	Colon	32	Yes	20	0	11	1	Yes
13	Small bowel colon	12	No	40	15	12	10	No
14	Small bowel colon	26	Yes	0	0	4	0	Yes
Mean+		22.5		21.4±5.6	5.5±2.0**	13.3±0.9	5.4±1.5++	

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* Patient relapsed off parenteral methotrexate
\+ Mean is ± the standard error of mean where applicable
** P = 0.0006 determined by paired t-test
++ P = 0.0001 determined by paired t-test

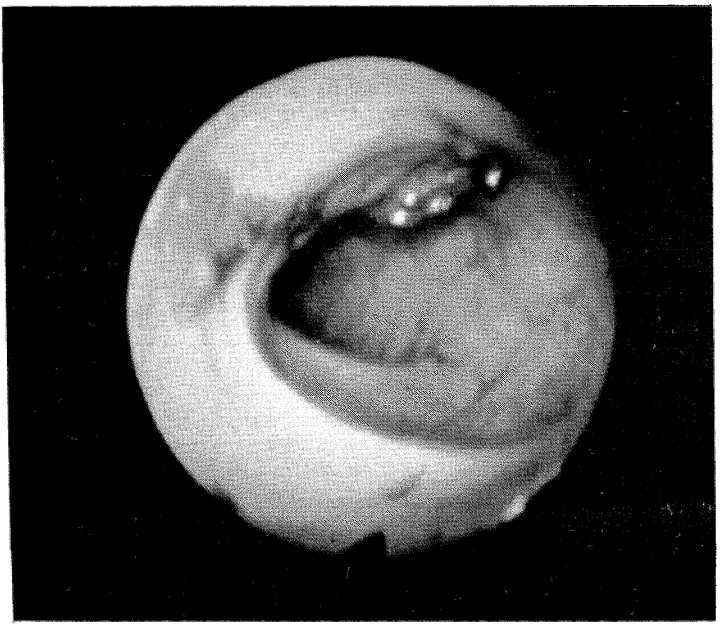

Figure 2. Complete healing of right colon at week 12, in patient depicted in Figure 1.

The current data further extends our experience utilizing oral methotrexate in previously refractory Crohn's disease patients who are switched to oral therapy.[15] Three-quarters of such patients remain in significant remission as defined by the modified CDAI and half have healed their rectal fistulae at one year. Relapses, nevertheless, occur and therapy was subsequently stopped in 3 patients who eventually required resection of obstructing and actively inflamed loops of bowel. Two of the 3 had had previous ileocolon resections.

In contrast to Crohn's disease in which symptomatic and endoscopic healing were often dramatic, chronic ulcerative colitis patients often maintained low-grade disease activity manifest by minor bleeding or diarrhea. Despite disease activity index falling from 12.4 to 5.4, and corticosteroid dosage from 39 to 12.7 mg at 12 weeks, only 3 patients could be completely withdrawn from steroids and only 1 had a normal appearing histology. A tendency for incomplete remission in patients with chronic ulcerative colitis treated with azathioprine or 6-MP has been previously noted.[21]

The current data suggest that oral methotrexate can maintain ulcerative colitis in remission, similar to its efficacy in Crohn's disease. Thus, 70% of chronically treated patients had no significant deterioration in their clinical status (activity index 3.8 at week 12, 3.0 at week 50) although low doses of corticosteroids (mean 9.8 mg) were often required concomitantly. In contrast to Crohn's disease, whether chronic immunosuppressive or methotrexate therapy should be used in a surgically curable disease such as ulcerative colitis remains problematic, and deserves further study.

Methotrexate side effects deserve special mention. Significant leukopenia development with increased susceptibility to infection occurred in a single patient, who developed pneumonitis. This should be preventable with leukocyte monitoring and will respond to leukovoren rescue, if necessary.[22] Minor leukopenia developed in 2 additional Crohn's patients, one of whom had liver and bone marrow granulomas plus hypersplenism. An additional patient had probable marrow suppression and accentuation of a chronic hemolytic anemia necessitating medication withdrawal at 4 weeks of therapy. Transient nausea, diarrhea, and abdominal cramping usually occurring within 24 hours of treatment occurred in 11% of patients. These symptoms may respond to lowering the dose or changing from oral to parenteral medication. Brittle nails and accentuation of hair loss occurred in one patient each.

Additional side effects deserve special mention. Transient AST elevations occurred in 11% of patients. While probably of no significance in the short-term, long-term methotrexate has been associated with the development of hepatotoxicity with fibrosis and cirrhosis.[23-31] Such liver changes appear to occur more commonly in patients who receive daily as opposed to weekly therapy, individuals who drink alcohol, and individuals who have received a cumulative dose in excess of 1.5-3 grams. Such toxicity has not been noted in arthritis patients treated with a weekly regimen for several years [32,33] but does not preclude the fact that liver biopsies may ultimately be required for patients requiring long-term therapy.

Prolonged administration of methotrexate may also be associated with additional toxicities. While the drug is not carcinogenic, it is teratogenic.[5] As such, it must be used in conjunction with birth control in individuals of either sex.

Finally, the major toxicity noted in this series was the development of hypersensitivity pneumonitis in a patient who had been on methotrexate for 1 year. Presenting with fever, dyspnea, pulmonary infiltrates, and a T cell alveolar infiltrate, this pneumonitis can be fatal if not recognized.[34,35] As such, patients being treated with methotrexate should be instructed to report lingering upper respiratory infections, dyspnea, or non-productive cough. A depressed carbon monoxide diffusing capacity (D_LCO) is an early diagnostic clue.[35] While rare, 17 cases have been compiled in the rheumatologic literature.

Unanswered Questions

The dosage regimen used for our patients was an arbitrary one and generally in excess of that utilized in the rheumatologic literature. It was chosen to assure that absence of clinical response was not related to inadequate medication and was given parenterally to assure both compliance and adequate tissue levels. Parenteral therapy and the 25 mg dose may have been fortuitous as switching to a lower oral dose was associated with ultimate relapse in a significant number of patients in this study. Nevertheless, could oral medication have been initiated, particularly in patients without a previous bowel resection? Was a 12 week trial adequate to assure lack of efficacy in

the non-responders? What is the minimum dose required to induce or maintain a remission? What are the long-term toxicities? Can we stop the drug and maintain a prolonged clinical remission? Can we use it short-term as sole therapy in less ill patients? Additional studies are required to define what place methotrexate will play in the treatment of inflammatory bowel disease.

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THERAPEUTIC STRATEGIES IN IBD: CASE DISCUSSION WITH COMPUTER-AIDED AUDIENCE PARTICIPATION

Moderator: Stephen B. Hanauer, USA

Panel: David Sachar, USA
Alan Thomson, Canada
Paul Rutgeerts, Belgium
Daniel Rachmilewitz, Israel

Introduction

The final session of the Inflammatory Bowel Disease meeting was an interactive session between a panel of medical experts and the audience, assisted by a computer-aided slide presentation, provided immediate feedback to predetermined questions regarding specific case-management decisions. Three common presentations of inflammatory bowel disease were presented to highlight evolving therapeutic strategies. A summary of each case, audience responses, and a synopsis of the ensuing discussion follow.

Case 1:

A 32-year-old female presents with a five year history of episodic rectal bleeding attributed to hemorrhoids. She had a three year history of intermittent bleeding associated with constipation and presented to a general practitioner with a two-month history of urgency, tenesmus, and rectal bleeding. Of note, she had stopped smoking cigarettes three months prior to her presentation. Her physical and perianal examinations were normal, as were the CBC and sedimentation rate. A rigid proctoscopy revealed erythema and granularity to the limit of the examination at 15 cm, and stool cultures for ova, parasites, enteric pathogens, and C. difficile were negative. Upon referral to a gastroenterologist, a flexible sigmoidoscopy revealed an abrupt end to the erythema and friability at 20 cm with normal appearing mucosa from 20 to 60 cm. Biopsies were performed which revealed normal mucosa at 25 cm and superficial inflammatory changes consistent with active ulcerative colitis at 15 cm.

Question: How would you manage this patient?

D. Rachmilewitz and J. Zimmerman (eds.), Inflammatory Bowel Diseases 1990, 267–274.

-- Oral therapy 6%
-- Rectal therapy 67%
-- Oral and rectal therapy 27%

Question: Which rectal therapy would you use?

-- Sulfasalazine 3%
-- 5-ASA 61%
-- Steroids 35%
-- 4-ASA 1%

Question: What form of rectal therapy would you recommend?

-- Enema 48%
-- Foam 32%
-- Suppository 20%

Question: Which oral therapy would you use?

-- Sulfasalazine 45%
-- 5-ASA 52%
-- Steroids 0
-- 4-ASA 3%

Case 1 (continued):

The patient responded to nightly 4 gm, 5-ASA enemas with dramatic relief in symptoms after two weeks. She continued with a trace of blood in her stool and complained of the inconvenience of nightly therapy. A flexible sigmoidoscopy revealed healing of the mucosa, except for persistence of inflammatory changes in the distal 5 cm. The patient responded to two, 500 mg 5-ASA suppositories nightly and, after three weeks, was completely healed.

Question: Would you give this patient maintenance treatment?

-- Yes 60%
-- No 40%

Question: What would you give for maintenance treatment?

-- Continue 1 gm suppositories 7%
-- Reduce nightly dose to 500 mg 32%
-- Reduce to 1 gm every other night 26%
-- Change to oral therapy 35%

Question: How long would you continue maintenance therapy?

-- Three months 11%
-- Six months 9%
-- One year 41%
-- Indefinitely 39%

Discussion:

The patient represented a common presentation of ulcerative proctitis. The recent availability of topical 5-ASA has already been recognized by practicing gastroenterologists as an effective, preferred (by 61% of the audience) therapy for distal ulcerative colitis. Data on the superior efficacy of 5-ASA enemas over steroid enemas was reviewed by Dr. Rachmilewitz, and Dr. Sachar reviewed the data on efficacy and spread of 5-ASA suppositories for proctitis. The need for maintenance therapy was highlighted and the audience was mixed regarding the choice of oral versus topical maintenance therapy. Few data are available on the ability to maintain distal colitis in remission with oral therapy after a response to topical therapy. In controlled trials, both oral and topical therapy with 5-ASA are effective maintenance treatments. The effect of cigarette smoking in the prevention of, and smoking cessation in the induction of remission of ulcerative colitis was reviewed.

Case 2:

A 31-year-old male was diagnosed as having total ulcerative colitis at age 17. He was treated successfully with steroids acutely, then maintained on sulfasalazine. He presented with three relapses in the past four years, despite maintenance sulfasalazine. Each relapse was treated successfully with steriods followed by sulfasalazine maintenance. Each relapse was more difficult to control and the patient had undergone periodic colonoscopy which revealed mild, pancolitis without dysplastic changes.

One month prior to his presentation, he had increased the dose of sulfasalazine from 2 to 3 gm because of insufficient prophylactic effect, but he was not able to tolerate the higher dose because of headache and nausea. With a reduction back to the 2 gm dose, he presented with increasing symptoms of colitis which were aggravated by a recent course of indomethacin for back pain.

Question: How would you treat this relapse?

-- Continue sulfasalazine, add high-dose steroids 10%
-- Stop sulfasalazine, treat with high-dose steroids 15%
-- Treat with high-dose steroids and 5-ASA 48%
-- Treat with high-dose 5-ASA alone 27%

Case 2 (continued):

The patient responded to high-dose steroids and sulfasalazine at a dose of 2 gm daily. Acetaminophen was substituted for the back pain. After six weeks his disease is brought under control.

Question: What would you do now for maintenance?

-- Continue sulfasalazine at 2 gm with low-dose alternate day steroids	14%
-- Try increasing sulfasalazine to highest tolerated dose	3%
-- Switch to 5-ASA at 0.75 gm per day	13%
-- Switch to 5-ASA at 1.5 gm per day	70%

Case 2 (continued):

Steroids were discontinued and the patient was put on oral 5-ASA (1 gm/day) as maintenance. The patient discontinued all medication after six months and returned with a flare-up one year later which was treated with 60 mg of prednisone. Upon tapering to 20 mg, he was found to have active ulcerative colitis of the distal 30 cm.

Question: In an effort to withdraw oral steroids, what would you add?

-- Oral 5-ASA	28%
-- Rectal 5-ASA	3%
-- Rectal steroids	3%
-- Oral + rectal 5-ASA	38%
-- Oral 5-ASA + rectal steroids	18%

Case 2 (continued):

The patient was placed on combination oral (1.5 gm) and rectal (500 mg suppositories b.i.d.) 5-ASA and responded. Six months later, a scheduled colonoscopy revealed indefinite dysplasia in the presence of mild pancolitis. He was treated with 3 gm, oral 5-ASA and repeat colonoscopy revealed high-grade dysplasia in a flat, raised placque. He underwent colectomy with formation of an ileoanal pouch and recovered without symptoms until five months post-surgery when "pouchitis" developed.

Question: How would you treat this pouchitis?

-- Metronidazole	34%
-- 5-ASA	54%
-- Sulfasalazine	0
-- Steroids	12%

Discussion:

Case 2 presents many aspects of the chronic treatment of ulcerative colitis. Many patients are unable to tolerate sufficient doses of sulfasalazine to maintain remission. Compliance with sulfasalazine is often reduced due to intolerance. Furthermore, non-steroidal anti-inflammatory drugs are recognized to aggravate the inflammation of inflammatory bowel disease, and are, at times, taken for headaches related to sulfasalazine.

It is recognized that many patients will have a variable extent of their colitis depending upon the phase of their illness. Some patients treated with oral steroids or sulfasalazine may continue with distal colitis, despite proximal healing. Oral and topical 5-ASA can be used in combination in these difficult to control patients. 1.5 gm per day of 5-ASA is comparable to 3 gm of sulfasalazine to induce remissions in patients with mild to moderate ulcerative colitis with less than half the number of reported side effects. Dr. Rutgeerts presented data from his study which showed that 750 mg per day of 5-ASA is equivalent to 1.5 gm of sulfasalazine for maintenance therapy.

Dr. Sachar reviewed the interpretation of dysplasia and cancer in ulcerative colitis and emphasized the need for rebiopsies when indeterminant changes are associated with active inflammation. Indications for surgery in ulcerative colitis include: intractable hemorrhage, toxic megacolon which does not respond to medical treatment, confirmed dysplasia or cancer, and complications or failure to respond to medical therapy.

While colectomy and ileostomy are considered a cure for ulcerative colitis, the new, sphincter-saving procedures with ileal reservoirs are recognized to have the potential for distal ileal inflammation ("pouchitis"). The exact etiology of pouchitis is uncertain; however, it is recognized to occur much more frequently in patients operated for ulcerative colitis than polyposis. Pouchitis may be related to bacterial overgrowth and production of bacterial products such as short-chain fatty acids and seems to respond to antibiotic therapy aimed at the treatment of anerobic bacteria (metronidazole). A few case reports have described response to 5-ASA, but severe inflammation may require a course of steroids in conjunction with antibiotics.

Case 3:

A 17-year-old student had visited an emergency room three times over four years with abdominal pain. One week before his brother's wedding, he presented to his physician with daily abdominal pain

located in the right lower quadrant and exacerbated by meals. His appetite was diminished and his bowel movements had become irregular with some diarrhea. He had lost 20 kg over the past 12 months, and on physical examination there was tenderness and fullness in the right lower quadrant. Laboratory studies revealed an hematocrit of 32%, hemoglobin 10.9, WBC 12.0, albumin 3.5 g dl, and a small bowel follow through demonstrated narrowing of the distal 30 cm of ileum with cobblestone formation. A CT scan revealed thickening of the small bowel loops in the right lower quadrant without evidence of an abscess and a colonoscopy demonstrated normal colonic mucosa to the ileocecal valve which was constricted preventing further passage. A biopsy of the ileocecal valve revealed a non-caseating granuloma.

Question: What therapy would you choose for this patient?

-- Medical therapy 45%
-- Diet therapy 0
-- Medical and diet therapy 47%
-- Surgery 8%

Question: What diet therapy would you choose?

-- Elemental diet 33%
-- Liquid polymeric 14%
-- Low-residue 53%

Question: What medical therapies would you choose?

-- Antibiotic 2%
-- 5-ASA 16%
-- Sulfasalazine 2%
-- Corticosteroids 31%
-- Antibiotic + steroids 10%
-- Antibiotic + 5-ASA 7%
-- Steroids + 5-ASA 29%
-- Steroids + sulfasalazine 3%

Case 3 (continued):

The patient was treated with oral prednisone, 40 mg daily, and improved as the steroids were withdrawn over three weeks. Six months after stopping therapy, he relapsed and was brought under control with high-dose steroids. The steroids were tapered to 10 mg of prednisone every other day and the patient was feeling well.

Question: What would you do next?

-- Maintain with steroids at this dose	9%
-- Continue to reduce steroids slowly	24%
-- Continue to reduce steroids and add another agent	67%

Question: If you choose to add another agent, what would it be?

-- Oral 5-ASA	87%
-- Oral sulfasalazine	7%
-- Antibiotics	6%
-- Immunosuppressives	0

Case 3 (continued):

The patient was tapered off steroids and maintained on oral 5-ASA (Claversal[R] 1.5 gm/day). He remained in remission for approximately one year and therapy was discontinued. After one additional year in remission, he relapsed, developed repeated obstructive episodes despite continuous high-dose steroids, and required an ileocecal resection with ileocolonic anastomosis.

Question: How would you manage this patient post-surgically?

-- No treatment	40%
-- Immunosuppressives	2%
-- 5-ASA	54%
-- Sulfasalazine	2%

Discussion:

Case 3 represents a typical presentation of ileitis with an initial response to medical treatment. The usefulness of diet therapy was reviewed and it appeared that the audience preferred to use diet therapy as adjunctive rather than primary treatment. There remains quite a diverse range of preferences for initial therapy of ileitis including the use of steroids alone, steroids with 5-ASA, or steroids with antibiotics.

The audience recognized the difficulty in maintainence therapy with Crohn's disease and the tendency to flare-up with tapering of steroids. Despite limited data in acute Crohn's disease, 5-ASA was felt to be an appropriate adjunctive agent to steroids. Dr. Thomson reviewed the multi-center study demonstrating efficacy of Claversal[R] at a dose of 1.5 gm daily in preventing relapses of inactive Crohn's

disease compared to placebo which led a majority of the audience to recommend maintenance therapy with 5-ASA after surgery, despite the absence of supportive data. Dr. Sachar and Dr. Rutgeerts reviewed data on post-surgical recurrences of Crohn's disease, the rate of which differs according to inflammatory or fibrotic nature of the disease. The need for studies to confirm efficacy of various pharmacologic agents in prolonging post-surgical remission was emphasized.

Index of Subjects

Developments in Gastroenterology

1. A. S. Peña, I.T. Weterman, C.C. Booth and W. Strober (eds.): *Recent Advances in Crohn's Disease.* Proceedings of the 2nd International Workshop on Crohn's Disease, held in Noordwijk/Leiden, The Netherlands (1980). 1981 ISBN 90–247–2475–9

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