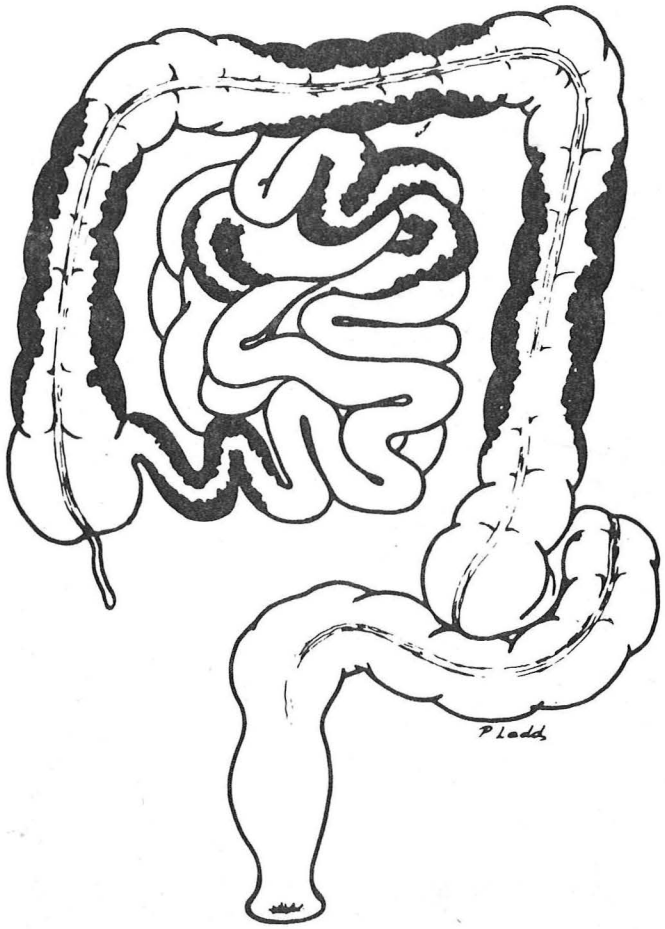
GI

CROHN'S DISEASE



MEDICAL GRAND ROUNDS

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Case 1

C.M., is a 26 year old lady who presented with episodes of abdominal pain, fever and diarrhea. She reported two types of abdominal pain. The first was a steady pain localized to the right lower quadrant. The second was cramping in nature and occurred after meals. She stated that she experienced 5-6 semi-formed stools each 24 hours. There was no obvious blood or mucus in the stools. She had lost 25 pounds during the past 4 months. Physical examination was normal except for a 3 x 4 cm mass in the right lower quadrant and a positive stool guaiac. Laboratory: Hemoglobin -10.2 gm/dl, Hematocrit - 30%, WBC - 10,200. Other laboratory studies were normal. Contrast examination of the small bowel was compatible with a diagnosis of Crohn's disease and is shown in Figure 1 of the Appendix.

Case 2

D.B., is a 30 year old man who was diagnosed in 1978 as having Crohn's disease. He was treated with prednisone and Azulfidine and symptoms, which consisted of abdominal pain and diarrhea, abated. He experienced symptomatic recurrences of disease in 1980, 1981 and 1982 and each time was treated with prednisone and Azulfidine. In August 1983, abdominal pain became more severe and he developed nausea and vomiting. He was hospitalized and a diagnosis of small bowel obstruction was made. The obstruction did not resolve and a laparotomy was performed. An eight cm area of diseased ileum with stenosis was removed as well as most of his right colon. He became asymptomatic but returned in March 1984 with recurrent Crohn's disease. Contrast examination of the small bowel is shown in Figure 2 (Appendix).

INTRODUCTION

Crohn's disease is one of the non-specific idiopathic inflammatory bowel diseases (IBD). In addition to Crohn's disease, ulcerative colitis (including ulcerative proctitis) is also included under the category of non-specific idiopathic IBD. There are a number of other causes of IBD. These include bacterial, viral, parasitic and fungal diseases as well as miscellaneous types of IBD such as ischemic colitis (see Classification, Table I).

The cause(s) of Crohn's disease and ulcerative colitis remains obscure years after the original descriptions of the diseases. In this Grand Rounds I will first define the various types of IBD and then limit my discussion, for the most part, to Crohn's disease. Throughout the discussion, however, comparisons will be made between Crohn's disease and ulcerative colitis.

CLASSIFICATION OF INFLAMMATORY BOWEL DISEASES

As mentioned previously the term IBD encompasses all inflammatory disorders affecting the small bowel and colon even though the term is used by many to denote only Crohn's disease and ulcerative colitis. A classification of inflammatory disorders of the intestine is listed in Table I.

TABLE I. CLASSIFICATION OF INFLAMMATORY BOWEL DISEASES

Idiopathic Inflammatory Bowel Disease	
	Crohn's Disease
	Ulcerative Colitis
Inflammation Caused by Infectious Agents	
Viruses -	Lymphogranuloma venereum
	Herpes simplex virus
	Norwalk virus
	Cytomegalovirus
Bacteria -	Shigella
	Salmonella
	Campylobacter species (jejuni, fetus)
	Pseudomonas
	Yersinia
	M. tuberculosis
	N. gonorrhoeae
	Treponema pallidum
Chlamydia	
Fungi -	Histoplasmosis
	Blastomycosis
Parasites -	*E. histolytica*
Inflammation Associated with Motor Disorders	
	Diverticulitis
	Solitary rectal ulcer
Inflammation Induced by Therapeutic Intervention	
	Effects of enemas and laxatives
	Drug-induced colitis (antibiotic-induced colitis, colitis due to methyldopa or gold salts)
	Colitis due to radiation
	Colitis in graft versus host disease
	Colitis following small intestinal bypass and diversion of the fecal stream
Miscellaneous Causes	
	Collagenous colitis
	Microscopic colitis (1)
	Necrotizing enterocolitis in cancer patients

In the strictest terms, the diagnosis of idiopathic IBD can be established only after many of the above diseases have been excluded. This does not mean

(at least in my opinion) that all patients should have cultures or serologic tests for each of the above organisms or that tests for all of the other causes of IBD should be performed. The work-up of a patient with IBD should include routine stool cultures (i.e. salmonella and shigella) and cultures for campylobacter and Yersinia. If sexually transmitted disease is suspected, cultures for N. gonorrhoeae and tests for T. pallidum should be performed. Chlamydia also should be a consideration. In addition, stools for ova and parasites should be collected. Clostridium difficile toxin should be assayed to determine if the patient has antibiotic-induced colitis. In an elderly patient, ischemia should always be in the differential diagnosis and in a patient with small bowel disease, lymphoma or carcinoid should be considered.

Once the more common causes of IBD have been excluded, idiopathic Crohn's disease or ulcerative colitis are likely considerations.

HISTORICAL PERSPECTIVE

Crohn's disease was first described in 1932 by Drs. Burrill B. Crohn, Leon Ginzberg and Gordon D. Oppenheimer (2). Prior to the original publication in which 14 cases were described, patients with what is now known as Crohn's disease were diagnosed as having "chronic appendicitis" or ileal tuberculosis. Pathologists had long been familiar with the gross and microscopic features of intestinal granulomas. In 1920 Tietze published a paper in which he cited 281 references from the world literature on the subject of intestinal granulomas (3) and in Dr. Crohn's own laboratory Drs. E. Moschowitz and A.O. Wilensky had studied and published a paper on nonspecific granulomas of the intestine (4). All of these early publications were devoted to the pathology of granulomas. The clinical aspects of the findings had been omitted and it was not until 1932 that Crohn along with Ginzberg and Oppenheimer put the findings together as a description of a new disease.

The first of the 14 cases in the original publication is summarized below:

> A 17 year old man was seen in 1930 for evaluation of fever, diarrhea, abdominal pain and a tender, palpable mass in the right lower quadrant of the abdomen. A diagnosis of "ileocecal tuberculosis" was made. Studies of the sputum, gastric contents and stools were negative for tubercle bacilli. Skin tests were negative as were the radiographs of the chest. The patient was treated with oxygen insufflation into the peritoneal cavity but this failed to alter the course of the disease. Dr. Crohn pleaded with Dr. Berg, the senior surgeon, to perform an exploratory laparotomy. Dr. Berg declined initially because previous attempts to operate on patients with ileal tuberculosis had led to disastrous results. However, since all modern tests for tuberculosis were negative, Dr. Berg relented. An exploratory laparotomy

was performed and for the first time a specimen of typical granulomatous ileitis was examined. All tests for tuberculosis were negative, including all cultures and inoculations into guinea pigs and other susceptible animals.

Within 2 years, Dr. Crohn and his colleagues had collected 13 identical cases which, along with the above case, constituted the original publication (2). Several of the original cases were patients who had undergone previous futile operations for "chronic appendicitis" and who had chronic intestinal fistulas that opened onto the abdominal wall. The fistulas always occurred in the scar of the previous surgery. One of the original patients had 11 abdominal wall fistulas. The case histories of these original 14 patients were presented by Dr. Crohn at the annual meeting of the American Medical Association in New Orleans in 1932. Other dates of historical interest are listed in Table II.

TABLE II. OTHER DATES OF HISTORICAL INTEREST

1933	-	Harris, Bell and Brunn (5) - described jejunal involvement in addition to ileal disease
1934	-	Kantor (6) - described radiographic findings in Crohn's disease and coined the term, "string sign"
1934	-	Colp (7) - described colonic involvement either segmentally or in contiguity from the terminal ileum
1937	-	Gottlieb and Alpert (8) - described involvement of duodenum
1949	-	Ross (9) - described granulomatous disease of the stomach

LOCATION OF CROHN'S DISEASE WITHIN THE INTESTINAL TRACT

This is illustrated in Figure 1. As indicated by data from the National Cooperative Crohn's Disease study, 30% of patients have only small bowel disease, 15% have only colon disease and 55% have small bowel plus colon disease (10).

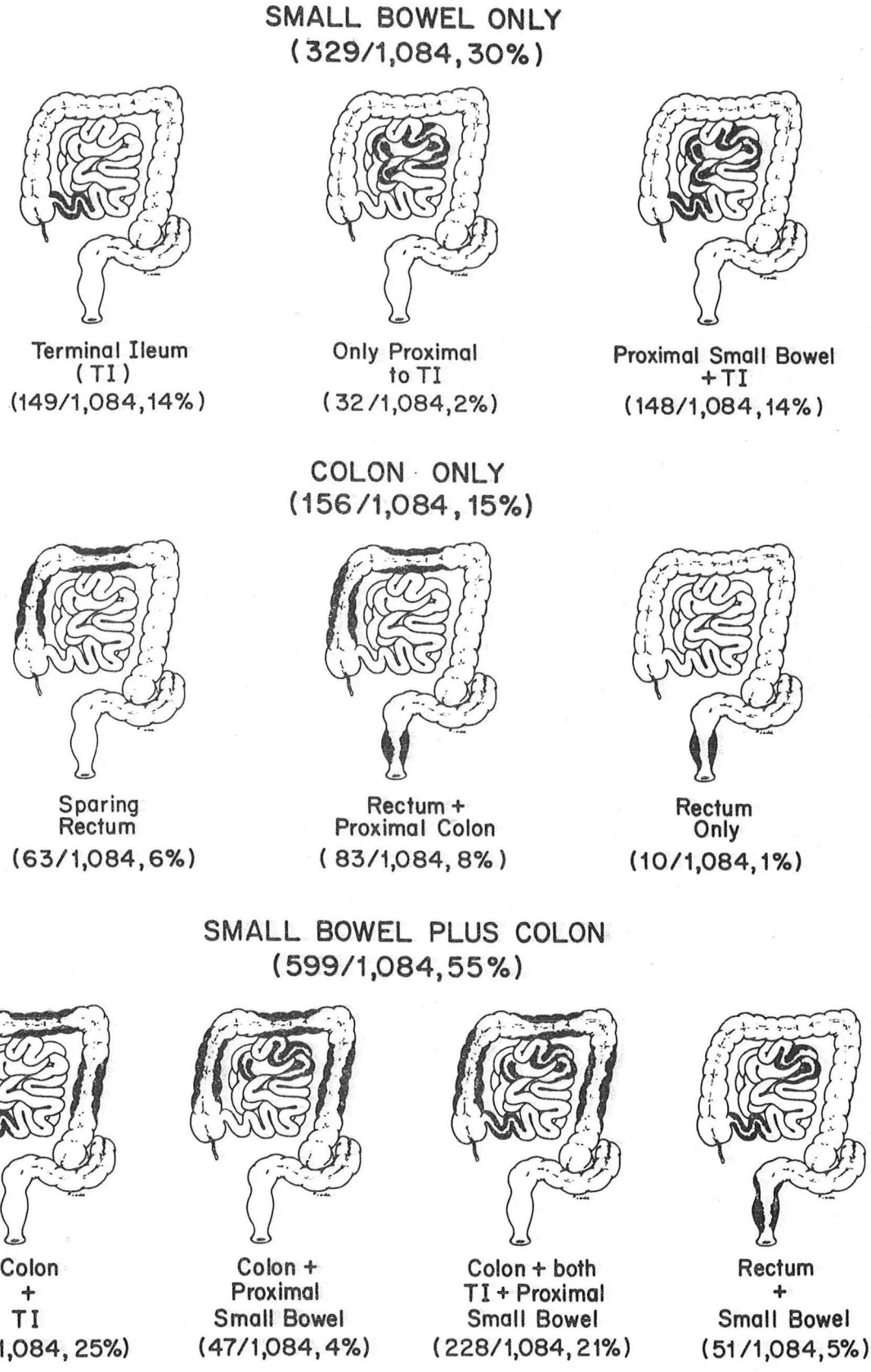

Figure 1. Location of Crohn's disease in 1,084 patients considered for randomization in the National Cooperative Crohn's disease study (from Ref. 10).

PATHOLOGY

Although sometimes the pathologist can characterize the pattern of inflammation and assign the condition to one of the categories listed in the classification above, the final diagnosis usually requires correlation between clinical findings, roentgenographic and/or colonoscopic interpretation, microbiologic data and response to therapy. In some patients there are reasons to obtain biopsies of the colon either at the time of proctoscopy or colonoscopy or of the terminal ileum at the time of colonoscopy. Reasons to do a biopsy include establishment of the presence of colitis, differentiating between idiopathic IBD and other inflammatory conditions, assistance in differentiating ulcerative colitis from Crohn's disease, documentation of the severity and activity of the disease, and detection of dysplasia and carcinoma which is more important in ulcerative colitis than in Crohn's disease. (See Medical Grand Rounds, Ulcerative Colitis and Colon Cancer: Risks, Detection, and Prevention, Mark Feldman, M.D., August 12, 1982).

There are several ways in which a biopsy may help differentiate Crohn's disease from ulcerative colitis: a) it may demonstrate granulomas (see Table III); b) may demonstrate aphthous lesions; c) may confirm skip areas; d) may confirm presence of a normal rectum (this is less important than previously believed since some patients with ulcerative colitis can also have normal rectums); e) may identify the pattern of inflammation (diffuse inflammation occurs more frequently in ulcerative colitis than in Crohn's disease while focal inflammation is more common in Crohn's disease).

TABLE III. INCIDENCE OF GRANULOMAS IN RECTAL BIOPSY OF PATIENTS WITH CROHN'S DISEASE (ADAPTED FROM HAGGITT, R.C., REF. 11)

SITE OF DISEASE	% RECTAL BIOPSIES WITH GRANULOMAS	REFERENCE
Small bowel	0.9	12
Small bowel and colon	7.5	
Colon	5.9	
Colon and rectum	30.0	
Small bowel	13.0	13
Small bowel and colon	13.0	
Colon only	37.0	
All sites	28.0	14
Colon	39.0	15
Colon	60.0	16
Small bowel	60.0	17
Colon	84.0	18

If a granuloma is found, the diagnosis of Crohn's disease is relatively secure. On the other hand, if a granuloma is not found, the pathologic results mean very little since, in clinical practice, granulomas will not be found in the majority of patients who ultimately are diagnosed as having Crohn's disease.

Occasionally, rectal or colonic biopsies may be useful in differentiating inflammation secondary to specific infectious agents (infectious colitis) from ulcerative colitis or Crohn's disease. Some general guidelines for differentiating infectious from idiopathic colitis are listed in Table IV.

TABLE IV. HISTOLOGIC FEATURES THAT MAY HELP IN DIFFERENTIATING INFECTIOUS COLITIS FROM ULCERATIVE COLITIS OR CROHN'S DISEASE (ADAPTED FROM HAGGITT, R.C., REF. 11)

HISTOLOGIC FEATURE	INFECTIOUS COLITIS	IDIOPATHIC IBD	
		ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Inflammation			
Focal	++	-	++
Neutrophils*	+++	++	+
Mononuclear cells	- or +	+++	+++
Edema	++	- or +	+++
Distortion of crypt - architecture/atrophy	-	+++	+
Mucus depletion	- or +	+++	- or +
Granulomas**	-	-	++

* Neutrophils in infectious colitis are often concentrated in the lamina propria and are not accompanied by marked increases in mononuclear cells. In Crohn's disease and ulcerative colitis, neutrophils tend to accumulate in the crypt lumen and epithelium. They are associated with increased mononuclear cells.

** Microgranulomas and foci of granulomatous inflammation which includes focal aggregations of macrophages may be seen in some infections such as those caused by salmonella and campylobacter. These granulomas differ from epithelial granulomas seen in Crohn's disease in that they are not as compact and discrete and they also lack giant cells. Epithelial granulomas can be seen in tuberculosis, Yersinia pseudotuberculosis and chlamydia trachomatosis.

Additional pathologic features differentiating ulcerative colitis from Crohn's disease are listed in Table V.

TABLE V. PATHOLOGIC FEATURES DIFFERENTIATING ULCERATIVE COLITIS FROM CROHN'S DISEASE
(ADAPTED FROM LENNARD-JONES, ET AL., REF. 19)

CHARACTERISTIC	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Inflammation	Mucosal and submucosal, except in toxic megacolon	Transmural
Submucosa	Normal or reduced width	Normal or increased width
Vascularity	Prominent	Seldom prominent
Lymphoid hyperplasia	Mucosa and submucosa	Transmural, plus pericolic lymph nodes are enlarged
Crypt abscesses	Common (> 70%)	Uncommon
Mucus secretion	Impaired	Slightly impaired
Paneth cell metaplasia	Common	Rare
Fissures	Absent	Common

PATHOGENESIS OF CROHN'S DISEASE

One of the earliest lesions in patients with Crohn's disease is believed to be a small ulceration which overlies lymphoid tissue, especially Peyer's patches. This lesion is associated with active crypt inflammation and contiguous granulomatous inflammation. The proximity of early, focal lesions to intestinal lymphoid tissue suggests that an infectious agent may gain access to the body via the cells of Peyer's patches. Granulomas seen in some patients may represent a non-specific immune-related defect in macrophage function.

There have been numerous attempts to create experimental models for Crohn's disease and ulcerative colitis. Inflammatory bowel disease occurs de novo in numerous animals and in many instances the diseases are due to an infectious agent. In most cases, however, these animal models do not represent human idiopathic inflammatory bowel disease. Also, there have been numerous attempts to injure the bowel experimentally by administering enzymes or chemicals, by giving various bacteria or viruses to animals, by producing vascular ischemia or lymphatic obstruction or by producing various immunologic manipulations. Almost all of these interventions have failed.

Experimental Enteritis and Colitis

Chemical Models

Carrageenan is used as a food-additive and is present in levels not exceeding 1% in chocolate products, pressure-dispensed whipping cream, evaporated milk, cheese products, ice cream, sherberts, salad dressings, jelly, beer, soups and many other foods (20). Carrageenan acts as a stabilizer in foods and adds bulk. The chemical is a hydrocolloid consisting of a sulfated polysaccharide of galactose and anhydrogalactose. It is found primarily between and within cell walls of red seaweeds. Once degraded (usually by dilute acid), carrageenan has a net negative charge. This allows it to react with positively charged molecules such as protein. Because of its effect on proteins, carrageenan can inhibit the proteolytic activity of enzymes such as pepsin and has been used in some European countries in the treatment of peptic ulcer disease. There have been no ill effects of this therapy in humans (21).

Ulcerative colitis associated with feeding carrageenan has been reported in guinea pigs, rabbits, rats and mice. Clinical manifestations have included weight loss, loose stools and both occult and visible blood in the stools. Ulcerations have been reported throughout the colon but primarily in the cecum. Histologic findings have included mucosal hemorrhages in the cecum, cellular infiltrates, edema, crypt abscesses and degeneration of surface epithelium. In other experiments, carrageenan has been shown to produce granulomas in the mucosa of the colon and cecum of guinea pigs. Granuloma formation was followed by development of mucosal ulceration.

The fact that "colitis" and granulomas have occurred in animals after treatment with carrageenan has stimulated interest in use of this chemical in developing animal models for studying idiopathic inflammatory bowel disease. There is controversy, however, regarding the similarity between carrageenan-induced colitis and human ulcerative colitis or Crohn's disease. For example, carrageenan-induced disease usually begins in the cecum of animals and is associated with a marked macrophage response. Human ulcerative colitis, on the other hand, usually begins in the rectum and is not associated with a marked macrophage response.

Amylopectin sulfate, derived from potato starch, also has been shown to produce colonic ulcerations and inflammation in animals. Additionally, sodium lignosulfonate, another sulfated compound, has caused colitis-like disease in animals. Amylopectin sulfate was tested several years ago in the United States as therapy for peptic ulcer disease. Trials were discontinued, however, probably because of the high incidence of colonic disease in guinea pigs and rabbits treated with the drug. Sulcralfate, a sulfated polysaccharide, used to treat patients with ulcer disease does not cause colitis in animals or humans.

Animal Models (Spontaneous Colitis)

Inflammatory bowel disease has been reported in a number of animal groups.

These include horses, dogs, pigs, rats, mice, lambs, cows and more recently, cotton top marmosets. Colitis in the latter animal is extremely interesting because it has been associated with colon carcinomas. Information related to inflammatory bowel disease in animals is summarized below.

Horses - The disease is usually fatal and is characterized by severe nonbloody diarrhea; cause is not known although believed due to endotoxins since endotoxins from E. coli will produce a similar disease; a stressful event often precedes colitis; Mycobacterium avium has been reported in one case.

Dogs - Terminal ileitis, ileocolitis and segmental granulomatous proctitis with perianal fistulas have been reported. Colitis in boxer dogs is the best described disease (22). It is characterized by exacerbations and remissions. Exacerbations are sometimes precipitated by pregnancy and change in food or environment. The cause is not known. Attempts have been made to compare colitis in boxer dogs to both ulcerative colitis and Crohn's disease (23). However, there is no transmural or mesenteric inflammation in boxer colitis nor have granulomas been described.

Pigs - Lesions resembling Crohn's disease have been described in swine (24). The incidence is about 1% of all animals slaughtered. There are similarities between porcine and human disease in that deep ulcerations occur in both diseases. The cause(s) has not been determined.

Rodents - Ileitis has been reported in the golden Syrian hamster. The disease differs from human disease in that severe coagulation necrosis of villi occur with extension into the submucosa and muscularis. The cause of this disease is not known.

Lambs - The mucosa of the terminal ileum becomes thickened and small ulcerations with pseudomembranes develop. Adjacent lymph nodes become hyperplastic and packed with macrophages or epithelioid cells with occasional giant cells.

Cattle - A disease secondary to Mycobacteria Johnei (Johne's disease) occurs in cattle and resembles Crohn's disease in man. It consists of a chronic granulomatous inflammation that involves the terminal ileum and extends into lymph nodes. It is contagious among cattle and can attack from 2 to 10% of a cattle herd (see paratuberculosis in discussion below).

Bacteria or Viruses as Etiologic Agents

The fact that Crohn's disease and ulcerative colitis occur in areas of the gastrointestinal tract where large numbers of aerobic and anaerobic bacteria reside makes it possible that one or more of these agents play a role in the pathogenesis of idiopathic inflammatory bowel disease. Also, the discovery of new microorganisms that cause "infectious colitis" has sparked new interest in the possibility that some organism(s) or one of their toxic products leads to Crohn's disease and/or ulcerative colitis. Some of these organisms are listed

under inflammation caused by infectious agents in Table I. Other organisms that have stimulated interest as possible etiologic agents, at least for infectious colitis, and possibly idiopathic IBD include Aeromonas hydrophila, Isospora, E. coli O157:H7, and Cryptosporidia.

Results of several studies have revealed bacterial overgrowth in certain patients with Crohn's disease. This has been true especially for some anaerobes such as peptostreptococcus magnus, eubacteria and bacteroides fragilis. Recent studies have revealed a mycobacteria similar to or identical with paratuberculosis johnei in a few patients with Crohn's disease and this is currently under investigation (25,26). Presently, this is the leading contender as the organism most likely to be the cause of Crohn's disease. Bacterial L forms, cell-wall deficient pseudomonas organisms, chlamydia and certain types of E. coli are also being investigated as possible factors in the development of Crohn's disease.

Viruses have also been considered as etiologic agents in patients with Crohn's disease (27,28). Serologic surveys have been performed in regard to adeno-, herpes-, paramyxo-, and picornavirus groups. There have been no differences between patients with Crohn's disease and controls in antibody titer to representative adenoviruses, Coxsackie B, Epstein-Barr, measles, influenza A-2 and B, mumps, parainfluenza 1-4, herpes simplex, respiratory syncytial, cytomegalovirus and five human mycoplasmas. Additionally, the presence of viruses or viral particles has not been found in electron microscopic examinations of tissues from patients with Crohn's disease. Molecular hybridization techniques have also been used in attempts to demonstrate adenovirus DNA in resected specimens from patients with Crohn's disease. These studies also have failed to demonstrate evidence of viruses.

Summary: Although numerous investigators have searched for years for an infectious etiology of Crohn's disease, there are major gaps in our understanding of gastrointestinal aerobic and anaerobic microflora, the mechanisms of bacterial-viral entry, adherence and penetration of the intestinal epithelium and the local gastrointestinal defenses against microbial and viral injury. Current investigation suggests that a paratuberculosis-like organism may be the cause of Crohn's disease.

Immunologic Alterations as Possible Pathogenetic Mechanisms.

Derangements in the immune system have been postulated as the cause of idiopathic inflammatory bowel disease (especially ulcerative colitis) for years. For example, it was believed that an immediate type of immunologic response to exogenous antigens, such as the ingestion of cow's milk or exposure to inhalants, might lead to ulcerative colitis (29). Most hypotheses related to immunologic alterations in the pathogenesis of Crohn's disease have included efforts to involve autoimmunity, lymphocyte sensitization, immunogenetic factors, immune complexes, defective macrophages or some combination of these mechanisms. Many of these efforts also have implicated bacteria, viruses or products of these organisms as inciting agents. These research efforts have led, however, to no consistent hypotheses as to how Crohn's disease might occur. Also, there has been no consistent association between HLA antigens and Crohn's disease except for a positive correlation with HLA B27 in patients with anky-

losing spondylitis and Crohn's disease. Additional studies relating genetic predispostion and Crohn's disease are needed, however, for a more complete understanding of the possible role of heredity in development of Crohn's disease.

Occasionally, ulcerative colitis or Crohn's disease has been noted in patients with severe hypogammaglobulinemia or selective IgA deficiency (30). In other experiments more immunoglobulin-containing lymphoid cells and larger concentrations of immunoglobulins have been found in the terminal ileum of patients with Crohn's disease than in specimens from control subjects. A relative decrease of IgA-containing cells and an increase in IgG and IgM cells was noted in the diseased tissue. Still other investigators have found normal distributions of immunocytes in both normal and diseased tissues from patients with Crohn's disease. Thus, there is controversy as to the relative populations of immunoglobulin-containing cells in patients with Crohn's disease.

Other studies have shown that proportions, as well as absolute numbers of peripheral blood B cells bearing surface IgA or IgM, were increased in patients with Crohn's disease. In another series of experiments, on the other hand, B cell populations in the peripheral blood were reduced in direct relation to the activity of Crohn's disease, its chronicity and effects of therapy (31). Changes in serum secretory IgA levels and salivary IgA production have also been noted in some patients with Crohn's disease.

Numerous experiments have been performed searching for serum antibodies to various tissues, foreign proteins or bacterial or viral organisms in patients with Crohn's disease. Antibodies to thyroid, gastric parietal cell, Epstein-Barr virus or viral gastroenteritis virus or antinuclear antibodies are not found more frequently in patients with Crohn's disease than in control subjects. Results of an early study indicated an increased incidence of antibodies to chlamydial antigens in patients with Crohn's disease. This, however, was not confirmed in subsequent studies. Experiments have shown a higher incidence of serum antibodies to synthetic double-stranded RNA in patients with Crohn's disease and in their relatives than in control families (32). The meaning of these findings, however, is not known.

Increased serum concentrations of the C4 component of complement have been described in patients with Crohn's disease, both during the active phase and when the disease was in remission. Results of other studies have found no differences in the in vitro synthesis of C3 and Clq in diseased tissues from patients with Crohn's disease compared to control levels. Findings in another study indicated that complement activation was correlated with disease activity (33).

Summary: The above is simply a brief summary of studies evaluating the role of the immune system in the pathogenesis of Crohn's disease. Obviously, much more work needs to be done before a consensus can be reached as to whether immunologic abnormalities play a role in the development of Crohn's disease.

Emotional Stress

In 1930, Murray suggested that psychogenic factors might play a role in the pathogenesis of ulcerative colitis (34). Since that time, there have been numerous studies evaluating the psychosocial aspects of patients with either ulcerative colitis or Crohn's disease. Today, most investigators do not believe that psychologic abnormalities cause Crohn's disease but that they may be important in the course of the disease, especially in some patients. For example, emotional factors may play a role in the severity of the disease, in patients' reaction to the disease or in patients' response to therapy.

A number of authors have reported characteristic personality features and coincidences between life stresses and onset of illness in patients with Crohn's disease. Other investigators, on the other hand, have found no such associations (35). In one study an elaborate system of scoring personality characteristics was used to test patients with ulcerative colitis or Crohn's disease and results in the patients were compared to those of a control group. No differences in personality traits were found between patients with ulcerative colitis, Crohn's disease or the controls (36,37). Because of these findings, as well as others, it is not likely that there is one personality disorder or personality trait that describes patients with inflammatory bowel disease.

The association of life-stress situations at the time of onset of idiopathic inflammatory bowel disease also has been evaluated. The experiences of 158 patients with ulcerative colitis, 69 patients with Crohn's disease and a control population were compared (38). No differences were found in the frequency of a broad range of stressful life events between the three groups. In another study, however, results from 50 consecutive patients with idiopathic inflammatory bowel disease were compared with a matched group of normal subjects as to the frequency of six kinds of life crises (39). Twenty-seven (54%) patients with inflammatory bowel disease and only 10 (10%) of controls had experienced bereavement, marriage, divorce, pregnancy, childbirth, or movement to a new community in the preceding 12 months. Only 3 of the patients with inflammatory bowel disease had not experienced a precipitating event prior to diagnosis of the bowel disease. Thus, results of this latter study suggest that some stressful life events may play a role in the overall natural history of idiopathic inflammatory bowel disease.

Working Hypotheses Related to Emotional Stress and Crohn's Disease. (Adapted from Almy, T.P., Ref. 35).

1. Somatopsychic - This relates to the secondary influence of illness on behavior. Almost all investigators agree that Crohn's disease effects the patient's behavior. Any illness characterized by diarrhea, abdominal pain, inanition, fever and prostration, especially when these symptoms occur in a previously healthy person, will understandably lead to a stressful situation. The difficulty of not straying far from a toilet without the possibility of experiencing incontinence and embarrassment constricts physical and social activity and may revive patterns of infantile behavior. In addition, it may erode the adult patient's self-confidence.

2. Psychophysiologic - Life-stress situations and associated emotional reactions occur simultaneously with Crohn's disease in individual patients but are not related necessarily to one another. Both the life-stress situations and the physiologic abnormalities brought on by Crohn's disease contribute, however, to the overall picture of illness.

3. Psychosomatic - This term refers to an adaptive response to stress in which the somatic component involves sustained malfunction and often tissue damage in a single organ or organ system. It is possible that this psychologic mechanism may constitute an important link, at least in some cases, in the exacerbation and/or perpetuation of Crohn's disease. So far,the evidence supporting this hypothesis is minimal and the mechanisms within the bodily reaction to stress which initiate or sustain tissue destruction and chronic inflammation in humans are not yet identified. It is possible that stressful life events somehow alter bodily defenses (e.g., immunologic mechanisms or defense mechanisms against microbial organisms or their toxins). There are examples of reactions to stress in lower animals. For example, the sea cucumber's mechanisms of defense includes extrusion of its gastrointestinal tract which it then regenerates. Also, colitis which occurs in the marmoset is believed to occur when the animals are in captivity and not when they are in their natural habitat. Presumably, captivity changes something, perhaps their emotional well-being, which, in turn, leads to colitis.

Summary: Emotional factors are unlikely as pathogenetic mechanisms in patients with Crohn's disease. However, it is possible that they are contributing factors in causing exacerbations of the disease.

CLINICAL FINDINGS

Incidence, Epidemiology and Demography

Crohn's disease has a worldwide distribution (Table VI). It is less common in underdeveloped countries. In contrast to ulcerative colitis which has stabilized in incidence, the incidence of Crohn's disease has increased during the past several years. This increase has occurred primarily in younger age groups. In general, there is no sex predominance although in some series there is a higher incidence in young females. In some reports children and teenagers make-up about one-third of Crohn's disease patients.

The most frequent age of onset is 15-30 years although the disease occurs occasionally in older patients. The fact Crohn's disease sometimes occurs in several members of a family suggests either an infectious cause or genetic predisposition.

TABLE VI. CROHN'S DISEASE: INCIDENCE, EPIDEMIOLOGY AND DEMOGRAPHY (ADAPTED FROM DONALDSON, R.M., REF. 40)

Worldwide distribution
Prevalence: 10-70 cases/10^5 population
Incidence: 0.5-6.3 cases/10^6 population/year
Increased frequency among Europeans
More common among Jews
More common among whites
Less common in rural areas and underdeveloped countries
Most frequent age of onset: 15-30 years
Increasing incidence over past 20 years (1.4-4 fold)

In addition to being less common in underdeveloped countries, Crohn's disease is also less common in rural areas. The liklihood of developing Crohn's disease appears to increase as people move to more industrialized countries. Originally, many patients with Crohn's disease were of western origin and Crohn's disease tended to be more common among Jewish populations. Now, however, family origin and ethnic relationships tend to be less important. There are, however, more Caucasions with Crohn's disease than Negroes. In general, there is an increased incidence of people who smoke cigarettes in patients with Crohn's disease while the opposite is true in those with ulcerative colitis.

Natural History

Based on data from the National Cooperative Crohn's Disease Study, an average interval of 35 months exists from the onset of symptoms to the diagnosis of Crohn's disease (10). Patients in this study were randomized to either active drugs (see Medical Therapy) or placebo. The placebo-treated patients provide information regarding the natural history of the disease, at least for a 24 month period, in patients on no medical therapy. Among patients who had active disease upon entry to the study and who were randomized to placebo, 32% achieved a spontaneous remission by the end of 17 weeks and 53% of these were still in remission at the end of 24 months. The percentage of patients with quiescent disease at the time of entry to the study and who remained in remission at various times after entry are shown in Figure 2. About 60% of patients who were in remission at the time of entry were still in remission at the end of 24 months even though they had been treated with placebo.

Results of another study indicate that up to 20% of patients with well-established Crohn's disease may remain in remission for up to 20 years after the first or even the second episode of active disease (41).

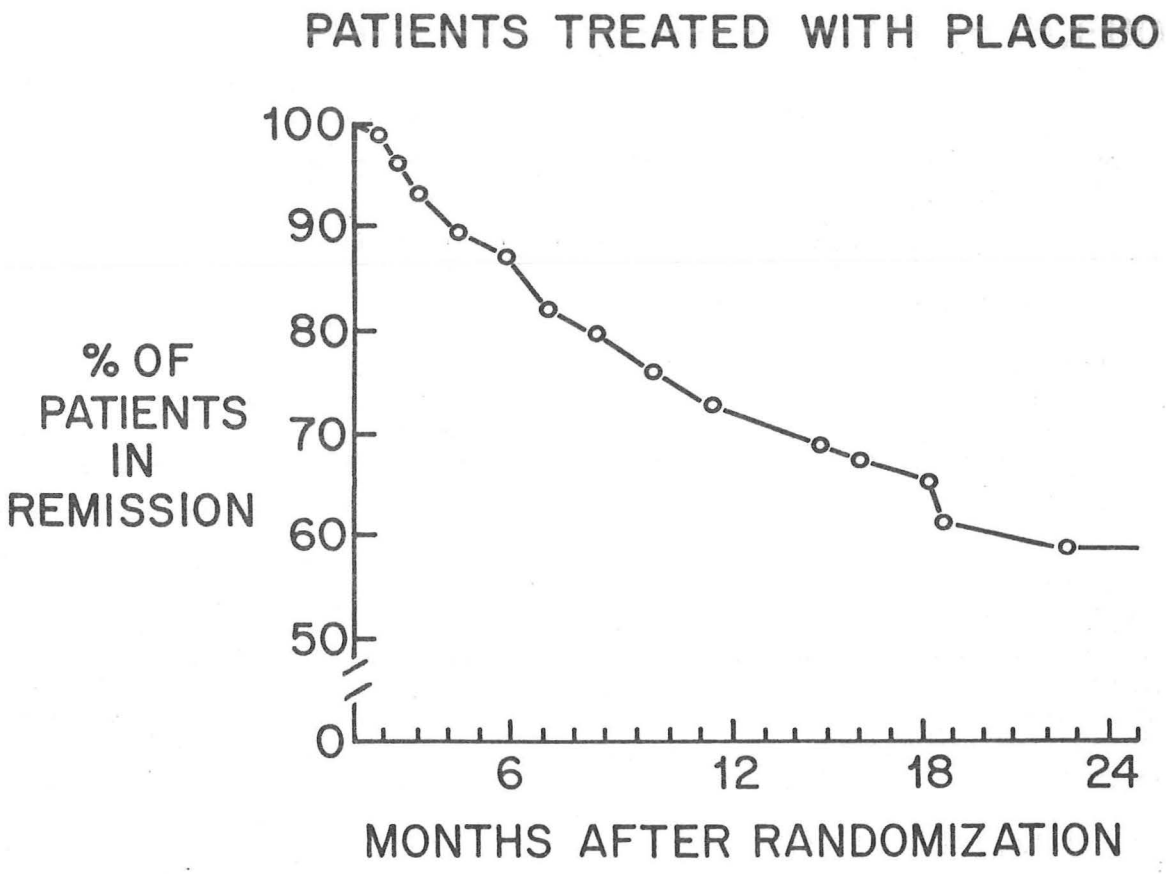

Figure 2. Percentage of patients treated with placebo who remained in remission after entering the study with quiescent disease (adapted from Ref. 10).

Although the clinical course varies from patient to patient, once the diagnosis of Crohn's disease is made, gradual deterioration occurs in many patients over a period of years. Blood loss is usually gradual and occult but this, combined with decreased food intake and nutrient malabsorption, often leads to anemia (see below). With time, intermittant episodes of partial or even complete small bowel obstruction occur in some patients and may lead to surgery (see Surgical Therapy). Progression to surgery occurs more rapidly in patients with ileal plus colonic disease than in those in whom only the small bowel or only the colon is involved.

Signs and Symptoms

Clinical manifestations of Crohn's disease in patients randomized to therapy in the National Cooperative Crohn's Disease Study are shown in Table VII.

TABLE VII. CLINICAL MANIFESTATIONS OBSERVED AT RANDOMIZATION TO THE NATIONAL COOPERATIVE CROHN'S DISEASE STUDY (REF. 10)

	TOTAL PATIENT GROUP (N=569) (%)	COLON-ONLY PATIENTS (N=60) (%)	UNTREATED PATIENTS (N=68) (%)
Diarrhea	92	92	93
Abdominal pain	95	93	94
Lower GI bleeding	41	62	32
Weight loss (>5 lb)	85	88	82
Fever	56	72	38
Anal fissure, abscess, or fistula	36	47	12
Other internal fistula	16	8	6
Enterocutaneous fistula	16	8	6
Arthritis or spondylitis	19	22	18
Iritis	4	7	3
Hepatitis, pericholangitis	4	5	0
Erythema nodosum/ pyoderma gangrenosum	5	8	3

Most patients present with recurrent episodes of diarrhea and abdominal pain. When the disease is confined to the ileum, diarrhea is usually moderate in severity with 5 to 6 bowel movements per day. Stools are usually soft and loose but may be watery. Urgency and incontinence may occur when the disease involves the colon and rectal bleeding is present in about 50-60% of patients with colonic involvement.

Abdominal pain is frequently localized to the right lower quandrant. It is usually steady and reflects disease in the terminal ileum. Cramping pain may be superimposed on the steady pain and may indicate intermittant, partial small bowel obstruction. Nausea and vomiting may occur as a manifestation of partial or complete small bowel obstruction. When the colon is involved, pain may be localized to one or both lower quadrants.

Fever is present in about 50% of patients. Fever is usually low-grade and rarely exceeds 102°F. Whether fever results from absorption of bacterial toxins or products of tissue breakdown or other mechanisms is not known.

Weight loss is a frequent finding in patients with Crohn's disease (Table VII). Decreased food intake as a result of anorexia (due to chronic disease) or because of fear of eating (eating food causes pain in some patients, especially those with partial small bowel obstruction) is one of the major causes of weight loss. Variable degrees of nutrient malabsorption also occur and are related primarily to the extent of small bowel involvement with disease. Protein-losing

enteropathy can also occur and this combined with decreased protein absorption leads to decreased serum concentrations of albumin and other proteins. Malabsorption of disaccharides also occur and leads to diminished calorie absorption and contributes to diarrhea via the osmotic effect of unabsorbed sugars.

Anemia is also a frequent finding in patients with Crohn's disease. Blood loss secondary to the inflammatory process is probably the most common explanation. However, malabsorption of folate, vitamin B_{12} and iron also can occur. Malabsorption of vitamin B_{12} occurs either as a result of ileal disease and/or because of bacterial overgrowth which can develop as a result of strictures and fistulas.

A mass in the right lower quadrant is a fairly common physical finding in patients with Crohn's disease. Usually, the mass is relatively small and represents a thickened terminal ileum. Matted loops of ileum may be involved in some patients and lead to development of a larger mass. Tenderness is frequently present in the right lower quadrant as a result of ileal disease or because of an inflammatory mass. The combination of a right lower quadrant mass, tenderness and fever may occur as a result of Crohn's disease, per se, but an abscess in the area of inflammed bowel is also a possibility and should be considered as a diagnostic possibility.

Differentiating Crohn's Disease from Ulcerative Colitis

When small bowel disease is present, differentiating Crohn's disease from ulcerative colitis is relatively easy since small bowel disease plus colon disease does not occur in patients with ulcerative colitis. When only the colon is involved the differential diagnosis is more difficult. The likelihood of having various signs and symptoms in the two diseases is listed in Table VIII.

TABLE VIII. INCIDENCE OF SIGNS AND SYMPTOMS IN PATIENTS WITH EITHER ULCERATIVE COLITIS OR CROHN'S DISEASE OF THE COLON (ADAPTED FROM REF. 42)

SIGNS OF SYMPTOMS	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Rectal bleeding	90-100%	Occult bleeding, common; gross bleeding, rare
Diarrhea	78-93%	66-90%
Abdominal pain	60-70%	45-87%
Weight loss	18-62%	55-75%
Fever	11-43%	36%
Vomiting	14-27%	35%

Other clinical characteristics that might be useful in differentiating patients with ulcerative colitis from those with Crohn's disease of the colon are listed in Table IX.

TABLE IX. CHARACTERISTICS THAT MIGHT BE HELPFUL IN DIFFERENTIATING ULCERATIVE COLITIS FROM CROHN'S DISEASE OF THE COLON (ADAPTED FROM REF. 42)

CHARACTERISTIC	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Diarrhea	Early, frequent small stools	Less distressing or absent
Abdominal pain	Predefecatory urgency	Colicky, postprandial
Palpable mass	Rare	Frequent, RLQ
Rectal involvement	95-100%	14%
Sigmoidoscopy	Diffuse ulcerations	Normal, or patches of lumpy edema or discrete, small ulcerations (aphthae)
Rectal biopsy:		
Inflammation	Diffuse, mucosal	Submucosal, more severe, edema, fibrosis
Granulomata	Uncommon	Common
Clinical course	Relapses-remissions, 65% Chronic continuous, 20-30% Acute fulminating, 5-8%	Usually slowly progessive; rarely fulminant
Distribution	Continuous with rectum	Segmental
Serosal Involvement	Unlikely	Common
Fibrous stricture	Uncommon	Common
Recurrence after resection	Rare	Frequent - 50%

Differences also exist between the two diseases in the liklihood of developing a complication. For example, perianal abscess, fissures and fistulas are more common in patients with Crohn's disease while colon cancer, pseudopolyps, free perforation and toxic megacolon occur more frequently in patients with ulcerative colitis. There is a greater likelihood of gallstones, kidney stones and hydronephrosis occurring in patients with Crohn's disease. The renal complications of Crohn's disease are discussed in greater detail on pages 26-28.

The differences in complications between ulcerative colitis and Crohn's disease of the colon are listed in Table X.

TABLE X. DIFFERENCES IN COMPLICATIONS BETWEEN ULCERATIVE COLITIS AND CROHN'S DISEASE OF THE COLON (ADAPTED FROM REF. 42)

COMPLICATION	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Perianal abscess, fissure, fistula	18%; more likely with severe attack, and total colon involvement	50-80%; may antedate bowel symptoms; may be multiple
Toxic megacolon	3-20%	Uncommon, 0-16%
Colonic carcinoma	Patients with pancolitis: 12.1% after 10 years 23.0% after 20 years	Uncommon; risk increased with onset under age 21
Pseudopolyposis	15-19%; up to 74%	Rare
Free perforation	1.6-2.8%; severe first attack, pancolitis	Rare
Internal fistula	Rare; small rectovaginal	Frequent; enteroenteric, enterovesicle, entercutaneous (usually in surgical scar), enterovaginal
Arthritis; peripheral sacroiliitis	12% 18-20%	20% 18%
Skin: erythema nodosum, pyoderma gangrenosum	5-10%	Less frequent
Gallstones	Incidence normal	Incidence increased
Nephrolithiasis	1.9-6.4%	4.4-10.1% (uric acid; oxalate)
Hydronephrosis	Unrelated	1.5% (usually obstruction of the right ureter secondary to inflammatory mass in RLQ)

Although differences exist between Crohn's disease of the colon and ulcerative colitis, sometimes it is difficult or even impossible, at least initially, to distinguish between the two diseases. In general, it is not important to make a distinction between the diseases during the early part of a patient's course. It does become important, however, if surgery is a consideration or if the patient has had the disease for several years and cancer is a concern.

Differentiating Ischemic Colitis, Ulcerative Colitis and Crohn's Disease of the Colon.

Occasionally, differentiating ischemic colitis from idiopathic inflammatory bowel disease of the colon is a consideration. This occurs especially in

elderly patients. Some of the characteristics seen in the three disease and their relative frequencies are listed in Table XI.

TABLE XI. DIFFERENCES IN THE FREQUENCY OF VARIOUS CHARACTERISTICS IN PATIENTS WITH ISCHEMIC COLITIS, ULCERATIVE COLITIS OR CROHN'S DISEASE OF THE COLON. (ADAPTED FROM REF. 42)

CHARACTERISTIC	ISCHEMIC COLITIS	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Onset	Very rapid	Gradual; occasionally rapid	Gradual
Age >50	80%	<10%	<5%
Rectal bleeding	Usually once	Frequently	Uncommon
Stricture formation	Common	Uncommon	Common
Prior cardiovascular disease	Common	Rare	Rare
Progress of disease	Acute; rapidly changing	Chronic	Chronic
Segmental involvement	Common	Rare	Common
Most common area of involvement	Splenic flexure; descending colon; transverse colon	Rectum; sigmoid; ascending and descending colon in contiguity	Terminal ileum and right colon; entire colon
"Thumb printing" on barium enema	Common	Rare	Uncommon

RADIOLOGIC MANIFESTATIONS OF CROHN'S DISEASE

The earliest radiologic manifestations include 1) small ulcers (aphthae), 2) edema of folds and 3) small nodules (see Figure 3 in Appendix). Aphthae are 2 to 3 mm raised plaques of tissue with a central ulceration. In their earliest form, aphthae are difficult to differentiate from lymphoid nodular hyperplasia. Nodules of lymphoid tissue are usually all the same or similar sizes and have round, central ulcerations. Aphthae, on the other hand, vary in size and have different shapes.

Edema of the folds leads to blunting, flattening, thickening, distortion and straightening of the valvulae conniventes (see Figure 4 in Appendix). As ulcerations progress, streaks of barium occur which are associated with longitu-

dinal and transverse ulcers. The criss-crossing of ulcerations give rise to the classic "cobblestone" appearance (see Figure 5 in Appendix). As ulceration continues, the intervening islands of mucosa which represent cobblestones are replaced by an irregular network of interlacing streaks of barium (43). Involved loops of bowel become moderately rigid and slightly narrowed. Separation of loops of bowel also occurs as a result of the same process (see Figure 6 in Appendix). Initially, narrowing of loops of bowel is due to edema, inflammation and spasm. Eventually, fibrosis occurs and the narrowing becomes more marked. This is known as the stenotic phase of Crohn's disease (see Figure 1 and 7 in Appendix). When this occurs, there may be dilatation of the small bowel proximal to the stenosis. Sometimes, loops of small bowel surround a mass. Usually, this is due to indurated mesentery, a marked increase in mesenteric fat and enlarged lymph nodes, although in some patients the mass effect may be due to an abscess (see Figure 7 in Appendix).

Skip areas are another characteristic radiographic finding in patients with Crohn's disease. These areas represent segments of normal intestine intervening between diseased segments. The length of the skip area may vary from a few inches to several feet.

Radiographic Differentiation Between Ulcerative Colitis and Crohn's Disease of the Colon

The radiologic manifestations of ulcerative colitis and Crohn's disease of the colon differ in several regards. These are listed in Table XII.

TABLE XII. RADIOLOGIC MANIFESTATIONS OF ULCERATIVE COLITIS AND CROHN'S DISEASE OF THE COLON (ADAPTED FROM REF. 42)

MANIFESTATION	ULCERATIVE COLITIS	CROHN'S DISEASE OF THE COLON
Distribution	Continuous with rectum	Often discontinuous (segmental, skip areas)
Rectum	Almost always involved	Often normal
Internal fistulas	Rare; small rectovaginal fistulas	Frequent
Strictures	Uncommon; suggests superimposed carcinoma	Frequent
Mucosa	Shallow ulceration; may have pseudopolyps	Longitudinal fissures; cobblestone appearance
Symmetry	Generally symmetrical	Often asymmetrical (one-wall involvement) (see Figure 3,Appendix)
Terminal ileum	Usually normal. If involved; dilated or normal in caliber, ("Backwash ileitis")	Often involved $\pm$ 65%; stenotic and irregular

INTESTINAL COMPLICATIONS OF CROHN'S DISEASE

Luminal Stenosis.

This can result from edema and inflammation and/or strictures secondary to scar formation. Small bowel obstruction occurs usually as a result of edema and inflammation in an area that is stenotic. Thus, small bowel obstruction is frequently transient and may respond to medical therapy. On the other hand, if edema and inflammation do not resolve or if the stenotic area is extremely narrow, surgery may be necessary. Small bowel obstruction is the most common reason for surgery in patients with Crohn's disease.

Internal Fistulas and Perianal Disease.

These are characteristics of Crohn's disease and rarely, if ever, occur in patients with ulcerative colitis. Fistulas are believed to result from the extramural extention of a fissure ulcer. If the communication remains localized, an abscess will form in the intraperitoneal space. On the other hand, if the communication extends to the surface (skin) or into adjacent viscera (another loop of small bowel, colon, rectum, bladder, vagina), a fistula will form. Some patients develop fistulas spontaneously. However, fistulas are more common in patients who have had previous surgical procedures. Enteroenteric fistulas between loops of small bowel can lead to malabsorption of nutrients either by allowing nutrients to bypass large segments of small bowel absorptive surfaces or by allowing stasis and bacterial overgrowth in the small intestine. Communication between the small bowel or colon and the urinary bladder can lead to persistent urinary tract infections, pneumaturia and other urinary symptoms. Of the patients in the National Cooperative Crohn's Disease Study, 16.3% had internal fistulas and 5.3% had enterocutaneous fistulas (44).

Perianal and perirectal fissures and fistulas occur commonly in patients with Crohn's disease and lead to devastating symptoms. The chances of patients with Crohn's disease developing an anorectal abscess, fissure or fistula ranges from 28 to 80% (45). Of the patients in the National Cooperative Crohn's Disease Study, 36.0% had had some type of perianal complication of Crohn's disease (44). Anorectal disease may be the first manifestation of Crohn's disease or may precede by months to years other manifestations of the disease.

A fistula in ano may arise as a result of a perianal abscess or may develop spontaneously. Discharge of fluid from the fistula may be intermittant or persistent and may irritate the surrounding skin and soil the clothes. The external opening of the fistula is usually within 5 cm of the anus. The opening into the rectum frequently can be palpated on digital exam or can be seen on proctoscopic examination. The fistula may become multiple and complex and may burrow through adjacent tissue to form several tracts which may extend into the vulva, groin, scrotum and penile urethra. Perianal and rectal disease is sometimes so severe that it destroys perianal skin, ischiorectal fat and the anal sphincter. Destruction of the anal sphincter can lead to incontinence.

Based on data from the National Cooperative Crohn's Disease Study, the likelihood of developing internal fistulas, enterocutaneous fistulas or perianal disease was greater in patients with small bowel plus colon disease compared to those with small bowel only disease (44).

Free Perforation.

This complication rarely occurs in patients with Crohn's disease although a few instances have been reported (46). When perforation occurs in the small bowel, the ileum is the usual site. Free perforations may occur proximal to an area of obstruction.

Malignant Neoplasms.

Cancer occurs about three times more frequently in patients with Crohn's disease than the expected incidence in the general population (47). The incidence is about 3.0% and is less than in patients with ulcerative colitis. It appears that the overall frequency of cancer in patients with ulcerative colitis is about fourfold greater than that in patients with Crohn's disease (48).

EXTRA-INTESTINAL COMPLICATIONS OF CROHN'S DISEASE

A large number of patients with Crohn's disease will have one or more extraintestinal complications at some time during the course of their disease. As with Crohn's disease, in general, the explanation for the extraintestinal complications are poorly understood. Twenty-four percent of patients randomized to therapy in the National Cooperative Crohn's Disease Study had had at least one extraintestinal manifestation at the time of randomization and 6% had a history of more than one extraintestinal manifestation (44). Multiple extraintestinal manifestations occurred in the same patient more frequently than would be expected due to chance alone ($P < 0.0001$) suggesting that a patient with one extraintestinal manifestation is at increased risk of developing others.

One group of extraintestinal manifestations appears to be related to the clinical activity of the inflammatory process, being present or active when the bowel disease is most active and subsiding when evidence of bowel disease diminishes. The activity of this group of disorders also seems to be related to the amount of bowel involved, i.e. they seem to occur more frequently in patients with more extensive bowel disease, especially colonic involvement (49). This group of extraintestinal complications include eye disorders, articular manifestations and skin manifestations. Each are discussed in more detail below.

The second major category of extraintestinal disorders arise mainly in patients with Crohn's disease of the ileum and occur because of some derangement in physiology. These include disorders due to malabsorption of nutrients such

as vitamin B_{12}, or fat or malabsorption of bile salts. There is a higher incidence of gallstones in patients with Crohn's disease and this is believed secondary to malabsorption of bile salts. Renal complications also can occur. Other extraintestinal complications include amyloid and liver disease.

Eye Manifestations

Three to 10% of patients with Crohn's disease of the colon and a small percentage of patients with Crohn's disease of the small bowel develop eye manifestations (50). Common eye lesions include conjunctivitis, iritis and episcleritis. Conjunctivitis is often seen at the beginning of an episode of bowel inflammation or may occur in the course of a clinical flare up. It has been assumed that eye lesions, articular manifestations and skin disease may be due to antigen-antibody immune complexes with deposition derived from the mucosa or absorbed through it. Direct proof of immune complex deposition in the affected extraintestinal locations is lacking at this time.

Articular Disease

Although the cause of joint manifestations is not known, analogies have been drawn between the articular disease associated with Crohn's disease and the arthritis associated with hepatitis B and jejunoileal bypass surgery for obesity. In patients with jejunoileal bypass surgery, immune complexes have been measured and the antigens appear to be derived from intestinal bacteria (51).

Peripheral arthritis. Recent evidence suggests that only peripheral arthritis is truly a complication of bowel disease whereas ankylosing spondylitis and idiopathic inflammatory bowel disease are two associated diseases occurring frequently in the same patient (50). The incidence of arthritis in patients with Crohn's disease ranges from 2.3 to 22.0% depending on the series. It is equally common in Crohn's disease and ulcerative colitis and is more common in patients with Crohn's disease who have colonic involvement than in those with only small bowel disease.

The arthritis is often a transient, acute, painful swelling that is usually monoarticular but may involve several joints (50). It is usually symmetrical when more than one joint is involved. Large joints of the legs, usually the knees, are involved most commonly. Residual deformity does not occur in arthritis associated with idiopathic IBD. A sterile, serous joint effusion without distinguishing features may occur.

Ankylosing Spondylitis and Sacroiliitis. As mentioned above, it is now believed that inflammation of the spine and Crohn's disease are two associated diseases occurring in the same patient. Not only does ankylosing spondylitis occur more frequently in patients with bowel disease than in control populations but bowel disease is more common in patients with ankylosing spondylitis than it is in control populations. The incidence of ankylosing spondylitis in patients with

Crohn's disease ranges from 3.0 to 12.6% which is about 30 times the incidence in the general population (50). In another series of 80 patients with ankylosing spondylitis, 17.5% had idiopathic inflammatory bowel disease (52).

Patients with Crohn's disease and ankylosing spondylitis have a high likelihood (50 to 90%) of having the histocompatibility antigen HLA-B27 (50). The incidence of HLA-B27 is also high in patients with ankylosing spondylitis without idiopathic inflammatory bowel disease but it is present in only 6 to 9% of patients with inflammatory bowel disease without ankylosing spondylitis, the same incidence as found in control populations (53). The usual male predominance of ankylosing spondylitis is not present in patients with ankylosing spondylitis plus inflammatory bowel disease.

Radiologic manifestations of ankylosing spondylitis include narrowing of the lumbar disc spaces, osteophyte formation and calcification of ligaments. In sacroiliitis there is narrowing of the joint space, erosions and sclerosis of the sacroiliac joints. In contrast to peripheral arthritis of Crohn's disease, ankylosing spondylitis and sacroiliitis are not clearly related to the extent or severity of bowel disease.

Skin Manifestations.

Erythema nodosum and pyoderma gangrenosum are the most common cutaneous manifestations (excluding perianal disease) of idiopathic inflammatory bowel disease. Erythema nodosum is more common in patients with Crohn's disease while pyoderma gangrenosum occurs more frequently in patients with ulcerative colitis.

Erythema Nodosum. As mentioned previously, this manifestation usually coincides with activity of the bowel disease and females are affected more frequently than males. The characteristic lesions are raised, red or reddish-blue, warm and tender nodules that are usually found on the anterior surface of the lower legs. The lesions are believed to be due to antigen-antibody complex disposition but specific antigens have not been identified.

Pyoderma gangrenosum. This is a severe lesion that rarely occurs in patients with Crohn's disease. It begins as a sharply demarcated, raised tender area which slowly enlarges. It becomes a deep, necrotizing, ulcerating, painful lesion. It has a characteristic elevated purplish margin. It usually occurs on the pretibial region of the lower legs but can occur elsewhere. In severe cases the lesion may penetrate deeply, cause osteomyelitis and necessitate amputation of the extremity.

Renal Complications.

There are three major renal disorders that occur in patients with Crohn's disease: 1) nephrolithiasis, 2) obstructive hydronephrosis and 3) renal amyloid.

Nephrolithiasis. The incidence of renal stones in patients with Crohn's disease

ranges from 4.4 to 10.1 percent (50) and consist of uric acid or calcium salts of oxalate or phosphate. Uric acid stones occur more frequently in patients with Crohn's disease who have had a colectomy and who have an ileostomy. They occur primarily because severe diarrhea leads to decreased volume of urine as well as decreased pH which results from bicarbonate loss in diarrheal fluid. Increased uric acid production from increased tissue breakdown secondary to inflammatory disease may be a contributing factor.

Mechanisms leading to oxalate stones are illustrated in Figure 3.

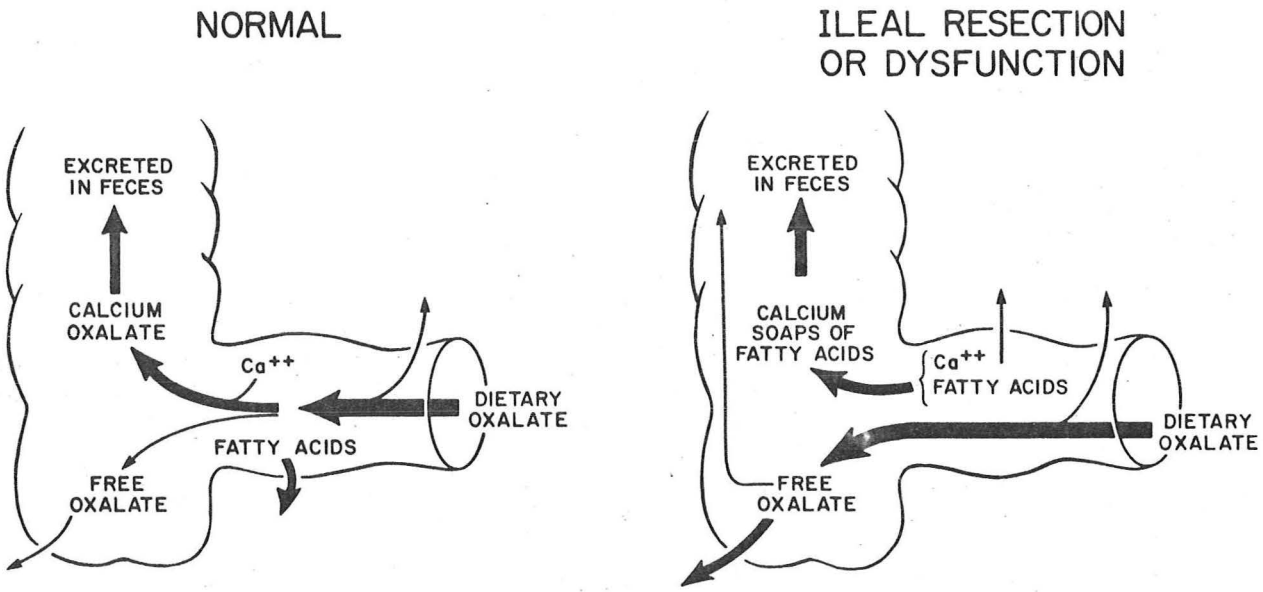

Figure 3. Mechanisms leading to enteric hyperoxaluria associated with ileal resection or ileal dysfunction (50).

Resection of at least 30 to 50 cm of ileum or extensive ileal disease causes hyperoxaluria in a large percentage of patients (54,55). In normal people (Figure 3, left) most dietary oxalate complexes with calcium in the gut lumen forming an insoluable salt of calcium oxalate. This is excreted in the feces. Only a small amount of free oxalate is absorbed. In patients with a severely diseased ileum or in those with ileal resection, calcium becomes bound to unab-

sorbed fatty acids. This leaves soluble dietary oxalate free for absorption. Most oxalate is absorbed in the colon. Thus, a relatively intact colon is usually found in patients with increased urinary oxalate excretion. A low urinary volume secondary to diarrhea enhances calcium oxalate precipitation in the kidney.

Obstructive Hydronephrosis. This usually occurs because of extension of the intestinal inflammatory process from the ileum and right colon to the area of the right ureter. Urinary tract symptoms are usually minimal and patients present with pain in the right thigh, flank or hip. They may have difficulty walking. Urinalysis is frequently normal. The diagnosis is made by intravenous pyelogram or sonogram. If the condition is not recognized, the kidney may be destroyed.

Renal Amyloid. This is rare but when it occurs in patients with idiopathic inflammatory bowel disease, it usually is in association with long-standing Crohn's disease. Amyloid should be considered in a patient with Crohn's disease who has impaired renal function and/or proteinuria. Amyloid in patients with Crohn's disease has also been found in the liver, spleen and other organs.

Liver Disease

Abnormal liver function tests and liver disease are more common in patients with ulcerative colitis but occur also in those with Crohn's disease. Up to 50% of patients with idiopathic inflammatory bowel disease have at least minor abnormalities on liver biopsy and/or liver function tests. Only 5 to 10% of patients have clinically significant liver disease. Three lesions primarily effect the biliary tract. These are pericholangitis, sclerosing cholangitis and bile duct carcinoma. Bile duct carcinoma has not been reported in patients with Crohn's disease.

Pericholangitis has been reported in up to 30% of patients with either chronic ulcerative colitis or Crohn's disase and who also have clinical or laboratory evidence of liver disease. The lesion is characterized by edema in the portal triads along with an inflammatory cell infiltrate. The infiltrate consists of lymphocytes, plasma cells and in some patients, polymorphonuclear leukocytes. Although the cause of pericholangitis is not known, it is believed due to passage of harmful material, perhaps, bacterial toxins or bile acids, through the diseased mucosa and into the portal vein.

Primary sclerosing cholangitis is a progressive, obliterative disease that usually involves the extrahepatic bile ducts but also may involve intrahepatic biliary radicals. Cholangiograms, usually performed by ERCP, show diffuse, irregular narrowings of the duct lumen. Microscopic examination shows fibrotic thickening of the duct wall which is characterized by a diffuse inflammatory infiltrate, consisting primarily of lymphocytes.

Treatment of the bowel disease does not help the liver disease.

Growth Retardation

This can occur in both ulcerative colitis and Crohn's disease but is more common in young patients with Crohn's disease. In one study, 17% of children and adolescents with Crohn's disease had retarded skeletal maturation and their height was below the third percentile (56). Growth retardation may precede other manifestations of Crohn's disease. Thus, inflammatory bowel disease should be considered as a diagnosis in evaluating young people with growth retardation. The cause of delayed growth is not known but poor nutrition, malabsorption of nutrients, secondary hypopituitarism and steroid therapy are all possible explanations.

Thromboembolic Disease

Venous and arterial thromboses occur more commonly in patients with Crohn's disease or ulcerative colitis than in control populations (50). Thromboembolic disease is more common in women than in men. Several factors may contribute to this complication. These include bed rest, surgical procedures and general debility. Increased coagulability has been demonstrated in patients with Crohn's disease or ulcerative colitis. Increased thromboplastin generation, higher levels of Factor V and VII, increased levels of fibrinogen, increased platelet count and a decrease in antithrombin III contribute to the hypercoagulable state (57-59). Disorders of coagulation seem to be related to the severity of the disease and improve, to some extent, with therapy of inflammatory bowel disease.

THERAPY

There is no known cure for Crohn's disease. Even resection of diseased small bowel and/or colon is not curative since recurrence develops in a relatively large percentage of patients (see Surgical Therapy). This is in contrast to ulcerative colitis, where if medical therapy fails, removal of the colon will lead to cure of the disease.

In Crohn's disease medical therapy will frequently suppress the disease process, relieve symptoms and in some patients induce a remission. Surgical therapy, on the other hand, should not be performed in patients with Crohn's disease unless it is absolutely necessary, for example, to relieve small bowel obstruction.

Since Crohn's disease cannot be cured, the physician should make every effort to control the disease. There are several goals of therapy. In patients who are acutely ill, the initial goals are to treat dehydration, electrolyte depletion, anemia and nutrient malabsorption. Attempts to relieve diarrhea, abdominal pain and fever should also be made. The long-term goals should be to induce a remission, prevent complications and re-establish an overall sense of well-being.

Medical Therapy

Hospitalization. Although this is not required, it is desirable for patients

who are acutely ill to be hospitalized. Studies have not been performed evaluating the effect of bed rest in inducing remission. However, in my opinion, patients who are acutely ill and who have fever, severe diarrhea, abdominal pain or other symptoms suggesting an acute attack should be confined to bed in the hospital for several days. Sometimes, a longer period of hospitalization is necessary. Hospitalization also may be useful to remove some patients from a stressful home or work environment.

Medications. Active Disease. Controlled clinical trials have been performed evaluating the efficacy of prednisone, sulfasalazine, sulfasalizine plus prednisone, azathioprine, 6-mercaptopurine and metronidazole in the treatment of active Crohn's disease. Results of several controlled clinical trials are summaried in Table XIII.

TABLE XIII. SUMMARY OF CONTROLLED CLINICAL TRIALS
IN THE TREATMENT OF ACTIVE CROHN'S DISEASE
(ADAPTED FROM DONALDSON, RM, REF. 40 AND DATA FROM SLEISENGER, MH)

Drug (Daily Dose)	Efficacy	Comments	Ref.
Prednisone (0.25-0.75 mg/kg)	+	Less effective in patients already treated with drugs or when disease was limited to colon.	60
Sulfasalazine (1.0 gm/15 kg)	+	Most effective in previously untreated patients. Less effective when disease was limited to small bowel.	60
(3.0 gm)	±	More effective in unoperated patients.	61
(4-6 gm)	+		62
(3.0 gm)	-	No placebo. Compared with metronidazole and was about as effective. Less effective if disease was limited to small bowel	63
Sulfasalazine (1.0 gm/15 kg) (0.25-0.75 mg/kg)	-	No placebo. Compared with prednisone alone, addition of sulfasalazine had no effect.	64
Azathioprine (2.0 mg/kg)	0		65
(2.5 mg/kg)	0		60
(3.0 mg/kg)	±	Given with glucocorticoids.	66
6-Mercaptopurine (1.5 mg/kg)	±	Slow response (at least two months) in most cases. Given with glucocorticoids Steroid "sparing" effect documented.	67
Metronidazole (800 mg)	-	No placebo. Found to be at least as effective as sulfasalazine. Less effective if disease was limited to small bowel).	63

* Efficacy: + = Significantly more effective than placebo.
0 = Not significantly different from placebo.
- = Compared with another drug rather than with placebo.

Perhaps, the best and most recent study, summarized in Table XIII, was the National Cooperative Crohn's Disease Study. As mentioned in the table and illustrated in Figure 4, prednisone or sulfasalazine but not azathioprine was significantly better than placebo in inducing a remission in patients with active disease. Response to azathioprine was better than placebo but the difference did not reach statistical significance.

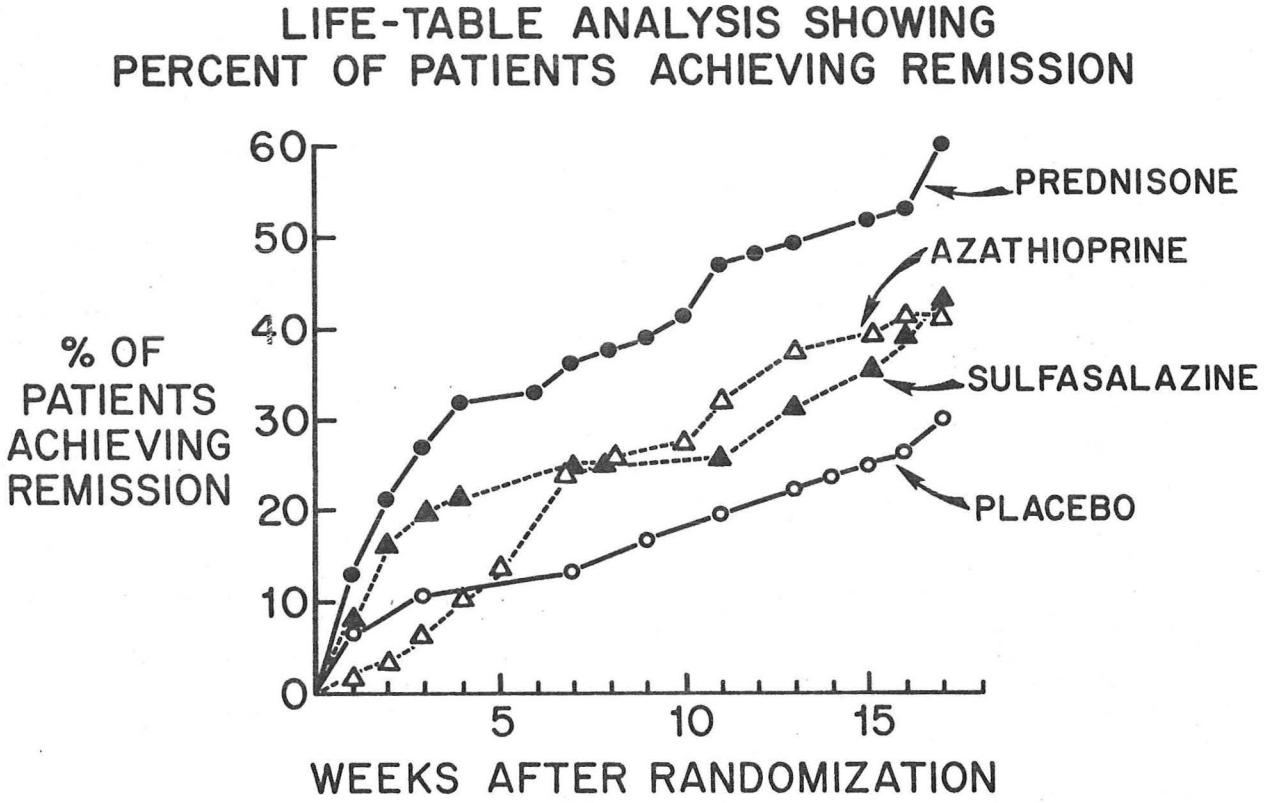

Figure 4. Life table analysis showing cumulative percent of patients in remission at each week of the study (adapted from Ref. 60).

Patients with colonic involvement were especially responsive to sulfasalazine while those with small bowel disease were especially responsive to prednisone. Whether this observation is clinically important is unclear. In my opinion, it is not necessary to differentiate small bowel disease from colon disease in selecting an appropriate drug.

Results of the European Cooperative Crohn's Disease Study were published recently (68). Patients with active disease were treated for 6 weeks and were

randomized to placebo, 6-methylprednisolone, sulfasalazine or the combination of 6-methylprednisolone and sulfasalazine. The dose of sulfasalazine was 3 gms daily while the dose of 6-methylprednisolone was 48 mg/day initially with tapering of the dose on a weekly basis so that by week 6 they were treated with 12 mg/day. Results indicated that 6-methylprednisolone was the most effective drug in patients who were previously treated for Crohn's disease, in patients with small bowel only disease and in those with small bowel plus colon disease. The combination of 6-methylprednisolone and sulfasalazine was the most effective in previously untreated patients and in those with disease localized to the colon. Sulfasalazine alone was the least effective of the drug regimens.

6-mercaptopurine (6-MP) also has been used in treating patients with Crohn's disease. Results of one study indicated that 6-MP plus glucocorticoids reduced symptoms and led to healing of fistulas more effectively than did placebo therapy (67). In addition, 6-MP appeared to have a steroid-sparing effect. Although azathioprine and 6-MP may be effective in treating some patients with Crohn's disease, their potential side effects may outweigh their possible benefits.

Medications. Maintenance of Remissions. Results of several controlled clinical trials evaluating various drugs in maintaining remissions in patients with Crohn's disease are summarized in Table XIV.

TABLE XIV. SUMMARY OF CONTROLLED CLINICAL TRIALS OF VARIOUS DRUGS IN MAINTENANCE OF REMISSION IN PATIENTS WITH QUIESCENT CROHN'S DISEASE (ADAPTED FROM DONALDSON, RM, REF. 40 AND DATA FROM SLEISENGER, MH)

Drug (Daily Dose)	Efficacy*	Comments	Ref.
Prednisone (0.25 mg/kg)	0		60
(7.5 mg)	0		69
Sulfasalazine (1.0 gm/15 kg)	0		60
(3.0 gm)	0		70
Sulfasalazine (1.0 gm/15 kg) plus prednisone (0.25-0.75 mg/kg)	-	No more effective than prednisone alone. Did not reduce steroid requirement	64
Azathioprine (2.0 mg/kg)	+	Some patients also received prednisone and/or sulfasalazine	71
(2.0 mg/kg)	+	Given with glucocorticoids; steroid "sparing" effect	72
(2.0 mg/kg)	+	Given with glucocorticoids; steroid "sparing" effect	73
(1.5 mg/kg)	0		60

* Efficacy: + = Significantly more effective than placebo.
0 = Not significantly different from placebo.
- = Compared with another drug rather than with placebo.

As shown in Table XIV (40) and also in Figure 5 below, none of the drugs were better than placebo in preventing a relapse of Crohn's disease in patients randomized to therapy in the National Cooperative Crohn's Disease Study.

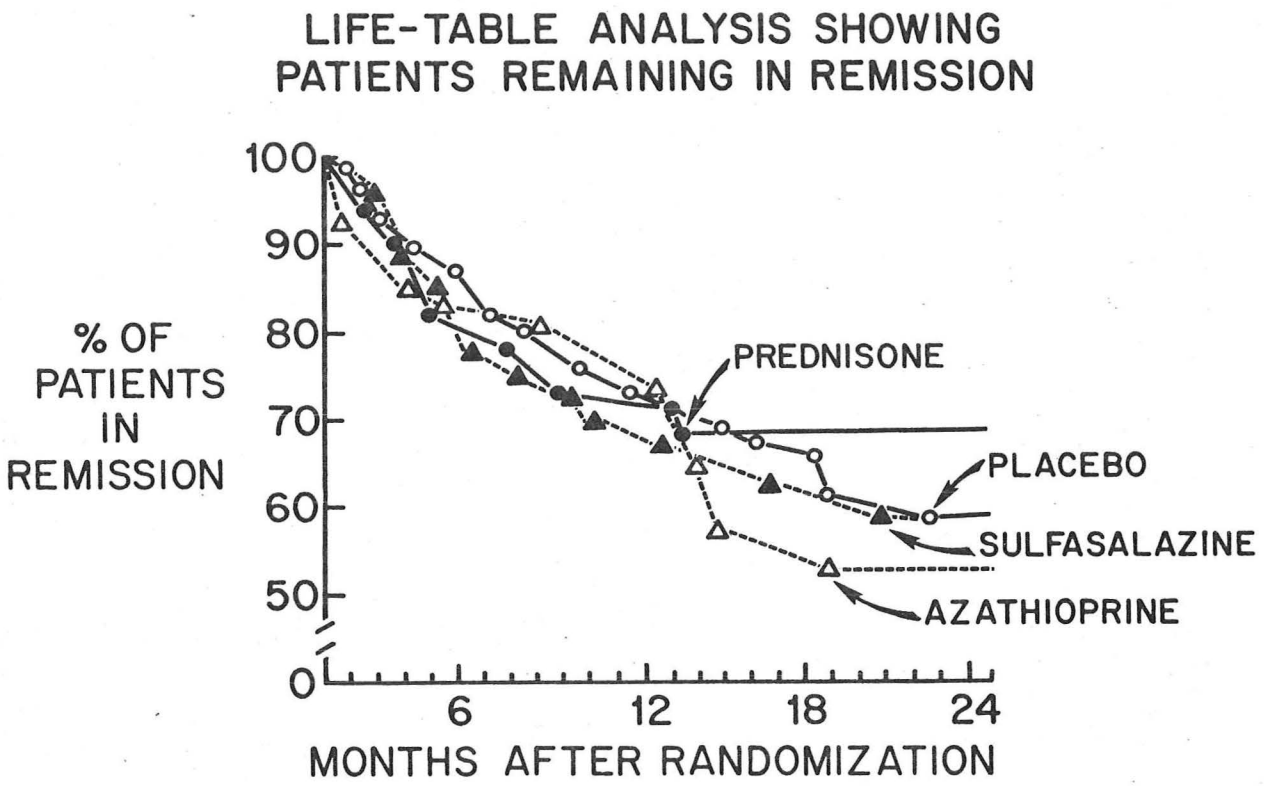

FIGURE 5. Life table analysis illustrating percent of patients remaining in remission (adapted from Ref. 60).

Results of the European Cooperative Crohn's Disease Study suggested that 6-methylprednisolone may be beneficial in maintaining a remission (68). However, the results were not convincing.

Treatment of Perianal Disease. In 1975, metronidazole was reported useful in the treatment of 5 patients with Crohn's disease (74). Since the original report, several other investigators have evaluated the effect of metronidazole in treating patients with Crohn's disease and the results have been variable (75-80). There was a suggestion, however, in several of these reports that the drug may be useful in treating perianal disease associated with Crohn's disease. In 1980, Bernstein, Frank, Brandt and Boley reported the effect of metronidazole in 21 consecutive patients with chronic unremitting perianal Crohn's disease

(81). Diarrhea, erythema and induration diminished in all patients and complete healing was obtained in 10 of 18 patients maintained on therapy. Patients were treated with 20 mg/kg/day of metronidazole.

In 1982, these same investigators reported their continued experience with metronidazole in the treatment of perianal disease (82). Their second report included data on 17 of the original 21 patients plus information on 9 additional consecutive patients. In this study they addressed and answered four questions:

a) Can the dose of metronidazole be reduced? Dosage reduction was associated with exacerbation of disease activity in all patients, but in all, the perineal manifestations healed promptly when the full dosage was reinstituted.

b) Can metronidazole be stopped without exacerbation of disease? Cessation of metronidazole was attempted in 18 patients after a mean of 8.8 months (range, 1.25-24 months) of therapy. Therapy was stopped because of healing in 8 patients, persistent paresthesias in 6 and because the medication was unpalatable in 1 patient. Three patients discontinued medication on their own. Perineal disease exacerbated in 13 patients after a mean of 3.4 months (range, 1 week-9 months). The drug was restarted in 7 of the 13 patients and the response was as originally observed. Four of the 18 patients in whom metronidazole was stopped remained healed 7-16 months after cessation of therapy. The other patient developed recurrent perineal disease 7 months after stopping the drug.

c) Does the effect of metronidazole persist for prolonged periods and can the disease relapse on full doses of the drug? Sixteen patients received metronidazole for at least 12 months. Eight of these 16 patients healed completely and remained healed: in 4 of these 8 the drug was eventually stopped and 4 continued to receive it. The other 8 patients had incomplete healing on the drug: 7 of these remain controlled on metronidazole and 1 patient had a transient exacerbation of disease while on the drug. This latter patient and another patient were the only ones who relapsed on full doses of the drug.

d) What are the long-term side effects of metronidazole therapy? Paresthesias were the only short- and long-term major side effect of the drug. These occurred in 50% of the patients. Other side effects included metallic taste, dark urine, decreased appetite, and headache.

Metronidazole is oncogenic in mice and rats but not in hamsters. There has been no evidence of oncogenic effects in retrospective reviews in humans. One patient who had been treated with intermittant metronidazole and sulfasalazine developed myelomonocytic leukemia with an absence of the 7th chromosome. Whether this was related to metronidazole or sulfasalazine is not known. One brief report suggested that sulfasalazine alone or in combination with metronidazole might cause chromosomal abnormalities more than metronidazole alone (83). This, however, requires further evaluation.

Diet. There is no evidence that specific foods or reactions to food are related to the pathogenesis of Crohn's disease. Furthermore, with two exceptions, there

is no evidence that dietary manipulations are important in the treatment of the symptoms related to Crohn's disease. The two exceptions occur in 1) patients with stenotic lesions in the small bowel or colon and 2) patients with lactose intolerance. Patients with stenotic lesions should be advised not to eat foods containing seeds or other undigestable or poorly digestable solids. If nuts are eaten, patients should be advised to chew them well. Acquired lactose deficiency can occur in patients with Crohn's disease and therefore this may be a contributing factor in the diarrhea experienced in some patients. If diarrhea is a major symptom in an individual patient, a lactose-free diet should be considered.

Emotional Support. As previously discussed, emotional factors are not related to the pathogenesis of Crohn's disease. However, environmental stress may play a role in the patients reactions to disease and in causing exacerbations of disease. Thus, it is important for physicians to be aware of the emotional needs of patients. It also is important for one physician to direct the care of the patient. Specialists and sub-specialists will likely be involved in care of patients with Crohn's disease but each patient needs one physician who will listen to them and who will direct their overall care.

Resources are available for patient education. The following is a list adapted from information provided by Dr. Howard Spiro.

A. National Foundation for Ileitis and Colitis, Inc.

444 Park Avenue South
New York, New York 10016
(212) 685-3440

BOOK: 1. The Crohn's Disease and Ulcerative Colitis Fact Book.

National Foundation for Ileitis and Colitis, Inc. Edited by Peter A. Banks, Daniel H. Present, and Penny Steiner.
Charles Scribner's Sons, New York, 1983.
$14.95 (Available from NFIC or Publisher)

2. Brochures:

a. Questions and Answers about Ileitis and Colitis

b. Questions and Answers about Diet and Nutrition in Ileitis and Colitis

c. Questions and Answers about Pregnancy in Ileitis and Colitis

d. Questions and Answers about Government Benefits for Ileitis and Colitis Patients

e. Questions and Answers about the Complications of Ileitis and Colitis

f. Questions and Answers about Emotional Factors in Ileitis and Colitis

g. Crohn's Disease, Ulcerative Colitis, and Your Child

h. Coping with Crohn's Disease and Ulcerative Colitis (a booklet for children and adolescents)

B. National Digestive Diseases Education Information Clearinghouse

1555 Wilson Boulevard, Suite 600
Rosslyn, Virginia 22209
(301) 496-9707

Information Sheets Available including "Ulcerative Colitis" and "Facts and Fallacies about Digestive Diseases".

C. United Ostomy Association
2001 West Beverly Boulevard
Los Angeles, California 90057

Brochures, films and slide tape presentations available.

D. Milner-Fenwick, Inc.

2125 Greenspring Drive
Timonium, Maryland 21093
(1-800-638-8652)

Patient Education Films (Sale or Lease)

1. Ulcerative Colitis (17 minutes)
2. Crohn's Disease (15 minutes)
3. Ostomy - A New Beginning (15 minutes)

Nutritional Therapy.

Nutritional deficits occur in patients with Crohn's disease for several reasons. These include increased need, decreased intake and increased loss of nutrients. With the institution of medications discussed above, inflammation of the bowel diminishes, symptoms decrease and overall nutritional status improves. In some patients, however, this does not occur and additional nutritional support is needed. Attempts to achieve this usually involve enteral feeding of refined diets or total parenteral nutrition. Some investigators believe that "putting the bowel at rest" by enteral feedings of refined diets or parenteral nutrition also is therapeutic in some patients especially those with severe perineal disease. Home parenteral nutrition has been used in treating patients with massive small bowel disease and/or resection.

Enteral Feedings with Minimal Residue Diets. These have been used in some centers as primary therapy for patients with Crohn's disease. As mentioned above, it is believed that if "bowel rest" is achieved Crohn's disease will

improve. A number of commercial formulas are available and a complete list can be found on pp. 450-451 of Ref. 84.

Controlled studies evaluating this therapy have not been performed. Anecdotal reports suggest that this approach may be useful in patients with severe disease and that it may be more helpful in patients with Crohn's disease than in those with ulcerative colitis (85-90). Controlled trials are needed, however, before this approach can be recommended as primary therapy.

The utility of enteral feedings with low residue diets is better established in patients with enteric fistulas (90-95). Again, much of the data is anecdotal. However, these diets lead to reduced fistula output and fistula closure has been documented in some patients with Crohn's disease. Unfortunately, in many instances the fistulas do not remain closed.

Total Parenteral Nutrition (TPN). This should be reserved for patients with severe disease in whom other measures such as enteral feedings of refined diets have been attempted and failed. A number of studies have evaluated the effect of TPN in patients with Crohn's disease. Results of these studies are summarized in Table XV.

TABLE XV. STUDIES EVALUATING THE USE OF TPN IN PATIENTS WITH CROHN'S DISEASE (ADAPTED FROM CLOUSE AND ROSENBERG, REF. 96)

NUMBER OF PATIENTS	CLINICAL REMISSION IN HOSPITAL (%)	LONG-TERM REMISSION (%)	FOLLOW-UP (MONTHS)	REFERENCE
21	67	57	42	97
50	38	--	--	98
16	75	44	10-48	99
29	90	76	24	100
59	47	46	35	101
36	75	61	4-24	102

In most studies listed in Table XV, parenteral nutrition and bowel rest were considered primary therapy. However, many of the patients were also treated with glucocorticoids. Thus, it is difficult to determine the true benefit of TPN. Although the number of patients evaluated has been small, TPN appears to be especially beneficial in inducing remissions in patients with only small bowel disease.

TPN also has been used in treating patients with enteral fistulas (103). In most series TPN led to reduced fistula drainage but the success rate of TPN in leading to fistula closure was not very high (99-101,104).

Home parenteral nutrition has been used in treating patients with short bowel syndrome secondary to Crohn's disease. In these patients home TPN has made a dramatic impact. Ideal body weight has been achieved in almost all patients in whom home TPN has been used. Home TPN has been useful also in treating children and adolescents with severe Crohn's disease and growth retardation (105).

Surgical Therapy

Crohn's disease recurs in a large percentage of patients after surgical resection. Because of this and also because mortality associated with surgery is relatively high (about 5%), surgery should not be performed unless absolutely necessary. Detailed discussions of indications for surgical therapy, surgical approaches and complications of surgery can be found in references 106-108.

Indications for surgery include:

1. Obstruction - This usually occurs in the small bowel but can occur in the colon. When a stricture occurs in the colon, cancer is always a consideration.

2. Abscess - This usually is associated with disease in the terminal ileum and occurs in the right lower quadrant.

3. Uncontrolled diarrhea, bleeding and/or protein loss - This is a rare indication for surgery in Crohn's disease. Occasionally, however, the degree of inflammation is so severe that surgery is necessary to correct these signs and symptoms.

4. Fistulas - Most fistulas should be managed medically, initially. Eventually, however, surgery may be required. Early surgery is indicated in patients with enterovesical fistulas to prevent recurrent urinary tract infections. Fistulas involving the rectum should be treated conservatively as long as possible since fecal incontinence occurs occasionally as a complication of surgery.

5. Free perforation - This is rare complication but when it occurs, it is an obvious indication for surgery.

Surgery for Crohn's Disease of the Colon. One of the most controversial aspects of surgical management of Crohn's disease relates to surgery for Crohn's disease of the colon. Part of the controversy involves the difficulty of distinguishing ulcerative colitis, which is cured by colectomy, from Crohn's disease of the colon, which may recur after colectomy. Another point of controversy revolves around how much of the colon should be removed in patients in whom the rectum is not involved. A total colectomy with permanent ileostomy could be performed. Alternatives include subtotal colectomy with primary ileorectal anastomosis or subtotal colectomy with temporary ileostomy and subsequent ileorectal anastomosis. At the present time, there is no correct answer and prospective, controlled studies are needed to determine the best surgical approach.

The incidence of recurrence after surgery for Crohn's disease of the colon varies markedly. In 1970 Glotzer reported no recurrences after colectomy (109). In a subsequent report, Korelitz and co-workers reported that 46% of the patients with Crohn's disease of the colon developed recurrent Crohn's disease after surgical resection (110). The differences in incidences of recurrence in these and other studies are likely related to differences in patient selection. It appears that recurrences are related directly to length of bowel involved and to the presence of rectal fistulas. Another problem, as mentioned earlier, may also be in differentiating Crohn's disease of the colon from ulcerative colitis.

SUMMARY

Excluding maligant neoplasms, Crohn's disease is probably the most devastating disease effecting the gastrointestinal tract. The cause of Crohn's disease is not known. Presently, the most promising investigation relates to discovery of a paratuberculosis-like organism in tissues from several patients with Crohn's disease. These studies must be confirmed, however, by further investigation. Also, there is no cure for Crohn's disease. Currently available medical and surgical therapies reduce symptoms and complications of disease in some patients but recurrences are frequent. In other patients, complications such as stenosis leading to small bowel obstruction, internal fistulas or peritoneal disease occur despite therapy and lead to debilitating symptoms. Even though there are few answers to questions regarding Crohn's disease at the present time, hopefully, this Grand Rounds will stimulate some individual or group of individuals to pursue the pathogenesis and ultimately, the cure of Crohn's disease.

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APPENDIX

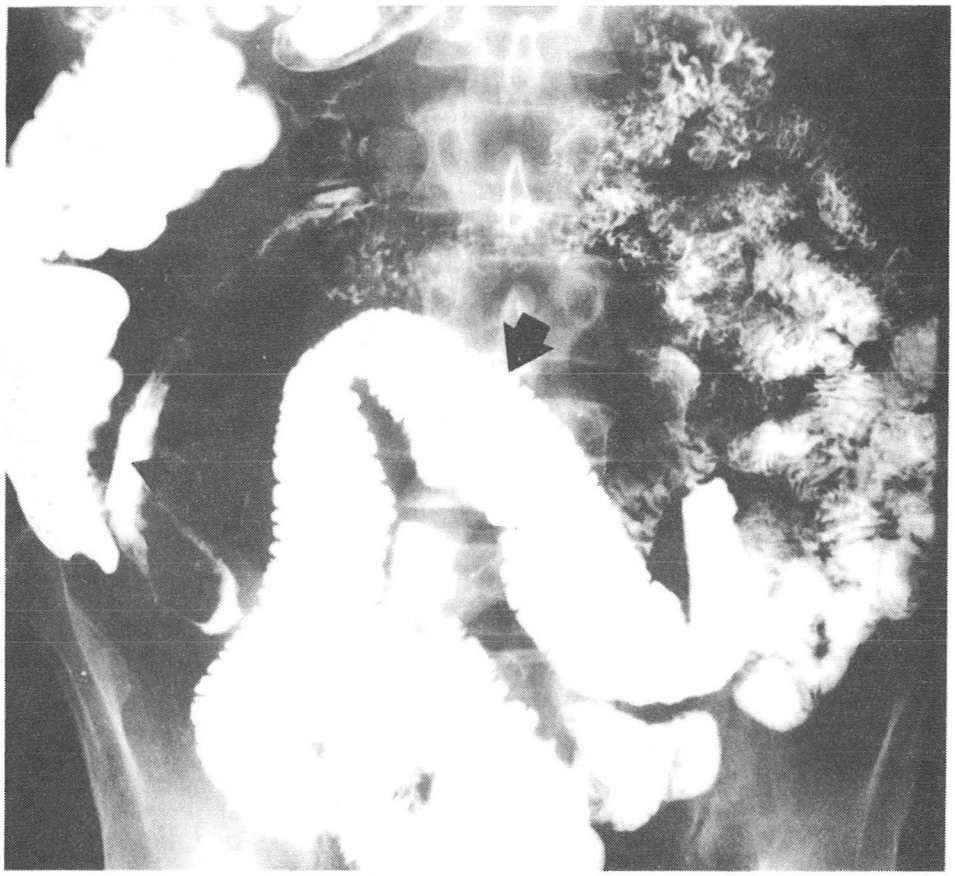

Figure 1. Contrast examination of the small bowel from Case 1 (page 1) illustrates diseased terminal ileum (arrow) and prestenotic dilatation (arrow).

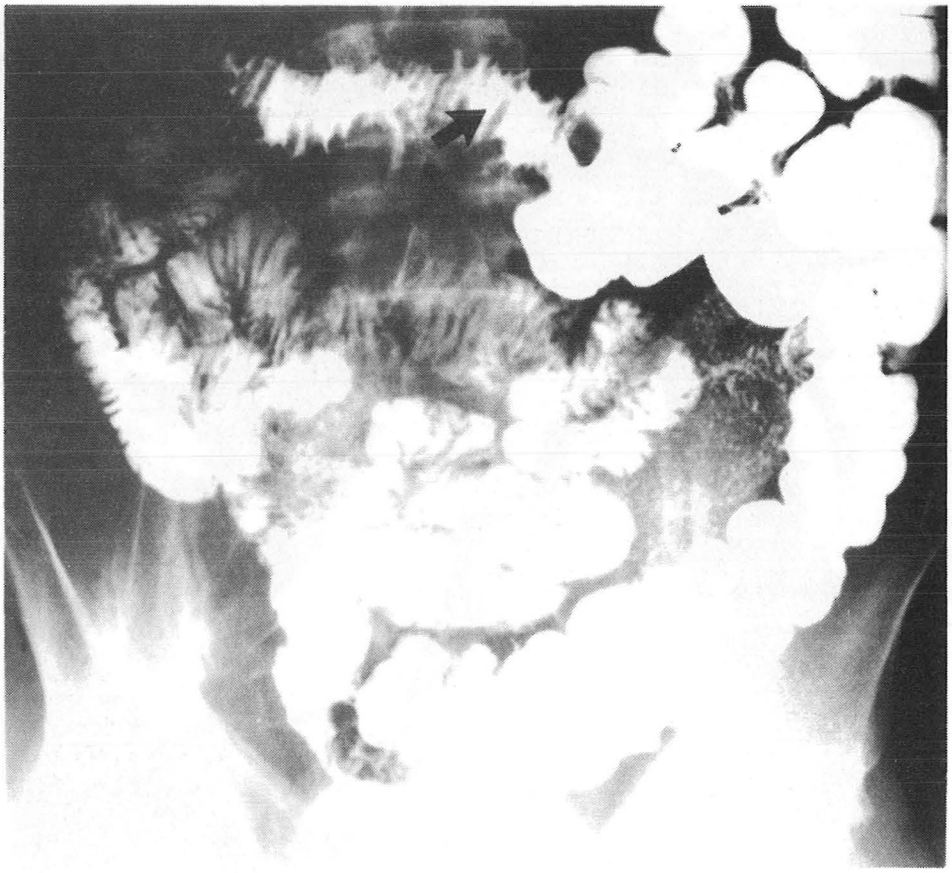

Figure 2. Contrast examination of the small bowel from Case 2 (page 1) illustrates recurrent disease (see arrow) at anastomosis of ileum and colon.

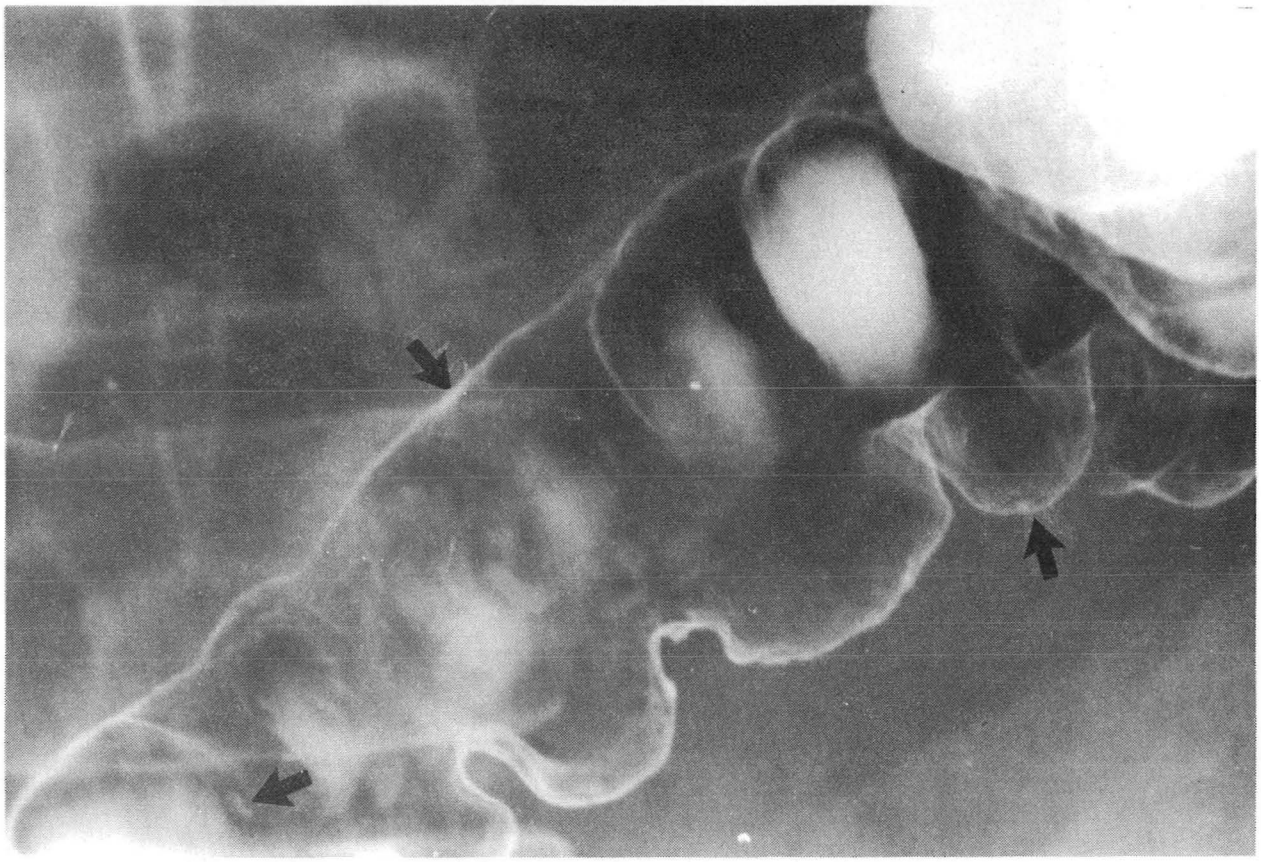

Figure 3. Double contrast barium enema of the hepatic flexure illustrates aphthae (arrow) and asymmetric involvement of colon characterized by disordered haustra: absence of haustra superiorly, presence of haustra inferiorly (see arrows).

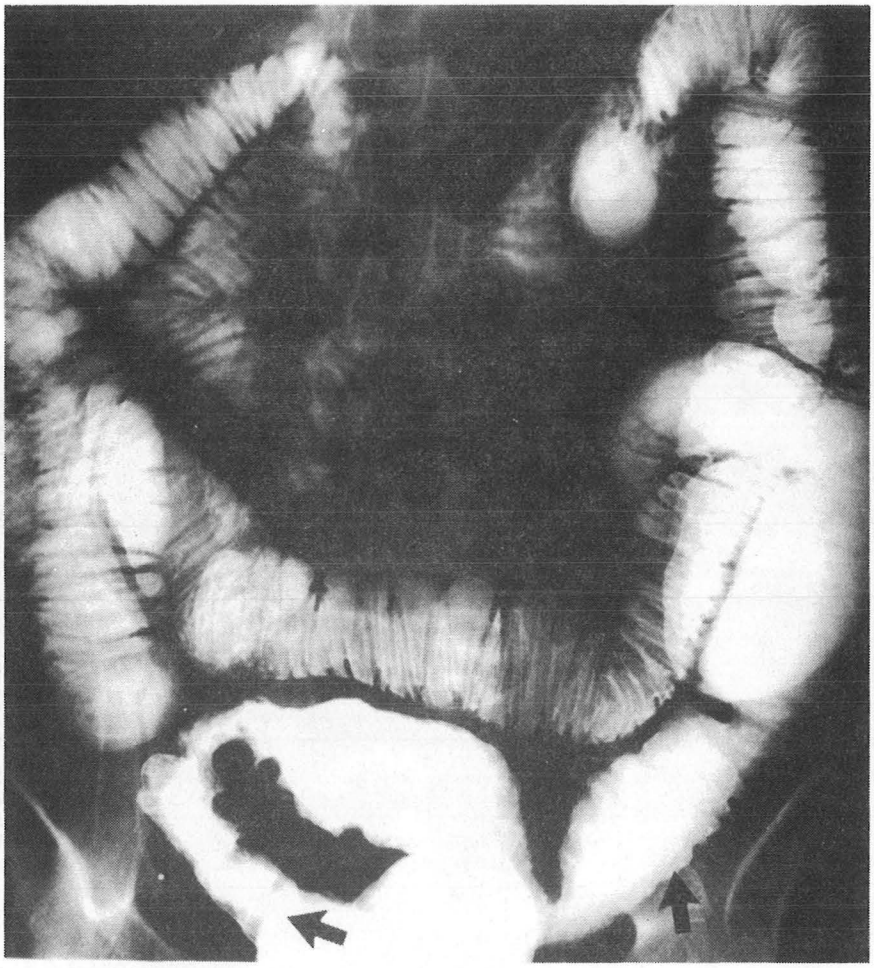

Figure 4. Barium edema in a patient with a subtotal colon resection and ileorectal anastomosis. Recurrent disease is shown in the rectum and small bowel (see arrows).

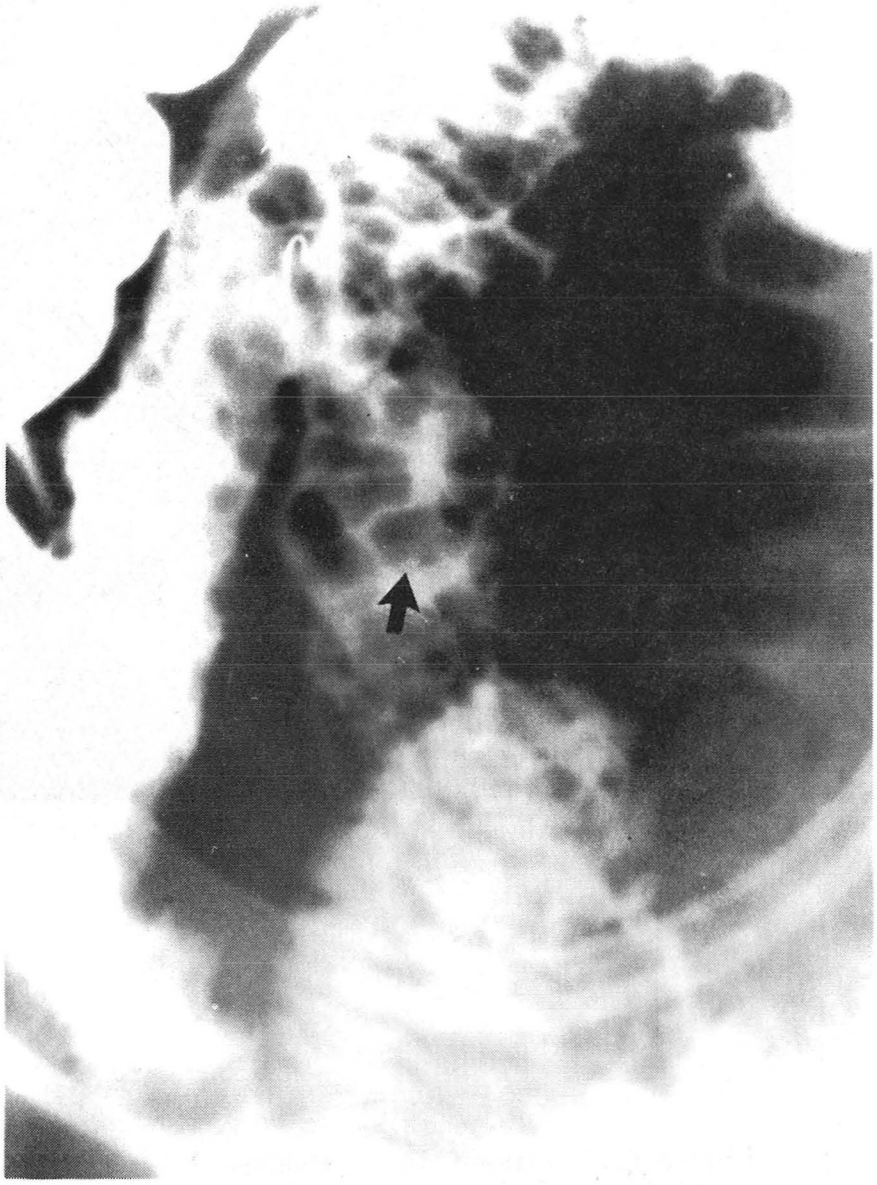

Figure 5. Barium examination of terminal ileum illustrates "cobblestone" appearance secondary to transverse and longitudinal ulcerations.

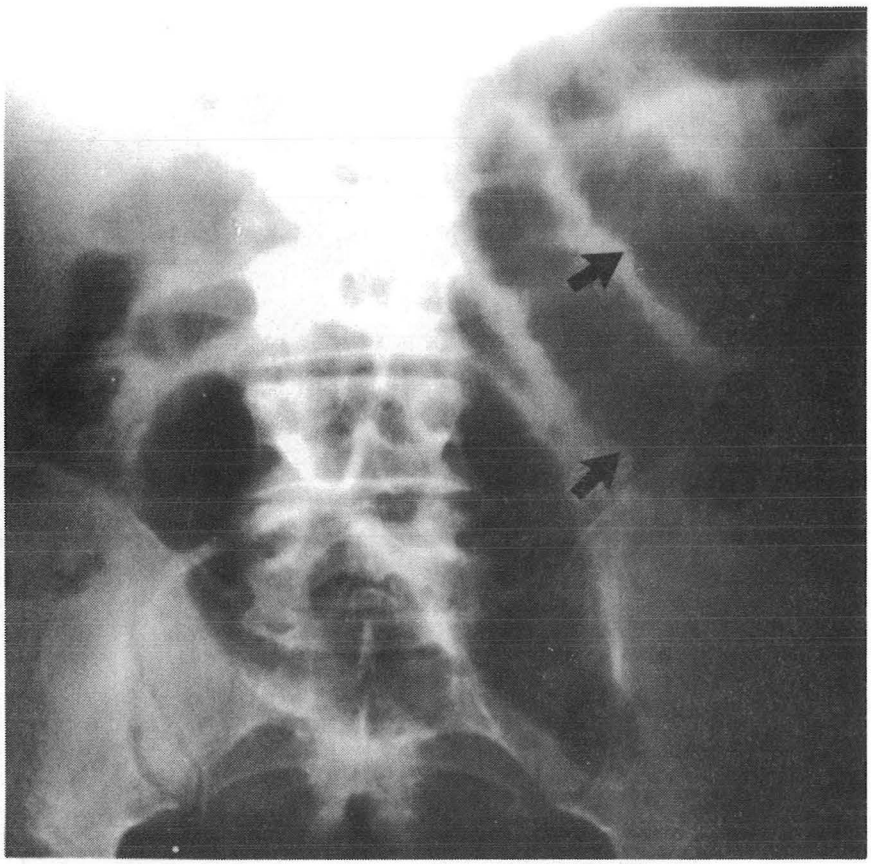

Figure 6. Supine film of abdomen illustrates separation of loops of small bowel. This results from edema and inflammation in the bowel wall and mesentery (see arrows).

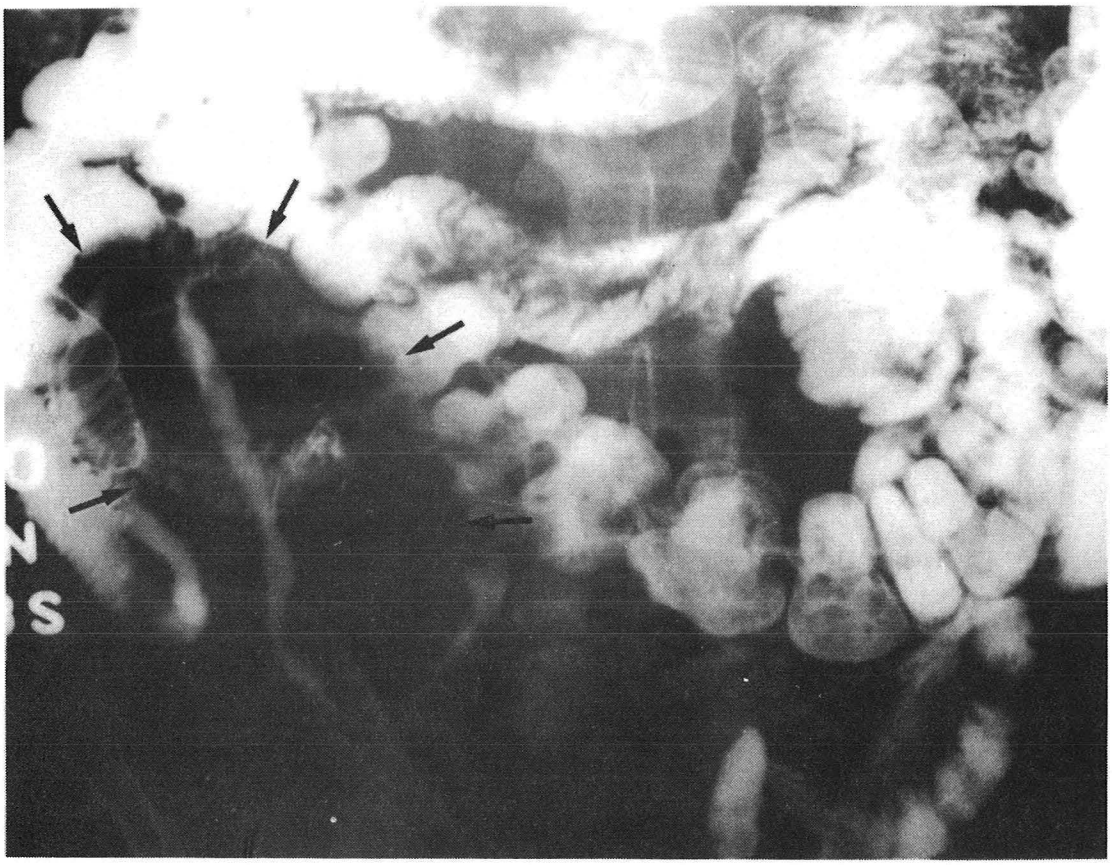

Figure 7. Small bowel examination illustrates right lower quadrant mass. This results from bowel wall inflammation, indurated mesentery, increase in mesenteric fat, enlarged lymph nodes and/or abscess (see arrows). Note stenotic small bowel.