# THE OUTCOME OF INFLAMMATORY BOWEL DISEASE

R G Farmer

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Crohn's disease and ulcerative colitis have become among the most frequently encountered chronic digestive diseases. Two important characteristics for inflammatory bowel disease are the tendency for exacerbation and remission (often unpredictable) and its occurrence in a relatively young population. The need for long-term follow-up studies of patients with inflammatory bowel disease is based on the chronicity of illness, types and frequency of complications present, need for prolonged medical therapy, and frequent requirement for operation and reoperation.

## EPIDEMIOLOGY AND GENETIC STUDIES

The incidence of Crohn's disease in the U.S.A. has gone up precipitously since the recognition that it could affect the large intestine, in the 1960's. Whether this was a real or imagined increase was the subject of a great deal of concern and many studies. Epidemiologic studies in the United States have been very difficult to obtain because of the decentralized health care system, the lack of disease registry throughout the country, and referral patterns, particularly to large tertiary care referral centers such as The Cleveland Clinic and others. However, such epidemologic data as has been obtained is in general conformity with that found in centers in which a defined population can be identified, notably in Scandinavia and in the U.K. What has been found is that the incidence of new cases per hundred thousand population increased from approximately two per year in 1960 to almost five per year by the late 1970's. Since that time there has been some evidence that the disease incidence reached a plateau or has actually declined to approximately 4.5 new cases per hundred thousand population per year. During this same period of time, the incidence of ulcerative colitis has remained about the same at 3-4 new cases per hundred thousand population per year. The prevalence of Crohn's disease has of course, been much higher than the incidence, because of the chronicity and recurrent nature of the symptoms requiring further medical attention. At The Cleveland Clinic, we have seen approximately a thousand cases a year for the past several years, but many of these are, of course, the same patients returning year after year and illustrates the difficulty of using a tertiary referral center to try and obtain incidence figures.

In addition to the incidence of the disease having been observed to increase, based on reports from many centers throughout the world, an additional aspect has been that the disease has been found to be far more common in certain geographic areas than in others, often for reasons which are not clear. The incidence figures quoted pertain to Northern Europe, the United Kingdom, and Northern U.S.A., and are not comparable to data from other parts of the world, where the incidence appears to be considerably lower.

One of the interesting characteristics of both ulcerative colitis and Crohn's disease over the years have been the apparent predilection for Jewish people. However, the diseases are by no means a 'Jewish disease' because the incidence in Sweden, with a very low Jewish population, is similar to that seen in New York.

A corollary to the predilection for Jews is the observation that patients with Crohn's disease are often (a) urban residents or suburban, (b) better educated than the general population, and (c) more affluent than the general population. While this sterotype has some validity, there are many exceptions and the question of urbanization (with presumably a stress or environmental factor related) as an etiologic factor in Crohn's disease has never been proved.

A further assessment of the Jewish preponderance in Crohn's disease is that persons affected are predominantly those of Northern and Eastern European descent Studies from Israel have shown a low incidence in the indigenous or Middle Eastern Jew and, in fact, the incidence of Crohn's disease generally in Israel is lower than the figures mentioned. Substantial Gentile involvement by the disease has also been recognized, and Caucasians are more commonly affected than other races. Again, however, some urban Blacks have been identified as having Crohn's disease, and the disease is now recognized in Japan although approximately ten per cent of the incidence of ulcerative colitis, figures approximating those seen in the United States in the 1940's and 1950's, one might speculate that as Japan becomes more "Westernized" one might anticipate more patients with Crohn's disease if one assumes that some element of Western culture might be causative or provocative. Likewise, in the Middle East, there are some cases of ulcerative colitis among Arabs, but Crohn's disease is extremely rare. In South Africa, the Caucasian population, particularly the Jewish subset, has an incidence of Crohn's disease similar to that described above, but only a few cases have been seen in Blacks and those have been recognized among the urban population. Data from Australia and New Zealand indicate a Caucasian incidence lower than that described in Scandinavia, but nonetheless significant, with a very low incidence among the Polynesians and Aboriginal populations. Whether or not the disease is recognized in China is not known; in India it appears to be quite rare. South American data has also emphasized the Jewish preponderance.

If one observes areas of the world in which infectious diarrhoea is relatively common, one finds an almost opposite relationship to the develoment of Crohn's disease. Thus in equatorial areas and locations in which amebic dysentery and other parasitic infestations are

Division of Medicine
The Cleveland Clinic Foundation
Cleveland
Ohio
USA
R G Farmer, MD, FACP, Chairman

relatively common, one also finds an inverse relationship to the presence of Crohn's disease.

All of this has, of course, led to a tremendous amount of speculation, which has centered, if one puts aside racial and ethnic considerations, on westernization and urbanization. A great variety of dietary factors have been assessed including whether or not the persons were breast fed as infants, the type of diet consumed with particular emphasis on carbohydrates and sugar content, and the content of fiber in the diet. All studies of this nature have proved inconclusive. In addition, whether there might be something in the environment which is ingested or inhaled and set up some type of allergic or immunologic reaction has likewise been investigated extensively, also with negative results, at least insofar as being an initiating mechanism. Although the search for a microbiologic agent and/or immunologic abnormality which might cause or precipitate the disease goes on, results have continued to be inconclusive.

By far the most commonly studied and evaluated aspect of the background of patients with Crohn's disease has been various forms of stress. The "stress theory" reached maximum popularity in the 1950's with the work of Engel who described the importance of a severed relationship for patients who develop ulcerative colitis (the presumption has been that whatever stress factors might precipitate ulcerative colitis do the same for Crohn's disease). This separation could result from the death of someone close to them, a disrupted relationship such as divorce or a romantic breakup, or a failure of some sort or another, often related to school work. The theory postulated that because of this disruption or separation phenomenon that the patient experienced a discontinuity of time and a feeling of "hopelessness and helplessness". Retrospective analysis of some patients with the onset of ulcerative colitis verified that such events had occurred to them previously. However, similar results were found with patients who developed lymphomas or myocardial infarctions. Mendeloff and his colleagues in the 1960's studied "life experiences" of patients with inflammatory bowel disease and the irritable bowel syndrome and found more similarities than differences. Nevertheless, there has emerged a stereotype of the patient with Crohn's disease as being frequently (a) Jewish, urban, well educated, and affluent, (b) having a possessive and domineering mother, and (c) being a compulsive, achieving, anxiety-laden and guilt-ridden person. While this sterotype is obviously an exaggeration, it does remain one of the great clichés of the illness. However, whether these characteristics are the result of the disease or the cause of the disease is open to speculation.

Another aspect of the disease which is of considerable importance is the predilection for a young population. The mean age of onset in a number of large series has been reported to be in the upper 20's and in The Cleveland Clinic experience, approximately 50% of all patients seen have onset of the disease between the ages of 15 and 30. Thus, many of the "stress" relationships can be explained by the development of a chronic illness, with remissions and exacerbations, need for medication and a frequent need for operation. In a patient who is attempting to develop economic and social independence, the very nature of the disease is to render the patient dependent at the time in his or her life when independence is desired. Further, this age group is among the most mobile of the entire population, and the disease tends to render the person less mobile at a vulnerable time in life as well.

One of the most interesting characteristics of Crohn's disease is its tendency for clustering in families. This has led to a number of genetic studies, but no markers have been found in the HLA or other systems studied which identify patients at potential risk for development of the disease. Nonetheless, longitudinal studies of families have indicated the phenomenon of clustering, both in a "vertical" manner (from generation to generation) and a "horizontal" manner (same generation to first cousin level). Kirsner's group indicated that a positive family history for a similar disease could be obtained in about 20% of their patients, and in The Cleveland Clinic Study, a positive family history as defined was found in over 30% in more than 280 families studied. (1, 2) The technique used was to interview patients who had been diagnosed as having Crohn's disease and/or the time having elapsed so that others with the disease were recognized were both presumptive factors in our study. However, specific genetic factors did not seem to pertain as the incidence of parent and child affliction with the disease was relatively low. Variations on this theme have been studied by others including looking at identical twins, married couples, and specific parent-child relationships. While all of these studies have tended to indicate the clustering phenomenon, there is nothing to suggest a specific genetic or inherited relationship. Therefore, the question of "genetic versus environmental factors" in the onset, development, precipitation, or perpetuation of Crohn's diesase or ulcerative colitis remains unsolved. (Table 1 and 2)

Table 1.
**ADDITIONAL FAMILY MEMBERS WITH IBD[1]**

| Original study[2] | Ulcerative Colitis | | | | Crohn's Disease | | | |
|---|---|---|---|---|---|---|---|---|
| 838 patients<br>Family history of IBD[2] | 316 patients<br>93 patients (29%) | | | | 522 patients<br>187 patients (35%) | | | |
| | Original Number[2] | New[1] | Total[1] | % | Original Number[2] | New[1] | Total[1] | % |
| Parents | 31 | 1 | 32 | 10.1 | 48 | 2 | 50 | 9.5 |
| Siblings | 19 | 4 | 23 | 7.2 | 39 | 4 | 43 | 8.2 |
| Relatives[3] | 43 | 10 | 53 | 16.7 | 100 | 12 | 112 | 21.3 |
| TOTAL | 93 | 15 | 108 | 34 | 187 | 18 | 205 | 39 |

Grand total
Original[2], 280 (34%)
Subsequent[1], 313 (37.3%)

[1] 1984
[2] 1974
[3] Aunts, uncles, first cousins — direct bloodline.

Table 2.
**ADDITIONAL FAMILY MEMBERS WITH IBD, IMMEDIATE FAMILY[1]**

| Original study[2] | Ulcerative Colitis | | | | Crohn's Disease | | | |
|---|---|---|---|---|---|---|---|---|
| 838 patients<br>Family history positive[2]<br>Immediate family | 316 Patients<br>50 Patients (15.8%) | | | | 522 Patients<br>87 Patients (16.6%) | | | |
| | Original Number[2] | New[1] | Total[1] | % | Original Number[2] | New[1] | Total[1] | % |
| Father-son | 4 | 1 | 5 | 1.6 | 14 | 0 | 14 | 2.7 |
| Father-daughter | 8 | 0 | 8 | 2.5 | 6 | 1 | 7 | 1.3 |
| Mother-son | 10 | 0 | 10 | 3.2 | 14 | 1 | 15 | 2.9 |
| Mother-daughter | 9 | 0 | 9 | 2.8 | 14 | 1 | 15 | 2.9 |
| Sibling-sibling | 19 | 4 | 23 | 7.3 | 39 | 4 | 43 | 8.2 |
| Total | 50 | 5 | 55 | 17.4 | 87 | 7 | 94 | 18.0 |

Grand total
Original 137 (16.3%)[2]
New, 12
New total, 149 (17.8%)[1]

[1] 1984
[2] 1974

## CLINICAL STUDIES

In the mid-1960s we at The Cleveland Clinic developed a registry of 615 consecutively seen patients with the new diagnosis of Crohn's disease. After following these patients for ten years we proposed the thesis that the initial anatomic involvement in Crohn's disease was a major determinant in prognosis. (3) Approximately 96% of these patients were followed for an additional ten years. (4) Analysis of the cases revealed the occurrence of clinical patterns of the disease process that were dependent on initial location of disease. Clinical patterns were established for the following anatomic location of disease: 1) ileocolic (involvement of right colon and distal ileum), 252 patients (41%); 2) small intestine (without colon involvement), 176 patients (28.6%); 3) colon (without small intestine involvement), 166 patients (27%); and 4) anorectal (without other demonstrable involvement initially), 21 patients (3, 4%). A small number of patients had gastroduodenal involvement. Statistically significant symptoms ($P < .001$) were rectal bleeding with colon involvement and rectal fistulas with ileocolic or colon involvement. Among statistically significant complications ($P < .001$) were perianal fistulas, internal fistulas, and intestinal obstruction with the ileocolic pattern; perianal fistulas, toxic megacolon, and arthritis with the colon pattern; and intestinal obstruction with the small intestine pattern. Surgery was required for 73% of patients with the ileocolic clinical pattern and for 51% of patients with each of the small intestine and colon patterns. Table 3 lists the indications for surgery.

Among these 615 patients, 316 had primary operations performed at The Cleveland Clinic between 1966 and 1969. In addition, in 1972 and 1973 there were 184 patients for whom the primary decision for surgery was made at The Cleveland Clinic, and the operation was then performed. Thus, in the six-year period (1966 to 1969 and 1972 to 1973) there were 500 patients who had indications for surgery. (5)

Among the 225 patients with the ileocolic pattern, 91% had specific surgical indications broken down as follows: internal fistula and abscess, 44%; intestinal obstruction, 35%; and perianal disease, 12%. Among the 130 patients with the small intestine pattern, two indications made up 87% of the surgical indications: intestinal obstruction, 55%, and internal fistula with abscess, 32%. Among the 127 patients with the colon pattern, a greater variety of surgical indications was observed. These included poor response to medical therapy (26%), internal firstula and abscess (23%), toxic megacolon (20%), perianal disease (19%), and intestinal obstruction (12%). For the patients with the anorectal pattern in whom colonic disease developed, the indications were either the perianal disease itself or poor response to therapy.

Comparison was made of the three major patterns, and the statistical significance of each surgical indication was defined. There were highly significant statistical differences in indications for surgery based on anatomic location of Crohn's disease (Table 4).

In our earlier study of recurrences and reoperation for patients with Crohn's disease (6) we found that recurrence after surgery in Crohn's disease is associated with the original location of disease. In this study 361 patients were followed for a mean of 11.5 years following the first operation for Crohn's disease. Among these patients, 40% had ileocolic location of disease, 30% small intestine disease, and 30% large intestine disease. There were 123 patients (34%) who had a recurrence requiring operation. The incidence of recurrence was lowest in patients with disease of the large bowel (24%) or small bowel (28.5%);

Table 3.
**INDICATIONS FOR SURGERY IN CROHN'S DISEASE**

Ileocolic Pattern
- Intestinal obstruction
- Internal fistula and abscess
- Perianal disease, severe

Small-Bowel Pattern
- Intestinal obstruction
- Internal fistula and abscess

Colonic Pattern
- Toxic megacolon
- Internal fistula
- Stricture with obstruction
- Perianal disease, severe
- Poor response to medical therapy and chronic disability; malnutrition

Anorectal Pattern
- Severe perianal disease

Other
- Hydronephrosis (ileal)
- Pyoderma (colon), severe
- Arthritis (colon), severe
- Eye manifestations (colon), severe
- Growth retardation (colon)
- Massive hemorrhage (rare)

Table 4.
**STATISTICAL DIFFERENCES IN INDICATIONS FOR SURGERY IN CROHN'S DISEASE**

| INDICATIONS FOR SURGERY | Clinical Pattern | | |
|---|---|---|---|
| | Ileocolic | Small Intestine | Colon |
| Perianal disease | + | 0 | + |
| Intestinal obstruction | + | + | 0 |
| Internal fistula and abscess | + | + | 0 |
| Toxic megacolon | 0 | 0 | + |
| Poor response to medical therapy | 0 | 0 | + |

the recurrence rate was highest for patients with ileocolic disease (44%). These data showed that for the first 8 years there was a 3.9% risk of recurrence requiring resection; after 8 years the risk declined to about 1.4% per year. The cumulative risk was about 42% at 15 years. However, 85% of all recurrences had occurred within the first 8 years following the initial operation, and the risk did not appear to increase as time elapsed. Further analysis of our data (7) revealed that the initial surgical indication of intestinal fistula was abscess, particularly when associated with ileocolic location of disease, and was associated with the highest risk of recurrence requiring further operation.

Evaluation was made of quality of life as assessed by the 502 surviving patients with adequate follow-up data. Questions directed to the patients related to their ability to function in relationship with their peers socially and economically, to the frequency and type of symptoms, to the frequency of medication used, and to the need for hospitalization (Table 5). Many patients were found to function on a suboptimal basis. Patients who fared best were those who had undergone one operation and who had no recurrence, and those who had not required surgery. There was also a relationship between disease location and prognosis: patients who had the most favorable prognosis, with both fewer complications and better quality of life, were those with localized ileal disease or segmental colonic involvement. Among 50 patients with segmental colonic disease, 33 (66%) described their quality of life as good, whether or not they had undergone an operation. Of the 123 patients with ileal disease location, 57 (46%) described their quality of life as good.

Table 5.
**QUALITY OF LIFE AT TIME OF FOLLOW-UP OF 592 PATIENTS**

| CONDITION | OPERATED (438) | NONOPERATED (154) |
|---|---|---|
| Good | 149 (40%) | 69 (53%) |
| Fair | 185 (50%) | 57 (44%) |
| Poor | 37 (10%) | 5 ( 3%) |
| TOTAL | 371 | 131 |

(Footnote)

Good = normal or nearly normal functioning, with comparison to peer group: (1) few if any symptoms and (2) no regular use of medications.

Fair = suboptimal overall functioning with symptoms or use of medications, or both, on a sporadic basis.

Poor = impaired functioning, with need for hospitalization or regular use of medications, or both.

In our most recent study (8) the long-term outcome of Crohn's disease was reviewed in 139 patients who were treated at The Cleveland Clinic for a minimum of 15 years. (Table 6) At the time of diagnosis, 38 (27%), 39 (28%), and 62 (43%) patients had small-bowel, large-bowel, and ileocolic patterns of disease, respectively. The disease progressed with time and eventually 104 (75%) patients had ileocolic disease. A total of 122 patients (88%) underwent at least one definitive operation for the disease. Forty-four (32%) patients had proctocolectomies and 65 (47%) have ileostomies. Associated manifestations of Crohn's disease occurred in a high proportion of patients: perianal disease in 78 (56%), intestinal fistulas in 45 (32%), and extraintestinal disease in 49 (35%). Six patients died of causes directly related to the disease. Specific complications tend to occur at definite times in the course of the disease. (Table 7)

Despite continued efforts to find predictive factors indicating prognostic variability in Crohn's disease, many aspects of the 'natural course' of the disease remain unpredictable, although some generalizations can be made. (Tables 8 and 9) Although surgical intervention in Crohn's disease may not be preventable, it may be predictable and can help the clinician communicate to his patient a realistic look at the prognosis. Certainly, the presence of disease itself is not an indication for surgery. Likewise, when surgical resection is indicated, extensive resections are not advisable unless absolutely necessary, because of the potential for recurrence. As has been emphasized by others, (9, 10) prevention of death and significant morbidity remains the primary concern of the clinician dealing with a patient who has Crohn's disease over a long period of time.

Based on our most recent long-term study, (4) we believe the following observations can be made:

1. The anatomic location of disease (clinical pattern) is a major determinant of clinical course, complications, and reasons for operation in patients with Crohn's disease.

2. Although long-term mortality is similar among the three clinical patterns, morbidity is greater with ileocolic location of disease, particularly in terms of need for operation.
3. Crohn's disease is associated with specific complications and especially obstruction with small intestine location, fistula/abscess with ileocolic location, and megacolon with colonic location of disease.
4. The most frequent complication encountered is perianal disease, which is an early manifestation of Crohn's disease. It is associated more with colonic and ileocolic patterns than with small intestine location of disease.
5. The most favorable long-term prognosis is for patients with segmental colonic or localized ileal disease.
6. Although not an epidemiologic survey, the importance of this study lies in the 615 initial patients with 96% follow-up for a minimum of 7 and a mean of 13 years after development of disease.

Table. 6
**DESCRIPTIVE STATISTICS FOR 139 PATIENTS WITH CROHN'S DISEASE GROUPED BY EXTENT OF DISEASE**

| Disease Pattern at Diagnosis | Number of Patients | Mean Follow-Up (Range, Years) |
|---|---|---|
| Small Bowel | 38 (27%) | 25 (15.1-43.5) |
| Large Bowel | 39 (28%) | 23 (16.0-38.2) |
| Ileocolic | 62 (45%) | 21 (15.2-38.5) |
| TOTAL | 139 | 23 |

Table. 7
**LONG-TERM COMPLICATIONS**

| | Small-Bowel Disease (N = 38) | Large-Bowel Disease (N = 39) | Ileocolic Disease (N = 62) | Total (N = 139) |
|---|---|---|---|---|
| Indications | No (%) | No (%) | No (%) | No (%) |
| Ureteric calculi | 8 (21) | 3 (8) | 12 (19) | 23 (17) |
| Gallstones | 6 (16) | 3 (8) | 10 (16) | 19 (14) |
| Short-bowel syndrome | 4 (11) | 1 (3) | 2 (3) | 7 (5) |
| Death | 6 (16) | 2 (5) | 2 (3) | 10 (7) |

Table. 8
**CROHN'S DISEASE COMPLICATIONS**

Early (less than 2 years) in course of disease:
- Perianal disease

Early to mid-course (0-5 years):
- Fistula/abscess
- Megacolon
- Extra-intestinal

Late in course (more than 5 years):
- Obstruction
- Renal and gallstones
- "Chronic illness"

Table. 9
**CROHN'S DISEASE**
**"NATURAL HISTORY**

Indicators of poor prognosis:
- Megacolon, sepsis, and malnutrition
- Sepsis and abscess with ileocolic disease
- Malnutrition with colonic disease

Indicators of good prognosis:
- Segmental colonic involvement
- Localized ileal involvement

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