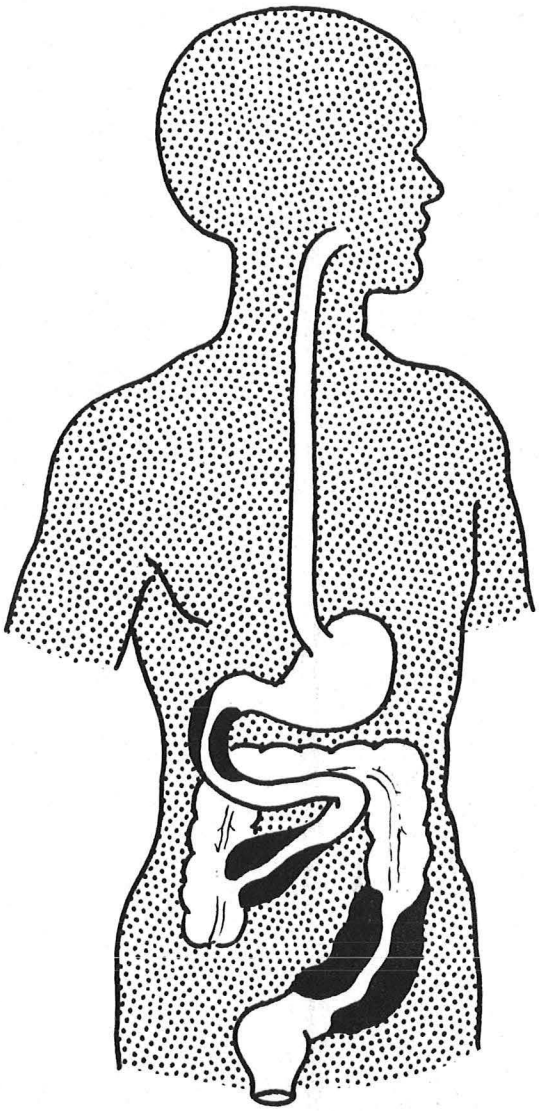

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Medical Grand Rounds

University of Texas
Health Science Center at Dallas

CROHN'S DISEASE

- REGIONAL ENTERITIS
- ILEOCOLITIS
- GRANULOMATOUS COLITIS

by

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I. INTRODUCTION

The term Crohn's Disease includes a variety of different clinical syndromes that have been called regional enteritis, terminal ileitis, granulomatous colitis, right-sided colitis and regional jejunitis. The typical pathological lesion is usually an inflammatory infiltration of the submucosal tissue with the presence of granulomas in a significant percent of the cases. Any area in the gastrointestinal tract may be involved including the mouth, esophagus, stomach, duodenum, biliary-tree, jejunum, ileum, cecum, appendix and colon. The major clinical syndromes, however, derive from involvement predominantly of either the ileum or the colon. The disease may run an acute fulminating course, although more commonly an acute recurrent or chronic clinical picture is seen. Patients affected with this disease commonly manifest recurrent fever, weight loss, diarrhea, gastrointestinal bleeding and sepsis. In general, therapy is directed at control of the disease rather than cure and consists primarily either of the administration of steroids and nonabsorbable sulfa drugs or surgical excision or bypass of the involved area of the gastrointestinal tract.

II. EPIDEMIOLOGICAL CONSIDERATIONS

In many ways Crohn's disease and ulcerative colitis manifest similarities with respect to general incidence within various populations and with respect to the age and sex distribution of patients manifesting the disease. Table 1

Table 1

Average Annual Incidence or First Hospitalization Rates of Crohn's Disease and Ulcerative Colitis (Number of cases per 100,000 per year)

		Crohn's Disease	Ulcerative Colitis
England	1951-1960	0.8	6.5
Norway	1946-1955		1.2
	1956-1960	0.2	2.3
	1964-1969	1.0	3.3
New Zealand			5.5
Baltimore	1960-1963	1.8	5.2

gives the annual incidence of new cases of both Crohn's disease and ulcerative colitis per 100,000 people. The data in this table were drawn almost exclusively from white populations. Three points are worthy of emphasis. First, in general terms the incidence of these two diseases is similar in different geographical locations, although it should be recognized that essentially all

of these patient populations are ultimately of European extraction. Second, Crohn's disease is usually less commonly seen in any population than ulcerative colitis. However, it should be pointed out that in the older series many of the cases of Crohn's disease of the colon were mistakenly diagnosed as ulcerative colitis; thus, it is apparent in Table 1 that in the two most recent series, one from Baltimore and the other from Norway, the incidence of Crohn's disease is approximately 1/3 to 1/2 that of ulcerative colitis. Third, there is a suggestion in several series that the incidence of Crohn's disease is increasing. This is seen in the carefully controlled epidemiologic studies presented from Norway in which between 1956 and 1969 the incidence of Crohn's disease increased 5 fold from approximately 0.2 to 1.0 cases per 100,000 population under circumstances where the incidence of ulcerative colitis increased much less, from 2.3 to 3.3 cases per 100,000. This may, of course, be the result of increased diagnostic accuracy and the recognition of Crohn's disease of the colon: nevertheless, several other series from northern Europe also confirm an apparent significant increase in the incidence of Crohn's disease.

As shown in Table 2 there are very significant differences in the incidence of Crohn's disease, as well as ulcerative colitis, in different ethnic and

Table 2

The Average Annual Incidence of Crohn's Disease and Ulcerative Colitis in White and Black Americans and in Jews (Number of cases per 100,000 per year)

	Crohn's Disease	Ulcerative Colitis
White, Male	2.5	3.9
White, Female	1.2	5.2
Black, Male	0.7	1.3
Black, Female	?	1.5
White, Jews, Male	20.0	23.8
White, Non-Jews, Male	3.2	5.7
White, Jews, Female	8.4	31.8
White, Non-Jews, Female	3.0	6.9

racial populations. In this carefully controlled study from Baltimore, it is apparent that there is a marked variation in the annual incidence of these two diseases in Blacks and in Jews when compared with non-Jewish Whites. For example, the incidence of Crohn's disease in Blacks was only 0.7 per 100,000 cases in Black males but equaled 2.5 in White males. There was a similar 3 fold lower incidence of ulcerative colitis in Blacks. In contrast, the incidence of Crohn's disease was 6 fold higher in Jewish males and 2-1/2 fold higher in Jewish females. Again, a similar disproportionately higher incidence was seen in Jewish men and women with respect to ulcerative colitis. This high incidence of Crohn's disease and ulcerative colitis in Jews has been confirmed in other series as has the relatively low incidence of these diseases in Blacks,

both Americans and Africans (in the Transvaal). Other, relatively poorly done studies also indicate that there is a low incidence of this disease in Orientals, in patients of Spanish-Mexican extraction, in American Indians and in Eskimos. Thus, as summarized in Table 3, Crohn's disease has an apparent incidence that

Table 3

Summary of the Relative Incidence of Crohn's Disease in Various Ethnic Groups

High Incidence	Jews
Medium Incidence	White-Non Jews of North European Extract
Low Incidence	Blacks Mexican Americans Eskimos Orientals

is 3 to 6 times higher in Jews than in White patients of European extraction while Blacks, and possibly Mexican-Americans, Orientals and North American Indians have an incidence which is significantly less. It should be emphasized, however, that despite these marked differences in incidence Crohn's disease, as well as ulcerative colitis, has been reported in every racial and ethnic group.

While Crohn's disease, as well as ulcerative colitis, commonly appear sporadically in the "at risk" population, it is also well established that the disease may cluster in some families. Thus, there are a number of reports of siblings, including twins, and parents from the same family that are affected with the disease. As summarized in Table 4, in a survey of approximately 985 cases, 4% of the patients came from families with other affected

Table 4

Frequency of Family History in U.C. and Crohn's Disease

	No. Cases	Percent
U.C.	3084	3%
Crohn's Disease	985	4%

members. This relationship is shown in detail for one report in the literature in Table 5. Finally, it is also now clear that different members of the same family may have Crohn's disease and ulcerative colitis. It was suspected that earlier reports of this occurrence were due to mis-diagnosis; however, more recent case reports strongly suggest that the diseases do indeed occur together in certain families at an incidence higher than would be predicted from chance alone. The importance of such clustering in particular families obviously suggests that some factor(s) is inherited that alters susceptibility to the onset of the disease. The nature of this factor(s), however, has not yet been elucidated.

Table 5

Crohn's Disease Occurring in Members of the Same Families

Relationship	Number of families
Parent-One Child	14
Parent-Multiple Children	2
Two Siblings	17
Three Siblings	4
Monozygotic Twins	4
Dizygotic Twins	2
Collateral Relatives	9
Husband and Wife	0

III. ETIOLOGY OF CROHN'S DISEASE

Over the past 20 years there have been many attempts to demonstrate the etiology of Crohn's disease. The common claims that this represents a psychosomatic disease or results from some abnormality in the immune response of the affected patients have never been substantiated. There have been several recent reports, however, strongly suggesting that an infectious agent may be involved. In two separate publications it has been reported that the inoculation of bacteria-free material obtained from diseased ileum into the wall of the small bowel of the rabbit produces an inflammatory reaction and granuloma formation. Such cellular infiltrates were not seen with the injection of similarly prepared material from human ileums not affected with Crohn's disease. In one preliminary publication a successful first passage has been achieved into a second group of rabbits using filtrates that have passed through either a 100 μ or 0.2 μ filter. Such studies, if confirmed in other laboratories, strongly suggest the presence of a transmiscible agent in human Crohn's disease. Certainly, such studies provide the most promising leads to date for the ultimate elucidation of the cause of this disease.

IV. PATHOLOGY OF CROHN'S DISEASE OF THE GASTROINTESTINAL TRACT

Crohn's disease may involve any area of the gastrointestinal tract, although it has a predilection for the terminal ileum. As shown by the data presented in Table 6 in 304 consecutive cases of gastrointestinal Crohn's disease the terminal portion of the small bowel was involved 90.8% of the time. The disease commonly crosses the ileal-cecal valve so that the cecum represents the second most common site of involvement at 48.3%. To a lesser degree the disease may extend proximally to involve the initial portion of the ileum (27.6%) and

Table 6

Organ Involvement in 304 Cases of Crohn's Disease

Organ	No. of Patients	Percentage
Terminal ileum	276	90.8
Cecum	147	48.3
Proximal ileum	84	27.6
Ascending colon	52	17.1
Jejunum	44	14.5
Transverse colon	34	11.2
Appendix	18	5.9
Descending colon	8	2.6
Sigmoid colon	4	1.3
Duodenum	3	0.98
Stomach	3	0.98
Skip areas	47	15.5

jejunum (14.5%). The most proximal portions of the gastrointestinal tract including the mouth, esophagus, stomach and duodenum are only rarely involved in the disease. Similarly, the most distal portions of the colon are involved infrequently. Thus, it is apparent that the primary site of involvement of the gastrointestinal tract with this disease is the ileum and right colon region. The particular clinical syndrome with which a given patient presents is determined by whether the disease in that particular patient is primarily localized to the terminal ileum or primarily involves the colon.

Grossly, the involved area of bowel usually appears to be thickened, edematous and grossly inflamed. The serosal surface commonly manifests dilated vessels and inflammatory exudate and there is adherence between the involved portions of bowel and adjacent structures such as the parietal peritoneum, dome of the bladder, vagina, or adjacent loops of uninvolved bowel. The adjacent portions of the omentum commonly are thickened, edematous and inflamed and there is usually significant adenopathy in the drainage area of the involved portion of bowel. On cut sections the bowel wall is obviously thickened and shows a variety of histological abnormalities. The most consistent histologic finding present in essentially all of the cases is a nonspecific inflammatory reaction. This consists of both mucosal and submucosal patchy infiltration by mononuclear cells and indirect evidence of tissue edema. The infiltrating cells commonly extend through the muscularis mucosa to involve the layers of muscle on the serosal surface of the bowel in the inflammatory process. The superficial mucosa may show ulcerations with the extension of deep, transmural clefts or fissures from the base of some ulcers through the inflammatory process of the submucosal tissue to the serosal surface of the bowel. These deep clefts presumably represent the precursor for the commonly encountered fistula and sinus tracts so characteristic of Crohn's disease. In addition, the submucosal cellular infiltrate may include large numbers of giant cells and histiocytes which are scattered throughout the submucosal layer as a diffuse, granulomatous inflammatory reaction. In approximately half of the cases there are more focal

aggregations of epithelioid cells and giant cells of the Langhans type which have the appearance of a noncaseating granuloma or tuberculoma. Thus, as summarized in Table 7, the major histologic features of Crohn's disease of

Table 7

Histological Criteria for Diagnosis of Inflammatory Bowel Disease

I. Criteria for Pathological Diagnosis of Crohn's Colitis:
   A. Major:
      1. Giant cell or epithelioid granulomas, intramural or within regional lymph nodes
      2. Intramural fissures or fistula
      3. Transmural mononuclear inflammation
      4. Transmural fibrosis (healed stage)
   B. Minor:
      1. Submucosal lymphangiectasia
      2. Chronic serositis in absence of prior surgery
      3. Muscle-wall thickening (>twice normal)
      4. Segmental involvement

II. Criteria for Pathological Diagnosis of Nonspecific Ulcerative Colitis:
      1. Mucosal ulceration
      2. Mucosal inflammation
      3. Submucosal inflammation or fibrosis (healed stage)

the bowel include the presence of giant cells or epithelioid granuloma within the bowel wall, deep fissures or fistula penetrating the bowel wall and the presence of extensive monocellular infiltrates within the submucosal tissue. Of these various features the most important from the standpoint of differentiating Crohn's disease from other inflammatory bowel diseases is the presence of granuloma. The incidence of such lesions in involved areas of the gastrointestinal tract in different age groups is summarized by the data in Table 8.

Table 8

Incidence of Granulomas and Giant Cells in Different Age Groups in 287 Cases of Crohn's Disease

		Granuloma in per cent of cases			Giant cells in per cent of cases		
Age Group	No. of Patients	Small Intestine	Colon	Lymph Nodes	Small Intestine	Colon	Lymph Nodes
0-19	99	62	29	28	46	23	18
20-39	134	41	17	23	27	10	7
40-79	54	26	12	20	31	8	8
Total	287	46	20	24	34	14	11

Generally speaking, it is apparent that the incidence of granuloma and giant cells is much commoner in younger patients than in older patients manifesting Crohn's disease. In addition, it is also apparent from these data that in any age group, Crohn's disease of the small bowel usually has a much higher incidence of granuloma formation than disease that involves other portions of the gastrointestinal tract. It should be emphasized that while the finding of granulomas in pathologic specimens strongly indicates that one is dealing with Crohn's disease, the absence of such granuloma is of relatively little differential value.

In contrast to these findings in Crohn's disease, the classical pathology of ulcerative colitis is different. Grossly, the exterior of the bowel may appear essentially normal and there is usually no involvement of the mesentery or regional lymph nodes. Also, there is no inflammatory exudate on the serosal surface so that adherence and fistula formation to adjacent viscera virtually never takes place. In the most common form of moderately severe ulcerative colitis, the disease extends at least to the mid-transverse colon and commonly involves the entire colon. The disease probably never involves small bowel, however. The earliest histological lesion is the appearance of scattered polymorphonuclear leukocytes about the base of the crypts. These cells can be seen moving outward between columnar mucosal cells into the crypt lumen. In a slightly more advanced stage there is dissolution of the basement membrane and destruction of the crypt epithelium with formation of crypt abscesses. At this stage it is common to see streamers of pus cells and mucus pouring out into the colonic lumen. With fusion of adjacent crypt abscesses there is microscopic and gross ulceration of the surface epithelium and bleeding from markedly distended superficial vessels. The abscesses commonly burrow beneath the mucosa to form mucosal bridges.

Thus, with respect to certain classical features Crohn's disease and ulcerative colitis present quite different pictures. Crohn's disease typically involves the ileal-cecal region and is manifest by a mononuclear cellular infiltrate of the submucosal tissue with granuloma and fistula formation. In contrast, classical ulcerative colitis is a very superficial lesion involving almost exclusively the mucosal surface in an ulcerating process. Unfortunately, when biopsies are taken in individual patients one commonly sees only superficial mucosal ulceration and a nonspecific inflammatory reaction. Such findings are seen in both Crohn's disease and ulcerative colitis, and, from a histological point of view do not help in the differentiation of these syndromes. Only the finding of granuloma in the submucosal tissue provide a relatively specific finding with which to differentiate Crohn's disease from ulcerative colitis. As will be discussed later, often this differentiation must be made on the basis of other clinical findings.

V. MAJOR CLINICAL SYNDROMES OF CROHN'S DISEASE

Crohn's disease of the gastrointestinal tract should be considered as a single clinical entity which, as summarized in Fig. 1, predominantly involves the distal ileum and cecum although it is apparent that essentially

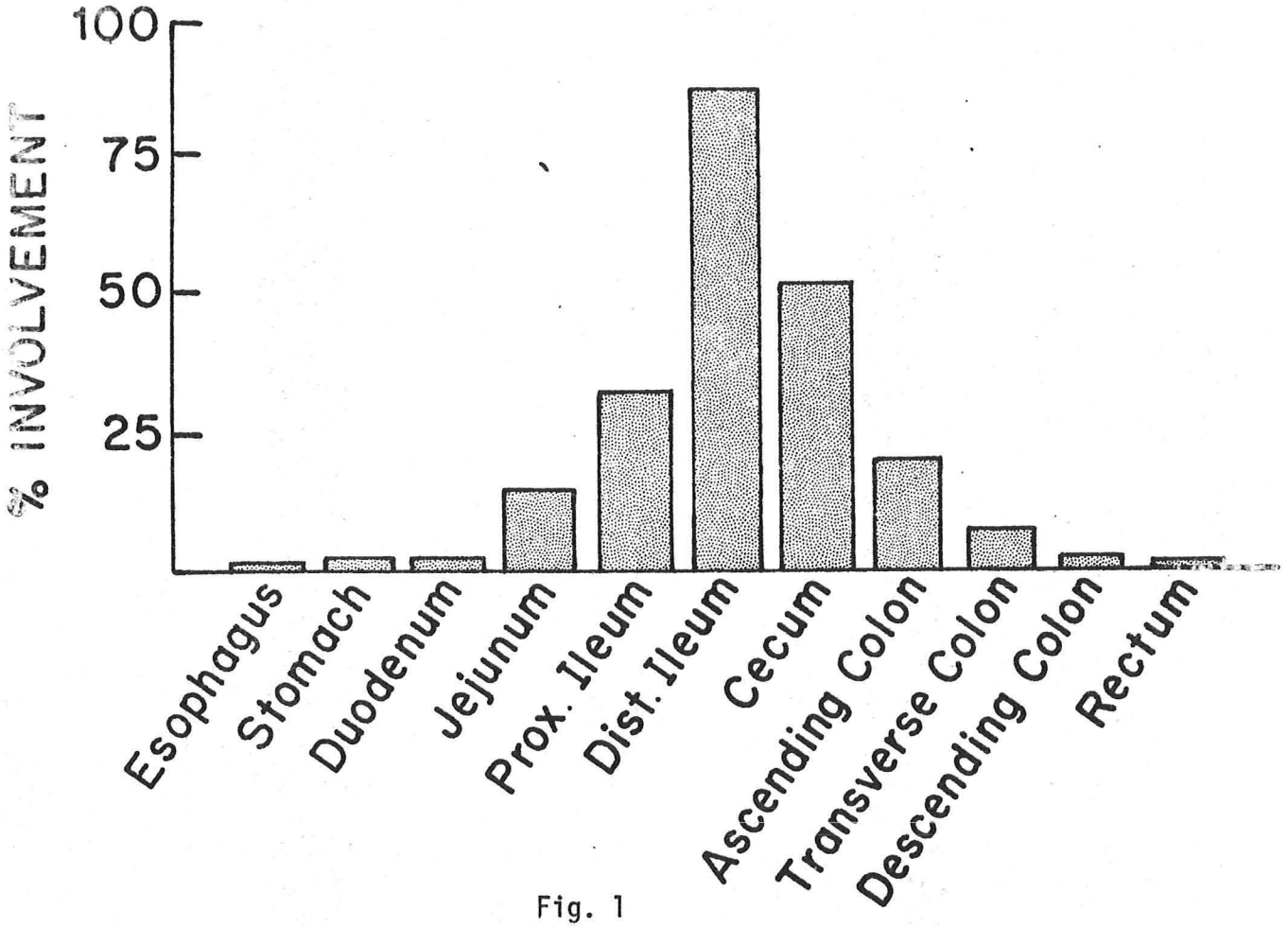

Fig. 1

every area of the gastrointestinal tract may be involved in the disease process. The clinical symptom complex with which a given patient presents is determined by the primary site of gastrointestinal involvement in that particular patient. The most common clinical syndrome involves a constellation of symptoms that derive from involvement primarily in the ileal-cecal region while the second most common clinical syndrome is seen in those patients with predominant involvement of the colon. Other less common syndromes exist, however, and will be reviewed in this section.

A. Crohn's Disease of the Mouth

While Crohn's disease is known to affect essentially any area of the gastrointestinal tract it was not until 1969 that lesions of the oral cavity were described. Since that time there have been a number of individual case reports describing lesions in patients who already had a diagnosis of Crohn's disease, usually of the ileum, or who later developed the disease. Typically, the lesion may present as either a nodular or "cobblestone" mass or as a

chronic ulceration somewhere in the buccal mucosa. In several cases the oral lesions preceded any other GI symptomology while in others the lesions came on after a definite diagnosis of ileal Crohn's disease had been made. While biopsy may simply show nonspecific inflammation and ulceration, apparently granulomas and giant cells are seen in the majority of cases strongly suggesting the possibility of Crohn's disease. Several of these lesions have responded to local steroid therapy while others responded to systemic steroids when there was evidence of disseminated bowel disease. It is apparent from these case reports that the spontaneous development of an oral mass or chronic oral ulcer should raise the possibility of oral Crohn's disease, particularly if there are other symptoms to suggest involvement of other portions of the gastrointestinal tract. A biopsy is apparently useful in that it commonly shows submucosal inflammatory infiltration typical of gastrointestinal Crohn's disease and, in a significant number of cases may show granuloma formation and giant cells.

B. Crohn's Disease of the Esophagus

Only a very few case reports have appeared in the literature concerning involvement of the esophagus in Crohn's disease. Essentially two types of lesions have been reported: ulcerating lesions predominantly located in the mid-esophagus and stenosing lesions occurring predominantly in the distal esophagus. The superficial biopsy of such lesions is usually not helpful since one sees only superficial, nonspecial "esophagitis". On the other hand, there are a number of individual case reports in which more extensive tissue examination has been possible either because the patient died and autopsy was performed or because there was surgical resection. In several of these cases typical mononuclear cellular infiltrate of the base of the ulcer or the stenotic lesion has been found with granuloma and giant cells. In addition, several cases have shown the extension of typical sinus tracts from the wall of the esophagus into mediastinal lymph nodes which also demonstrated enlargement, cellular infiltration and granuloma formation. Usually such esophageal involvement becomes manifest in patients who already have obvious clinical or laboratory evidence of Crohn's disease elsewhere in the gastrointestinal tract but, as with the oral lesions, the patient may present with dysphagia as the initial complaint of involvement of the gastrointestinal tract in this granulomatous reaction. Presumably the esophageal lesions will respond to steroid therapy although there is little information in the literature specifically dealing with this point.

C. Crohn's Disease of the Stomach

A relatively small number of cases also have been reported in which Crohn's disease apparently involves the stomach. Typically, the antrum rather than the body of the stomach is involved. X-ray findings include antral narrowing with functional gastric outlet obstruction occurring in a few patients. Occasionally, the upper GI series also reveals one or more gastric ulcers and marked hypoperistalsis of the stomach. The duodenum is also involved in the majority of cases. At gastroscopy the antrum usually appears relatively rigid and the mucosa manifests granularity and cobblestoning. Erosions or frank, discrete ulcerations are occasionally seen.

Table 9

Clinical Features of 17 Cases of Crohn's Disease Involving the Stomach

1) Sex Distribution	
male	- 12
female	- 5
2) Typical X-Ray Findings	
antral narrowing	- 10
severe outlet obstruction	- 2
ulceration	- 4
hypoperistalsis	- 3
duodenal involvement	- 13
3) Gastroscopic Findings	
antral granularity	
cobblestoning	
erosions and ulcerations	

These various findings commonly raise the differential problem of Crohn's disease versus gastric carcinoma, lymphoma or some other granulomatous, infiltrative disease. A full thickness biopsy of the antral wall again commonly shows the typical findings of submucosal mononuclear infiltration and granuloma formation. In the presence of obvious Crohn's disease elsewhere in the gastrointestinal tract such findings are probably sufficient to establish the diagnosis of Crohn's disease involving the gastric antrum: however, in the absence of Crohn's disease elsewhere in the GI tract the differential diagnosis must include other granulomatous reactions that may be seen in conjunction with disseminated sarcoidosis, certain infections and certain malignancies. If the lesion in the antrum is established as being due to Crohn's disease then the course is generally benign and surgery is not indicated unless there is severe gastric outlet obstruction. Generally, the lesion in the stomach responds to systemic steroids if these are begun for treatment of more disseminated disease elsewhere.

D. Crohn's Disease of the Duodenum

Crohn's disease involving the duodenum also is relatively uncommon. As shown in Table 10 in the majority of cases in which involvement of the duodenum has been identified there has been coexisting disease of other portions of the gastrointestinal tract. Only very uncommonly, in 5 reported cases, has Crohn's disease been found to be isolated to the duodenum alone. The cases usually become evident clinically after examination of the upper gastrointestinal tract with barium: the duodenal loop may manifest an irregular edematous appearance or may show a typical "string" sign, i.e., marked irregular narrowing of the intestinal lumen. Often the x-ray findings of duodenal involvement are only incidental to more significant clinical disease elsewhere in the gastrointestinal tract. However, occasionally the duodenal

Table 10

Incidence of Involvement of Other Areas of the Small Intestine in 44 Patients with Crohn's Disease of the Duodenum

	Number of Cases
Duodenum Alone	5
Jejunum	17
Ileum	2
Multiple Areas Including Stomach, Jejunum and/or Ileum	20

narrowing produces signs and symptoms of bowel obstruction with nausea and vomiting. Usually the presence of abnormalities in the duodenum in patients with proven Crohn's disease elsewhere in the gastrointestinal tract presents no special problem in diagnosis. However, in that small percentage of cases that presents with Crohn's disease primarily localized to the duodenum, a more difficult differential problem exists and includes such possibilities as lymphoma, carcinoma at the head of the pancreas, postbulbar peptic ulcer deformity, etc. Certainly, the possibility of isolated Crohn's disease of the duodenum should be included in the differential diagnosis in any patient who presents with a narrowed, deformed segment of duodenum.

E. Crohn's Disease of the Appendix and "Acute Terminal Ileitis"

In the original reports of Crohn as well as in many recent medical and surgical reviews a number of cases of "acute terminal ileitis" have been reported in which patients commonly present with the acute onset of fever, malaise, nausea and vomiting, right lower quadrant pain and tenderness and leucocytosis. The majority of these cases were diagnosed preoperatively as having acute appendicitis but during exploration were found to have acute inflammation, edema and thickening of the terminal ileum. Usually, the disease did not appear to cross the ileal-cecal valve although clearly cases also were reported in which there was involvement of the cecum and/or the appendix in this inflammatory process. There is general agreement that the great majority of these cases (50-95%), undergo complete resolution of the process and do not progress to disseminated Crohn's disease of the small bowel when followed for prolonged periods of time. The strong suspicion has developed, therefore, that many of these cases of "acute terminal ileitis" are due to some etiology other than that responsible for classical Crohn's disease of the small bowel. Indeed, one recent series from Finland reported that of 17 patients followed for an average of 11 years there was no evidence of chronic Crohn's disease in any of the subjects.

More recently, particularly in the European literature, it has become apparent that infection with Yersinia, both *Y. pseudotuberculosis* and *Y. enterocolitica*, can produce both a mesentery lymphadenitis and acute terminal ileitis. Numerous case reports have now appeared in the European literature and a lesser number in the U.S. literature in which both children and adults presenting with a right lower quadrant pain syndrome have been found to have mesentery lymphadenitis from which both strains of Yersinia have been cultured. In addition, in 1966 Winblad, and colleagues, reported that a number of cases with acute terminal ileitis have striking rises in the agglutination titers for Yersinia. Sjöström reported that *Y. enterocolitica* was apparently responsible for the acute terminal ileitis found in 21 of 29 cases: after a follow-up of several years, none of these cases developed chronic Crohn's disease. In contrast, in those 8 cases with acute terminal ileitis where Yersinia infection was not found, 5 went on to develop apparent disseminated chronic Crohn's disease. A similar provocative study was recently published from Great Britian and is reproduced in modified form in Table 11. As shown in lines A-C, 95-97%

Table 11

Serological Titers to Y. enterocolitica In Various GI Syndromes Including Patients Presenting with Right Lower Quadrant Pain Syndromes

Syndrome	Number of Patients	Maximum Titer to *Y. enterocolitica*					
		≤1/40		1/40 - 1/80		≥1/160	
A. Controls (Inpatients)	1,351	1316	(97%)	24	(1.8%)	11	(0.8%)
B. Controls (blood donors)	431	420	(97%)	10	(2.3%)	1	(0.2%)
C. Diarrhea	148	140	(95%)	3	(2.0%)	5	(3.3%)
D. Crohn's Disease	22	22	(100%)	0		0	
E. Right Lower Quadrant Syndrome							
- Acute Ileitis	25	7	(28%)	7	(28%)	11	(44%)
- Mesenteric Adenitis	8	3	(38%)	2	(25%)	3	(38%)
- Appendicitis	45	38	(84%)	4	(9%)	3	(7%)
- No Pathology	17	14	(82%)	0		3	(18%)

of either normal control patients or patients with simple diarrhea have serological titers to *Y. enterocolitica* equal to or less than 1/40. Furthermore, 100% of 22 patients with proven chronic Crohn's disease of the GI tract also

had low titers to this organism. Line E shows the results, however, in 95 cases who presented with an acute febrile illness and right lower quadrant pain and were operated on with the presumptive diagnosis of acute appendicitis. Twenty-five of these patients proved to have an acute terminal ileitis and 72% of these cases had significantly elevated titers to *Y. enterocolitica*. Similarly, 8 patients were found to have an acute mesenteric adenitis and 63% of these had marked elevation of the titer to Yersinia. In contrast, 84% of patients that appeared to have uncomplicated appendicitis had low titers to this organism. Taken together, these data strongly suggest that the majority of patients who present with acute terminal ileitis have, in fact, an acute bacterial infection, apparently commonly due to various strains of Yersinia, while only a small percentage of the cases actually have Crohn's disease of the terminal ileum. The great majority of all of the reported cases of mesenteric adenitis or ileitis due to Yersinia have appeared in the European literature and only a few recent reports concerning this problem have appeared in the U.S. medical literature. Nevertheless, it is well documented that a number of animal species in the U.S. carry Yersinia and it becomes of considerable importance to evaluate the quantitative significance of Yersinia infection in cases of acute terminal ileitis occurring in the United States.

Table 12 summarizes the differential diagnostic possibilities that must be taken into consideration in that group of patients who present with an acute febrile illness, leucocytosis and right lower quadrant discomfort who

Table 12

Differential Diagnostic Considerations in Patients Presenting with an Acute Picture of Right Lower Quadrant Pain, Fever and Leucocytosis

1) Acute Appendicitis

2) Mesenteric Adenitis (? *Y. pseudotuberculosis* or *enterocolitica*)

3) Acute Terminal Ileitis (? *Y. pseudotuberculosis* or *enterocolitica*)

4) Crohn's Disease of the Ileum

5) Crohn's Disease of the Appendix

6) Other Infectious Diseases of the Ileo-Cecal Region such as Amoebiasis, Actinomycosis and Tuberculosis

are commonly operated upon with a presumptive diagnosis of acute appendicitis. The most common diagnosis found at surgery will be classical, acute appendicitis. Less commonly, the primary diagnosis will be mesenteric lymphadenitis: while a number of viruses and bacteria have been implicated, a significant number of these presumably are due to Yersinia infection. A third possible finding at surgery is acute terminal ileitis, commonly without

extension of the inflammatory process to the cecum or appendix. On the basis of current information it seems likely that the great majority of these cases, possibly 75%, may be due to acute infection with Yersinia while a minority of the cases, possibly averaging about 25% (or much less), are due to Crohn's disease that will ultimately disseminate and develop into chronic regional enteritis. The actual figures for the relative occurrence of the latter two possibilities have not been firmly established for the United States. Finally, very rarely there may be isolated Crohn's disease involving only the appendix at the time of surgery. The majority of these cases, when followed, ultimately develop evidence of disseminated Crohn's disease.

F. Crohn's Disease of the Ileum and Colon

In the past, Crohn's disease has been considered primarily a disease of the terminal small bowel; however, during the past 5 years this concept has changed considerably with the recognition that Crohn's disease may involve the colon as well as other regions of gastrointestinal tract. As shown in Fig. 1, the highest incidence of involvement of the gastrointestinal tract is in the terminal portion of the small bowel and the cecum. The incidence of involvement rapidly drops off as one goes either more proximally in the small intestine or more distally in the colon. It is not surprising, therefore, that the major clinical syndromes relating to Crohn's disease derive from involvement of these same regions of the gastrointestinal tract. Thus, current concepts concerning Crohn's disease indicate that there are three separate syndromes of major clinical importance. As summarized for three series appearing from 1971 to 1974 (Table 13) patients present primarily

Table 13

Site of Involvement of Crohn's Disease when Initially Seen by the Physician

	Fromm (1971)		Ananitakis (1973)		de Domball (1974)		Mean Values	
Total Number Cases	92		75		321		488	
Small Bowel Only	40	(43%)	42	(56%)	136	(42%)	218	(45%)
Colon Only	5	(5%)	8	(11%)	70	(22%)	83	(17%)
Small Bowel and Colon	47	(51%)	25	(33%)	115	(36%)	187	(38%)

with involvement of only the terminal small bowel (ileitis), with involvement only of the colon (granulomatous colitis) or with evidence of involvement of both the terminal small bowel and colon (ileocolitis). In all three series the most common site of involvement is the terminal small bowel (45% of the cases): however, involvement of both the terminal small bowel and colon is very nearly as common (38%). Involvement exclusively of the colon occurs

less frequently and accounts for roughly only 1/5 to 1/10 of the reported cases. When the colon is involved, the distribution of the disease is extremely variable as shown in Figures 2 and 3. In those syndromes characterized by

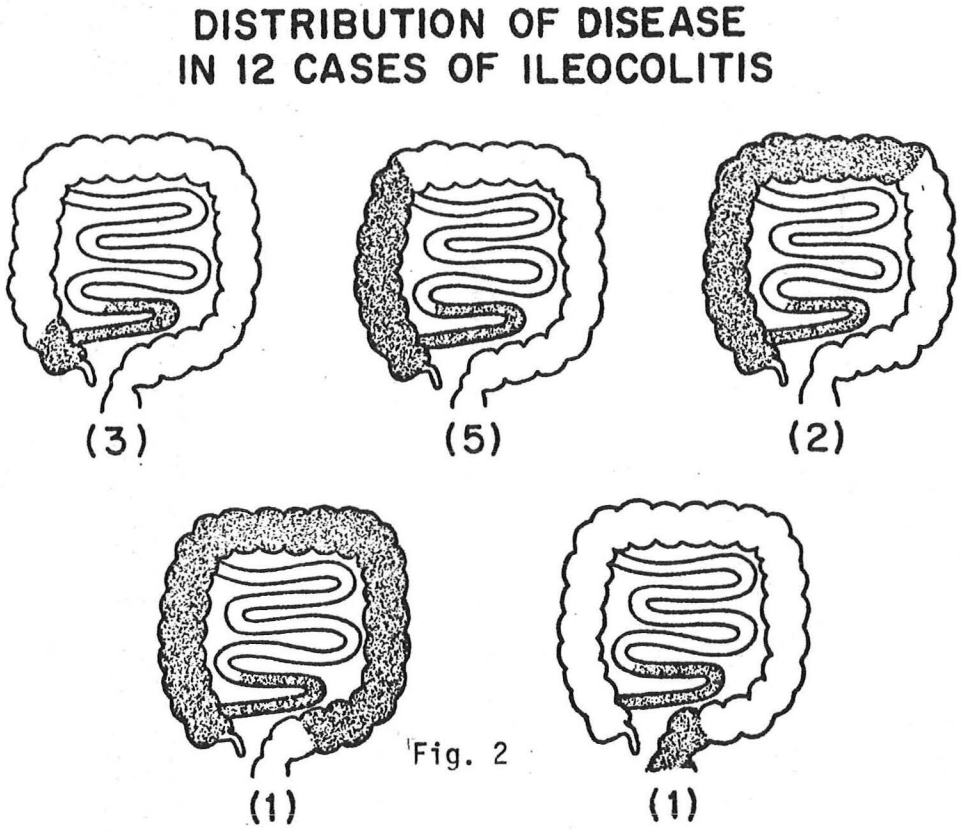

Fig. 2

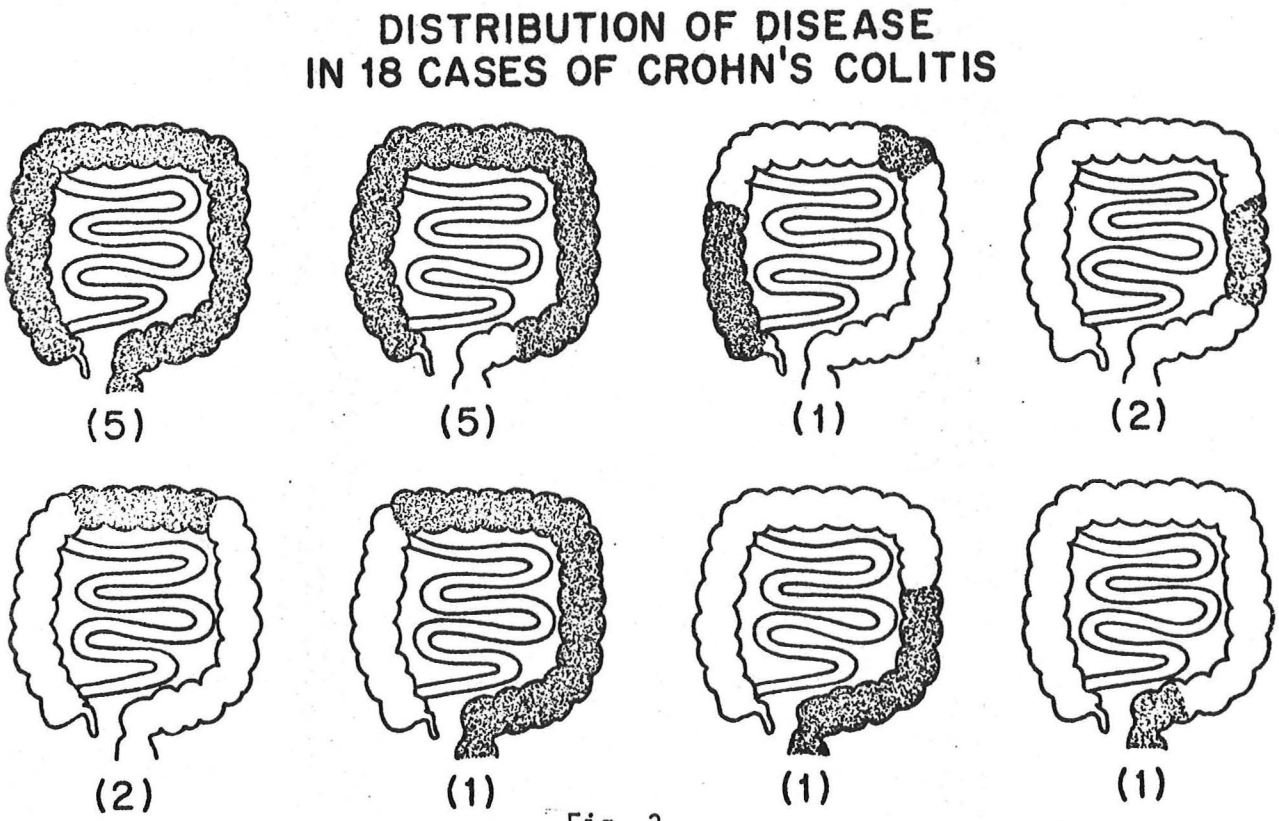

Fig. 3

an ileocolitis the disease almost invariably crosses the ileal-cecal valve as a continuous process to involve the cecum, ascending colon, transverse colon or entire colon to a variable degree. Only very rarely is the ileum and distal colon involved without intervening disease. As seen in Fig. 3, in those cases with Crohn's disease limited to the colon, the distal rectum is commonly spared whereas more proximal portions of the colon may be involved to a varying degree as a continuous or discontinuous process. Such terms as "right-sided colitis" and "segmental colitis" are commonly applied to this type of distribution. Very uncommonly the disease may involve the rectum and extend proximally for varying distances in a distribution that is similar to that seen with involvement of the colon in ulcerative colitis.

The age of onset and sex distribution is not significantly different in any of these major clinical syndromes. As summarized by the data seen in Fig. 4,

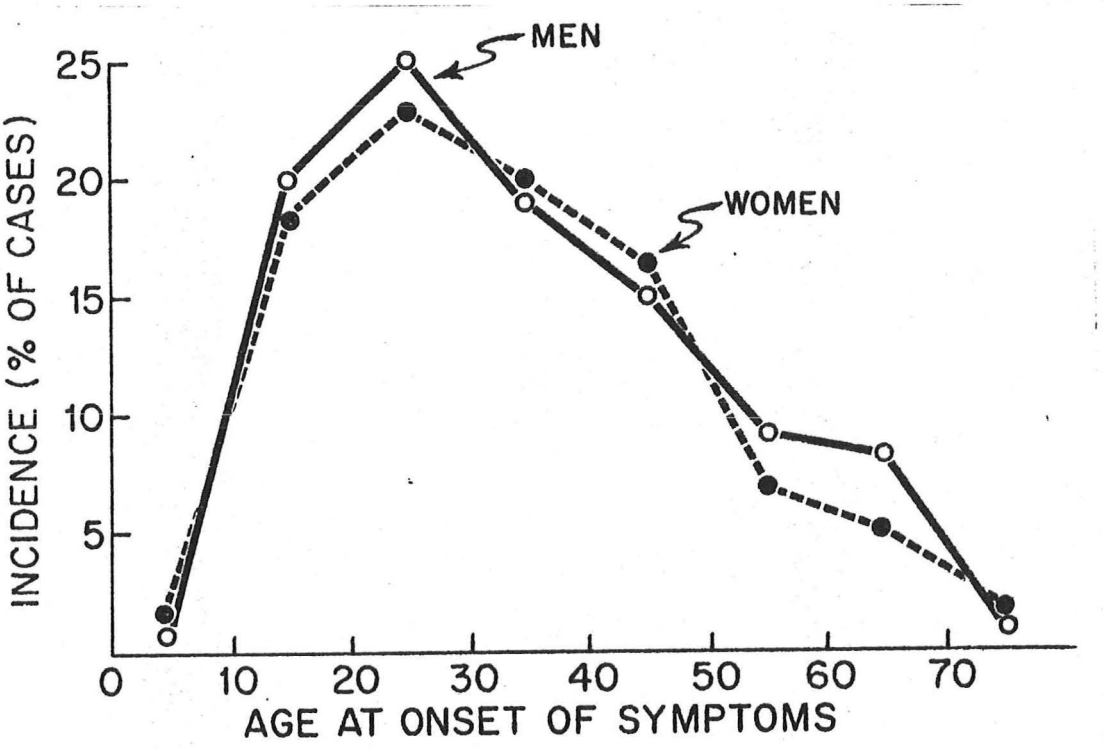

Fig. 4

the peak age of onset of initial symptoms is in the 2nd, 3rd and 4th decades. It should be emphasized, however, that fully 1/3 of the cases of Crohn's disease have the onset of initial symptoms beyond the age of 40. Both men and women appear to be affected with a similar incidence although occasional series have reported a slight predominance of one sex.

To some degree, the initial symptoms depend upon the area of bowel involvement. As summarized in Table 14, in individuals who primarily have a terminal ileitis, abdominal pain, diarrhea and weight loss are present in the

Table 14

Incidence of Initial Signs and Symptoms of Crohn's Disease

	Small Bowel Alone (40 patients)	Small Bowel Plus Colon (47 patients)	Colon Alone (18 patients)
Abdominal Pain	88%	81%	66%
Diarrhea	75%	81%	90%
Weight Loss	55%	64%	75%
Anemia	38%	49%	50%
Nausea and Vomiting	50%	38%	?
Fever	35%	42%	53%
Minor Bleeding	28%	25%	40%
Major Bleeding	3%	14%	15%
Abdominal Mass	20%	10%	20%
Constipation	15%	14%	?
Anorexia	15%	12%	Common

great majority of patients. These individuals also may manifest nausea and vomiting fairly commonly. Anemia and guaiac positive stools also are fairly common although frankly bloody diarrhea is rare. Patients with ileocolitis have similar but commonly more severe symptoms: again, recurrent abdominal pain and frequent watery diarrhea are the most common initial manifestations of the disease. Weight loss, nausea and vomiting, anemia and fever also occur frequently. Patients who present with granulomatous colitis commonly have less abdominal pain, particularly the periumbilical cramping pain so characteristic of terminal ileitis. They nearly all have frequent, small volume diarrhea which is usually guaiac positive although infrequently grossly bloody. Again, fever is a surprisingly common finding. Fistula formation, as indicated above in the section on Pathology, is a characteristic feature of Crohn's disease regardless of the area of involvement. Such fistula may be internal, connecting the affected area of gastrointestinal tract to other loops of uninvolved bowel or to structures such as the bladder or vagina or may empty externally as sinus tracts in the perineal region or anterior abdominal wall. The high frequency of fistula formation in all series is indicated by the data presented in Table 15 where fully 1/3 of patients with Crohn's disease have some type of internal or external fistula. The apparent decrease in the incidence of fistula formation between 1954 and 1971 probably reflects an increasing awareness of this disease with the diagnosis of Crohn's disease in milder forms. Finally, another extremely common problem encountered in all forms of Crohn's disease is the presence of perianal lesions, both anal fissures and fistulae, in the perineal region. As summarized in Table 16, however, there is a significant difference in the incidence of perianal lesions depending upon the site of the primary Crohn's disease. Approximately 1/4 of cases with Crohn's disease of the small bowel manifest this complication whereas the majority of patients with Crohn's disease of the colon have anal fistulas or fissures. Patients with chronic ulcerative

Table 15

Incidence of Fistula in Crohn's Disease of All Types

Date of Series	Percentage Incidence		
	Internal	External	Total
1954	--	--	48
1958	--	--	42
1958	--	--	48
1964	18	17	35
1965	14	14	28
1965	12	19	31
1966	10	23	33
1968	20	21	41
1969	--	--	31
1969	12	17	29
1971	9	17	26
	Mean		36 ± 4%

colitis also may have perianal disease but the incidence is probably much lower, possibly of the order of 10%, than patients with granulomatous colitis.

Table 16

Incidence of Anal Lesions (fissures and fistulae)

	Date of Series	Incidence (%)
A. Predominantly Small Bowel Disease		
	1962	11
	1962	18
	1965	8.5
	1965	14.3
	1968	29
	1969	27
	1969	12.5
	1970	76
Total Mean		24.5 ± 8

Table 16 (cont)

	Date of Series	Incidence (%)
B. Predominantly Colonic Crohn's Disease		
	1964	81
	1965	43.7
	1967	75
	1968	50
	1968	50
	1968	50
	1970	93
Total Mean		63.3 ± 7

Thus, the overwhelming majority of patients with either ileitis, ileocolitis or colitis alone initially present with diarrhea and abdominal pain. Much less commonly there may be few or no gastrointestinal complaints and the patient may present with a variety of other symptoms. These are summarized in Table 17. For example, in children, Crohn's disease may be initially

Table 17

Unusual Initial Manifestations of Crohn's Disease

1) Failure to Grow in Children
2) Iron Deficiency or Megaloblastic Anemia
3) Fever of Unknown Origin
4) Edema with Protein-Losing Enteropathy
5) Weight Loss of Unknown Origin
6) Perianal Disease
7) Recurrent Erythema Nodosa
8) Arthritis
9) Progressive Liver Disease
10) Obstruction of the Urinary Tract
11) Gallstones
12) Ulcerating Lesions of Mouth, Vulva, Penis

manifest by failure to grow and develop properly. In both children and adults Crohn's disease may present as an iron deficiency or megaloblastic anemia, as fever of unknown origin, or with weight loss of unknown origin. As summarized above, perianal disease is extremely common in patients with inflammatory bowel disease so that initial complaints in some patients may derive primarily from perianal disease. Occasionally, one of the extracolonic manifestations of Crohn's disease may bring the patient to the physician. These symptoms

include recurrent erythema nodosum, a rheumatoid arthritis-like syndrome, ankylosing spondylitis, progressive obstructive liver disease, obstructive disease of the urinary tract, or even the formation of gallstones in a relatively young patient. These various complexes are all discussed in more detail below.

VI. MAJOR EXTRAINTESTINAL COMPLICATIONS OF CROHN'S DISEASE

A. Abscesses and Fistula

As noted in Table 15, fistula formation is characteristic of Crohn's disease involving any area of the bowel. These fistula may occur internally and give rise to loculated collections of pus in virtually any area of the abdominal cavity. They may burrow posteriorlly to produce abscesses in the muscle or superiorlly to produce either liver abscesses or subdiaphragmatic abscesses. One of the most common sites for intraabdominal abscesses is the inferior portion of the peritoneal cavity where a walled-off abscess may occur in the lower portion of either gutter or in the pelvis. Such abscesses may involve contiguous structures such as the rectum, ureters or vagina. The complication of abscess and/or fistula formation may occur spontaneously but, much more commonly, may follow a surgical procedure. Thus, the simple drainage of any abscess is almost inevitably followed by the formation of a permanent fistula or sinus tract. Similarly, any operative procedure that involves laparotomy without primary resection of the affected bowel or any resection procedure that goes through disease is likely to be complicated by the development of a postoperative fistula. The optimal surgical treatment of fistula or deep abscesses involves excision of the tract or abscess cavity along with the contiguous segment of diseased intestine.

B. Arthritic Disease Associated with Inflammatory Bowel Disease

Inflammatory bowel disease of any type, including both Crohn's disease and ulcerative colitis, are associated with a significant incidence of arthritic complaints. Symptoms referable to joint involvement occasionally appear simultaneously with the onset of the chronic bowel syndrome, more commonly appear after the appearance of the GI disease and, rarely, may precede the symptoms of bowel dysfunction. As shown in Table 18, the symptoms associated with chronic inflammatory bowel disease generally fall into three

Table 18

Musculoskeletal Involvement in Chronic Inflammatory Bowel Disease

Overall Incidence in Patients with U.C.	20%
Arthralgias and Arthritis ("Colitic arthritis")	60%
Ankylosing Spondylitis	25%
Miscellaneous Forms, Unrelated to U.C.	15%

categories: these include a specific form of arthritis often referred to as "colitic arthritis", ankylosing spondylitis and various nonspecific myalgias and arthralgias. As summarized in Table 19, "colitic arthritis" is usually

Table 19

Summary of Characteristics of Colitic Arthritis

Joints Involved	Commonly large joints (knees, ankles and elbows) involved asymmetrically
Relationship to Colitis	More common in U.C. of long duration and extensive colon involvement. Rarely precedes U.C.
Prognosis	That of colitis, rarely does arthritis produce permanent deformity
Sex Incidence	Equal to incidence of U.C.
Relationship to Other Extracolonic Diseases	Associated with eye, mouth and skin lesions
Laboratory Findings	↑ WBC Anemia ↑ ESR Rheumatoid factor absent Antinuclear factors may be present X rays of joints minimal to no change
Synovial Fluid	Turbid but sterile 5000-7000 WBC/cm^3 mostly PMN Fair mucin clot Reduced viscosity Normal sugar or slightly decreased

manifest as pain and swelling in various joints, commonly large joints, which may be asymmetrical. Typically, there is little or no destruction of the joint, and the rheumatoid factor is usually absent. The severity of the joint involvement commonly parallels the severity of the underlying bowel disease and usually subsides with specific treatment of the inflammatory bowel syndrome either with surgery or with steroids.

Ankylosing spondylitis is also fairly commonly seen in association with inflammatory colon disease and apparently is more common in men affected with

the disease than females. In one series approximately 5% of a group of patients with disseminated Crohn's disease had clinical and x-ray evidence of this disorder. Patients with Crohn's disease and ankylosing spondylitis have a frequency of HL-A 27 antigen of 27% which is 3 fold higher than control patients (8.5%) but considerably lower than patients with ankylosing spondylitis alone (90%).

There is little doubt that any form of chronic inflammatory bowel disease is associated with a significant incidence of complicating arthritis. It is important to emphasize that a small number of these cases present with complaints primarily related to the arthritic disease, and bowel symptoms may be totally absent. Thus, in patients who present with a rheumatoid arthritis-like picture and a negative rheumatoid factor in the serum or have the onset of symptoms referable to ankylosing spondylitis, one should investigate the gastrointestinal tract carefully using both xray and sigmoidoscopy to look for possible inflammatory bowel disease. In one recent series, for example, in 33 patients who presented with ankylosing spondylitis and who were asymptomatic with respect to their GI tract six, or 18%, were found to have inflammatory colon disease when subjected to examination by barium enema and sigmoidoscopy.

C. Skin Diseases Associated with Inflammatory Bowel Disease

The skin also commonly is involved in a variety of nonspecific and relatively more specific lesions in patients who have chronic inflammatory bowel disease. Table 20 outlines the findings in 101 patients with disseminated Crohn's disease. Again, when both Crohn's disease and ulcerative colitis

Table 20

Skin Conditions in 101 Patients with Crohn's Disease

Diagnosis	Males	Females	Total	Percentage
Acne	8	4	12	11.9%
Rosacea or Telangiectasia Alone	2	6	8	7.9%
Infections	7	3	10	9.9%
Psoriasis	3	2	5	5.0%
Atopy	4	4	8	7.9%
Non-Atopic, Dermatitis, Dry Skin, Ichtyosis, Prurigo	6	9	15	14.9%
Anal and Perianal Conditions	11	17	28	27.7%
Vascular Conditions (excluding Telangiectasia)	10	9	19	18.8%
Mouth Lesions	9	10	19	18.8%
Finger Clubbing	none	2	2	2.0%
Hyperpigmentation	none	4	4	4.0%
Others	2	6	8	7.9%

are considered together, the incidence of significant skin lesions varies from 2.4 to 34% in various large series. Generally, the various skin lesions that have been reported can be broken down into four major groups. The most common manifestation of chronic bowel disease is the occurrence of either masses or ulcerations within the oral mucosa. In ulcerative colitis aphthous ulcers of the mouth are very common and in Crohn's disease there may be either the spontaneous development of thickened folds or masses that actually contain inflammatory exudates (see section above on Involvement of the Mouth in Crohn's Disease) or nonspecific ulcerations. A second fairly common lesion is pyoderma gangrenosa. It is said that approximately 50% of individuals presenting with this skin lesion have overt chronic inflammatory bowel disease. It seems likely that this figure would be even higher if patients who were asymptomatic were investigated for the presence of underlying disease such as ulcerative colitis. Finally, patients also may present with two other kinds of lesions: recurrent urticaria and recurrent erythema nodosum.

In general, these lesions often appear in association with recurrence of the gastrointestinal syndrome. Occasionally, lesions such as urticaria or erythema nodosum may appear in crops and herald the onset of a recurrent attack of acute diarrhea. Generally, the skin lesions respond to treatment of the underlying bowel disease with either steroids or surgery. Again, it should be emphasized that the appearance of aphthous ulcers, pyoderma gangrenosa or erythema nodosum should raise the suspicion in the mind of the physician that there is underlying, occult inflammatory bowel disease in an otherwise essentially asymptomatic patient. Such patients should be carefully investigated with both proctoscopic examination and x-ray examination.

D. Eye Lesions Occurring in Association with Inflammatory Bowel Disease

Various conditions of the eye, usually inflammation of the uveal tract, are another relatively common manifestation of underlying chronic inflammatory bowel disease. As shown in Table 21, the most commonly diagnosed specific diseases are episcleritis and iritis. It is likely that the incidence of eye involvement is more common, particularly in Crohn's disease, than such data would indicate since many of the lesions are not apparent except to detailed investigation of the anterior tract by slit-lamp examination. In general, the highest incidence of ocular complications appears to occur in patients having severe attacks of colitis. In contrast to other extracolonic complications, however, eye lesions appear to be more common during the first several years of symptomatic bowel disease and become relatively less common after a very prolonged, chronic course. The ocular complications usually respond to local steroid therapy or to specific therapy of the underlying colon disease.

Table 21
Frequency of Eye Lesions in 465 Patients with Inflammatory Bowel Disease

Episcleritis	7
Iritis	5
Blepharo-Keratitis	2
Choroiditis	1
Dacryostenosis	1
Interstitial Keratitis	1
Overall Incidence	3.6%

Cases also have been reported in which the onset of the uveitis preceded the onset of symptoms referable to the GI tract. This again raises the problem of diagnosing occult bowel disease in patients who have recurrent uveitis of unknown etiology.

E. Liver Dysfunction and Chronic Inflammatory Bowel Disease

Liver dysfunction both asymptomatic and symptomatic occur in Crohn's disease as well as in chronic ulcerative colitis. In one recent series of 50 consecutive patients with regional enteritis, 30% had abnormal liver function tests, primarily consisting of an elevation of the alkaline phosphatase and bromsulphathalein test. None of these patients had clinically significant liver dysfunction. In 19 subjects in which liver biopsy was done, chronic pericholangitis or triaditis was the most common lesion and was seen in 15 subjects. Fatty infiltration and mild portal fibrosis were seen in a lesser number of cases. Only 2 subjects showed noncaseating granuloma. Almost identical findings were reported in 62 additional patients with Crohn's disease in a series from England published in 1972. Thus, Crohn's disease is commonly associated with liver function abnormalities, particularly with an elevation of the alkaline phosphatase but apparently serious symptomatic liver dysfunction is uncommon. A number of other reports, however, strongly suggest that there is a liver lesion of potential clinical importance in patients who have chronic inflammatory colitis, usually of the ulcerative colitis type. Such disease may manifest itself with one of two generally different syndromes. Some patients present with a predominantly obstructive picture and have severe itching, markedly elevated bilirubin, elevated alkaline phosphatase and near normal values for the SGOT. A second, less common syndrome is that of a apparent recurrent cholangitis in which the patient presents with fever, an elevated white count, an enlarged tender liver, elevated bilirubin, elevated alkaline phosphatase and SGOT. At surgical exploration or at autopsy there is usually no evidence of obstructive biliary disease in these patients. Both of these syndromes tend to recur and tend to be independent of the severity of the underlying colitis. Again, it should be emphasized that the bowel symptoms may be minimal or nonexistent and the patient may present primarily with symptoms referable to the liver.

F. Gallstones in Patients with Crohn's Disease of the Terminal Ileum

Biliary cholesterol is solubilized by solution into a mixed micelle primarily constructed from bile acids and phospholipids. The ability of such micelles to fully solubilize cholesterol is limited and, in general, when the molar percent of cholesterol in bile exceeds approximately 10% the bile becomes thermodynamically unstable and there is a tendency for cholesterol to crystallize out in a microcrystalline phase. This presumably leads to crystallization of cholesterol about a nidus of protein in the gallbladder with eventual formation of gallstones containing predominantly cholesterol. It is now well documented in a variety of clinical settings that patients who make bile that is supersaturated with respect to cholesterol have a high incidence of cholesterol gallstones.

Maintenance of a thermodynamically stable bile critically depends upon maintenance of the enterohepatic circulation of bile acids. This circulation,

in turn, requires functional integrity of active transport sites localized in the ileum for the essentially complete reabsorption of bile acids from the intestinal contents. In the presence of significant disease of the terminal ileum, as commonly occurs when Crohn's disease involves this area of the bowel, there is partial or complete interruption of the enterohepatic circulation of bile acids with the consequence that the pool size of bile acids in the body drops dramatically. Under these circumstances the liver continues to secrete cholesterol into the bile but because of an inadequate pool of bile acids the bile is relatively supersaturated with respect to cholesterol. Under these circumstances it is to be anticipated that gallstone formation would occur at an earlier age and with a higher frequency than the population-at-large. Several recent reports have now shown that in patients with Crohn's disease of the terminal ileum there is an incidence of gallstones that is from 2 to 4 times higher than would be anticipated in a group of control subjects of similar sex and age (Table 22). Thus, the physician caring for patients who

Table 22

Prevalence of Gallstones in Patients with Regional Enteritis-Granulomatous Ileocolitis (RE-GIC), Granulomatous Colitis-Ulcerative Colitis (GC-UC) and Hospital Control Population

	Number of Patients		
	RE-GIC	GC-UC	Hospital comparison population
Gallstones	29	7	12
No Gallstones	74	79	91
Total Patients	103	86	103
% with Gallstones	28.2	8.1	11.7

have significant terminal ileitis or who have had surgical resection of the ileum because of Crohn's disease should be aware of this high incidence of gallstones and should be alert to the possibility of the development of acute or chronic cholecystitis. Furthermore, if such patients present with obstructive jaundice the differential diagnosis necessarily must include obstruction due to gallstones in the common duct as well as cholestatic liver disease secondary to the inflammatory bowel disease, a reaction to one of the many drugs that the patient might be taking, hepatitis, etc.

G. Malabsorption and Malnutrition in Patients with Crohn's Disease

As indicated above, patients with Crohn's disease commonly manifest significant weight loss as a major symptom of the underlying bowel disease. To some extent this weight loss is contributed to by the anorexia, protein-losing enteropathy and chronic inflammation that is characteristic of this disease. Some patients, however, develop significant malabsorption: this

complication is not seen in patients who have Crohn's disease localized to the colon or in patients with chronic ulcerative colitis but, rather, is seen in those patients who primarily have extensive involvement of the terminal ileum. At least two separate mechanisms account for the malabsorption and steatorrhea that is occasionally seen in such subjects. As summarized in Table 23 some

Table 23

Possible Causes of Malabsorption in Crohn's Disease

A) Ileal Dysfunction Syndrome
   a) Ileal Crohn's disease
   b) Ileal resection

B) Intestinal Stasis Syndrome
   a) Stricture formation
   b) Surgical blind loop
   c) Entero-enteric or entero-colic fistula

---

subjects manifest an ileal dysfunction syndrome. As outlined in the preceding section, ileal integrity is required for maintenance of the enterohepatic circulation of bile acids. Interruption of ileal integrity either because of involvement of this area of the small bowel with extensive Crohn's disease or because of ileal resection leads to a sharp reduction in the size of the circulating bile acid pool. This, in turn, leads to a relative bile acid deficiency in the proximal small intestine during the process of digestion and, consequently, causes malabsorption of lipids. Such a syndrome characteristically is manifest by a relatively mild degree of steatorrhea, in the range of 6 to 20 g of stool fat per 24 hrs, a very low Schilling test, usually less than 2% of the injected dose, and an essentially normal value for the xylose absorption test, usually greater than 4.5 g per 5 hr urine specimen.

A second major reason for the appearance of malabsorption in these patients is the development of an intestinal stasis or blind loop syndrome. This syndrome arises under any circumstance in which there is massive bacterial proliferation, particularly bacteriodes, in the proximal small bowel. This takes place in the setting of Crohn's disease with stricture formation and partial small bowel obstruction, following the formation of a surgical blind loop during bypass surgery or with the development of an entero-enteric or entero-colic fistula. The massive overgrowth of bacteria in the proximal small bowel has two important metabolic consequences: a) bile acids are rapidly metabolized by deconjugation and dehydroxylation so that the effective bile acid concentration in the intestinal contents is sharply reduced and b) there is binding of the intrinsic factor-B_{12} complex. Consequently, this syndrome is characterized by mild steatorrhea, usually of the order of 10 to 20 g of stool fat per 24 hrs, a very low Schilling test, usually less than 1% of the administered dose, and a normal or abnormal value for the xylose absorption test. These findings are similar to those found in the ileal dysfunction syndrome. However, the two can be distinguished by measuring the response of these 3 tests to the administration of a broad-spectrum antibiotic such as tetracycline for 3 days. Typically, all of the abnormal tests normalize if the underlying defect is due to an intestinal stasis syndrome whereas

antibiotic administration has essentially no affect on these tests of absorption if ileal dysfunction is the primary disorder.

Usually, malabsorption is not a major diagnostic problem in cases that have obvious chronic bowel disease. On the other hand, uncommonly, weight loss and malabsorption, in the absence of striking GI symptoms, may be the initial presenting complaint of a patient with Crohn's disease of the ileum.

H. Involvement of the Kidney in Crohn's Disease

The major syndromes giving rise to renal complications in Crohn's disease are summarized in Table 24. Relatively uncommonly, the renal tract may be

Table 24

Renal Complications in Crohn's Disease

A) Involvement of the Kidney or Ureters by Fistula or Abscesses (rare)	Usually arises from involvement of the retroperitoneal or perirenal space with fistula or abscesses. May be direct communication between bowel and urinary tract or perinephric abscess.
B) Renal Amyloidosis (probably uncommon)	May be asymptomatic in many patients but may become clinically apparent because of the appearance of a nephrotic syndrome and/or progressive renal failure.
C) Obstruction of Ureters (fairly common)	Seen in patients with significant ileo-cecal Crohn's disease. The right ureter is involved when there is significant ileo-cecal disease. Intravenous pyelograms usually show a right hydronephrosis. At operation the ureter is usually obstructed in the area of the right lower gutter because of retroperitoneal fibrosis and inflammation. Patients, unfortunately, are commonly asymptomatic with respect to the renal tract obstruction although they commonly have symptoms referable to the Crohn's disease.
D) Renal Stones (fairly common)	Commonly oxalate stones due to hyperoxaluria which, in turn, appears to be due to increased absorption of dietary oxalate in the presence of significant ileo-cecal Crohn's disease.

involved by direct extension of the Crohn's disease into the retroperitoneal or perirenal spaces. Fistula tracts may give rise to direct communications between the ureter or renal pelvis and some portion of the gastrointestinal tract. There also may be formation of peri-ureteral or peri-renal abscesses with inflammatory changes in the contiguous renal structures.

Another serious complication of chronic Crohn's disease of the gastrointestinal tract is the development of secondary amyloidosis with significant renal involvement. This is said to be a relatively uncommon complication although in one recent autopsy series amyloidosis was found in 5 of 17 patients who died as the result of Crohn's disease of the intestine. Amyloid deposition may occur in otherwise asymptomatic patients; however, when the disease becomes clinically evident it is usually manifest by either the onset of a nephrotic syndrome and/or by progressive renal failure.

The third, and most common serious complication of Crohn's disease is involvement of the ureter in the inflammatory process with obstruction to urinary outflow. Using radioactive renorgraphy one recent series demonstrated ureteral stasis in 50% of patients with ileo-cecal Crohn's disease. In another series evidence of definite ureteral obstruction was found in 27 of 106 patients referred to a large surgical service: this high incidence of involvement is probably not representative since these were all patients who had extensive, very symptomatic ileo-cecal disease. Nevertheless, it is apparent from a number of series that this is a fairly common and serious complication of granulomatous entero-colitis. The great majority of patients, unfortunately, are asymptomatic with respect to their urinary tract and only a minority of patients complain of flank pain or dysuria. Most patients, however, have a palpable right-lower quadrant mass. Excretory urograms show obstruction of the right ureter in the majority of cases with hydronephrosis. At exploration most of these patients are found to have direct extension of the inflammatory process through the parietal peritoneum into the retroperitoneal space with extensive retroperitoneal fibrosis. In about 1/4 of the cases there is frank abscess formation in the retroperitoneal space. The ureter is commonly enclosed in a dense layer of inflammatory-fibrotic tissue. Treatment usually consists of freeing the ureter from the fibrous mass or drainage of the ureter to the anterior abdominal wall by various surgical procedures. It is apparent that this complication is frequent enough that the physician should be constantly aware of the possibility of right ureteral obstruction in any patient with significant ileo-cecal disease.

Fourth, another fairly common complication of extensive ileo-cecal Crohn's disease is the formation of renal calculi. Commonly these are oxalate stones and hyperoxaluria is a common finding in patients who have extensive involvement of the terminal ileum. Three general theories have been put forth to explain these findings. First, it was suggested that the increased amounts of glycine conjugated bile acids that reached the colon in the presence of significant ileal disease or ileal resection might give rise to increased glycine absorption and, hence, increased oxalate formation by the liver. Recent studies, however, have shown that the administration of radiolabeled glycine to such patients does not give rise to radiolabeled oxalate in the urine. Second, it was more recently postulated that interruption of the enterohepatic circulation of bile acids might, in a secondary fashion, alter normal control mechanisms for oxalate synthesis in the liver so that there was overproduction

of this compound and, hence, hyperoxaluria. Again, more recent data suggest that this second possibility also is not correct. The most recent data indicate that the hyperoxaluria seen with ileal resection or ileo-cecal Crohn's disease primarily derives from enhanced absorption of dietary oxalate. Placing patients on an oxalate-free diet or administering cholestyramine which binds intraintestinal oxalate essentially eliminates the hyperoxaluria seen in these subjects. While the cause of enhanced oxalate absorption under these conditions is not well understood, recent unpublished information suggests that in the presence of significant ileal dysfunction the excessive amounts of unabsorbed free fatty acids in the gut contents bind significant amounts of dietary calcium. Under such circumstances absorption of dietary oxalate is markedly increased and causes hyperoxaluria. Again, the physician should be aware of this fairly common and potentially serious complication. The degree of hyperoxaluria is directly related to the extent of ileal involvement or to the size of the ileal resection that was performed. Actual oxalate stone formation is most likely to occur in those patients with extensive ileal disease of long standing or in patients who have had a rather extensive ileectomy.

I. Pneumatosis Coli of Crohn's Disease

Rarely, Crohn's disease may be a cause of pneumatosis intestinalis and presumably results from the dissection of intraluminal gas into the bowel wall. It is also seen in the presence of carcinoma, obstructive lung disease, intestinal obstruction, collagen disease and a variety of other disorders. This is a very uncommon complication of Crohn's disease.

J. Acute Toxic Dilatation of the Ileum and Colon in Crohn's Disease

Acute toxic dilatation of the colon is a well recognized complication of chronic ulcerative colitis. It commonly occurs in the setting of an acute exacubation of the disease and is manifest by abdominal distention, progressive dilatation of the colon on plain film and increasing abdominal pain and tenderness. This serious complication commonly progresses to perforation and death unless there is prompt surgical intervention. Early reviews of Crohn's disease of the colon suggested that this serious complication did not occur in this disease. However, there are now a number of scattered individual case reports indicating clearly that acute toxic dilatation of the colon may occur in patients whose primary diagnosis is Crohn's disease or granulomatous colitis. Nevertheless, it is still probably true that acute toxic dilatation is relatively less common in colitis due to Crohn's disease than in that due to chronic ulcerative colitis. Rarer yet is the serious complication of acute toxic dilatation of the ileum in patients with Crohn's terminal ileitis. Only a few case reports have appeared in which patients presented with severe toxicity, marked ulceration of the terminal ileum, progressive abdominal distention and progressive dilatation of the terminal small bowel.

K. Massive Gastrointestinal Hemorrhage in Crohn's Disease

Occult bleeding occurs in the vast majority of patients with either ileal, ileo-cecal or colonic Crohn's disease. Frank bleeding with bloody diarrhea is extremely uncommon in ileal and ileo-cecal Crohn's disease but may occur in Crohn's colitis. The frequency of frankly bloody diarrhea, however, in Crohn's

colitis is said to be less common than in patients affected with chronic ulcerative colitis, although several recent series would question this. Rarely, massive rectal bleeding may be the initial presenting complaint of the patient with Crohn's disease of the gastrointestinal tract. There are probably no more than 10 such reported cases and they involve ileal, ileo-cecal as well as colonic Crohn's disease.

L. Acute Perforation of the Intestine in Regional Enteritis

As discussed above, Crohn's disease is characteristically a transmural disease which causes inflammatory involvement of the serosal surface of the bowel. As a consequence, the affected areas of the intestinal tract commonly become adherent to the surrounding loops of bowel, to the abdominal wall or to other abdominal viscera. As a consequence, as the disease burrows through the wall of the affected area of the bowel it commonly results in the formation of fistula, sinus tracts and localized abscesses but only very rarely perforates free into the peritoneal cavity. Usually, this complication occurs in patients who have a well established diagnosis of Crohn's disease of the small bowel or colon. Occasionally, however, the signs and symptoms of chronic bowel disease are minimal and the patient may present initially with abdominal pain and evidence of air in the peritoneal cavity. Exploration under these circumstances will usually yield the proper diagnosis of Crohn's disease involving some area of the gastrointestinal tract.

M. Acute Pancreatitis Occurring in Patients with Crohn's Disease

Pancreatitis is another uncommon complication of Crohn's disease and has been described in patients with distal ileal disease as well as in patients treated with immunosuppressant drugs. Of particular interest is the recent description of acute pancreatitis occurring in 3 of 10 patients who had primary Crohn's disease of the duodenal loop. It is apparent that this diagnosis should be considered in individuals who have Crohn's disease of the proximal small intestine when pain, nausea and vomiting become a major part of the clinical picture.

N. Carcinoma of the Bowel in Patients with Crohn's Disease

It is well established that patients with chronic ulcerative colitis have a higher than normal incidence of colon carcinoma. The highest incidence of malignant degeneration occurs in those patients with the chronic continuous form of the disease and with involvement of the entire colon. The incidence of carcinoma is time-related and exceeds 10% in such patients who have been asymptomatic for at least 10 years. The incidence of carcinomatous degeneration in Crohn's disease, even in Crohn's disease of the colon, is said to be considerably lower. Nevertheless, there is now an ever-increasing number of individual case reports of carcinoma occurring in patients with an established diagnosis of Crohn's disease of the gastrointestinal tract. Between 1956, when the first such case was reported, and 1974 there were 27 reported cases of carcinoma occurring in patients with an established diagnosis of Crohn's disease. A summary of these cases is given in Table 25. On the average, the patients were symptomatic from their underlying bowel disease for approximately 14 years.

Table 25

Carcinoma Occurring in Crohn's Disease

	Carcinoma Complicating Regional Enteritis	Primary Carcinoma of Small Intestine
Average age, yr	44	55
Sex		
Male	17	--
Female	9	--
Unknown	1	--
Average duration of symptoms prior to carcinoma diagnosis	14.07 yr	8 mo
Diagnosis established, %		
Preoperative	7	40
Intraoperative	7	40
Postoperative	72	20
Autopsy	10.5	--
Unknown	3.5	--
Site, %		
Ileum	59.3	19.7
Jejunum	33.3	28.0
Duodenum	3.7	32.8
Colon	3.7	----
Prognosis		
5-yr survival, %	3.7	20-22
Average length of survival, mo.	6.56	30

Approximately 90% of the reported carcinomas occurred in the ileum or jejunum while only about 4% of the cases involved the duodenum or colon. More than 80% of the time the diagnosis was made postoperatively in the resected specimens and the mean 5-yr survival was only 3.7%. One population study suggests that the incidence of colon-rectal cancer is 20 times more prevalent in patients with Crohn's disease than in a comparable control population. Thus, while there now seems to be little doubt that malignant degeneration can take place and be superimposed upon Crohn's disease involving any region of the bowel, this still constitutes a relatively uncommon complication and occurs with a frequency that is probably still much less than that seen in patients with chronic ulcerative colitis.

O. Pregnancy and Crohn's Disease

Two recent series involving 119 pregnancies in 60 women suggest that patients who have Crohn's disease do relatively well. In general, the incidence of acute attacks was not significantly different in pregnant and non-pregnant patients and approximately 83% of the pregnancies resulted in a normal full-term delivery. Both series come to the conclusion that, in general, a pregnancy does not constitute an unusual risk to the woman with Crohn's disease nor is there any evidence that there is a high potential risk to the fetus. Generally, most of these women had no significant symptoms relative to their Crohn's disease during the pregnancy but approximately 40% of them suffered a relapse after delivery.

VII. LABORATORY MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS OF CROHN'S DISEASE IN THE GASTROINTESTINAL TRACT

Crohn's disease involving any region of the gastrointestinal tract causes a variety of abnormalities that involve many different systems. The specific diagnosis of Crohn's disease involving the ileum or the ileum and the right colon is relatively simple and primarily depends upon the demonstration of rather characteristic radiological findings on a barium enema and upper small bowel series. Specific diagnosis of Crohn's disease involving the colon is more complex since it becomes extremely important, in terms of the long-term prognosis, to differentiate granulomatous colitis from chronic ulcerative colitis, amoebiasis and other forms of colitis. Various biochemical, hematological and radiographical findings that have implications with respect to diagnosing Crohn's disease and with respect to long-term treatment are outlined below.

A. The Anemia of Crohn's Disease

The major hematologic findings in a large group of patients with Crohn's disease is given in Table 26. Anemia of varying severity is found in the great majority of patients with active Crohn's disease. This is a very complex anemia, however, and in different patients may be due to iron deficiency, folate deficiency or vitamin B_{12} deficiency. Serum iron levels are reduced below normal in approximately 65% of the cases and presumably is a manifestation of chronic, continual low grade loss of blood from the gastrointestinal tract in Crohn's disease. Approximately 40% of these patients also manifest a decrease in iron stores in the bone marrow. Approximately 1/6 of the patients manifest low serum vitamin B_{12} levels: the degree of vitamin B_{12} depletion generally relates to the extent of ileal involvement with Crohn's disease or to the size of the ileal resection that was undertaken for treatment of the primary illness. A recent finding of considerable interest reported from several institutions is that fully 2/3 of the patients with Crohn's disease have significant depression of serum folate levels and about 1/3 of these patients manifest low red blood cell folate levels. Using ^{3}H-folic acid about 1/2 of the patients with Crohn's disease have been

Table 26
Hematological Findings in 63 Patients with Crohn's Disease (St. Bartholomew's Hospital)

A. Anemia Present Females	54%
Males	79%
B. Low Serum Iron Levels	65%
Low Total Iron Binding Capacity	22%
Low Bone Marrow Iron Stores	39%
C. Low Serum Vitamin B_{12}	16%
D. Low Serum Folate Levels	64%
Low RBC Folate Levels	35%
E. Megaloblastic Bone Marrow	39%
Due to Folate Deficiency	61%
Due to B_{12} Deficiency	33%
Due to Both	6%

shown to malabsorb folate: in addition, it has also recently been demonstrated that the administration of azulfadine, a drug commonly used to treat Crohn's disease, causes a further reduction in the absorption of this compound (Fig. 7). Thus, it is not surprising that approximately 40% of patients with active Crohn's disease were found to have a megaloblastic bone marrow. In approximtely 2/3 of these patients the megaloblastic anemia was attributed to folate deficiency while in the remaining 1/3 it was attributed to a B_{12} deficiency state. However, several recent reports have emphasized the complex nature of the anemia manifest in these patients so that many will have varying degrees of iron deficiency, folate deficiency and vitamin B_{12} deficiency as well as marrow depression associated with the chronic inflammation present in the bowel.

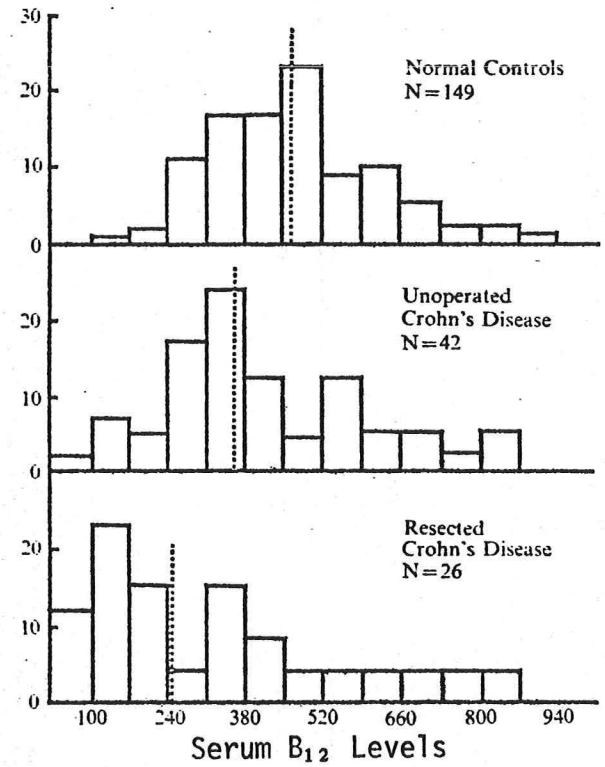

Fig. 5

Frequency Distribution of Serum B_{12} Levels in Patients with Crohn's Disease

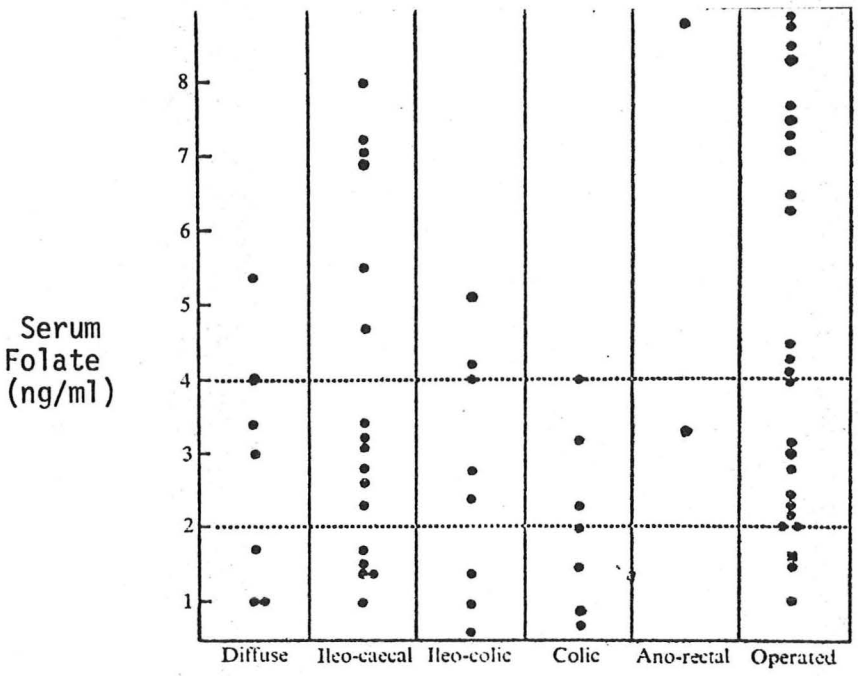

Fig. 6

Serum Folate Levels
Related to Site of Disease

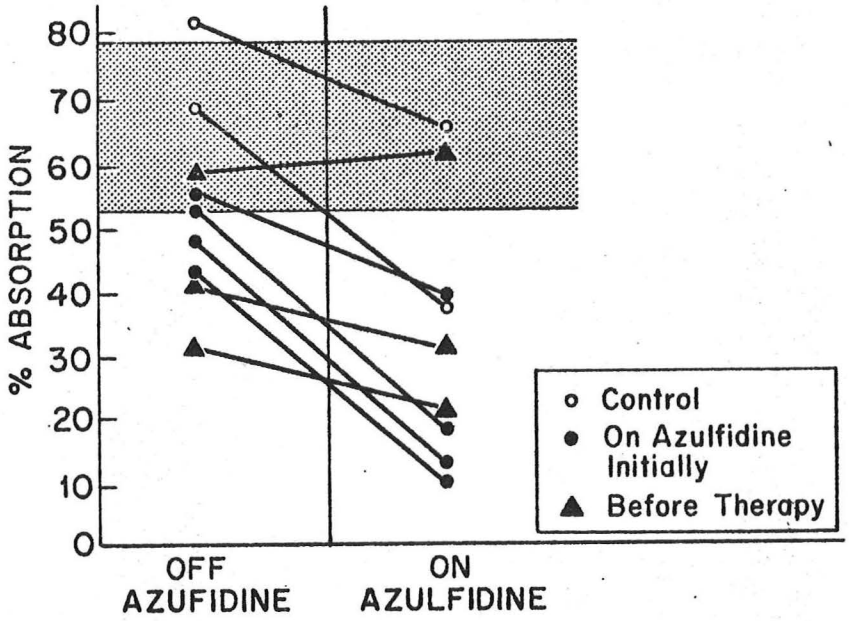

Fig. 7

^{3}H-Folic Acid Absorption
in Patients with Crohn's Disease

B. Electrolyte and Volume Abnormalities in Crohn's Disease

Generally, three major problems are seen in patients with chronic diarrheal syndromes. First, if the patients have had a relatively prolonged or severe diarrheal syndrome it is likely that they will manifest serious volume depletion. This is particularly likely to occur in those patients who are toxic and who have been having frequent watery diarrhea. Second, massive potassium depletion is also fairly common so that serum potassium levels are usually low on admission to the hospital. As illustrated in Fig. 8 the amount of potassium lost in stool water is generally proportional

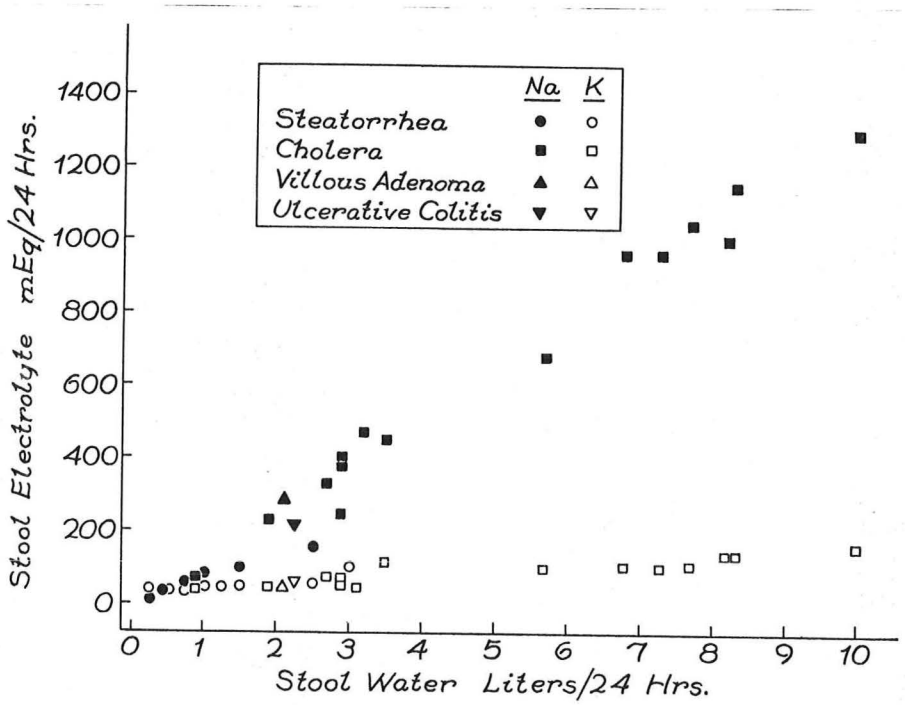

Fig. 8

to the volume of the diarrhea: this combined with poor intake because of anorexia, nausea and vomiting leads to profound potassium depletion in many of these patients. Third, the patient may also have marked depletion of the RBC volume and may require whole blood as well as isotonic sodium chloride and potassium replacement. However, this is much less of a problem in Crohn's disease where grossly bloody diarrhea is less prevalent than in chronic ulcerative colitis.

C. Hypoalbuminemia and Protein-Losing Enteropathy in Crohn's Disease

Hypoalbuminemia is a common finding in patients with Crohn's disease and generally correlates with the severity and extent of involvement in given patients. The cause of the hypoalbuminemia is complex and, in a given patient, may be the result of a) chronic inflammation, b) poor protein intake, c) intestinal malabsorption or d) excessive protein loss through the gastrointestinal tract. In one recent study excessive protein loss in the

gastrointestinal tract, i.e., protein-losing enteropathy, was demonstrated in 21 of 30 patients with Crohn's disease. As illustrated in Fig. 9, the

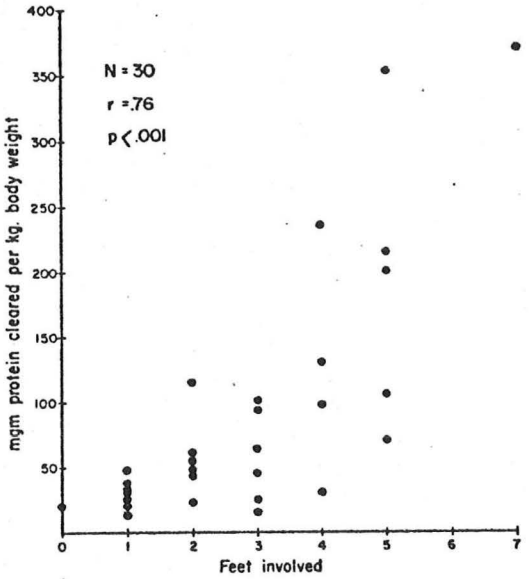

Fig. 9

Relationship of Protein Loss in GI Tract to Amount of Intestinal Involvement with Crohn's Disease

degree of protein loss was fairly well correlated with the extent of obvious clinical involvement in the intestine by Crohn's disease. Usually, the patient compensates fairly well for the excessive protein loss but occasionally the serum albumin level drops sufficiently low so as to result in clinically important peripheral edema.

D. Tests of Malabsorption in Crohn's Disease

As discussed above, malabsorption and steatorrhea may occur in Crohn's disease for several reasons including ileal dysfunction, either because of involvement of the ileum in the basic pathologic process or because of resection, or the intestinal stasis syndrome. For these reasons the major tests of malabsorption including the quantitative stool fat excretion test, xylose absorption test, and Schilling test show abnormalities fairly commonly. As summarized for 30 cases of Crohn's disease in Table 27, the majority of patients with significant Crohn's disease manifest steatorrhea. In the majority of these cases, however, the steatorrhea is mild and of little clinical consequence. However, with extensive involvement of the ileum in Crohn's disease or following extensive ileal resection, massive steatorrhea may develop along with the watery diarrhea characteristic of ileal dysfunction. Approximately 1/2 of the patients also manifest an abnormally low result for xylose absorption. Again, however, the great majority of these cases have values in the range of 3.5 to 4.9 g per 5 hr urine specimen and seldom are very low values in the range of 1.0 to 2.0 g per 5 hr urine specimen ever seen. Such very low values imply extensive involvement of the jejunum in the

Table 27

Tests of Malabsorption in 30 Cases of Crohn's Disease

	Percent	Range
A. Patients with Steatorrhea	57%	5.1 - 81 g per 24 hrs
B. Patients with Low Xylose Absorption	47%	2.3 - 4.9 g per 5 hrs
C. Patients with Low B_{12} Absorption	57%	1.0 - 6.5% per 24 hrs

Crohn's disease or, alternatively, partial obstruction of the small intestine by the Crohn's process with development of an intestinal stasis syndrome. Finally, approximately 1/2 of the patients also show an abnormally low value for the B_{12} absorption or Schilling test. Such findings are compatible with extensive involvement of the ileum with Crohn's disease: however, occasionally there is poor correlation between the apparent degree of bowel involvement and the Schilling test, e.g., the vitamin B_{12} absorption test is sometimes low in patients who have Crohn's disease predominantly involving the colon. It may be that in a number of these cases it is bacterial overgrowth in the proximal small bowel that leads to an abnormally low value rather than extensive destruction of ileal reabsorptive function.

E. Serum Lysozyme in Crohn's Disease

Lysozyme (muramidase) is an enzyme of lysosomal origin that is present in the exocrine secretions such as saliva and tears, in many tissues and in cells such as monocytes and granulocytes. It has been reported to be elevated in serum in various granulomatous diseases such as tuberculosis and sarcoidosis as well as in malignant disorders such as leukemia. One recent publication indicates that serum lysozyme levels may be significantly elevated in Crohn's disease but not in ulcerative colitis. This is illustrated in Fig. 10. If this finding is confirmed in other laboratories measurement of serum lysozyme levels may prove to be of great value in differentiating ulcerative colitis from Crohn's disease involving only the colon.

F. Carcinoembryonic Antigen and α_1-Fetoprotein in Crohn's Disease

Both carcinoembryonic antigen (CEA) and α_1-fetoprotein (AFP) are fetal antigens that have been found in the blood in a high proportion of patients with certain entodermal tumors. Such antigens, in theory, might be of use in detecting malignant degeneration in patients with either Crohn's disease or ulcerative colitis. However, in one recent study of sera obtained from 108 patients with inflammatory bowel disease 14% of 51 patients with ulcerative colitis and 19% of 52 patients with Crohn's disease had significant

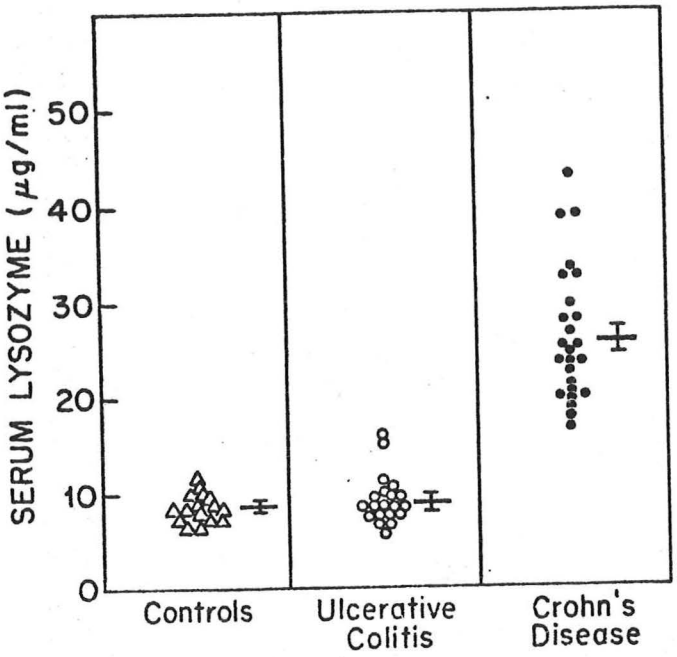

Fig. 10

Serum Lysozyme Concentration in a Population of Control Subjects and Patients with Ulcerative Colitis and Crohn's Disease

elevations of CEA. Only one of the patients with ulcerative colitis had proven carcinoma of the colon. Similarly, 9% of the patients with ulcerative colitis and 5% of the patients with Crohn's disease had detectable amounts of AFP. While, at this time, it is not certain what the meaning of these elevations are in patients with inflammatory bowel disease it is clear that such elevations cannot be taken as evidence for GI malignancy in the presence of inflammatory bowel disease. Obviously, such patients should be followed and an attempt to relate elevation of these antigens to the patients' clinical course, degree of bowel involvement and possible ultimate malignant degeneration.

G. Sigmoidoscopic Examination of Patients with Crohn's Disease

Sigmoidoscopic examination is usually the initial and one of the most important diagnostic procedures undertaken in patients with inflammatory bowel disease. It is used to establish the diagnosis of colon involvement in an inflammatory process and to evaluate the extent of such involvement in the sigmoid-rectal region. Unfortunately, despite much published information to the contrary, there is a great deal of overlap in the appearance of the rectal mucosa in various inflammatory lesions such as amoebiasis, chronic ulcerative colitis and Crohn's colitis. The principle function of sigmoidoscopy is to establish the diagnosis of "colitis" both by the subjective appearance of the rectal mucosa (the presence of a granular, friable mucosa, gross ulceration, etc.) and by objective testing (the demonstration of polymorphonuclear leukocytes on smears or scrapings of the rectal mucosa). In patients who present with Crohn's disease limited to the ileum or to the ileum and right colon there is usually little evidence of abnormalties on sigmoidoscopic examination. However, at least one recent publication

suggests that even in these forms of the disease one may find polymorphonuclear leukocytes in rectal smears. In patients who have obvious granulomatous colitis there may be a diffuse, ulcerated inflammatory process evident throughout the distal colon. Less commonly, the friability and ulceration is patchy with normal intervening areas of colonic mucosa. Occasionally, one finds an essentially normal distal rectal mucosa with evidence of colonic involvement higher in the rectum or in the recto-sigmoid region. Unfortunately, amoebiasis, chronic ulcerative colitis and clindamycin-induced colitis can present with a similar picture. It is clear from the reported literature that the overlap in appearance of the rectal mucosa in these various forms of colitis is so great that one should be very cautious about making a specific diagnosis of the etiology of the colitis on the sigmoidoscopic appearance of the mucosa alone. Similarly, the usual histological findings in rectal biopsies are relatively nonspecific. In all of these syndromes one finds evidence of nonspecific ulceration and submucosal inflammatory cell infiltration. Essentially the only specific histologic findings that provide evidence for a specific kind of colitis is the finding of 1) granuloma and 2) amoeba. As pointed out earlier, however, granuloma are found in a minority of the cases felt to be Crohn's disease of the colon so that the absence of such a granulomatous reaction certainly does not rule out the diagnosis of Crohn's disease.

H. X-Ray Findings in Crohn's Disease of the Gastrointestinal Tract

In classical Crohn's disease of the terminal ileum x-rays usually reveal a narrow, distorted segment of intestine with evidence of mucosal ulceration and, possibly, obstruction. Less commonly, there may be less prominent narrowing but definite "cobblestoning" of the mucosal pattern. This lesion usually begins at the ileo-cecal valve and extends proximally for variable distances. Often, the lesion crosses the ileo-cecal valve, however, to involve the cecum or right colon. This region of bowel typically shows narrowing with marked distortion and ulceration of the mucosal pattern. When the colon is involved in Crohn's disease the extent of involvement is quite variable and, as summarized in Figs. 2 and 3 may be localized to the cecum, to the right colon or may involve various parts of the colon as a "skip" lesion. There may be diffuse involvement of the entire colon or involvement of all of the colon with sparing of the most distal rectal segments. Often the mucosa shows definite ulceration that varies from very subtle, barely visible ulcers to deep "spike" ulcers penetrating perpendicularly into the wall of the bowel. Again, when one is dealing with ulcerating disease localized to the colon one must differentiate among several diagnoses including ulcerative colitis, amoebiasis, Crohn's disease of the colon, shigellosis and antibiotic-induced colitis. Unfortunately, there are no specific x-ray findings that are unequivocally associated with any of these diseases. However, the following findings on x-ray examination of the bowel would strongly suggest that the most appropriate diagnosis is Crohn's disease of the colon: 1) the finding of any definite small bowel disease associated with ulceration in the colon, 2) the finding of predominantly right-sided colitis, 3) the finding of "skip" lesions in the colon or 4) relative sparing of the distal rectal segment.

VIII.

DIFFERENTIAL DIAGNOSIS OF CROHN'S DISEASE AND A RATIONAL APPROACH TO THE PATIENT

In the setting of an appropriate clinical picture, the diagnosis of Crohn's ileitis or ileo-colitis usually does not present a major problem in differential diagnosis. The onset of a diarrheal syndrome with systemic manifestations and x-ray findings of a narrowed and ulcerated ileum is usually sufficient to make the diagnosis. There are, rarely, other diseases that may mimic these findings, however. It should be emphasized that gastrointestinal tuberculosis has essentially the same distribution of involvement as Crohn's disease and can mimic in every way the signs and symptoms of this disease. However, infection of the gastrointestinal tract is extremely uncommon in the United States and there is often a history of exposure or of pulmonary tuberculosis to suggest this possibility. Primary lymphoma of the gastrointestinal tract may present as a diffuse infiltrating lesion in the distal small bowel and also can mimic the clinical and radiographical picture of Crohn's disease. Much less commonly other tumors such as primary adenocarcinoma or carcinoids may be mistaken for Crohn's disease. When there is primary involvement of the cecal region then a number of infectious diseases such as amoebiasis, actinomycosis, pericecal abscess or various tumors must occasionally be considered.

A far more difficult differential diagnosis is involved, however, in patients who present with Crohn's disease primarily localized to the colon. From the standpoint of both treatment and ultimate prognosis it becomes extremely important to differentiate among the several possibilities. In the setting of the patient population seen at Parkland Hospital it is now apparent that the clinical picture of acute or chronic "colitis" with frequent liquid bowel movements and mucopurulent discharge with or without gross bleeding can be seen with at least five specific disease entities all of which occur with reasonably similar frequencies. As shown in Table 28 this differential diagnosis includes idiopathic ulcerative colitis, idiopathic Crohn's disease involving the colon, shigellosis, amoebic colitis and colitis induced by the antibiotics clindamycin and lincocin. Much less commonly, other illnesses such as vascular insufficiency of the colon and infiltrating malignancy may mimic these diseases but, for practical purposes, these possibilities can be ignored in the initial workup. The specific procedures that should be undertaken in such patients are outlined in Table 29. All patients should be immediately sigmoidoscoped. This should be undertaken without any kind of preparation. The purpose of sigmoidoscopy is 4 fold: 1) it is first necessary to establish the diagnosis of "colitis" by evaluating the subjective appearance of the colonic mucosa, i.e., the presence of erythema, ulceration, exudation, friability, etc. 2) If the colonic mucosa appears relatively normal then a mucosal smear should be done to assess the presence or absence of polymorphonuclear leukocytes. The ability

Table 28

Differential Diagnosis of "Colitis"

1) Idiopathic Ulcerative Colitis
2) Idiopathic Crohn's Disease of Colon
3) Shigellosis
4) Amoebiais
5) Antibiotic Induced

Table 29

Diagnostic Procedures in Patients with "Colitis"

	Reason	Conditions
1) Sigmoidoscopy	Establish Diagnosis of Colitis a) Mucosal Appearance b) Mucosal Smear c) Culture for Pathogenic Bacteria d) Mucosal Scrapings for Amoeba	Do Not Prep Do Not Biopsy
2) Barium Enema with Ileal Spill	Delineate Distribution of Disease	Do Not Do In Seriously Ill Patient
3) Small Bowel Series	Look for Small Bowel Lesions	Do Not Do In Seriously Ill Patient
4) Biopsy of Mucosa	Look for Compatible Pathology Look for Granuloma Look for Amoeba	

to express pus cells from the colonic mucosa is prima facie evidence of the existence of "colitis" regardless of the subjective appearance of the colonic mucosa. 3) Cultures can be obtained at this time for pathogenic bacteria, i.e., shigella and salmonella. 4) Mucopurulent material or scrapings can be obtained directly from the ulcerated mucosa for warm stage, wet prep examination for amoebic trophozoites. Unless the patient is very toxic and extremely ill the next diagnostic procedure of choice is usually barium enema with ileal spill. The barium enema will allow the physician to evaluate the extent and anatomical distribution of the ulcerating disease of the colon and small bowel. If the diagnosis still remains uncertain, then a small bowel series for evaluation of possible involvement of more proximal portions of the small intestine is indicated.

The findings of major differential importance are outlined in Table 30. Generally, shigellosis is an acute colitis which is self-limited so that the clinical course is usually less than one week. Furthermore, the patient can usually be safely maintained with appropriate attention to fluid and electrolyte balance for 24 hours until cultures establish the diagnosis of acute shigella colitis. For practical purposes, however, if a patient presents with a history of continuous or intermittent diarrhea for a number of weeks or months shigellosis can be excluded as a likely diagnosis. Acute or chronic colitis due to clindamycin or lincocin can mimic in every way acute idiopathic ulcerative colitis or Crohn's disease. In this disease, however, at sigmoidoscopy one commonly sees pearly, greyish patches scattered irregularly over the colonic mucosa. On histologic examination these rather unique patches prove to be pseudomembranes: thus, the finding of such lesions at

Table 30

Differential Points in Patients with Crohn's Disease

Disease	Weak	Strong
1) Shigellosis		1) Length of Symptoms 2) Culture of Shigella
2) Antibiotic Colitis	1) Isolated Yellowish Gray Patches - Pseudomembranes	1) History of Antibiotic Administration
3) Amoebic Colitis	1) Isolated Ulcers 2) Few WBC's 3) Distribution of Disease	1) Identification of Amoeba 2) Positive Serology 3) Response to Specific Therapy
4) Idiopathic Colitis a) Ulcerative Colitis b) Crohn's Disease	1) Distribution of Disease	1) Exclusion of Other Forms of Colitis 2) Small Bowel Lesions in Crohn's Disease 3) Finding of Granuloma

sigmoidoscopy should certainly arouse suspicion that one is dealing with antibiotic-induced acute colitis and every effort should be made to elicit a history of antibiotic administration. It should be emphasized, however, that all of the other forms of colitis, including amoebiasis, uncommonly manifest pseudomembranes. The definitive diagnosis of amoebic colitis depends upon a) the identification of trophozoites of *Entamoeba histolytica* in mucosal secretions, b) the presence of a diagnostically high serological titer or c) prompt response to specific anti-amoebic therapy. It should be emphasized that amoebic colitis can mimic in every way the proctoscopic and radiographic appearance of ulcerative colitis or Crohn's disease. Finally, the diagnosis of idiopathic colitis, either chronic ulcerative colitis or Crohn's disease, is essentially a diagnosis of exclusion. If the other specific forms of colitis can be ruled out, then one must make every attempt to further differentiate ulcerative colitis from Crohn's disease of the colon. Ulcerative colitis is usually localized exclusively to the colon and almost invariably involves the rectum, extending proximally in the colon for varying distances. Those findings that would suggest that one is dealing with Crohn's disease are: 1) the finding of a definite small bowel involvement, 2) predominantly right-sided colitis, 3) segmental colitis, 4) sparing of the distal rectum, or most importantly, 5) the finding of granuloma in the rectal biopsies.

IX. TREATMENT OF CROHN'S DISEASE

Over the past 25 years there has been a marked change in the philosophy of treatment of Crohn's disease. Initially, this disease was considered to be a curable entity and radical surgery was undertaken relatively soon in most of the cases diagnosed as Crohn's ileitis or ileo-colitis. It became apparent, however, that there was a very high frequency of recurrence so that now any

form of therapy, medical or surgical, is primarily aimed at controlling the disease rather than curing it. Initially, most patients respond to drug therapy but, eventually, a relatively high proportion of patients require some sort of surgical intervention on one or more occasions. Surgeons, generally, have become more conservative and direct their procedures at those that are appropriate for the immediate relief of the patient's acute problems and attempt to minimize the amount of normal bowel that is resected.

A. Drug Therapy of Crohn's Disease

The most useful and commonly utilized drugs for the treatment of Crohn's disease, regardless of its location in the gastrointestinal tract, are summarized in Table 31. Basically, however, most patients with significant Crohn's

Table 31

Medical Management of Crohn's Disease

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1) Diet - in specific patients it may be useful to reduce undigestible fiber content, particularly in the face of obstructive ileal disease: if malabsorption is present, can reduce amount of fat intake.

2) Symptomatic Relief of Pain and Diarrhea
   a) Metamucil - 1 teaspoon with water each morning
   b) Anticholinergics
   c) Narcotics - Deodorized tincture of opium
      Paregoric
      Codeine
   d) Combination - Lomotil

3) Specific Therapy for Inflammation
   a) Prednisone - with acute attack give 40-60 mg each day for 2-3 weeks. Then begin very slow reduction in dosage over a period of several months to the minimum dose required to maintain patient essentially symptom-free.
   b) ACTH - 40 units in 1000 cc of 5% dextrose in water given as a slow IV drip over 12 hrs
   c) Steroid Enemas - a 2 oz. enema of oil or water containing either 100 mg of hydrocortisone hemi succinate or 50 mg of prednisolone phosphate may be given in the morning and evening or at a lesser frequency to control distal colitis.
   d) Azulfidine - usually given in combination with low doses of prednisone in amounts of 2.0 to 4.0 g per day.

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disease are treated with a combination of steroids and azulfidine. In contrast to the situation in ulcerative colitis, very few control studies have been undertaken using these two drugs either singly or in combination so it is very difficult to ascertain whether or not the ultimate course of the disease has been altered by such therapy. Generally, some dietary alterations are indicated

in many patients. The patient probably should avoid fibrous, undigestible vegetables particularly if there is marked ileal narrowing and partial small bowel obstruction. If malabsorption is a prominent part of the picture, it is reasonable to reduce the amount of fat in the diet and, at the same time increase the amount of protein. Symptomatic relief of a portion of the diarrhea and of the cramping abdominal pain that is so common in these patients can usually be successfully treated with a variety of medications. Occasionally, the administration of metamucil alleviates the symptoms in mild cases. More commonly, however, either anticholinergics or various narcotic agents are required to suppress bowel motility and partially control the pain and diarrhea. Lomotil, a combination of a narcotic and antispasmodic, is particularly useful in this regard. Some caution is required in the use of these drugs since excessive dosage may lead to complete small bowel obstruction or, in the case of colitis, has been implicated as inducing acute toxic dilatation of the colon. Clearly, the drug of choice for the treatment of the acutely ill patient who has an exacerbation of fever and diarrhea is steroids, usually prednisone, in a dose of 40 to 60 mg per day given over a period of 2 to 3 weeks until the symptoms are under control. This dosage is then reduced very slowly over a period of several months to the minimum dose required to maintain the patient essentially symptom-free. ACTH is still used by some physicians to treat acute exacerbations: however, there is no objective evidence that ACTH is superior to prednisone. In patients who have inflammatory disease primarily localized to the distal colon, steroid enemas may be used rather than systemic steroids. Various preparations are available and usually consist of either 100 mg of hydrocortisone hemisuccinate or 50 mg of prednisolone phosphate dissolved in a water or oil enema. Finally, most physicians also administer azulfidine in a dose of 2.0 to 4.0 g per day to patients being treated with continuous low-dose prednisone. This drug has been shown to be affective in reducing the number of acute attacks in patients with ulcerative colitis but has not been shown to have a similar affect in patients with Crohn's disease. Nevertheless, the combination of azulfidine and prednisone is probably the most commonly utilized form of drug management in the long-term treatment of patients with any type of Crohn's disease.

Two other forms of drug therapy may be effective in highly selected cases. First, a number of cases with extensive ileal disease or extensive resection may have a severe watery diarrhea that is the result of an ileal dysfunction syndrome and bile acid-induced enteropathy. Such patients may respond to the administration of cholestyramine in doses of 4 to 12 g per day. Second, immunosuppressant drugs, particularly azathioprine have been utilized with some success. Individual case reports have suggested that this drug may be valuable in certain patients: however, two control series using relatively small numbers of patients have given conflicting results in that one series showed no affect while the other showed an apparent favorable effect in suppressing the number of acute attacks. At this point in time the use of this drug should clearly be considered an experimental procedure and should be utilized only in very special circumstances in patients who, for various reasons, cannot be maintained on conventional steroid therapy and in whom conventional surgical therapy is contraindicated for some reason.

The initial response to drug treatment is usually good in that in various series from 75 to 95% of patients respond to high-dose steroid therapy

with a reduction in toxicity, diminished bleeding and alleviation of the diarrhea. The long-term outlook, however, is relatively poor in that most patients will pursue a clinical course of either chronic or intermittent symptomatic disease even when maintained on low doses of steroids.

B. Surgical Management of Crohn's Disease

A large percentage of patients with significant involvement of the gastrointestinal tract and Crohn's disease eventually undergo one or more surgical procedures. Since these surgical procedures are usually undertaken as a result of continually active disease or complications such as intestinal obstruction, it is not surprising that the immediate operative mortality rate is relatively high. As summarized for nine separate series in Table 32, the

Table 32

Operative Mortality in Crohn's Disease of All Types

Date of Series	No. of Patients Treated Surgically	No. of Major Operations	Patient Mortality (%)
1954	402	564	5.5
1960	304	346	2.0
1962	257	325	3.1
1966	72	57	5.5
1967	73	91	6.8
1969	147	213	7.5
1969	195	244	6.2
1971	254	459	7.1
1971	244	415	9.9
	Mean		5.9 ± 1

mortality varies from 2.0 to 9.9% and averages 5.9% for all series. The reasons for surgery and the type of surgical procedure undertaken necessarily relates to the primary site of involvement in a given group of patients.

As summarized for three separate series in Table 33, in patients who primarily have ileal Crohn's disease the most common cause for the initial surgical procedure is obstruction of the small bowel. The complications of internal and external fistulae and the formation of intraabdominal inflammatory masses are two other common indications for surgery. Uncommonly, significant GI blood loss or free perforation necessitate the intial surgical procedure in such patients. Two general kinds of surgical procedures have commonly been utilized for the treatment of ileal Crohn's disease. As shown

Table 33

Indications for Initial Surgery in Patients with Crohn's Disease, Principally of the Ileum

	Series		
	1960 (304 patients)	1963 (88 patients)	1965 (85 patients)
Obstruction	84%	42%	47%
Fistulae, internal and external	25%	21%	6%
Abdominal Mass	17%	36%	25%
GI Bleeding	9%	3%	3%
Perforation	3%	1%	13%

in Fig. 11 various bypass procedures have been used in which the fecal stream is diverted into the colon while the diseased small bowel is left behind. Alternatively, the disease is resected and the terminal end of the small intestine is anastomosed either into the right colon or into the transverse colon.

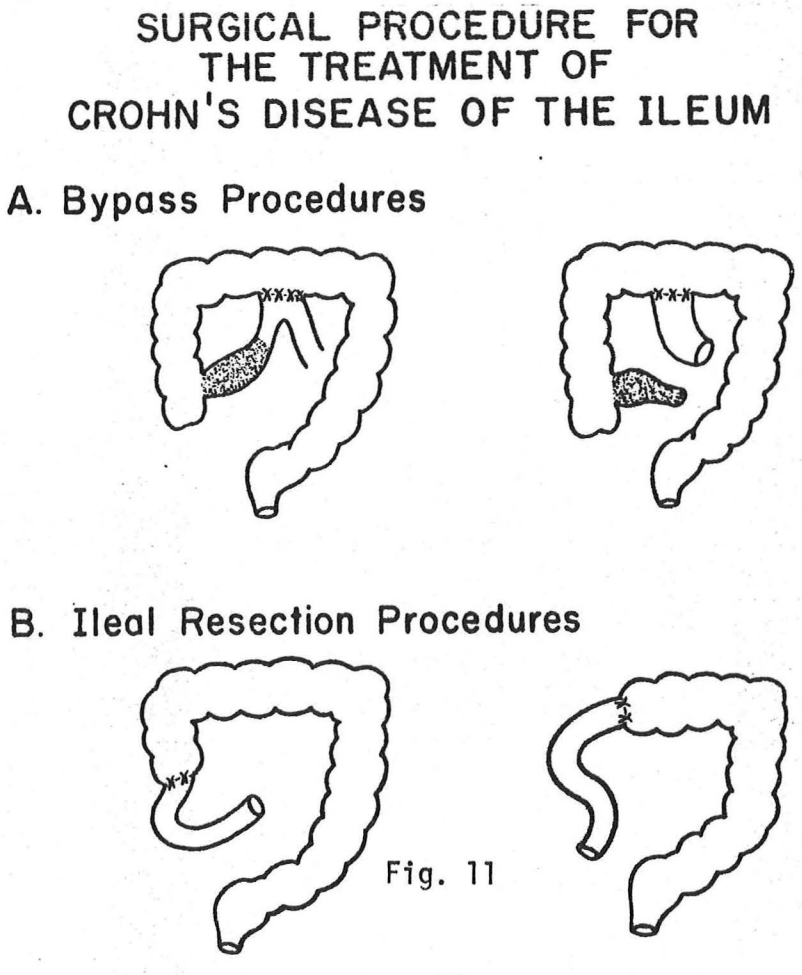

Fig. 11

It is well established that after either of these primary surgical procedures there is a high incidence of recurrent disease. As shown in Fig. 12 for

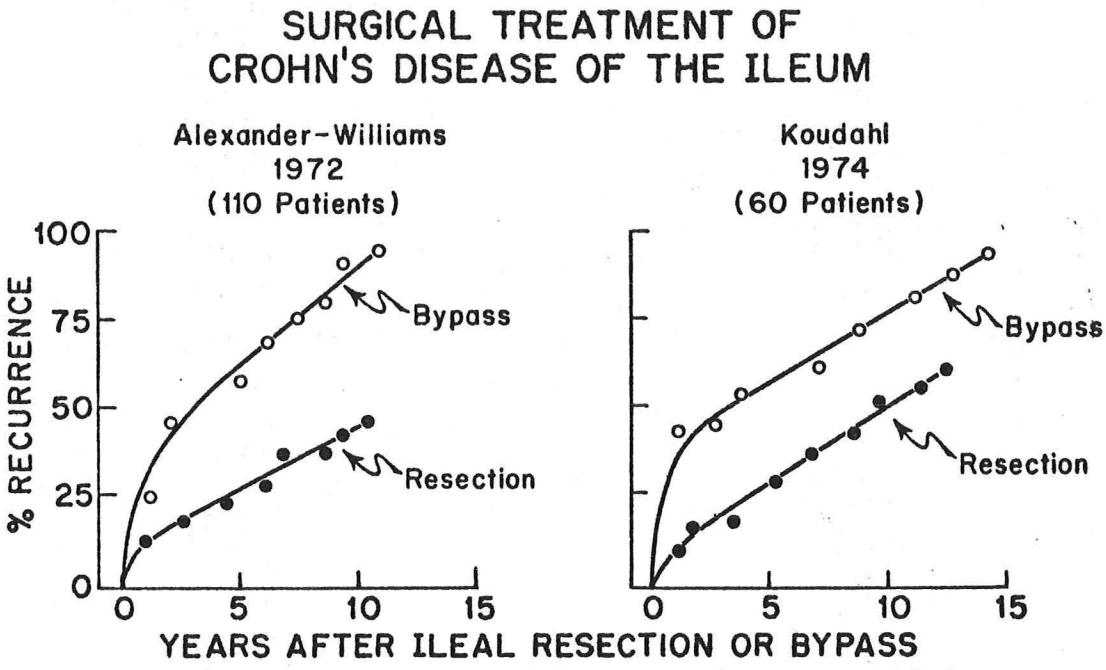

Fig. 12

two very recent series published in 1972 and 1974, in those patients treated with ileal bypass the incidence of recurrence approaches 100% when patients are followed for 10 to 15 years. Primary surgical resection of the involved ileum gives considerably better results although recurrent disease, usually in the region of the anastomosis, commonly occurs and the incidence is related to the duration of followup. On the basis of such data most surgeons feel that surgical resection of the affected ileum is the operation of choice: however, for technical reasons it is still occasionally necessary to bypass disease in the right lower quadrant. The prognosis in such cases is considerably worse than patients treated with primary resection.

Thus, with respect to the surgical treatment of ileal Crohn's disease these curves illustrate two very important points: first, following surgery there is an immediate recurrence rate within the first 1 year to 18 months of approximately 10 to 25%. Second, in all cases the cumulative percent of recurrence continues upward as a linear function of the years of followup. That is to say, in all major surgical series that have been reported there is a constant annual recurrence rate of approximately 4 to 6% per year so that essentially all patients will have recurrent disease if followed for sufficiently long periods of time.

As summarized in Table 34, the indications for the initial surgical procedure in patients with Crohn's disease principally localized to the colon are

Table 34

Indications for Initial Surgery in Patients with Crohn's Disease, Principally of the Colon

1) Continuous Disease with Failing to Respond to Drugs
2) Acute Recurrent Disease or Acute Progressive Disease
3) Severe Perianal Disease
4) Obstruction, Bleeding or Perforation (all uncommon)

different. In contrast to the situation with ileal Crohn's disease the major reason for colon surgery in this circumstance is continuous active clinical disease which fails to respond well to appropriate drug therapy. Again, two general surgical approaches have been utilized, as illustrated diagrammatically in Fig. 13. In a number of cases, particularly those with sparing of the

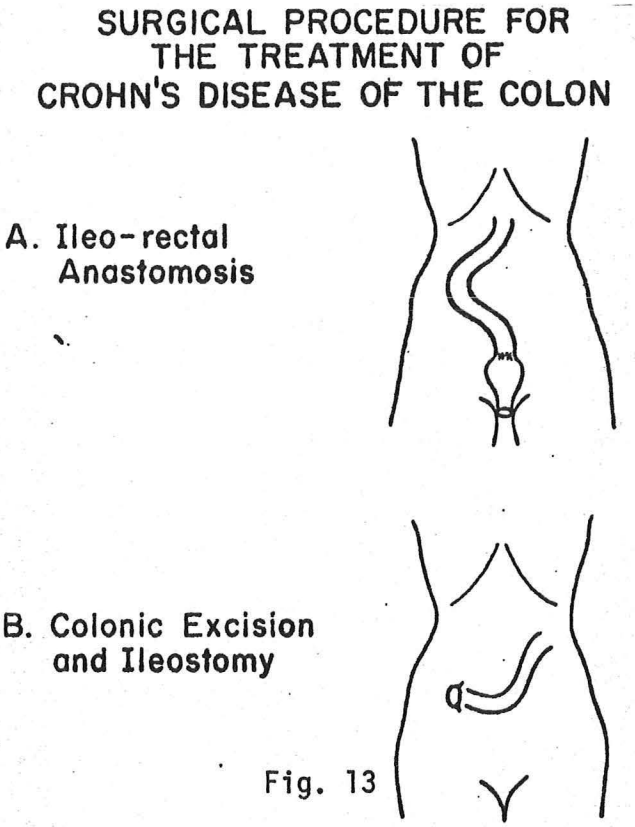

Fig. 13

rectum, a subtotal colectomy has been performed followed by an ileal-rectal anastomosis. The second surgical approach is that of a total colonic excision and formation of a permanent ileostomy.

As summarized in Table 35 the results obtained with the ileal-rectal anastomosis are clearly very poor. In these two recent series the recurrence

Table 35

The Results of Treating Crohn's Disease, Predominantly of the Colon, with Subtotal Colectomy and Ileo-Rectal Anastomosis

Series	Year	Recurrence Rate					
		Colon Disease Alone			Colon + Ileum		
		Number Cases	Mean Follow-up (yrs)	Recurrence Rate %	Number Cases	Mean Follow-up (yrs)	Recurrence Rate %
Baker	1971	10	6.2	80%	15	6.2	87%
Burman et al	1971	11	6.3	45%	14	6.3	71%

rate varied from 45 to 87% after an average followup of only six years. As shown diagrammatically in Fig. 14 the principle site of recurrence is in the retained rectal stump although recurrences also are seen in the more proximal portions of the small intestine.

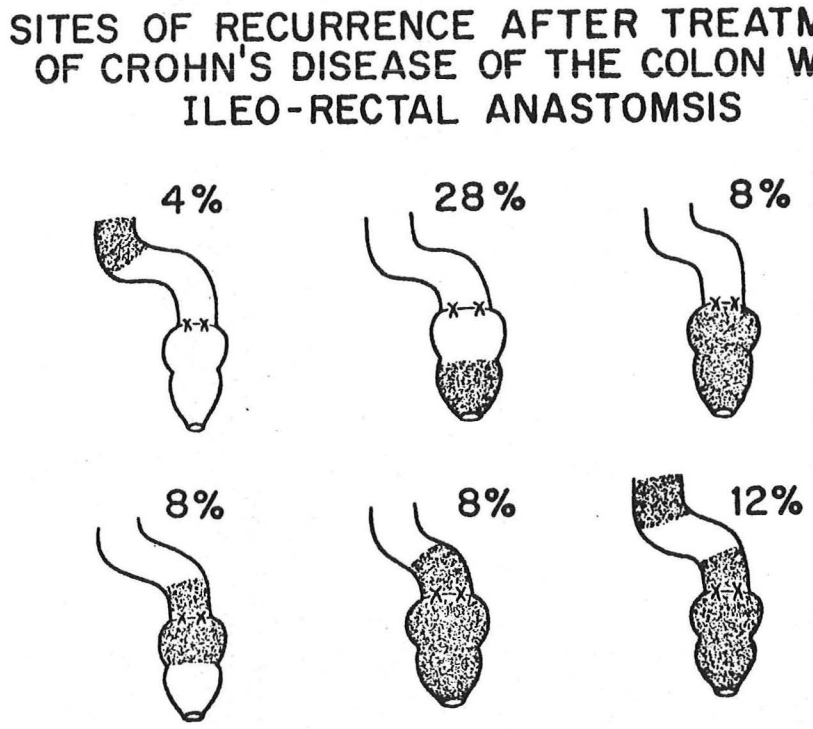

Fig. 14

Results such as these have lead most surgeons to conclude that Crohn's disease of the colon should be treated with total colon excision and the

formation of a permanent ileostomy. Furthermore, several series published in 1970 to 1973 suggested that the results of such surgery were excellent and that, in fact, Crohn's disease of the colon should not be considered to be different from chronic ulcerative colitis of the colon with respect to the long-term prognosis. Such data are summarized in Table 36 where, it can be seen, the recurrence rate varied from only 4 to 17% in patients so treated.

Table 36

The Results of Treating Crohn's Disease, Predominantly of the Colon, with Colon Resection and Permanent Ileostomy

Series	Year	Recurrence Rate					
		Colon Disease Alone			Colon + Ileum		
		Number Cases	Mean Follow-up (yrs)	Recurrence Rate %	Number Cases	Mean Follow-up (yrs)	Recurrence Rate %
Glotzer	1970	21	11.0	? 5%	21	11.0	? 5%
Ritchie	1973	19[1]	8.1	0%	8[1]	8.1	0%
		25[2]	8.1	8%	12[2]	8.1	17%
Nugent	1973	28	12.8	4%			

[1]One stage protocolectomy
[2]Staged protolectomy

Such data has given rise to the currently prevalent view that Crohn's disease of the colon has a significantly better prognosis than Crohn's disease of the ileum after resection.

Such an optimistic viewpoint has not been substantiated by a number of other series as outlined by the data in Table 37. As is apparent, in those patients who had Crohn's disease localized to the colon alone, the recurrence rate varied from 12 to 43% while in those cases with ileal colitis at the time of surgery the recurrence rate was higher and varied from 35 to 41%. Obviously, the percent recurrence is a function of time and, as shown in Fig. 15, in those patients that have now been followed for a period of 10 to 15 years it is apparent that the recurrence rate is similar to that seen with Crohn's disease of the small bowel. There is an initial recurrence of approximately 10 to 15% in the first 1 to 2 years after the colectomy and a constant annual recurrence rate varying from 3 to 7% per year thereafter.

It has also been argued that while recurrence may occur after colectomy for colonic Crohn's disease the recurrence tends to be clinically milder than

Table 37

The Results of Treating Crohn's Disease, Predominantly of the Colon, with Colon Resection and Permanent Ileostomy

Series	Year	Recurrence Rate					
		Colon Disease Alone			Colon + Ileum		
		Number Cases	Mean Follow-up (yrs)	Recurrence Rate %	Number Cases	Mean Follow-up (yrs)	Recurrence Rate %
De Dombal	1971	30	? 2-15	12%	64	? 2-15	41%
Fielding	1972	43	13.7	43%	40	13.7	47%
Korelitz	1972	--	--	--	67[1]	?	46%
Steinberg	1974	33	? 1-15	30%	37	? 1-15	35%
Steinberg	1975	73[2]	9.1	31%	--	--	--

[1]May include patients with ileal disease also.
[2]Includes cases with both colon disease alone and colon + ileum.

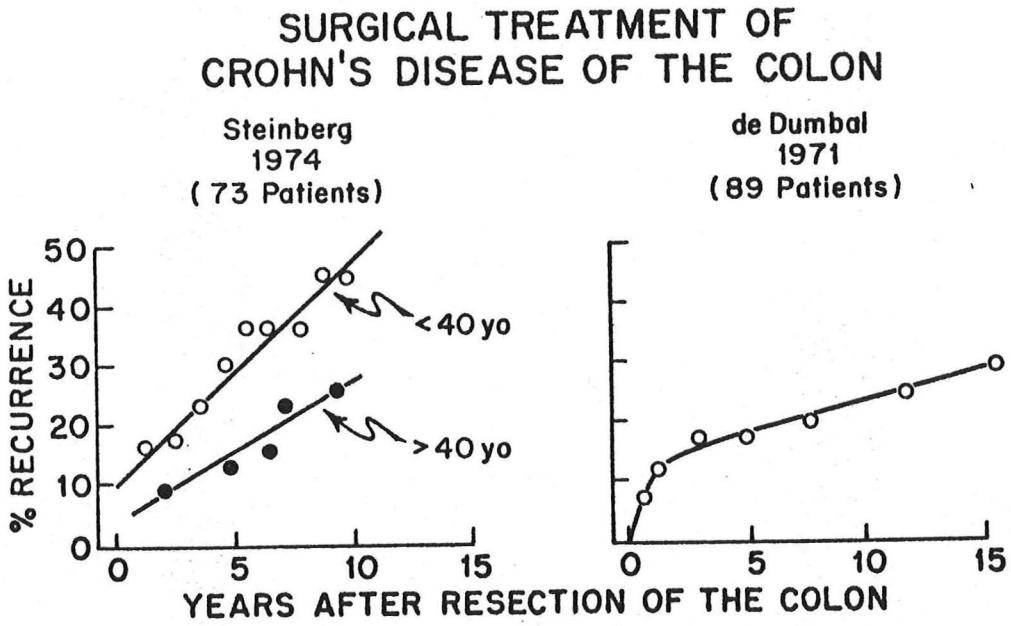

Fig. 15

that seen with ileal Crohn's disease. Again, the data suggest that this is not true and, certainly, patients who have colectomy for Crohn's disease clearly do more poorly than patients who have colectomy for ulcerative colitis. As shown, for example, in Table 38 the immediate operative complications are similar in patients operated on for Crohn's disease and ulcerative colitis:

Table 38

Outcome of Colectomy and Ileostomy for Inflammatory Colon Disease

	Crohn's Disease of Colon	Ulcerative Colitis
A. Immediate Postoperative Mortality		
a) Emergency operation	33%	24%
b) Elective operation	3%	3%
B. Postoperative Sepsis		
a) Wound	13%	12%
b) Intraperitoneal	8%	9%
c) Perineal	30%	32%
d) Total	34%	35%
C. Late Mortality	9%	10%

thus, the elective mortality in both situations is about 3% and there is a significant incidence of postoperative sepsis in both situations equal to approximately 35%. As shown in Table 39, however, it is apparent that in patients whose primary diagnosis was Crohn's disease of the colon, ileostomy

Table 39

Frequency of Reoperation After Colectomy and Ileostomy for Inflammatory Colon Disease

	Crohn's Disease of Colon (64 patients)	Ulcerative Colitis (65 patients)
A. Number of operations	75	34
B. Operations per patient	1.2	0.5
C. Cause of Reoperation		
a) Obstruction	20%	17%
b) Perineal Sepsis or Sinus Tract	3%	6%
c) Dehiscence	22%	18%
d) Ileostomy reconstruction	33%	9%
e) Recurrent disease	39%	0%

reconstruction was necessary in 33% of the cases (as opposed to 9% of the cases whose primary diagnosis was ulcerative colitis) and reoperation for recurrent disease occurred in 39% of those patients with Crohn's disease (as opposed to 0% of those patients whose primary diagnosis was ulcerative colitis). Thus, in most modern series, patients having a colectomy for Crohn's disease have a reoperation rate that is 2 to 3 times higher than that seen in patients who have a colectomy for ulcerative colitis.

Thus, in summary, the primary purpose of surgery is to treat the major complications of Crohn's disease such as intestinal obstruction, massive bleeding or perforation or for the temporary control of disease that has responded poorly to the administration of steroids and azulfadine. The outlook after such surgery should be guarded, however, since there is a high frequency of recurrent disease the incidence of which increases each year after the surgery was performed. Data suggest that the recurrence rate may be lower after colectomy for Crohn's disease localized to the colon: however, it is clear that such patients do much less well than patients who have had colectomy for ulcerative colitis. Patients who have had colon resection for ulcerative colitis and who survive the initial operative complications can be assured that their disease has been essentially cured: no such assurance can be given to patients who have colonic resection because of granulomatous colon disease.

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