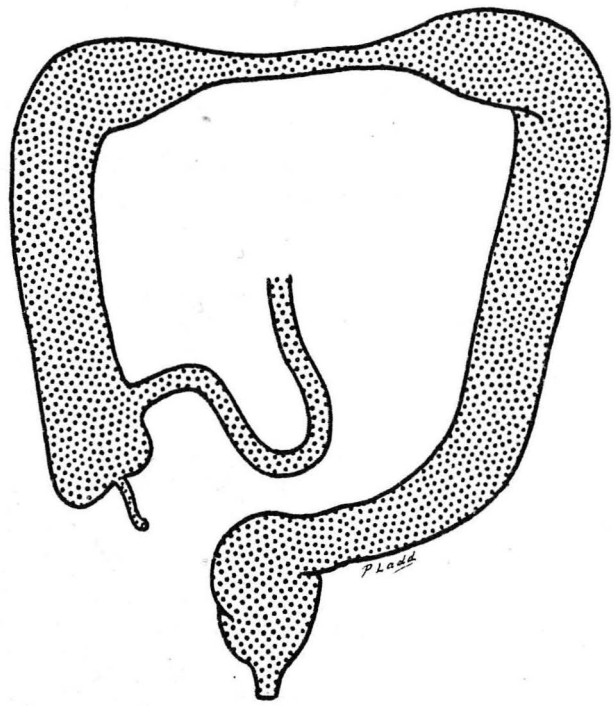
ULCERATIVE COLITIS AND COLON CANCER: RISKS, DETECTION, AND PREVENTION



MEDICAL GRAND ROUNDS

University of Texas
Southwestern Medical School

August 12, 1982 *Mark Feldman, M.D.*

TABLE OF CONTENTS

INTRODUCTION AND DEFINITIONS

There are two types of inflammatory bowel disease which are relatively common and of unknown cause: ulcerative colitis and Crohn's disease. Ulcerative colitis is limited to the colon and thus is potentially curable by proctocolectomy. This disease begins in the rectum and extends proximally for variable distances. If the disease involves only the rectum, the term ulcerative proctitis is used. In these patients, proctoscopic examination will reveal distal rectal abnormalities (ulcers, edema, friability, bleeding), above which normal rectal or sigmoid mucosa can be visualized. Barium enema is usually normal. In other patients, the disease extends beyond the rectosigmoid, but does not involve the entire colon. This is usually referred to as left-sided colitis. Finally, ulcerative colitis may involve the entire colon from rectum to cecum and may even involve a few centimeters of terminal ileum ("backwash" ileitis). This type of ulcerative colitis is called pancolitis or extensive colitis. These three sub-types of ulcerative colitis, shown schematically in Figure 1, are important to recognize because they have somewhat different clinical pictures. For example, patients with pancolitis tend to be sicker, require surgery more often and have a higher mortality and incidence of carcinoma than patients with left-sided colitis or ulcerative proctitis. Although many patients with ulcerative colitis remain in the sub-type in which they initially present, some patients will develop more extensive disease with time. For example, 10% of patients with ulcerative proctitis will extend their disease more proximally and develop left-sided colitis or pancolitis. Thus, it is important to evaluate extent of disease periodically, especially during clinical relapses.

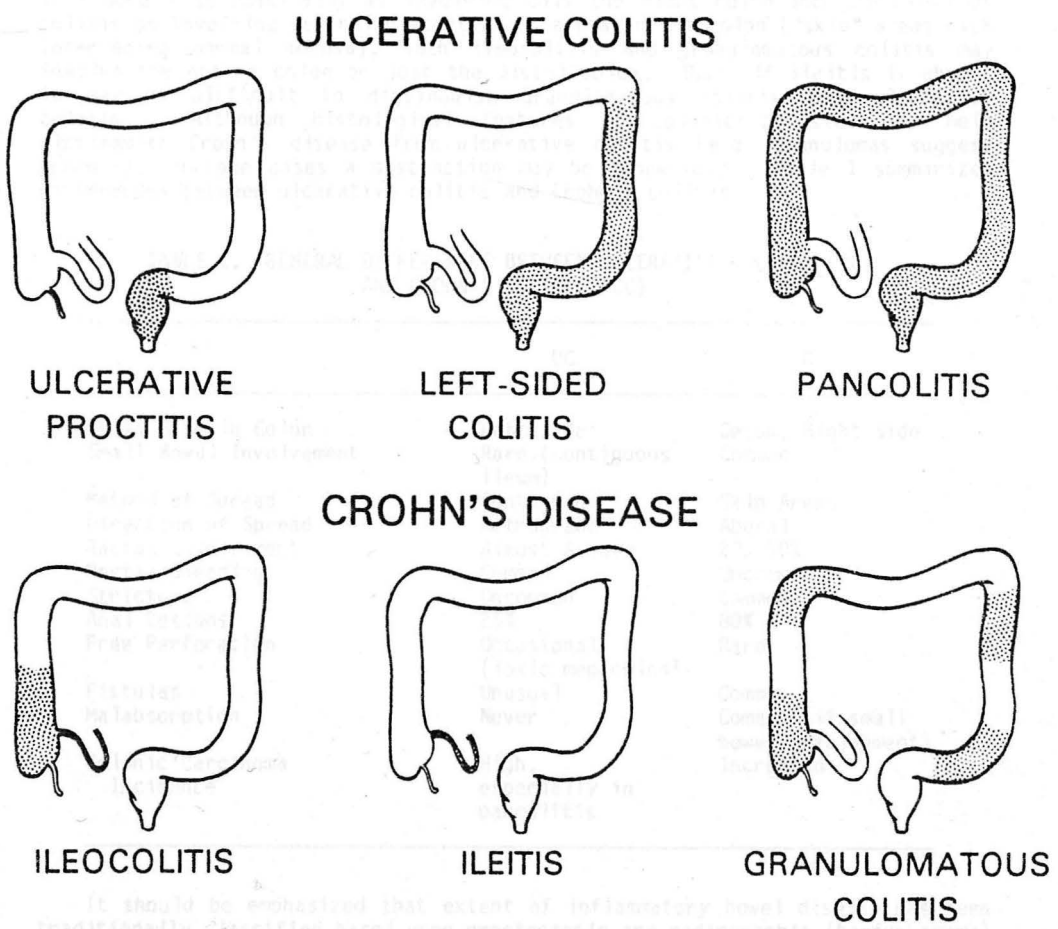


FIGURE 1. Subtypes of Ulcerative Colitis and Crohn's Disease.

Unlike ulcerative colitis, in which ulceration and inflammation are limited to the colonic mucosa, Crohn's disease is characterized by transmural inflammation which may involve any region of the gastrointestinal tract. Three major sub-types are recognized (Figure 1): ileocolitis, ileitis without colitis, and colitis without ileitis (granulomatous colitis). Although ileocolitis is shown in Figure 1 schematically as involving only the right colon and granulomatous colitis as involving several discontinuous areas in the colon ("skip" areas with intervening normal mucosa), both ileocolitis and granulomatous colitis may involve the entire colon or just the distal colon. Thus, if ileitis is absent it may be difficult to distinguish granulomatous colitis from ulcerative colitis. Although histological features of colonic biopsies may help distinguish Crohn's disease from ulcerative colitis (e.g. granulomas suggest Crohn's), in some cases a distinction may be impossible. Table 1 summarizes differences between ulcerative colitis and Crohn's colitis.

TABLE 1. GENERAL DIFFERENCES BETWEEN ULCERATIVE COLITIS (UC) AND CROHN'S COLITIS (CC)

	UC	CC
Usual Site in Colon	Left Side	Cecum, Right Side
Small Bowel Involvement	Rare (contiguous ileum)	Common
Method of Spread	Contiguous	Skip Areas
Direction of Spread	Retrograde	Aboral
Rectal Involvement	Almost Always	20%-50%
Rectal Bleeding	Common	Uncommon
Stricture	Uncommon	Common
Anal Lesions	25%	80%
Free Perforation	Occasional (Toxic megacolon)	Rare
Fistulas	Unusual	Common
Malabsorption	Never	Common (if small bowel involvement)
Colonic Carcinoma Incidence	High, especially in pancolitis	Increased

It should be emphasized that extent of inflammatory bowel disease has been traditionally classified based upon proctoscopic and radiographic (barium enema) findings and almost all information which is available concerning prognosis and complications is based upon this type of classification. If a patient with ulcerative proctitis on proctoscopy and a normal barium enema is subjected to colonoscopy, he might be found to have an abnormal endoscopic and histologic appearance of his entire colon. When estimating risk of cancer, for example, it is unclear whether such a patient should be considered to have pancolitis or just ulcerative proctitis.

References

Farmer, R.G., and Brown, C.H. Emerging concepts of proctosigmoiditis. Dis. Col. Rect. 15:142-146, 1972.

Glotzer, D.J., Gardner, R.C., Goldman, H., Hinrichs, H.R., Rosen, H., and Zetzel, L. Comparative features and course of ulcerative and granulomatous colitis. N. Engl. J. Med. 282:582-587, 1970.

Kirsner, J.B., and Shorter, R.G. (eds.). Inflammatory Bowel Disease, 2nd Edition. Lea and Febiger, Philadelphia, 1980.

Nugent, F.W., Veidenheimer, M.C., Zuberi, S.J., and Garabedian, M.M. Clinical course of ulcerative proctosignoiditis. Hosp. Med. 8:8-20, 1972.

INCIDENCE OF ULCERATIVE COLITIS AND CROHN'S DISEASE IN THE UNITED STATES

The incidence of a disease is the percentage of the population at risk who newly develop the disease during a particular time period (e.g., 1 year, in which case the statistic is the annual incidence). This is contrasted with the prevalence of a disease, which is the percentage of the population with the disease at a given point in time (point prevalence) or over a period of time (period prevalence or, in the case of a year, annual prevalence). For chronic diseases such as inflammatory bowel disease, the annual prevalence greatly exceeds the annual incidence. For acute diseases with a brief course, e.g., bacterial meningitis, the incidence and prevalence rates are very similar.

There is considerable variation in the incidence of inflammatory bowel disease throughout the world. Moreover, the risk of cancer developing in ulcerative colitis appears to be much higher in certain countries (e.g., United States and England) than in other countries (Israel, Czechoslovakia). We will focus on incidence data from the United States. Females are affected slightly more often than males, whites more than blacks, and Jews much more than non-Jews.

When studying incidence it is important to detect all patients who develop the disease within a defined geographic area. Patients living in a geographic area but diagnosed elsewhere will lead to an artifically low incidence rate per 100,000 population. Also, patients diagnosed in doctors' offices rather than in the hospital will lead to an underestimation of incidence unless doctors' records rather than just hospital charts are also reviewed. It is also important that patients actually have the disease in question. Thus, acceptable criteria for defining a "case" need to be used.

Sedlack and his associates attempted to define the incidence of inflammatory colonic disease in a defined and relatively stationary population in Olmsted County, Minnesota (the Mayo Clinic cares for this population almost exclusively). During the 30-year period from 1935-1964, 108 residents developed inflammatory colon disease. I have divided their patients into three groups (A-C, Table 2).

TABLE 2. INFLAMMATORY COLON DISEASE IN OLMSTED COUNTY, MINNESOTA, 1935-1964

Group	Involvement	Number	Annual Incidence per 100,000 population	Number with Cancer
A	Ulcerative Proctitis	58	6.3	0
B	Ulcerative Colitis (Left-sided or Pancolitis)	31	3.4	5
C	Crohn's Colitis	19	2.1	0
	TOTAL	108	11.8	5

The annual incidence was 11.8 cases per 100,000 population at risk but in more than half of these cases (58 of 108, or 53%) the disease never progressed beyond a proctitis. It is of interest that 5 of the 108 patients developed carcinoma of the colon (expected number = 0.4 carcinomas) and all of the cancers occurred in group B which had more extensive ulcerative colitis. Because, as will be reviewed subsequently, it is this group which has the highest cancer risk, it is apparent from Table 2 that the majority of cases of inflammatory bowel disease which occur in the community have an extent of disease which is minimal (group A) and which therefore puts them in a low cancer-risk group.

The workers in the Olmsted County study also noted that the incidence of inflammatory colon disease was apparently increasing with each decade of the study (Table 3), especially in groups A and B.

TABLE 3. ANNUAL INCIDENCE OF INFLAMMATORY COLON DISEASE BY DECADE IN OLMSTED COUNTY, MINNESOTA

Group	Average Annual Incidence Per 100,000		
	1935-1944	1945-1954	1955-1964
A (Ulcerative Proctitis)	4.0	5.6	8.2
B (Extensive Colitis)	2.0	3.9	3.8
C (Crohn's Colitis)	2.4	2.5	1.5
TOTAL	8.4	12.0	13.5

A more recent study of the incidence of ulcerative colitis and Crohn's disease in the United States was published by Garland et al. Fifteen widely different geographic areas were selected for study of annual incidence rates during 1973. Populations in these areas ranged from 11,670 (Eunice, Louisiana) to 1,070,103 (Albuquerque, New Mexico) and the areas also varied widely in climate and in ethnic, racial and social characteristics. Each area was considered to be a "full coverage area", i.e., the hospitals surveyed were sole providers for the defined population. Overall, a population of 1,070,103 was included and 102 new cases of ulcerative colitis and Crohn's disease developed in 1973 (9.5 per 100,000). This incidence figure is similar to the Olmsted County figure. Unfortunately, ulcerative colitis was not divided into sub-types. There were interesting geographic variations in this study. For example, in Portland, Maine (population: 60,873) there were 4 new cases of ulcerative colitis and 3 new cases of Crohn's disease in 1973 (11.4 per 100,000) whereas in Eunice, Louisianna there were no new cases of either disease in 1973.

The annual age-specific incidence of ulcerative colitis in the United States in 1973 is shown in Figure 2 (for simplicity, men and women are combined).

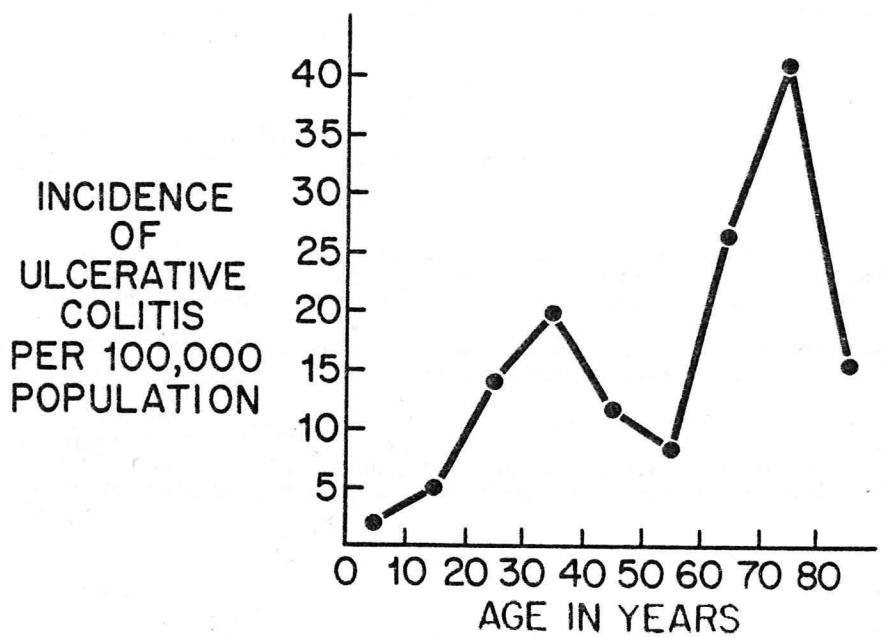


FIGURE 2. From C. F. Garland, et al.

It is apparent that the incidence of ulcerative colitis has a biomodal distribution, with one peak in early adulthood and a second peak in older age. Although not shown in Figure 2, Crohn's disease appears to have a tri-modal distribution (peaks at ages 20-29, 50-59, and 70-79). It is conceivable that what we call idiopathic ulcerative colitis or Crohn's disease is more than one disease, accounting for the bi- or tri-modal patterns seen. It is also possible that there are different precipitating factors for these diseases at different ages.

It is unclear if there is a correlation between age at onset of ulcerative colitis and extent of colonic involvement. Many authors believe that onset of disease before age 20 is more likely to be associated with extensive colitis. This is important because extent of colitis and duration of colitis are the two most important factors which determine subsequent cancer risk. Nevertheless, the data in Table 2 and in Figure 2 serve to remind us that many patients with ulcerative colitis have limited involvement (rectum only) or an onset of disease relatively late in life (after age 60). These patients have little risk of developing cancer and colectomy should be performed only for other indications. On the other hand, the important sub-group of patients with extensive colitis which begins at a relatively young age are at considerable risk for developing and dying from cancer prematurely.

References

Carleson, R., Fristedt, B., and Philipson, J. Ulcerative colitis, a primary 20-year series. Acta Chir. Scand. 125:486-487, 1963.

Gilat, T., Zemishlany, Z., Ribak, J., Benaroya, Y., and Lilos, P. Ulcerative colitis in the Jewish population of Tel-Aviv Yafo. II: The rarity of malignant degeneration. Gastroenterology 67:933-938, 1974.

Garland, C.F., Lilienfeld, A.M., Mendeloff, A.I., Markowitz, J.A., Terrell, K.B., and Garland, F.C. Incidence rates of ulcerative colitis and Crohn's disease in fifteen areas of the United States. Gastroenterology 81:1115-1124, 1981.

Mendeloff, A.I., Monk, M., Siegel, C.I., and Lilienfeld, A. Some epidemiological features of ulcerative colitis and regional enteritis. Gastroenterology 51:748-756, 1966.

Nedbal, J., and Maratka, Z. Ulcerative proctocolitis in Czechoslovakia. Am. J. Proctology 19:106-114, 1968.

Sedlack, R.E., Nobrega, F.T., Kurland, L.T., and Sauer, W.G. Inflammatory colon disease in Rochester, Minnesota, 1935-1964. Gastroenterology 62:935-941, 1972.

RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE AND CANCER

An example of a representative patient with carcinoma complicating ulcerative colitis is presented below. His clinical course is summarized in Figure 3.

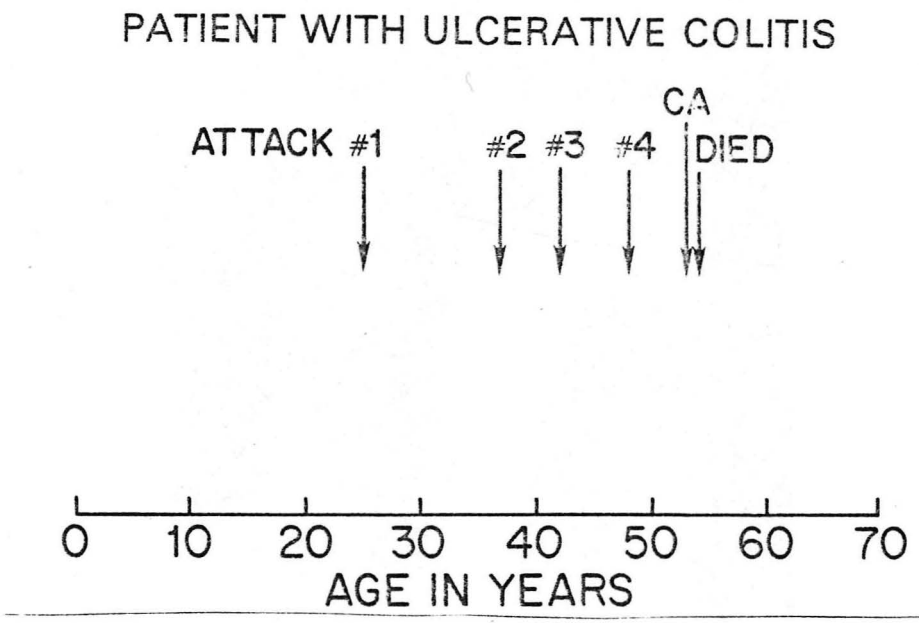


FIGURE 3

Case Report 1. A 25 year old man developed bloody diarrhea and was hospitalized for 3 months and diagnosed as having ulcerative colitis. He remained asymptomatic until age 37 when low-grade fever, diarrhea (12 bloody bowel movements per day), mild abdominal pain and tenesmus developed. Proctoscopy showed an ulcerated, friable, erythematous rectal mucosa and a smear showed numerous white and red blood cells but no ova or parasites. Bacterial cultures were negative for pathogens. Rectal biopsy showed acute and chronic inflammation with crypt abscesses. Barium enema showed extensive ulcerations throughout the colon (pancolitis) with a normal terminal ileum. Sulfasalazine (Azulfidine) was prescribed and there was clinical and proctoscopic improvement. He relapsed again with the same symptoms at age 42 and responded to prednisone therapy. At age 48 he again relapsed and was hospitalized. Proctoscopy showed rectal granularity and rectal biopsy showed acute and chronic inflammation. He again responded to a course of prednisone. At age 53, he again began having bloody diarrhea and mild lower abdominal pain and was admitted to the Dallas VAMC (#449-24-9465). Rectal examination revealed a hard anterior rectal mass which bled to touch. Biopsy of this mass showed a mucinous adenocarcinoma. Barium enema examination is shown in Figure 4. Liver scan and liver function tests were unremarkable. A proctocolectomy (total colectomy) and ileostomy were performed. The rectal tumor extended through to the serosal surface and 16 of 27 lymph nodes contained metastatic carcinoma. The liver was normal and he was considered Dukes' C. He died one year later at age 54. At autopsy there was diffuse intra-abdominal and pelvic mucinous adenocarcinomatosis.

FIGURE 4. Constricting, polypoid rectal carcinoma in patient with ulcerative colitis.

Comments. This man developed rectal cancer 28 years after the onset of extensive ulcerative colitis and he died from the cancer shortly thereafter. With regard to his colitis, his clinical course had been chronic but intermittent, with long symptom-free intervals.

Risk of Carcinoma in Inflammatory Bowel Disease

The first report of colonic carcinoma in ulcerative colitis was by Crohn and Rosenberg in 1925. Until approximately 1960, however, there was controversy whether there was an increased risk of colon cancer in ulcerative colitis. Numerous studies since 1960 have confirmed this association and have allowed a quantitation of cumulative risk.

Many early studies of cancer in ulcerative colitis were marred by their design. I would like to give a hypothetical (but realistic) example of the

type of studies published in the 1950's and early 1960's relating cancer and ulcerative colitis. Let us assume that Dr. X is finishing his gastroenterology fellowship in City Y. While in city Y, Dr. X has worked closely with the eminent Dr. Z, a world-renown authority on ulcerative colitis. Now, the new medical school in State B is recruiting a gastroenterologist and is especially anxious to have one interested in ulcerative colitis and so Dr. X moves to B. He begins seeing colitis referrals from all over B and within 10 years has seen 300 cases. At this point, he decides to publish his experience and notes that 9 of his 300 cases of ulcerative colitis had developed cancer in the last 10 years and he reports an "incidence" of cancer of 3% (9/300). This might, on face value, indicate that cancer is quite uncommon in ulcerative colitis. Obviously, there are many problems with Dr. X's study.

First, his study population has no controls and is also not likely to be representative of all cases of ulcerative colitis in B. He probably attracted more complicated, bizarre, and wealthy patients than would be representative of the overall colitis population (referral bias). Second, his study did not take into account (a) that some of his 300 patients may have moved to another city or state for medical care (and may have developed cancer elsewhere); (b) that some of his patients had required proctocolectomy because of medically-unresponsive disease (removing these patients from cancer risk because their colon is out); (c) that patients had had variable durations of disease prior to seeing Dr. X; and (d) that a 10-year follow-up period is relatively short. The only way to prevent these shortcomings is to study a representative population using well-accepted criteria for the disease (preferably with a control group) and to apply actuarial (life-table) methods for calculating cancer risk. These methods take into account duration of disease, variable follow-up, end-points (death, cancer, colectomy, emigration) and are a powerful statistical tool. Such a study can be done retrospectively or prospectively (growing old with the patients). The former is easier, the latter is more desirable.

A classical controlled study of the natural history of ulcerative colitis was carried out by Nefzger and Acheson. They carefully traced 525 male patients with ulcerative colitis (UC) newly diagnosed in 1944 while in the U.S. Army and a control group of 517 men without colitis who were matched for age and Army rank. Patients were followed until 1960 for death or cancer development. During this 16 year period, twice as many patients with UC died compared to the control group ($P < 0.001$). Causes of death were as follows (Table 4):

TABLE 4. CAUSE OF DEATH IN U.S. ARMY STUDY (1944-1960)

	UC Group (N=525)		Control Group (N=517)	
Ulcerative Colitis	15		0	
Cancer	23		5	
Colon or Rectal Cancer		17		0
Other Cancer		6		5
Other Causes	18		21	
TOTAL DEATHS	56		26	

Thus, 17 of 525 (3.4%) patients died of cancer of the colon and rectum compared to none in the control group. The average age at which colon cancer developed was 36 years (range, 23-49 years). The number of years of symptomatic UC prior to developing cancer were: 6-10 years, 4 patients; 11-15 years, 7 patients; 16-20 years, 1 patient; and 21-25 years, 5 patients. Unfortunately, patients were not divided into colitis sub-types.

In the study by Nefzger and Acheson, one patient with colitis died of cancer of the bilary tree. More recent studies by Prior et al have confirmed that patients with ulcerative colitis have an increased risk of developing hepatobilary cancer (observed to expected ratio, ??:1), rectal cancer (11:1) and colon cancer (11:1), but they do not have an increased risk of developing other types of cancer. This study also found evidence that men with colitis get fewer than expected cases of lung cancer for unclear reasons.

As mentioned earlier, the actuarial method is the most powerful and relevant tool for determining cancer risk. The first application of this technique to cancer in ulcerative colitis was by Devroede and his associates. They studied 396 children (< 14 years of age) with ulcerative colitis who were referred to the Mayo Clinic. Obviously, this is an unrepresentative population sample because the Mayo Clinic is a tertiary referral center. Nevertheless, the study is quite interesting. Children were followed for up to 43 years. Patients were not included in the study if they had (a) a normal proctoscopy on initial examination; (b) skip areas on barium enema at any time during follow-up (suggesting Crohn's disease); (c) an abnormal terminal ileum on barium enema; or (d) other features compatible with granulomatous colitis. Two major endpoints - survival and the development of cancer - were recorded and several factors which might influence outcomes were analyzed (sex, age at onset of symptoms, and extent of disease at time of diagnosis). Results are summarized in Figure 5, with survival probability on the left and cancer probablility on the right.

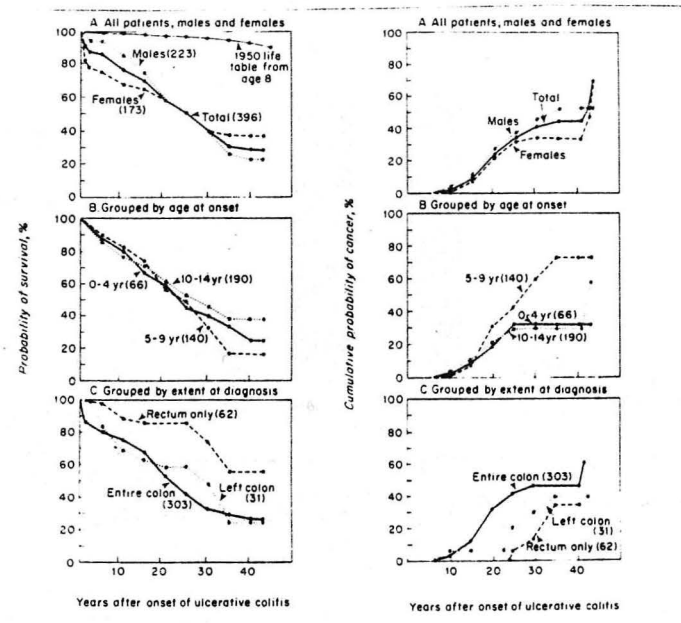


FIGURE 5. Probability of survival (left) and cancer (right) in children with ulcerative colitis. From Devroede et al., 1971.

As indicated on the left side of Figure 5 (panel A), survival of children with ulcerative colitis was significantly shortened compared to a control group (labelled "1950 life table from age 8"). Survival was not significantly affected by sex or age at onset of colitis (panel B) but survival was affected by extent of disease at time of diagnosis. Patients with involvement of the rectum only (ulcerative proctitis) had a better survival than those with more extensive disease (panel C). Note, however, that the group with ulcerative proctitis comprised only 16% (62/396) of the patients, whereas 77% (303/396) had pancolitis at the time of diagnosis.

The right side of figure 5 indicates that males and females had similar probabilities for developing cancer (A). Age at onset seemed to be a factor, children with onset of colitis between ages 5 and 9 having a greater risk of cancer than older and younger children (B). Not all studies have confirmed that age of onset is an independent risk factor for cancer apart from duration of disease. There was a marked difference in the cumulative probability of cancer when patients were grouped by extent of disease at diagnosis (C). Children with pancolitis (the majority) had a minimal risk of cancer up to 10 years of disease (3%), but thereafter this risk increased sharply (20% per decade or 2% per year) so that by 30 years (i.e. age 40 or so) approximately half of these patients had developed carcinoma. Patients with left-sided colitis and ulcerative proctitis had a lower risk of developing cancer and it tended to occur later. However, these patients were not immune to development of cancer. Only 49% of patients with cancer survived one year and 24% survived 5 years. The ages at which cancer developed are shown in Figure 6.

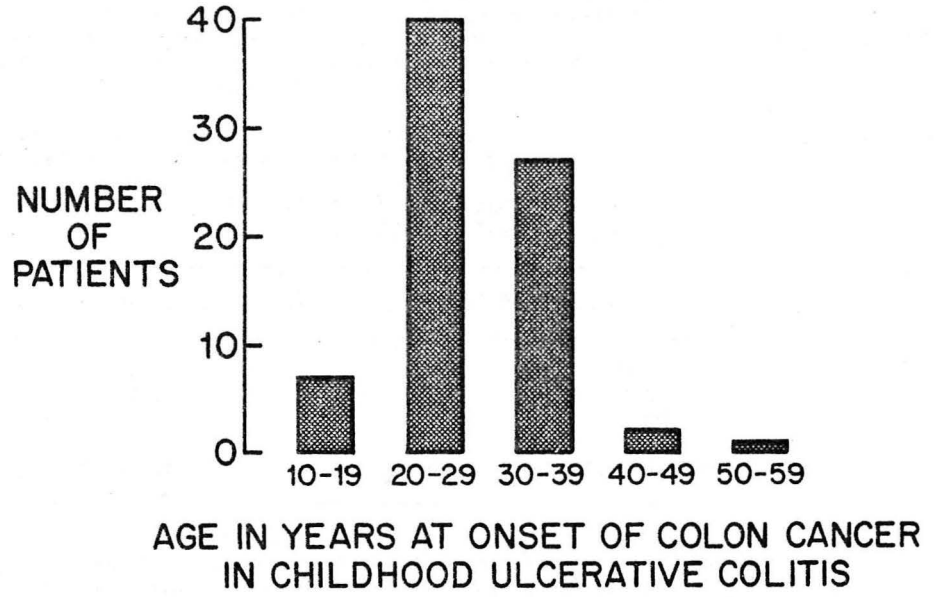


FIGURE 6. From G.J. Devroede et al., NEJM 285:17, 1971.

In contrast to the Mayo Clinic study by Devroede which followed only children with ulcerative colitis, a study by Greenstein et al from the Mt. Sinai School of Medicine evaluated cancer risk in children and adults with pancolitis or left-sided colitis as a function of duration of disease (Table 5).

TABLE 5. PERCENTAGE OF PATIENTS DEVELOPING CANCER AS A FUNCTION OF DURATION OF COLITIS

Duration of Colitis (yr)	Left-sided Colitis (N=109)	Pancolitis (N=158)
0-9	0	0.6
10-19	0	12.1
20-29	5.5	23.0
> 30	44.4	60.0

Patients with left-sided colitis were free of cancer for 20 years, but 4/9 patients followed for more than 30 years developed cancer (44.4%). Patients with pancolitis were virtually free of cancer with duration of colitis less than 10 years, after which cancer incidence increased at a rate of at least 10% per decade (1% per year). Six of 10 patients with pancolitis followed for more than 30 years developed cancer (60%).

Butt et al reviewed three European studies of patients with pancolitis and expressed data as percentage risk of cancer per year (Table 6).

TABLE 6. RISK OF COLONIC CANCER IN PANCOLITIS AS A FUNCTION OF DURATION OF DISEASE

Duration of Colitis (yrs)	Annual Percentage Risk of Cancer
<10	0.2%
10-19	1.4%
>20	2.8%

(from Butt JH, et al. Med. Clin. N. Amer. 64:1203-1220, 1980)

These figures are similar to those of Greenstein et al (Table 5). One study from the University of Minnesota by Dennis has suggested that, after 10 years of disease, the risk of cancer development is as high as 4.1% per year. Because most series are from referral centers, it is difficult to know the true cancer risk for the overall population. A Table indicating risk of cancer at any age as a function of age at onset of colitis is provided below (Table 7). This table applies to pancolitis and is only a guideline for calculating risk.

TABLE 7. CANCER RISK AT DIFFERENT AGES IN PANCOLITIS AS A FUNCTION OF AGE AT ONSET (from data of Devroede, Greenstein, and Butt)

	Percent Cumulative Cancer Risk by Age (yr)						
Age at Onset (yrs)	15	25	35	45	55	65	75
5	2	20	40	60	80	100	100
10	0	12	32	52	72	92	100
15	-	2	20	40	60	80	100
20	-	0	12	32	52	72	92
25	-	-	<1	10	20	40	60
30	-	-	-	6	16	36	46
35	-	-	-	<1	10	20	40
40	-	-	-	-	6	16	36
45	-	-	-	-	<1	10	20
50	-	-	-	-	-	6	16
55	-	-	-	-	-	<1	10
60	-	-	-	-	-	-	6
65	-	-	-	-	-	-	<1

Some studies, such as the one by MacDougall, have not found an increased risk of cancer in left-sided colitis or ulcerative proctitis, although the follow-up period of 1-16 years may have been too short (cancers in this setting often appear much later). Cancer-free survival with left-sided colitis and universal colitis (pancolitis) in Greenstein's study are shown in Figure 7.

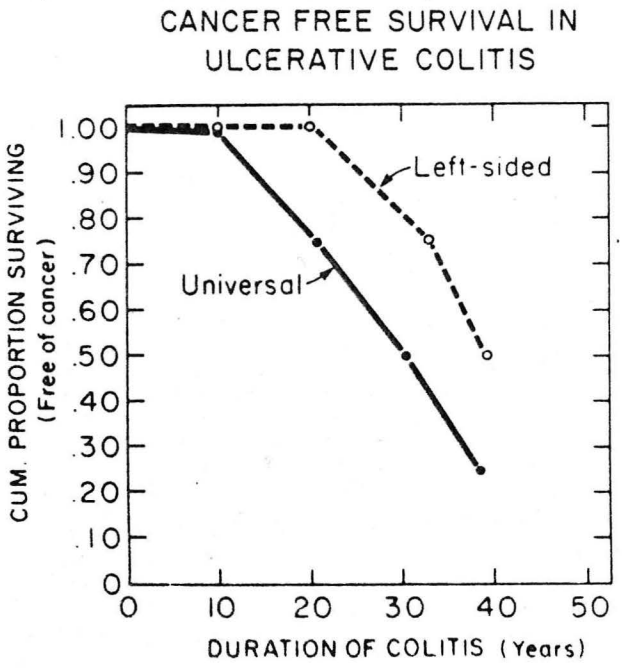


FIGURE 7. From Greenstein, et al., 1979.

Recently, Greenstein et al calculated relative risk ratios (observed divided by expected) for cancer in inflammatory bowel disease. The results are shown in Table 8.

TABLE 8.

Inflammatory Bowel Disease	Cancer Type	Relative Risk
ULCERATIVE COLITIS		
Pancolitis	Colon	26.5 to 1
Left-Sided Colitis	Colon	8.6 to 1
CROHN'S DISEASE		
Colitis or Ileocolitis	Colon	6.9 to 1
Ileitis or Ileocolitis	Small Bowel	85.8 to 1
Ileitis without Colitis	Small Bowel	114.5 to 1

Extra-intestinal cancers occurred with an expected frequency in patients with inflammatory bowel disease. Note that patients with Crohn's colitis or ileocolitis also appear to have an increased risk of colon carcinoma and that patients with Crohn's disease involving the ileum have approximately a 100-fold greater risk of developing small bowel carcinoma than the general population. However, because small bowel carcinoma is so rare, even with a 100-fold increased risk very few patients with Crohn's disease develop small bowel carcinoma.

As already stated, the two major factors which determine cancer risk in ulcerative colitis are duration of disease and extent of disease. It is important to recognize that it is sometimes difficult for a patient to date when the disease began. It is easier for them to remember when it was diagnosed or when they were first hospitalized. When calculating cancer risk, most investigators use the date of onset of symptoms rather than the date of diagnosis. Also, extent of disease may change during the course of the illness. For example, Watts et al in Leeds, England found that disease which initally involved only the rectum often (20% of the time) spread to the more proximal colon during relapses, whereas the reverse (pancolitis on first attack, less extensive colitis on subsequent attacks was uncommon (3%). Although ulcerative proctitis may spread to a more extensive colitis somewhat less often in the U.S.A. (5-10%), this point should be remembered and risk should probably be calculated based upon extent of disease at any time during the patient's course.

Other than duration and extent of disease, other factors have been looked at as possible modulators of cancer risk. As already stated, some studies do not find age at onset an independent risk factor whereas others do. Children tend to have more extensive disease when they initially present and they are also followed longer. For these reasons the cumulative risk is greater in children.

Clinical severity of disease does not appear to be a strong risk factor.[+] In fact, patients with especially severe clinical manifestations are more likely to undergo early in their course an emergency or elective proctocolectomy than are patients with relatively quiescent disease, thus removing the former patients from cancer risk. Many patients who develop cancer have been having minimal problems with their colitis. One study by Edwards and Truelove suggests that the risk of cancer is greater if the initial attack of colitis was severe.

The different types of clinical patterns of ulcerative colitis have been studied with regard to risk of cancer. These patterns are summarized in Figure 8.

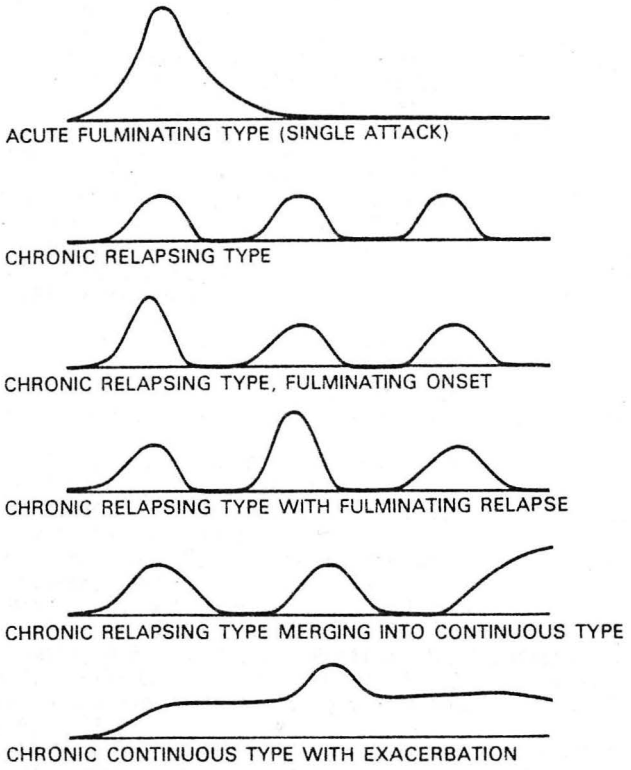


FIGURE 8. Clinical Patterns in Ulcerative Colitis. (Modified from Bockus Textbook of Gastroenterology.)

([+] The fact that disease severity is not closely related to cancer risk suggests that estimates of cancer risk based upon patients referred to University Hospitals (sicker patients) may be reasonable estimates for risk in patients with milder disease who are therefore not referred).

Edwards and Truelove found that the patients with the chronic continuous form of the disease had a higher risk of cancer than those with the chronic relapsing types. It is unknown to what extent medical therapy (sulfasalazine, prednisone) of ulcerative colitis affects cancer risk in these patients, nor is it known whether repeated exposure to ionising radiation (barium enemas) used to follow these patients plays any role in cancer development.

References

Bargen, J.A., Sauer, W.G., Sloan, W.P., and Gage, R.P. The development of cancer in chronic ulcerative colitis. Gastroenterology 26:32-37, 1954.

Brooke, B.N., and Chir, M. Malignant change in ulcerative colitis. Dis. Col. Rect. 4:393-398, 1961.

Butt, J.H., Lennard-Jones, J.E., and Ritchie, J.K. A practical approach to the risk of cancer in inflammatory bowel disease. Reassure, watch or act? Med. Clinics of North America 64:1203-1220, 1980.

Crohn, B.B., and Rosenberg, H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). Am. J. Med. Sci. 170:220-228, 1925.

Counsell, P.B., and Dukes, C.E. The association of chronic ulcerative colitis and carcinoma of the rectum and colon. Brit. J. Surg. 39:485-495, 1952.

Dennis, C., and Karlson, K.E. Cancer risk in ulcerative colitis: Formidability per patient-year of late disease. Surgery 50:568-571, 1961.

Devroede, G.J., Taylor, W.F., Sauer, W.G., Jackman, R.J., and Stickler, G.B. Cancer risk and life expectancy of children with ulcerative colitis. N. Engl. J. Med. 285:17-21, 1971.

Devroede, G.J., Dockerty, M.B., Sauer, W.G., Jackman, R.J., and Stickler, G.B. Cancer of the colon in patients with ulcerative colitis since childhood. Canadian J. Surg. 15:369-374, 1972.

Devroede, G.J., and Taylor, W.F. On calculating cancer risk and survival of ulcerative colitis patients with the life table method. Gastroenterology 71:505-509, 1976.

Diaz, R.J., Farmer, R.G., and Brown, C.H. Carcinoma of the colon and ulcerative colitis. Am.J. Dig. Dis. 10:643-656, 1965.

Edling, N.P.G., and Eklof, O. Distribution of malignancy in ulcerative colitis. Gastroenterology 41:465-466, 1961.

Edwards, F.C., and Truelove, S.C. The course and prognosis of ulcerative colitis. Gut 5:1-22, 1964.

Fielding, J.F., Prior, P., Waterhouse, J.A., and Cooke, W.T. Malignancy in Crohn's disease. Scand. J. Gastro. 7:3-7, 1972.

Greenstein, A.J., Smith, D.B., Smith, H., Pucillo, A., Papatestas, A.E., Kreel, I., Geller, S.A., Janowitz, H.D., and Aufses, A.H., Jr. Cancer in universal and left-sided ulcerative colitis: Factors determining risk. Gastroenterology 77:290-294, 1979.

Greenstein, A.J., Sachar, D.B., Smith, H., Janowitz, H.D., and Aufses, A.H., Jr. A comparison of cancer risk in Crohn's disease and ulcerative colitis. Cancer 48:2742-2745, 1981.

Goldgraber, M.B., Humphreys, E.M., Kirsner, J.B., and Palmer, W.L. Carcinoma and ulcerative colitis, a clinical-pathologic study. II. Statistical analysis. Gastroenterology 34:840-846, 1958.

Goldgraber, M.B., and Kirsner, J.B. Carcinoma of the colon in ulcerative colitis. Cancer 17:657-665, 1964.

Hinton, J.M. Risk of malignant change in ulcerative colitis. Gut 7:427-432, 1966.

Hughes, R.G., Hall, T.J., Block, G.E., Levin, B., and Moossa, A.R. The prognosis of carcinoma of the colon and rectum complicating ulcerative colitis. Surg. Gyn. Obst. 146:46-48, 1978.

Jones, J.H. Colonic cancer and Crohn's disease. Gut 10:651-654, 1969.

Kewenter, J., Ahlman, H., and Hulten, L. Cancer risk in extensive ulcerative colitis. Ann. Surg. 188:824-828, 1978.

Lennard-Jones, J.E., Misiewicz, J.J., Parrish, J.A., Ritchie, J.K., Swarbrick, E.T., and Williams, C.B. Prospective study of outpatients with extensive colitis. Lancet 1:1065-1067, 1974.

Lightdale, C.J., Sternberg, S.S., Posner, G., and Sherlock, P. Carcinoma complicating Crohn's disease. Report of seven cases and review of the literature. Am. J. Med. 59:262-268, 1975.

MacDougall, I.P.M. The cancer risk in ulcerative colitis. Lancet 2:655-658, 1964.

Michener, W.M., Gage, R.P., Sauer, W.G., and Stickler, G.B. The prognosis of chronic ulcerative colitis in children. N. Engl. J. Med. 265:1075-1979, 1961.

Nefzger, M.D., and Acheson, E.D. Ulcerative colitis in the United States Army in 1944. Gut 4:183-192, 1963.

Prior, P., Gyde, S.N., Macartney, J.C., Thompson, H., Waterhouse, J.A.H., and Allan, R.N. Cancer morbidity in ulcerative colitis. Gut 23:490-497, 1982.

Rosenqvist, H., Ohrling, H., Lagercrantz, R., and Edling, N. Ulcerative colitis and carcinoma coli. Lancet 1:906-908, 1959.

Sackett, D.L., and Whelan, G. Cancer risk in ulcerative colitis: Scientific requirements for the study of prognosis. Gastroenterology 78:1632-1635, 1980.

Sachar, D.B., and Greenstein, A.J. Cancer in ulcerative colitis: Good news and bad news. Ann. Int. Med. 95:642-644, 1981.

Stahl, D., Tyler, G., and Fischer, J.E. Inflammatory bowel disease - Relationship to carcinoma. In: Current Problems in Cancer, Volume 5, Hickey, R.C., and Clark, R.L. (eds.), Year Book Medical Publishers, Chicago, 1981, pp. 5-72.

Weedon, D.D., Shorter, R.G., Ilstrup, D.M., Huizenga, K.A., and Taylor, W.F. Crohn's disease and cancer. N. Engl. J. Med. 289:1099-1103, 1973.

Welch, C.E., and Hedberg, S.E., Colonic cancer in ulcerative colitis and idiopathic colonic cancer. JAMA 191:815-818, 1965.

Possible Carcinogenic Mechanisms in Ulcerative Colitis

Increased Epithelial Turnover. Under normal conditions there are three zones in the colonic crypts: a deep proliferative cell zone, a transitional cell zone in which cells differentiate and cease proliferating, and a superficial mature cell zone near the luminal surface. The normal turnover time from base to surface is approximately 90 hr (3.8 days). Using a ^{3}H-thymidine double-labeling technique followed by autoradiography, the turnover time in patients with active ulcerative colitis was found to be reduced to 34 hr ($P < 0.01$) and there was an expansion of the proliferative zone toward the upper part of the crypts.

A recent study by Serafini et al at St. Mark's Hospital showed that ulcerative colitis patients in clinical and histological remission had an abnormal proliferative pattern similar to that described for patients with active colitis. Histological remission was defined as no crypt abscesses, no intraepithelial neutrophils, no increase in neutrophils in the lamina propria, a well-developed goblet cell population and no evidence of dysplasia or epithelial regeneration. Their results are summaried in Table 9.

TABLE 9. PATTERN OF EPITHELIAL CELL PROLIFERATION (from Serafini et al)

	^{3}H-Thymidine Labelled Cells per Crypt		Ratio
	Lower 2/3	Upper 1/3	Lower / Upper
Control (N=7)	6.6	1.5	4.2
Colitis in Remission (N=18)	3.8	3.2	1.2
Active Colitis (N=8)	4.5	3.0	1.5

Even patients in remission with a short history of colitis had an abnormal proliferative pattern. Similar abnormal patterns of epithelial cell proliferation in the colon have been described in colonic polyposis, during colonic mucosal regeneration following radiotherapy, and during treatment of mice with the carcinogen dimethylhydrazine. The authors concluded that this abnormal proliferative pattern predisposes to neoplastic development (perhaps in the presence of a luminal carcinogen) but is not a sign per se of neoplasia.

Abnormal Biochemical Regulation of DNA Synthesis. The abnormal pattern of ^{3}H-thymidine uptake just described suggests that factors which regulate DNA synthesis may be altered in ulcerative colitis. To study this, Alpers et al have organ cultured mucosal explants from ulcerative colitis patients who were in clinical remission and from non-colitis controls. They found that, under normal circumstances, phosphodiesterase inhibitors such as theophylline or papaverine inhibited the uptake of ^{3}H-thymidine by colonic mucosa. This inhibition is presumably mediated by cyclic AMP generation. For example, 5 mM theophylline reduced thymidine incorporation by the normal colonic mucosa to 72% of the control incorporation rate. The effect of 5 mM theophylline on thymidine incorporation in mucosa from ulcerative colitis patients (left-sided and pancolitis) is shown in Table 10 as a function of disease duration. Similar results were obtained using papaverine.

TABLE 10. EFFECT OF 5 mM THEOPHYLLINE ON ^{3}H-THYMIDINE INCORPORATION OF MUCOSAL EXPLANTS

GROUP	NUMBER	INCORPORATION AT 20 HR (% CONTROL)
1. Normal	18	72 ± 4
2. Left colitis of short duration (< 10 yrs)	5	70 ± 4
3. Pancolitis of short duration (< 10 yrs)	8	69 ± 3
4. Left colitis of long duration (> 10 yrs)	5	97 ± 3
5. Pancolitis of long duration (> 10 yrs)	8	95 ± 5

In patients with a short disease duration (groups 2 and 3), DNA synthesis was inhibited normally by theophylline. On the other hand, none of the patients with disease of long (> 10 yrs) duration suppressed DNA synthesis with theophylline or papaverine (groups 4 and 5). Three patients with ulcerative colitis of long duration and precancer histologically were also studied. None showed suppression of DNA synthesis (thymidine uptake) with phosphodiesterase inhibitors. Thus, independent studies have shown that DNA synthesis is regulated in an abnormal fashion in ulcerative colitis patients in remission. The relationship between these abnormalities in DNA synthesis and malignant degeneration is uncertain.

Chronic Inflammation. The increased risk of colonic cancer in ulcerative colitis (and Crohn's) is not unique to these disorders. For example, colonic schistosomiasis (a disease very prevalent in China) is associated with a markedly increased risk of carcinoma. Ulcers occur in this disease as a result of ova deposition in the colonic mucosa. Several features of colon cancer in schistosomiasis (association with pancolitis of greater than 10 years duration, multicentricity, early age at onset of cancer) resemble those of ulcerative colitis. Because hematochezia is uncommon in ordinary schistosomiasis, this symptom should alert the physician to the presence of colon cancer in schistosomiasis.

It has also been suggested by Camacho that chronic amebiasis involving the cecum (amebic granuloma or ameboma) predisposes to carcinoma of the cecum. Thus, it is possible that chronic, indolent infection or inflammation in the colon, regardless of etiology, predisposes to malignancy.

Role of Bile Acids and Cholesterol Metabolites. It has been suggested that colonic bacteria are capable of producing carcinogens from dietary animal fats including cholesterol or from bile acids.

Accordingly, fecal concentrations of cholesterol and microbial metabolites of cholesterol (coprostanol, cholestane - 3β, 5α, 6β-triol) and of bile acids have been measured and found to abnormal in ordinary colon cancer patients and in patients with familial polyposis coli, most of whom develop cancer (see Reddy, 1976).

More recently, Reddy et al have reported quantitation of fecal excretion of cholesterol (and its metabolites) and bile acids in Caucasian patients with ulcerative colitis as well as in healthy relatives of these patients, in patients with other digestive diseases (Crohn's, irritable colon, diverticular disease, rectal ulcer), and in healthy controls. They found normal bile acid excretion but increased excretion of cholesterol and its metabolites in colitis patients (only values for cholesterol and the bacterial metabolite, coprostanol, are shown in Table 11).

TABLE 11. FECAL EXCRETION OF CHOLESTEROL AND ITS METABOLITE COPROSTANOL (mg/g DRY FECES)

	CHOLESTEROL	COPROSTANOL
UC (N=15)	12.5*	26.6*
Relatives (N=15)	2.9	13.8
Other GI Diseases (N=15)	3.3	11.9
Healthy Controls (N=40)	3.2	12.9

(from Reddy, B.S., et al.)

Both cholesterol and coprostanol, neutral sterols of animal origin, were significantly (*) elevated in patients with ulcerative colitis (UC) compared to all other groups. Another metabolite of cholesterol, cholestane - 3β, 5α, 6β-triol, was also increased in UC. Also, the ratio of cholesterol to its metabolites was higher in UC than in the other groups, a finding also seen in familial polyposis coli. Levels of β-sitosterol and campesterol (plant-derived sterols) were normal in UC patients. The authors have speculated that there may be interactions between bacterial metabolites of cholesterol and colonic epithelial cells which result in carcinoma. They have suggested that an epoxide of cholesterol, a precursor of cholestane - 3β, 5α, 6β-triol -may be the carcinogen. Additional work in this exciting area is needed.

References

Alpers, D.H., Philpott, G., Grimme, N.L., and Margolis, D.M. Control of thymidine incorporation in mucosal explants from patients with chronic ulcerative colitis. Gastroenterology 78:470-478, 1980.

Bleiberg, H., Mainguet, P., Galand, P., Chretien, J., and Dupont-Mairesse, N. Cell renewal in the human rectum. In vitro autoradiographic study on active ulcerative colitis. Gastroenterology 58:851-855, 1970.

Camacho, E. Amebic granuloma and its relationship to cancer of the cecum. Dis. Col. Rect. 14:12-16, 1971.

Ming-Chai, C., Chi-Yaun, C., Pei-Yu, C., Jen-Chun, H. Evolution of colorectal cancer in schistosomiasis. Cancer 46:1661-1675, 1980.

Eastwood, G.L., and Trier, J.S. Epithelial cell renewal in cultured rectal biopsies in ulcerative colitis. Gastroenterology 64:383-390, 1973.

Reddy, B.S., Mastromarino, A., Gustafson, C., Lipkin, M., and Wynder, E.L. Fecal bile acids and neutral sterols in patients with familial polyposis. Cancer 38:1694-1698, 1976.

Reddy, B.S., Martin, C.W., and Wynder, E.L. Fecal bile acids and cholesterol metabolites of patients with ulcerative colitis, a high-risk group for development of colon cancer. Cancer Research 37:1697-1701, 1977.

Serafini, E.P., Kirk, A.P., and Chambers, T.J. Rate and pattern of epithelial cell proliferation in ulcerative colitis. Gut 22:648-652, 1981.

Clinical Features of Carcinoma in Ulcerative Colitis

Signs and Symptoms. Unfortunately, as demonstrated in Case Report 1, the symptoms of colonic carcinoma closely resemble those of ulcerative colitis. Thus, diagnosis is often delayed considerably. Symptoms of ulcerative colitis patients admitted to the hospital with or without cancer are shown in Table 12.

TABLE 12.

	With Cancer (N=30)	Without Cancer (N=237)
Diarrhea	100%	96%
Bleeding	100%	95%
Abdominal Pain	67%	78%
Toxemia	43%	56%
Intestinal Obstruction	43%	7%
Abdominal Mass	30%	3%
Abdominal Tenderness	30%	41%

(from Greenstein AJ, et al.)

Only intestinal obstruction and abdominal mass occurred significantly more often in those with cancer than in those without cancer.

Age at Onset of Cancer. The average age of onset of colon cancer in colitis is 35 to 40 years whereas in idiopathic colon cancer the average age of onset in approximately 60 years.

Location and Number of Cancers. Cancers of the colon in the non-colitis population are most common in the rectum and sigmoid colon. On the other hand, numerous studies have shown that patients with ulcerative colitis who develop colonic cancer have a more even distribution of carcinomas throughout the colon. In one study, the distribution of colon cancer in age-matched patients with and without ulcerative colitis in Sweden were compared by Hulten et al. (Figure 9). In idiopathic colon carcinoma (open circles) the majority of cancers were in the rectosigmoid (14 of 22), with lesser numbers in the right colon (6 of 22) and transverse colon (2/22). The distribution was more uniform in ulcerative colitis-associated carcinoma (closed circles).

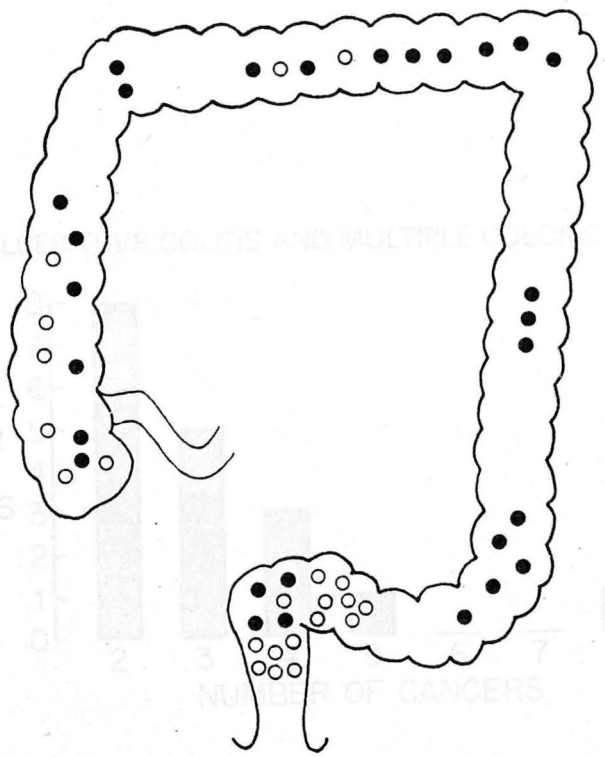


FIGURE 9. Distribution of colon cancer in age-matched patients with idiopathic colon cancer (O) and patients with colitis-associated colon cancer (●). Distribution of cancers is more uniform in colitis-associated cancers. From Hulten, et al.

One implication of this study is that the proctoscope will fail to reach the site of cancer in the majority of ulcerative colitis patients.

Cancers may be multiple in location at the time of presentation. Although in ordinary colon carcinoma, approximately 2.5% of patients will have more than one cancer (synchronous lesions), this figure is much higher in ulcerative colitis. Riddell and Morson found that 18 of 73 colitis patients with cancer had multiple cancers (25%). The numbers of separate cancers in these 18 patients are shown in Figure 10. Bargen also found multiple cancers in 43 of 178 patients with colon cancer and colitis (24%). Cases have been described in which the entire colon contained carcinoma. The relationship between cancer and colonic precancer ("dysplasia") will be discussed subsequently.

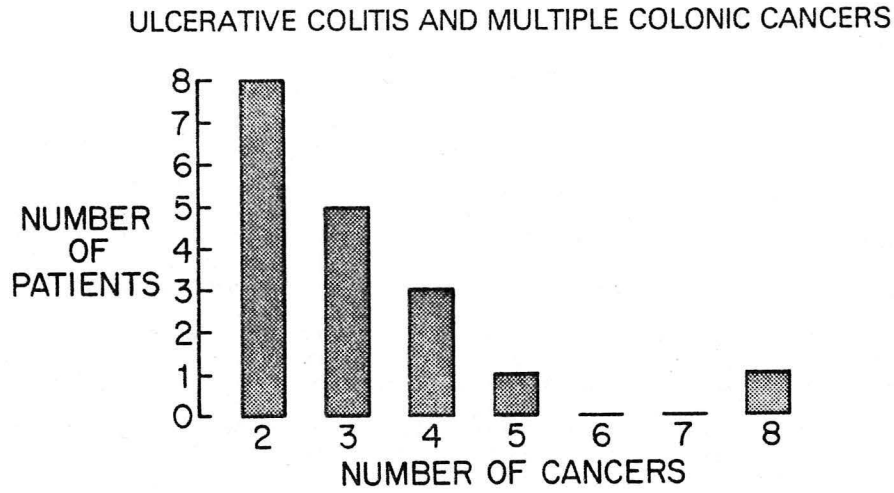


FIGURE 10. From Riddell and Morson.

Clinical Pathology of Cancers. Although the majority of cancers which occur in the colon of patients with ulcerative colitis are ordinary adenocarcinomas, other types of cancer have also been reported. These include the mucinous variety of adenocarcinoma (Case Report 1), lymphoma (of the non-Hodgkins and Hodgkins type), squamous cell carcinoma, and mixed adenosquamous carcinoma (adenoacanthoma). A patient with squamous cell carcinoma in the sigmoid colon complicating long-standing ulcerative colitis will be discussed subsequently (Case Report 2). Carcinomas in ulcerative colitis are often flat and diffusely infiltrative without sharp edges (making them difficult to see on x-ray or endoscopy), in contrast to the usual annular or polypoid colonic cancer in patients without colitis. In some cases, cancers in colitis cannot be seen grossly by the surgical pathologist and only microscopic sections reveal the cancer.

In general, perhaps because carcinomas in ulcerative colitis are more difficult to recognize clinically, radiologically, and endoscopically, they tend to present at a more advanced Dukes' stage and at a more undifferentiated histologic grade than ordinary colonic cancers. This may account for the poor survival of these patients, but other factors may also be involved (see below). Recent studies which have screened patients at risk periodically using biopsies of the rectum and colon to look for precancerous changes (dysplasia) or early carcinomas may be detecting cancers at an earlier stage.

There is no relationship between inflammatory pseudopolyps and cancer. In one study by Bargen, 114 of 178 patients with colitis and colon cancer had no pseudopolyps. The relation between adenomatous polyps and colon cancer in colitis will be discussed subsequently.

Survival. Most studies have compared the survival of patients with colon cancer and ulcerative colitis to the survival of patients with ordinary colon cancer. Some of these studies have found that colitis-cancer patients had a shorter survival than non-colitis cancer patients and other studies have found similar 5-year survivals in the two groups. However, even if the survival rates are approximately the same, this is especially alarming in ulcerative colitis because the average age at cancer diagnosis is so young.

Because colitis-cancer patients and ordinary cancer patients are so different in age, it is important to evaluate age as a factor which could affect survival in colon cancer. To do this, Hulten and his associates compared survival from colon cancer in 25 patients (15 male, 10 female) with colitis and cancer (mean age 29 years; range, 19-39 years) and in 22 young patients (15 male, 7 female) with ordinary colon cancer (mean age 29.5 years; range 10-40 years). The five-year survival rates were low in both groups: 3/25 (12%) in colitis-associated cancer and 5/22 (23%) in ordinary cancer, an insignificant difference. Thus, colon cancer in younger people may have an especially virulent course, since the 5-year survival in most series of older patients is approximately 50%.

References

Bargen, J.A., and Gage, R.P. Carcinoma and ulcerative colitis: Prognosis. Gastroenterology 39:385-393, 1960.

Cornes, J.S., Smith, J.C., and Southwood, W.F.W. Lymphosarcoma in chronic ulcerative colitis with report of two cases. Brit. J. Surg. 49:50-53, 1961.
Friedman, H.B., Silver, G.M., and Brown, C.H. Lymphoma of the colon simulating ulcerative colitis. Am. J. Dig. Dis. 13:910-917, 1968.
Greenstein, A.J., Sachar, D.B., Pucillo, A., Vassiliades, G., Smith, H., Kreel, I., Geller, S.A., Janowitz, H.D., and Aufses, A.H., Jr. Cancer in universal and left-sided ulcerative colitis: Clinical and pathologic features. Mt. Sinai J. Med. 46:25-32, 1979.
Hulten, L., Kewenter, J., Ahren, C., and Ojerskog, B. Clinical and morphological characteristics of colitis carcinoma and colorectal carcinoma in young people. Scand. J. Gastroent. 14:673-678, 1979.
Patterson, F.K. Adenoacanthoma and ulcerative colitis: Case report and review of the literature. Southern Med. J. 66:681-684, 1973.
Riddell, R.H., and Morson, B.C. Value of sigmoidoscopy and biopsy in detection of carcinoma and premalignant change in ulcerative colitis. Gut 20:575-580, 1979.
Ritchie, J.K., Hawley, P.R., and Lennard-Jones, J.E. Prognosis of carcinoma in ulcerative colitis. Gut 22:752-755, 1981.
Wagonfeld, J.B., Platz, C.E., Fishman, F.L., Sibley, R.K., and Kirsner, J.B. Multicentric colonic lymphoma complicating ulcerative colitis. Dig. Dis. 22:502-503, 1977.

DIAGNOSIS OF COLONIC CANCER AND PRECANCER IN ULCERATIVE COLITIS

It would be ideal to diagnosis the presence of carcinoma in a colitis patient on the exact day that cancer developed. The approach to such a hypothetical patient would be to immediately perform a proctocolectomy. This operation would remove the cancer and any other synchronous cancers and would prevent additional cancers from developing. Because diagnostic techniques have not yet reached this level of perfection, we must either diagnosis cancer some time after it has developed or attempt to diagnosis cancer before it will develop, perhaps at a precancer stage. Intuitively, these approaches have certain disadvantages. Diagnosis of cancer too long after it develops may be too late. On the other hand, a diagnosis of "precancer" may lead to proctocolectomy and ileostomy in patients who never will develop cancer, unless precancer always becomes cancer. We will discuss diagnosis of established cancer and diagnosis of precancer in ulcerative colitis separately.

Diagnosis of Cancer

Radiology (Barium Enema). Diagnosis of carcinoma of the colon by barium enema is more difficult than in patients without colitis. At the Mayo Clinic, only 29 of 49 patients thought to have carcinoma radiologically actually had carcinoma (20 of 49 false positives). On the other hand, in patients with the scirrhous, infiltrating, linitis - plastica type of cancer, the diagnosis may not be suspected radiologically (false negatives). Besides scirrhous carcinomas, other types of cancers described radiologically in colitis patients are constricting, annular, sessile, and polypoid. The constricting type, which can be several inches long, is the commonest.

In one study of 30 colonic cancers (occurring in 23 patients with ulcerative colitis studied at the University of Chicago), a lesion was identified radiologically in 21 instances (70%), but the lesion was felt by the radiologist to be carcinoma in only 12 of 30 (40%). It was especially common for the radiologist to miss a cancer in the rectum or sigmoid colon.

Part of the problem related to radiological interpretation of cancer in colitis revolves around controversy over strictures. Some investigators believe that benign strictures occur not uncommonly in patients with ulcerative colitis, especially early in the course and following a severe attack. There is controversy whether benign strictures are due to mural fibrosis or to smooth muscular spasm without fibrosis. Other workers believe that benign stricture formation in ulcerative colitis is very unusual and that such a stricture should suggest either carcinoma or Crohn's (granulomatous) colitis.

Proctoscopy. Because the majority of colonic cancers in ulcerative colitis are beyond the reach of the proctoscope, proctoscopy is an inefficient way of detecting cancer. The only exception to this statement is the patient who has already undergone subtotal colectomy and ileoproctostomy, an operation still commonly performed for ulcerative colitis in some countries. In this situation, it is reasonable to follow patients for the development of rectal cancer by proctoscopy. In one study by MacDougall, 237 such patients were followed for 1-16 years after colectomy and ileoproctostomy using proctoscopy and 5 developed rectal cancer (observed to expected ratio, 67:1), indicating that these patients are at increased risk.

Colonoscopy. It is possible to examine the entire colon with the colonoscope. There is surprisingly little literature on the role of colonoscopy in diagnosis of cancer in ulcerative colitis. The endoscopist is faced with the same problem as the radiologist. The colon is often diffusely abnormal. In addition, 10-20% of patients with ulcerative colitis have inflammatory pseudopolyps, especially in the transverse and descending colon. Moreover, cancers in colitis do not always look like ordinary cancers in the colon - they may be flat and scirrhous and blend in with the inflammed mucosa rather than appear as a polypoid or ulcerated mass adjacent to normal mucosa. Cancers in colitis can be easily missed by colonoscopy. Thus, the usefulness of colonoscopy and proctoscopy may be mainly to obtain histological specimens for the diagnosis of pre-cancer (see below).

Colonic Lavage for Cytology. There is very little experience with this technique so that the number of false positive and false negative cytologies cannot be stated. An expert cytopathologist is needed (see Katz et al).

Carcinoembryonic Antigen (CEA). Patients with colonic cancer often have elevated levels of CEA in their serum. Thus, the use of CEA to diagnosis cancer in ulcerative colitis, possibly at an early stage, has been evaluated. Unfortunately, up to 30% of patients with inflammatory bowel disease (ulcerative colitis or Crohn's disease) but without cancer have elevated CEA levels (> 2.5 ng/ml). CEA is especially likely to be elevated during active disease and may return to normal during remission. One report suggested that a preliminary extraction of serum with perchloric acid prior to CEA assay eliminated false posi-

tive CEA elevations but did not lead to false negatives. However, only 2 patients with colitis and cancer were included in this report. In one report, colonic tissue was reported to stain positively for CEA in patients with colon carcinoma or precancer (dysplasia) but not in patients with reactive colonic dysplasia secondary to inflammation (reactive hyperplasia).

References

Crowson, T.D., Ferrante, W.F., and Gathright, J.B., Jr. Colonoscopy: Inefficacy for early carcinoma detection in patients with ulcerative colitis. JAMA 236;2651-2652, 1976.

de Dombal, F.T., Watts, J.M., Watkinson, G., and Goligher, J.C. Local complications of ulcerative colitis: Stricture, pseudopolyposis, and carcinoma of colon and rectum. Brit. Med. J. 1:1442-1447, 1966.

Fennessy, J.J., Sparberg, M.B., and Kirsner, J.B. Radiological findings in carcinoma of the colon complicating chronic ulcerative colitis. Gut 9: 388-397, 1968.

Goulston, S.J.M., and McGovern, V.J. The nature of benign strictures in ulcerative colitis. N. Engl. J. Med. 281:290-295, 1969.

Granqvist, S., Granberg-Ohman, I., and Sundelin, P. Colonoscopic biopsies and cytological examination in chronic ulcerative colitis. Scand. J. Gastroent. 15:283-288, 1980.

Granqvist, S., Gabrielsson, N., Sundelin, P., and Thorgeirsson, T. Precancerous lesions in the mucosa in ulcerative colitis.

Hodgson, J.R., and Sauer, W.G. The roentgenologic features of carcinoma in chronic ulcerative colitis. Am. J. Roentgenol. 86:91-96, 1961.

Isaacson, P. Tissue demonstration of carcinoembryonic antigen (CEA) in ulcerative colitis. Gut 17:561-567, 1976.

Katz, S., Katzka, I., Platt, N., Hajdu, E.O., and Bassett, E. Cancer in chronic ulcerative colitis. Diagnostic role of segmental colonic lavage. Dig. Dis. 22:355-364, 1977.

Khoo, S.K., Hunt, P.S., and Mackay, I.R. Studies of carcinoembryonic antigen activity of whole and extracted serum in ulcerative colitis. Gut 14:545-548, 1973.

Rule, A.H., Straus, E., Vandevoorde, J., and Janowitz, H.D. Tumor-associated (CEA-reacting) antigen in patients with inflammatory bowel disease. N. Engl. J. Med. 287:24-26, 1972.

Shearman, D.J.C. Colonoscopy in ulcerative colitis. Scand. J. Gastroent. 8: 289-291, 1973.

Turner, M.D., Kleinman, M.S., and Thayer, W. Serum carcinoembryonic antigen (CEA) in patients with chronic inflammatory bowel disease. Digestion 9: 116-123, 1973.

Diagnosis of Precancer (Dysplasia)

Because it is so difficult to diagnosis cancer at an early stage in ulcerative colitis, attention has been turned to the possibility of detecting a group of patients with colonic precancer i.e. patients who have a high probability of developing cancer and who therefore, once identified, might be candidates for elective proctocolectomy as either prophylaxis for cancer or treatment of small, early, clinically-unrecognized cancers. Ideally, a group of patients who are high risk (extensive disease of long duration) would be screened periodically for pre-cancerous changes in the colon which, if present, would select them for colonic extirpation. The following modalities for precancer detection have been employed: rectal biopsy, colonoscopy with blind and directed colonic biopsy, double-contrast radiology, and lactic dehydrogenase (LDH) isoenzyme analysis of colonic tissue. Each will be reviewed.

Rectal Biopsy. In 1967, Morson and Pang, working in St. Mark's Hospital of London, published an extremely important and controversial study of the precancer-cancer relationship in ulcerative colitis. They defined precancer (dysplasia) based upon histologic appearances of rectal mucosa as follows: (a) goblet cells and mucus secretion are reduced; (b) nuclei of the epithelial cells, rather than being lined up in parallel (polarity) at the base of the cell, lose polarity and become stratified; (c) nuclei are also enlarged, hyperchromatic, variable in size, and have prominent nucleoli and course chromatin; (d) glands (crypts) lose their parallelism and begin to branch, bud laterally, invaginate into the submucosa, or grow vertically (toward the lumen) in a villous pattern. The amount of inflammation in the lamina propria is highly variable and it may be absent. It is important to emphasize that severe inflammation can lead to reactive epithelial changes very similar to those described as precancer (dysplasia). Thus, the diagnosis of precancer or dysplasia should be made with caution or not at all in area with marked inflammation (especially acute inflammation). Morson and Pang found two types of precancerous mucosa: a flat mucosa (more common) and a sessile-polypoid mucosal surface visible to the naked eye (less common).

Some workers prefer to grade precancer as borderline, mild, moderate and severe (Figure 11).

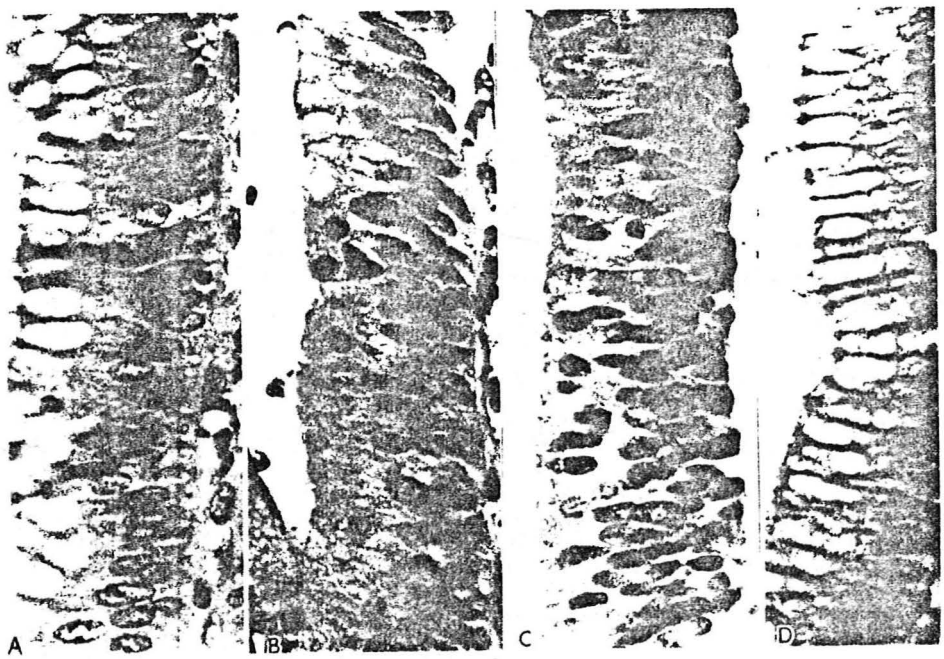


FIGURE 11. A. Mild dysplasia. B. Moderate dysplasia. C. Severe dysplasia. D. Borderline (very mild) changes. From Blackstone et al.

Some pathologists use the term precancer and carcinoma in situ synonomously and others do not. The terminology is still evolving in this field and there is not yet a universal agreement on nomenclature. (This makes the literature somewhat confusing but does not detract from the importance of the subject.)

The findings in Morson and Pang's study can be summarized as follows:

1. They studied retrospectively resected colon specimens from 23 patients with colitis and colon cancer and found precancer changes elsewhere in the colon (especially left colon and rectum) in all 23. However, they mention in their discussion one patient who had colonic cancer without dysplasia in the resected specimen.

2. Of 172 colectomy specimens from patients with ulcerative colitis but no cancer studied retrospectively, 12 had precancerous changes in the colon, and all 12 had had pancolitis (12 of 134 with pancolitis had precancer without cancer, or 9%).

3. Of 148 consecutive rectal biopsies studied retrospectively, 16 (11%) had precancer. None of those 16 patients, all of whom eventually had a colectomy, had cancer.

4. A semi-prospective study was carried out in a subgroup of patients with pancolitis of greater than 8 years duration who underwent rectal biopsy. Nine patients were found to have precancer on biopsy of the rectum (7, flat type, 2 polypoid type). All 9 of these patients underwent surgery (in some cases only because of the precancer findings and in other cases for other reasons) and 5 were found to have cancer in the resected colon (1 rectal, 2 sigmoid, 2 descending colon). The other four patients had dysplasia confirmed in the resected specimen but no cancer. Thus, precancer in the rectum "predicted" the presence of cancer in the rectosigmoid or left colon in 5 of 9 patients.

To summarize the findings of Morson and Pang, almost all patients with cancer and ulcerative colitis had dysplasia; 10% of patients with ulcerative colitis had dysplasia without cancer at the time they were studied or operated upon; more than 50% of patients with pancolitis of long duration and rectal dysplasia had cancer.

Following the paper by Morson and Pang, many laboratories throughout the world began studying this question. In 1972, Evans and Pollack reported that none of 4 patients who had ulcerative colitis and carcinoma of the right or transverse colon had dysplasia in the rectum on the resected specimen or on a subsequent rectal biopsy. This raised the possibility that the histology of the rectal mucosa may not always reflect the presence of pre-malignancy or malignancy in the remainder of the colon.

In 1974, Myrvold in Sweden reported results of preoperative rectal biopsy (3-4 biopsies taken) in comparison with findings in the subsequent colectomy specimen. Forty-six patients with extensive colitis about to undergo elective proctocolectomy were studied. Their results are summarized in Table 13.

TABLE 13.

Preoperative Rectal Biopsy	Colectomy Specimen	
	Precancer	Cancer
No Precancer (N=40)	11	0
Precancer (N=6)	6	4

Several points about this study merit mentioning: (1) Precancer, when present on pre-operative rectal biopsies, was often seen in only 1 or 2 of the 4 biopsies, indicating potential sampling errors if only 1 or 2 biopsies are taken; (2) precancer in the colectomy specimens was often very patchy in distribution and often spared the rectum; (3) none of the 4 cancers were diagnosed clinically or by barium enema and two of these patients had had colitis less than 10 years. This study confirms that a rectal biopsy may miss the presence of colonic dysplasia, but that rectal dysplasia, when present, was often associated with colon cancer. This series has now been extended to 110 patients (Kewenter et al) with similar results. A cumulative risk of precancer and cancer as a function of disease duration for this selected group of patients has been calculated (Figure 12).

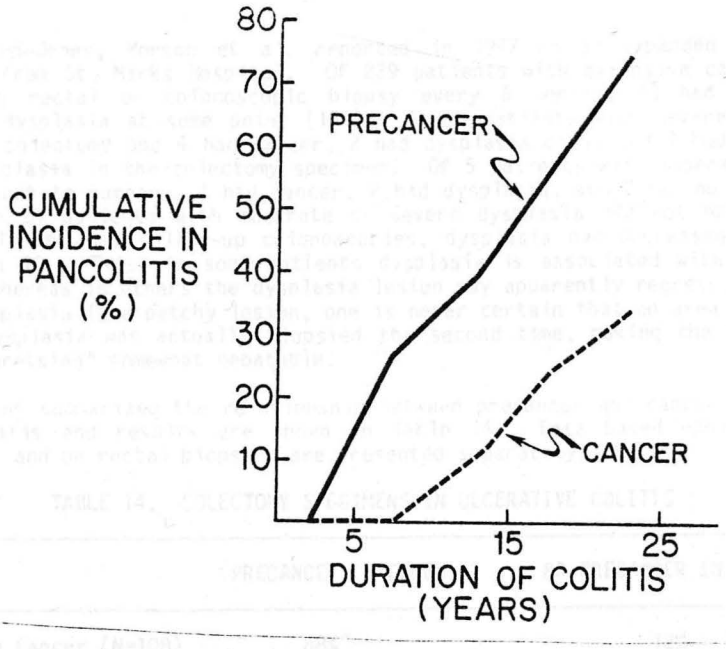


FIGURE 12. Cumulative incidence of precancer and cancer as a function of duration of colitis in patients with pancolitis (from Kewenter et al).

Other authorities, such as Yardley, have also emphasized that precancer can be a patchy lesion and that the sessile, polypoid type of precancer can be hard to distinguish grossly from carcinoma. He found that the majority of ulcerative colitis patients with precancer on rectal biopsy (29/34) has an associated severe acute inflammation, raising the possibility of reactive hyperplasia as opposed to true dysplasia.

In 1979, Nugent et al. published a 2-part retrospective and prospective study of dysplasia in ulcerative colitis. In the retrospective study of colectomy specimens, 18 of 23 patients with colitis-associated cancer had moderate or severe colonic dysplasia (78%) whereas only 6/57 patients who underwent colectomy and did not have cancer had dysplasia (11%). They then did a prospective colonoscopic study in which serial biopsies were taken throughout the colon and in the rectum of patients with pancolitis (N=36), Crohn's colitis (N=12) and patients without inflammatory bowel disease (N=12). None of the patients without inflammatory bowel disease or with Crohn's colitis had dysplasia, whereas 8/36 patients with pancolitis had dysplasia (22%). In all 8 patients dysplasia involved both the colon and rectum. Of the 8 patients with dysplasia, 6 had a colectomy and 2 had carcinoma. The other 2 patients did not have surgery.

Lennard-Jones, Morson et al. reported in 1977 on an expanded series of patients from St. Marks Hospital. Of 229 patients with extensive colitis subjected to rectal or colonoscopic biopsy every 6 months, 33 had severe or moderate dysplasia at some point (14%). Seven patients with severe dysplasia have had colectomy and 4 had cancer, 2 had dysplasia only, and 1 had no detectable dysplasia in the colectomy specimen. Of 5 patients with moderate dysplasia who went to surgery, 1 had cancer, 2 had dysplasia, and 2 had no dysplasia. The other 21 patients with moderate or severe dysplasia did not have surgery and, of 11 who had follow-up colonoscopies, dysplasia had decreased or disappeared in 10. Thus, in some patients dysplasia is associated with an occult cancer, whereas in others the dysplasia lesion may apparently regress. However, since dysplasia is a patchy lesion, one is never certain that an area which contained dysplasia was actually biopsied the second time, making the use of the word "regression" somewhat debatable.

Dobbins summarized the relationship between precancer and cancer in ulcerative colitis and results are shown in Table 14. Data based upon colectomy specimens and on rectal biopsies are presented separately.

TABLE 14. COLECTOMY SPECIMENS IN ULCERATIVE COLITIS

	PRECANCER IN COLON	NO PRECANCER IN COLON
Colon Cancer (N=108)	88%*	12%
No Colon Cancer (N=345)	13%	87%

(* only 66% had precancer in the rectum)

RECTAL BIOPSY SPECIMENS IN ULCERATIVE COLITIS

	CANCER IN COLON	NO CANCER IN COLON
Precancer (N=53)	32%	68%
No precancer (N=884)	< 1%	99%*

(* many of these patients did not have colectomy, so this is a maximum figure)

Thus, cancer without precancer occurs but is apparently rare. On the other hand, precancer without cancer is quite common and, as already mentioned, may be a reversible lesion. Because of these data, negative rectal and colonoscopic biopsies are reassuring but do not totally guarantee against cancer. On the other hand, a positive rectal biopsy for dysplasia means that 1/3 of such patients may have cancer (which could be at a curable stage) whereas 2/3 will not have cancer. Of course, some of these patients may eventually develop cancer if their colons are left in situ. Most experts feel that the presence of dysplasia on a biopsy, even severe dysplasia, is not an indication per se for colectomy unless (1) inflammation is absent; (2) the dysplasia persists on repeat biopsy or occurs in more than one area of the colon; and/or (3) dysplasia is associated with a grossly visible (macroscopic) lesion.

Another way to look at dysplasia (precancer) is: how should the clinician react to a negative biopsy report or to a positive report for dysplasia? First, it is important that he familiarizes himself with the nomenclature used by the pathologist because it is not yet standardized. The pathologist's experience with dysplasia in the colon is also important. The following are guidelines for the clinician.

A negative rectal or colonic biopsy for dysplasia:

1. True negative.
2. Dysplasia present but missed with biopsy because lesion is patchy or spares rectum (false negative).
3. Cancer present without dysplasia [this occurred in 5 of 937 (0.5%) of patients reviewed by Dobbins].

A positive rectal or colonic biopsy for dysplasia:

1. Might be secondary to acute inflammation (reactive dysplasia).
2. Might be unassociated with cancer and possibly even resolve with time.
3. Might indicate underlying cancer somewhere in colon even though colonoscopy and barium enema are negative.

A patient with "mild" dysplasia who developed cancer associated with ulcerative colitis is presented below. The case is presented to emphasize how difficult decisions are in this situation and how important it is to follow a patient closely when colectomy is not performed for dysplasia.

Case Report 2

A 25 year old women developed diarrhea and was found to have "colitis" on proctoscopy. Over the next several years, she began having intermittent attacks of diarrhea (up to 30 bowel movements per day) and abdominal cramps without rectal bleeding. At age 45, following a typical attack a barium enema showed pancolitis and a dilated terminal ileum (backwash ileitis) and proctoscopy showed active inflammation. Rectal biopsy was compatible with ulcerative colitis. Her symptoms responded to prednisone and sulfasalazine. At age 46, a barium enema showed a 3-4 cm stricture in the mid-descending colon. Colonoscopy could not

confirm the stricture, but random biopsies showed mild dysplasia in the descending and sigmoid colon and in the rectum with only minimal inflammation. She was advised to have yearly colonoscopy examinations with repeated colonic biopsies but because she felt well she did not return for follow-up until 3 years later (age 49) with bloody diarrhea, weight loss and a mass palpable in the left lower abdominal quadrant. She was found to have a bleeding, necrotic tumor in the sigmoid colon at colonoscopy and biopsies revealed squamous cell carcinoma. At laparotomy the tumor had invaded through the wall of the colon and had metastasized to regional lymph nodes and the liver. The rest of the resected colon was compatible with ulcerative colitis.

Colonoscopy. As already reviewed, colonoscopy or proctoscopy can be used to take random biopsies of flat mucosa with the goal of detecting premalignant changes in patients with ulcerative colitis. A similar approach has recently been reported by Craft in a few patients with Crohn's (granulomatous) colitis. Moreover, some types of precancer, the sessile-villous or polypoid type, can be recognized macroscopically by pathologists (and perhaps by endoscopists).

In 1975, Teague and Read reported their results of colonoscopy in 150 patients with ulcerative colitis. Of these patients, 48 had pancolitis (32%) and 54 had had disease for more than 8 years (36%). Thus, this was a relatively heterogenous group of patients and not weighted toward extensive or long-duration cases. Polypoid lesions were found in 32 patients (21%): inflammatory polyps (pseudopolyps) in 25; adenomatous polyps (probably synonomous with polypoid dysplasia) in 4, and polypoid carcinoma in 3. The importance of adenomatous polyps in relation to cancer in colitis was first pointed out in 1959 by Dawson and Pryse-Davies.

Another series was recently reported by Blackstone and his associate at the University of Chicago. They colonoscoped 112 patients with extensive colitis of greater than 7 years duration (high-risk group). Five to 8 blind biopsies were taken at colonoscopy from flat areas and any macroscopic lesions (e.g. polyp) were also biopsied three times. Twenty-seven patients (24%) had dysplasia in an area of flat mucosa on random biopsy (1 severe, 6 moderate, and 20 mild dysplasia). Only 7 of these 27 patients underwent colectomy and 1 of these 7 had cancer (he had had moderate dysplasia). In the other 20 patients, colonoscopy was repeated; dysplasia was less severe or absent in 12 and the same in 8.

Twelve patients in Blackstone's series (or 11%) had macroscopically-evident lesions at colonoscopy which on biopsy were found to contain dysplastic epithelium. (It is not stated, unfortunately, how often a lesion was seen and biopsied without dysplasia being present.) Of these 12 patients with a dysplasia-associated lesion or mass (DALM), 5 had had an abnormal barium enema which led to colonoscopy, 1 had had rectal bleeding which led to colonoscopy, and 6 were detected as part of a routine cancer surveillance study which included colonoscopy. Macroscopically, the lesion was either a single polypoid mass, a segment of colon 5 to 15 cm long with a carpeting of polyps, or a plaque-like lesion. Dysplasia was graded as severe (N=2), moderate (N=5), or mild (N=5). Interestingly, 10 of the 12 patients had no dysplasia on rectal biopsy. The outcome of the 12 patients with DALM is summarized in Table 15.

TABLE 15. OUTCOME OF PANCOLITIS PATIENTS WITH DYSPLASIA-ASSOCIATED LESION OR MASS (DALM) VISUALIZED AT COLONOSCOPY (from Blackstone et al)

	NUMBER OF PATIENTS	NUMBER WITH CANCER
Single Polyp	5	5
Carpet of Polyps	5	2 (1 had 2 cancers, 1 had 3)
Plaque	2	0 (1 refused surgery)
TOTAL	12	7

Thus, 7 of 12 patients with DALM had cancer, always in the area of the lesion or mass (except for one patient with a DALM in the sigmoid and 3 separate cancers in the sigmoid, descending colon and cecum). None of the cancers had been diagnosed on colonoscopic biopsy (only dysplasia). Dukes' staging of cancers in these 7 patients were B in 4 (extending through the muscular wall of the colon into the serosa or perirectal fat), C in 2 (nodal involvement) and unknown in 1. This study, though not truly done prospectively, suggests that patients should undergo colectomy if they have a macroscopic lesion at colonoscopy which is dysplastic on biopsy.

It has been suggested by Butt and Morson that precancer in flat mucosa may be an early stage after which dysplasia associated with macroscopic change develops. In support of this, they reported that colon cancers found in association with dysplastic flat mucosa are more likely to be Dukes' A (confined to the wall of the colon) than cancers in association with dysplastic macroscopic lesions (66% vs. 26%, respectively, $P < 0.05$). It is important for the endoscopist to learn to recognize these macroscopic lesions and to biopsy them several times.

Radiology. A recent report from Chicago suggested that a carefully performed double-contrast barium enema examination of the colon can detect dysplasia-associated lesions and masses. Radiologically, macroscopic dysplasia tended to be nodular and irregular areas with sharply angulated edges. Grossly, these lesions represented dysplastic plaques, nodules, or polyps. The authors felt they could distinguish dysplastic lesions from inflammatory polyps which tend to be rounded without angulated margins (pseudopolyps) or to be bulbous or clubbed at the end (filamentous polyps). However, radiological distinction of dysplasia from inflammatory polyps may be difficult and they may occur simultaneously in the same patient. Both dysplasia and pseudopolyps tend to occur in patients with extensive colitis of long duration. Thus, biopsy of suspicious areas should be carried out. Frank and his associates felt that double-contrast barium enema may be more sensitive than colonoscopy in detecting dysplastic lesions, but additional comparative studies are necessary to justify this claim.

LDH Isoenzyme Patterns. The pattern of LDH isoenzymes is abnormal in tissues or sera from patients with colonic, bronchogenic, and uterine cancer. Under normal circumstances, there is a preponderance of rapidly migrating isoen-

zymes I and II over slower migrating isoenzymes IV and IV. In malignancy, there can be a preponderance of IV and V or of isoenzyme III. Lewis et al. reported that the normal ratio of LDH IV and V isoenzymes to LDH I and II isoenzymes in rectal mucosa was 0.79. In patients with pan-ulcerative colitis but no evidence of precancer or cancer the ratio was 1.04 ($P < 0.05$ vs. controls). Even more striking was a group of patients with colitis and precancer on rectal biopsy. Their LDH ratio of IV plus V to I plus II was 2.30 ($P < 0.001$ vs. control or pancolitis without precancer). Because the precancer group also had a significantly lower than normal total LDH concentration in rectal mucosa (60 vs. 154 IU/gram, $P < 0.01$), the $\frac{IV + V}{I + II}$ ratio probably increased more as a result of low levels of isoenzymes I and II than elevated levels of IV and V isoenzymes. Additional studies are needed to confirm these findings.

References

Blackstone, M.O., Riddell, R.H., Rogers, B.H., and Levin, B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: An indication for colectomy. Gastroenterology 80:366-374, 1981.

Butt, J.H., and Morson, B. Dysplasia and cancer in inflammatory bowel disease. Gastroenterology 80:865-868, 1981.

Butt, J.H., Konishi, F., Morson, B.C., Lennard-Jones, J.E., and Ritchie, J.K. The frequency, appearance and clinical significance of macroscopical changes associated with dysplasia and carcinoma (MADC) complicating chronic ulcerative colitis (CUC). Gastroenterology 80:1119, 1981.

Cook, M.G., and Goligher, J.C. Carcinoma and epithelial dysplasia complicating ulceration colitis. Gastroenterology 68:1127-1136, 1975.

Craft, C.F., Mendelsohn, G., Cooper, H.S., and Yardley, J.H. Colonic "precancer" in Crohn's disease. Gastroenterology 80:578-584, 1981.

Dawson, I.M.P., and Pryse-Davies, J. The development of carcinoma of the large intestine in ulcerative colitis. Brit. J. Surg. 47:113-128, 1959.

Dobbins, W.O. Current status of the precancer lesion in ulcerative colitis. Gastroenterology 73:1431-1433, 1977.

Evans, D.J., and Pollock, D.J. In-situ and invasive carcinoma of the colon in patients with ulcerative colitis. Gut 13:566-570, 1972.

Frank, P.H., Riddell, R.H., Feczko, P.J., and Levin, B. Radiological detection of colonic dysplasia (precarcinoma) in chronic ulcerative colitis. Gastrointest. Radiol. 3:209-219, 1978.

Gewertz, B.L., Dent, T.L., and Appelman, H.D. Implications of precancerous rectal biopsy in patients with inflammatory bowel disease. Arch. Surg. 111: 326-329, 1976.

Kewenter, J., Hulten, L., and Ahren, C. The occurrence of severe epithelial dysplasia and its bearing on treatment of longstanding ulcerative colitis. Ann. Surg. 195:209-213, 1982.

Lennard-Jones, J.E., Morson, B.C., Ritchie, J.K., Shove, D.C., and Williams, B.M. Cancer in colitis: Assessment of the individual risk by clinical and histological criteria. Gastroenterology 73:1280-1289, 1977.

Lewis, B., Morson, B.C., February, A.W., Jones, J.H., and Misiewicz, J.J. Abnormal lactic dehydrogenase isoenzyme patterns in ulcerative colitis with precancerous change. Gut 12:16-19, 1971.

Morson, B.C., and Pang, L.S.C. Rectal biopsy as an aid to cancer control in ulcerative colitis. Gut 8:423-434, 1967.

Morson, B.C. Rectal and colonic biopsy in inflammatory bowel disease. Am. J. Gastroent. 67:417-426, 1977.

Myrvold, H.E., Kock, N.G., and Ahren, C. Rectal biopsy and precancer in ulcerative colitis. Gut 15:301-304, 1974.

Nugent, F.W., Haggitt, R.C., Colcher, H., and Kutteruf, G.C. Malignant potential of chronic ulcerative colitis. Gastroenterology 76:1-5, 1979.

Otto, H.F., and Gebbers, J.-O. Pracancerose epitheldysplasien bei colitis ulcerosa. Virchows. Arch. A Path. Anat. Histol. 377:259-276, 1978.

Teague, R.H., and Read, A.E. Polyposis in ulcerative colitis. Gut 16:792-795, 1975.

Yardley, J.H., and Keren, D.F. "Precancer" lesions in ulcerative colitis. A retrospective study of rectal biopsy and colectomy specimens. Cancer 34: 835-844, 1974.

Yardley, J.H., Bayless, T.M., and Diamond, M.P. Cancer in ulcerative colitis. Gastroenterology 76:221-225, 1979.

RECOMMENDATIONS FOR MEDICAL THERAPY AND FOLLOW-UP OF THE INDIVIDUAL PATIENT WITH INFLAMMATORY BOWEL DISEASE

Early On (years 1-5). Many kinds of physicians treat patients with ulcerative colitis: pediatricians, family practitioners, internists, gastroenterologists, and surgeons. When the care of a patient transfers from one physician to another (e.g. pediatrician to internist, or, internist to gastroenterologist) it is important that all relevant records documenting extent and duration of disease are transferred with the patient.

When the physician first sees a patient with a new onset of apparent inflammatory bowel disease, he must exclude several specific diagnoses before diagnosing an idiopathic condition such as ulcerative colitis or Crohn's disease. A list of the major disorders which figure in the differential diagnosis are listed in Table 16 along with the type(s) of inflammatory bowel disease that they may mimic.

TABLE 16. SPECIFIC CAUSES OF INFLAMMATORY BOWEL DISEASE

I. INFECTIOUS
   - Bacterial
     - Salmonella (colitis, ileitis)
     - Shigella (colitis)
     - E. Coli, invasive types (enterocolitis)
     - Camplyobacter (colitis)
     - Clostridium difficile (pseudomembranous colitis)
     - Staphylococcus (enterocolitis)
     - Yersinia (ileitis, colitis)
     - Gonorrhea (proctitis)
     - Syphilis (rectal ulcer, or chancre)
     - Tuberculosis (ileocecitis)
   - Fungal
     - Histoplasmosis (ileocecitis resembling TB)
     - Actinomycosis (ileocecitis resembling TB)
   - Parasitic
     - Amebiasis (cecitis, generalized colitis)
     - Schistosomiasis (proctitis, colitis)
   - Viral and Chlamydial
     - Herpes simplex, type 2 (proctitis)
     - Lymphogranuloma venereum (LGV) (proctitis)

II. RADIATION INJURY

III. BOWEL ISCHEMIA (ischemic colitis)

IV. DRUG OR TOXIN-INDUCED INJURY TO BOWEL (e.g. mercury poisoning)

Thus, the physician confronted with a patient with new-onset inflammatory disease of the bowel must take a careful history including questions related to heavy metal ingestion, radiation exposure, foreign travel, homosexual intercourse ("gay bowel syndrome"), and antibiotic exposure (which would favor Clostridium difficile-induced pseudomembranous colitis or perhaps staphylococcus

enterocolitis). The stool should be examined for ova and parasites and cultured for appropriate bacterial pathogens. Special incubation conditions are necessary for campylobacter, yersinia, gonococcus, and tuberculosis. In some cases serologic testing for amebiasis, LGV or syphilis; dark field examination of material from rectal ulcers looking for spirochetes; or a test for a cytopathic toxin in the stool which can be neutralized by clostridium antitoxin are necessary. Rectal or ileocolonic biopsies (and culture of the biopsy material) may be required to establish a diagnosis of tuberculosis, yersinosis, histoplasmosis, actinomycosis, or herpes simplex infection.

If specific causes of inflammatory bowel disease listed in Table 16 can be excluded, it is likely that the patient has idiopathic inflammatory bowel disease - either ulcerative colitis or Crohn's disease. The anatomic distribution of the disease (Figure 1) as well as clinical differences (Table 1) and histology of mucosal biopsies will help distinguish these two. It should be mentioned, however, that there are patients who develop an acute, evanescent colitis of unknown etiology which does not recur (see Bonfils et al.). Therefore, a patient should not be labelled as having nonspecific inflammatory bowel disease until the disease has been shown to be idiopathic and chronic (> 3 months).

Another word of caution is in order. When a patient with inflammatory bowel disease symptomatically relapses, it is usually assumed that the disease relapse has been triggered by emotional stress, an infection (usually upper respiratory) or other major change (pregnancy, surgery, etc). However, some patients relapse because of a superimposed intestinal infectious process that may respond to specific therapy. Thus, patients with nonspecific ulcerative colitis may develop amebiasis, salmonellosis, or Clostridium difficile infection which would respond to metronidazole, trimethoprim-sulfamethoxazole, or vancomycin, respectively. The role of Cl. difficile in the genesis of relapses in ulcerative colitis is being investigated in many laboratories (see References below).

During the early years after the diagnosis of inflammatory bowel disease the patient should be treated medically. Both sulfasalazine and steroids are effective in ulcerative colitis and Crohn's although these medications are not always necessary in mild cases. In ulcerative colitis, there is evidence that sulfasalazine prevents recurrences (see Truelove). Neither sulfasalazine nor prednisone prevents relapses of Crohn's disease and these drugs should therefore be used only to treat acute attacks. Recommendations for medical therapy of inflammatory bowel disease are summaried in Table 17.

TABLE 17. MEDICAL THERAPY OF INFLAMMATORY BOWEL DISEASE*

	ULCERATIVE COLITIS	CROHN'S
Acute Attack		
Very Mild	Symptomatic (e.g. Lomotil)	Symptomatic
Mild-Moderate	Sulfasalazine	Sulfasalazine
Moderate-Severe	Prednisone+	Prednisone+
Prevention of Relapses	Sulfasalazine	None

(* rectal steroids are useful in patients with proctitis)
(+ IV hydrocortisone or prednisolone may be necessary in ill, hospitalized patients).

Surgery during the early years should be reserved for patients with (1) acute fulminant colitis that is medically-unresponsive; (2) toxic megacolon that does not rapidly respond to medical therapy; (3) intestinal perforation, obstruction, or massive hemorrhage; (4) persistent chronic disease that does not respond well to medical therapy or that requires relatively high doses of systemic steroids chronically to prevent relapses (intractability). Approximately 10% of patients with ulcerative colitis (and a higher percentage of patients with Crohn's disease) require surgery early in their course.

Cancer as a complication of ulcerative colitis is very uncommon during the first 5 years of the disease. However, there is another entity in which patients with obstructing lesions in the colon (e.g. cancer) develop secondarily a colitis proximal to the obstruction. The distal (non-obstructed) colon is normal. This entity should not be confused with ulcerative colitis. An example of proximal colitis secondary to an obstructing colon cancer is presented below.

Case Report 3. A 46 year old man noticed the onset of abdominal pain and a right upper quadrant abdominal mass and was admitted to the Dallas VAMC (#453-50-8580). Examination revealed a large (15x8x8 cm) hard right upper quadrant mass separate from the liver. Barium enema showed an annular carcinoma nearly obstructing the hepatic flexure of the colon and a markedly dilated cecum and ascending colon with abnormal mucosal folds on the lateral aspect of the ascending colon and cecum. Emergency surgery was perfomed because of impending colonic obstruction. A large mass was found emanating from the hepatic flexure of the colon and a right hemicolectomy was performed. The hepatic flexure contained adenocarcinoma which had metastasized to the liver. The proximal colon was edematous and contained a patchy ulcerative colitis. The distal colon was normal without changes of chronic ulcerative colitis.

Comments. Colitis proximal to an obstructing carcinoma developed. The mechanism for the colitis is uncertain but it is probably related to mucosal ischemia secondary to bowel distention.

Later On (Year 6 and Beyond). Because approximately 5% of cases of carcinoma complicating ulcerative colitis occur between the 6 and 10 year mark, I believe that surveillance for cancer should begin after the disease has been present for 5 or 6 years if the patient is in a high risk-group (pancolitis). It is important to explain to the patient the necessity for careful follow-up, but a presentation which is too aggressive may lead to an excessive fear of cancer and poor patient compliance. Some patients may decide not to return if they realize that a possible consequence of close follow-up is a colectomy and ileostomy. Other patients will be very compliant in their follow-up. Still others may opt for elective colectomy at this stage, especially if they had a lot of trouble with their colitis in the first 5 years. Because the risk for cancer from 6 to 10 years is relatively small, this four-year period will also help establish whether or not a patient will be compliant in follow-up.

Patients with left-sided colitis are also at increased risk, although somewhat later than those with pancolitis. I believe that these patients should begin to undergo close surveillance after 15-20 years of disease. Patients with ulcerative proctitis do not need special cancer surveillance, with the possible exception of patients whose disease began in childhood (Figure 5).

What tests should be done at the onset of surveillance? At the first session, the patient should probably undergo an air-contrast barium enema and colonoscopy with multiple biopsies of any macroscopic lesions and 8-10 random (blind) biopsies from flat areas throughout the colon and rectum. These procedures will serve as a valuable baseline, will familiarize the patient with the surveillance program, and in rare cases will detect an unsuspected cancer or focus of precancer.

If the air-contrast barium enema and colonoscopy are negative and biopsies do not show dysplasia, the patient should be seen at yearly intervals for surveillance. Which test(s) to perform when the patient returns are controversial. Factors such as diagnostic yield, cost, and patient comfort are all important. Some experts prefer to perform proctoscopy and rectal biopsy yearly (or even every 6 months) and perform colonoscopy and/or barium enema only every 2 years. The advantages of proctoscopy are its ease, its lack of need for extensive bowel preparation and its low cost. Disadvantages include sampling errors (colonic dysplasia may spare the rectum) and, on rare occasions, severe rectal bleeding post-biopsy. Advantages of colonoscopy are access to the entire colon and excellent optics for observing macroscopic changes which can be biopsied. Disadvantages include need for patient sedation, complications such as perforation, high cost (at least in the USA) and physician time. Advantages of radiology are examination of the entire colon, detection of strictures or dysplasia-associated lesions or masses which may not be appreciated at colonoscopy, and the ability to keep permanent film records for future comparisons. Disadvantages of radiology are moderately high cost, patient discomfort and exposure to radiation. An internist may choose to follow the patient with yearly proctoscopy and rectal biopsy and an air-contrast barium enema perhaps every 1-2 years. A gastroenterologist may prefer yearly colonoscopy with colonic and rectal biopsies. The optimal way of following these patients has not been established.

If the patient continues to have no evidence of cancer or precancer at the 10-year mark, a decision should be made whether to continue this course of yearly follow-up or to proceed with elective colectomy. Patients who have demonstrated good early compliance with the surveillance regimen and who have relatively quiescent disease can be followed medically. Neither the physician nor patient should be lulled into complacency during the next several years because it is during this time that the risk of cancer increases sharply. On the other hand, if the patient has demonstrated poor compliance (see Case Report 2), serious consideration should be given at this point to elective colectomy. Patients who have had a great deal of trouble from their colitis may be more willing to accept colectomy than those with clinically-mild disease. As will be discussed, operations which include colectomy but allow continence (no ileostomy bag) are being developed. As these new operations become perfected and more available, it is likely that physicians and patients will be more willing to accept elective colectomy as a cancer-preventing operation in ulcerative colitis than at present. An aggressive surgical approach in patients with extensive colitis of long duration can eliminate cancer as a problem in ulcerative colitis (see Bonnevie).

As has already been reviewed, the majority of patients with ulcerative colitis will not have dysplasia on rectal or colonic biopsy. Therefore, the presence of dysplasia on any biopsy should immediately raise suspicion. If the dysplasia is associated with a macroscopic lesion, if the dysplasia is severe, and/or if the dysplasia is associated with little or no inflammation, even more consternation is warranted. A few experts recommend immediate colectomy at this point. The majority recommend a repeat biopsy - either immediately or in 6 to 12

months because dysplasia, even severe dysplasia, may apparently resolve with time. It is important that the clinician review the histogical sections with the pathologist, discuss the implications and options with the patient and reach a joint decision. In order to make a rational decision it is important to know the surgical options, including each operation's advantages and disadvantages. These will be discussed in the next section.

References

Bartlett, J.G. Clostridium difficile and inflammatory bowel disease. Gastroenterology 80:863-865, 1981.

Bolton, R.P., Sherriff, R.J., and Read, A.E. Clostridium difficile associated diarrhoea: A role in inflammatory bowel disease? Lancet 1:383-384, 1980.

Bonfils, S., Hervoir, P., Girodet, J., Le Quintrec, Y., Bader, J.P., and Gastard, J. Acute spontaneously recovering ulcerating colitis (ARUC). Report of 6 cases. Dig. Dis. 22:429-436, 1977.

Bonnevie, O., Binder, V., Anthonisen, P., and Riis, P. The prognosis of ulcerative colitis. Scand. J. Gastroent. 9:81-91, 1974.

Feldman, P.S. Ulcerative disease of the colon proximal to partially obstructive lesions: Report of two cases and review of the literature. Dis. Col. Rect. 18:601-612, 1975.

Hurwitz, A., and Khafif, R.A. Acute necrotizing colitis proximal to obstructing neoplasms of the colon. Surg. Gyn. Obst. 111:749-752, 1960.

Keighley, M.R.B., Youngs, D., Johnson, M., Allan, R.N., and Burdon, D.W. Clostridium difficile toxin in acute diarrhoea complicating inflammatory bowel disease. Gut 23:410-414, 1982.

Lebedeff, D.A., and Hockman, E.B. Rectal gonorrhea in men: Diagnosis and treatment. Ann. Int. Med. 92:463-466, 1980.

Meyers, S., Mayer, L., Bottone, E., Desmond, E., and Janowitz, H.D. Occurrence of clostridium difficile toxin during the course of inflammatory bowel disease. Gastroenterology 80:697-700, 1981.

Sohn, N., and Robilotti, J.G., Jr. The gay bowel syndrome. Am. J. Gastroent. 67:478-484, 1977.

Summers, R.W., Switz, D.M., Sessions, J.T., Jr., Becktel, J.M., Best, W.R., Kern, F., Jr., and Singleton, J.W. National cooperative Crohn's disease study: Results of drug treatment. Gastroenterology 77:847-869, 1979.

Trnka, Y.M., and LaMont, J.T. Association of clostridium difficile toxin with symptomatic relapse of chronic inflammatory bowel disease. Gastroenterology 80:693-696, 1981.

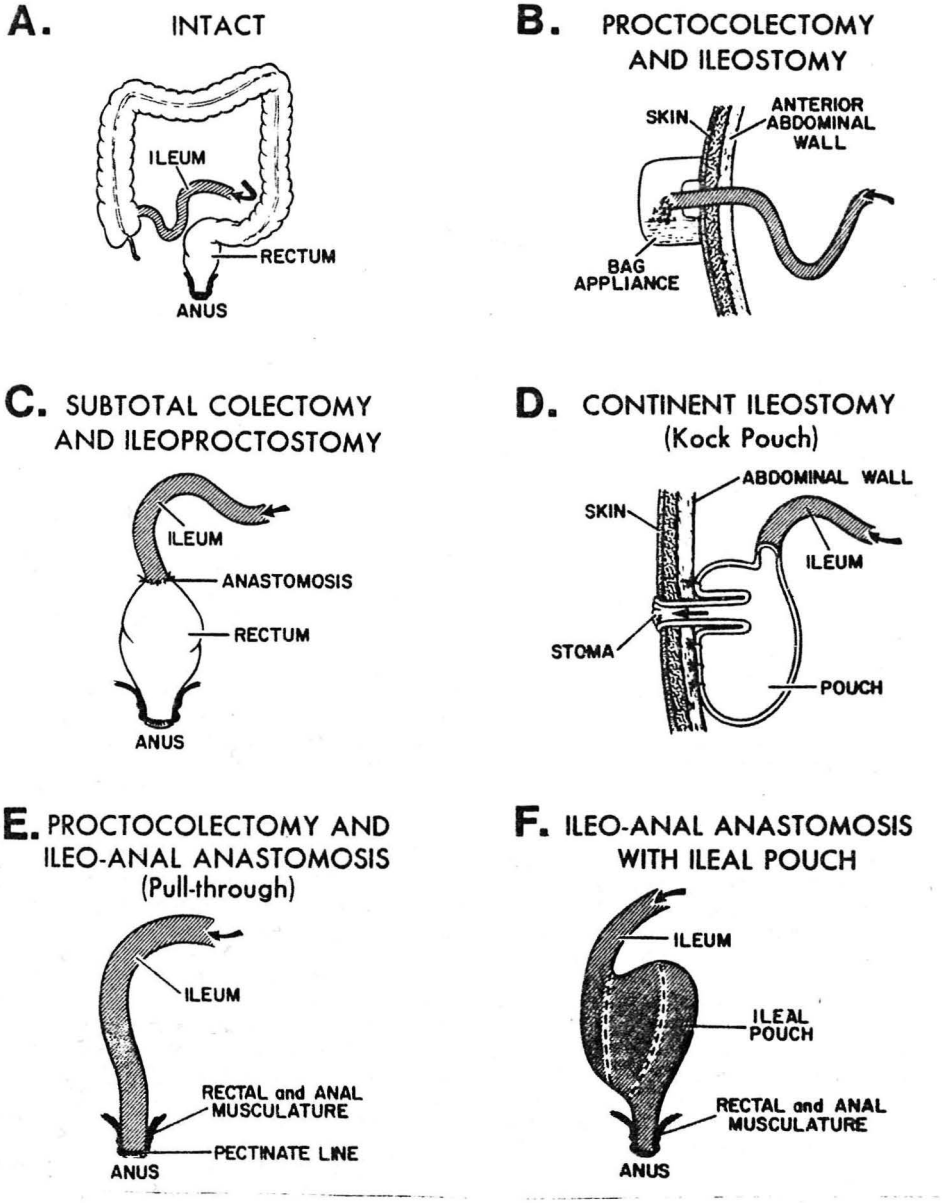
Truelove, S.C., Watkinson, G., and Draper, G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. Brit. Med. J. 2:1708, 1962.

Tucker, P.C., Webster, P.D., and Kilpatrick, Z.M. Amebic colitis mistaken for inflammatory bowel disease. Arch. Intern. Med. 135:681-685, 1975.

Wolloch, Y., Zer, M., Lurie, M., and Dintsman, M. Ischemic colitis proximal to obstructing carcinoma of the colon. Am. J. Proctology Gastroent. Colon Rect. Surg. March-April:17-32, 1979.

SURGERY IN ULCERATIVE COLITIS

The major operations used to treat patients with ulcerative colitis are shown in Figure 13 (B-F).



Proctocolectomy and Ileostomy (Figure 13B): This is the most common operation used to treat ulcerative colitis. The advantages of the procedure are that the entire colon is resected (eliminating risk of carcinoma) and that no intra-abdominal enteric suture lines are present. One disadvantage is the necessity for a permanent ileostomy and bag appliance and its attendant local complications and psychological consequences. The applicances may be uncomfortable and odoriferous and are unsightly. The bag must be worn day and night. However, modern enterostomal care has enabled many of these patients to return to a full and active life. One player in the National Football League has an ileostomy because of ulcerative colitis. Enterostomal therapists and "ostomy" clubs have facilitated patient adaptation to an ileostomy. Nevertheless, many patients (especially adolescents and young adults) are terrified by the implications of a permanent ileostomy.

Another disadvantage of proctocolectomy and ileostomy relates to the occurrence of sexual dysfunction. This occurs as a result of excision of the rectum which can damage pelvic autonomic nerves. Men are especially likely to develop this problem and become impotent, although women may also have sexual problems postoperatively. The major symptoms in males are erectile impotence and inability to ejaculate. The major symptom in women is dyspareunia. In addition to neurological injury to the sexual apparatus, the presence of a stoma may lead to physical difficulties which make intercourse difficult or to psychologic reactions in either the patient or spouse. In one study, 46 males with rectal excision for ulcerative colitis were interviewed. Most (35/46) had normal sexual function, but 3 (7%) had had transient disturbances postoperatively and 8 (17%) had varying degrees of permanent impairment. Three patients (7%) became completely impotent. The incidence of postoperative impotence is related to the age of the patient (i.e. impotence is less common in men under age 45 than in those above age 45).

The mortality rate of elective proctocolectomy and ileostomy is approximately 3%. This mortality rate increases to appoximately 15-20% when the operation is performed as an emergency. A 3% chance of dying, a 5-10% chance of permanent impotence, and a permanent ileostomy bag are factors which discourage many physicians and patients from undergoing elective colectomy and ileostomy as a prophylaxis against cancer.

Subtotal Colectomy and Ileoproctostomy (Figure 13C)

On the surface, this operation has many advantages over proctocolectomy and ileostomy: (1) preservation of the anus and rectum; (2) avoidance of an external stoma; (3) avoidance of impotence because rectal dissection is not performed; (4) avoidance of perineal wound problems which occur with proctectomy; (5) ability to remove the rectum at a later date "if necessary"; and (6) decrease of colonic surface area for carcinoma to develop. Because of these advantgages, the procedure has been adopted by many British surgeons. However, the procedure also has disadvantages: (1) two operations are usually necessary: a first stage with resection, ileoproctostomy, and proximal diverting loop ileostomy to protect the ileo-rectal anastomosis, and a second stage with closure of the ileostomy after 2-3 months; (2) there is a high incidence of anastomotic leakage with fistulae or pelvic abscess formation; (3) severe diarrhea occurs in some patients; (4) the disease may progress in the rectal

stump requiring subsequent excision; (5) cancer may develop in the rectal stump. Approximately half the patients eventually require an ileostomy but the other half do quite well, albeit with 7 or more stools per day.

Only a minority of patients with ileo-rectal anastomosis will develop cancer. For example, MacDougall followed 237 such patients for 1-16 years and 5 developed rectal cancer (2%). Aylett had 7 cancers develop in a series of 369 patients (2%). Although this incidence of rectal cancer is much higher than expected in a non-colitis population, the data indicate that most patients do not develop rectal cancer. It is unknown whether periodic proctoscopy with rectal biopsy looking for dysplasia will allow early detection of rectal cancer in these patients. This operation seems (to the author) to be a viable alternative to the standard poroctocolectomy and ileostomy only if (a) the rectum is only mildly involved with colitis; (b) the patient will be compliant with at least yearly proctoscopic examinations; and (c) the patient understands that diarrhea will almost certainly occur postoperatively. The mortality rate is probably less than 3%.

Proctocolectomy and Continent Ileostomy (Kock pouch) (Figure 13D)

In this operation, the surgeon manufactures an internal "bag" or reservoir out of the terminal 40 centimeters of ileum, the reservoir being emptied 3 or 4 times a day by passing a catheter through an abdominal stoma. Thus, there is a stoma but no need for a bag appliance. Ideally, there is no escape of feces or flatus from the reservoir between intubations. The reservoir is constructed by approximating the proximal 30 centimeters of a 40 cm segment of terminal ileum, opening the ileum and folding the distal half of the over the proximal half, creating the pouch. Before the pouch is closed, the distal 10 cm segment of ileum is in part intussuscepted backward into the pouch, creating an external nipple 3-4 cm long to establish continence. The nipple is held in place by multiple silk sutures. The pouch is anchored to the parietal peritoneum immediately below the stoma. Initially, the pouch has a 100 ml capacity but this usually increases in 3-6 months to 500-600 ml.

This is still a very new procedure and many modifications of Kock's original operation are being reported. The mortality rate in Kock's series has been 7 of 275 (3%) and in other series mortality has ranged from 0-8%. There is considerable morbidity with the procedure and many patients (up to 50%) are not completely continent. Second and third revision-type operations related to the stoma are the rule rather than the exception. Many surgeons are disenchanted with the procedure and some have abandoned it. The operation should not be used in patients with Crohn's disease because recurrent ileal disease in the reservoir may result in resection of a large amount of small bowel leading to malabsorption.

Proctocolectomy and Ileo-anal Anastomosis (Figure 13E)

In 1947, Ravitch and Sabiston proposed an operation for patients with ulcerative colitis and familial polyposis coli which included: (a) colectomy; (b) proximal partial proctectomy; (c) excision of the mucosa and submucosa (but not the muscle) from the distal rectum; and (d) a pull-through of the terminal ileum through the cuff of distal rectal muscle for anastomosis to the pectinate line in the anal canal. This is essentially an anal ileostomy. Theoretical

advantages were removal of all malignancy-prone mucosa with preservation of anal sphincteric mechanisms and lack of need for an external bag appliance. However, problems with the operation (which like ileorectal anastomosis is usually done in two stages) are diarrhea, severe rectal urgency, and incontinence.

Because of the side-effects the operation was not received enthusiastically (although very few patients actually received this operation). Thirty years later, however, Martin at the University of Cincinnati reported results in 17 children with ulcerative colitis treated with this procedure. Patients were operated upon for medical intractability rather than as prophylaxis against cancer. Martin felt it was important to get the rectum in optimal condition prior to surgery with systemic or rectal steroids, parenteral hyperalimentation or even a preliminary, temporary diverting ileostomy (with subtotal colectomy). After the ileo-anal anastomosis, severe diarrhea and incontinence were common for up to 12 months. Postoperative complications (sepsis, bowel obstruction, and stricture) were also common but only 2 of 17 patients eventually required permanent ileostomy and the other 15 have all become continent. Similar results in children have been reported at the Mayo Clinic by Telander and Perrault.

Since Martin's paper there has been a rebirth in interest in this procedure[+] and some surgeons are performing the operation in one stage rather than two. More than 50 cases have been reported without any surgical mortality. It appears that blood loss, which is fairly common with proctectomy, is less with this procedure. The typical patient has 6-9 bowel movements per day, perhaps 1 or 2 bowel movements at night and no incontinence. A few patients have occasional episodes of incontinence, usually at night. Because of the high frequency of bowel movements, some surgeons have begun to experiment with construction of an ileal reservoir (similar to the Kock pouch but without a nipple) in the pelvis (see Fonkalsrud and also Parks et al. as well as Figure 13F). Experience with this new procedure is limited. Proctocolectomy, rectal mucosal excision, and ileo-anal anastomosis is currently being evaluated by Dr. Phil Huber in our Department of Surgery.

The choice of operation for cancer prophylaxis in ulcerative colitis should depend upon physician and patient preference and available surgical expertise. If a patient with ulcerative colitis is known to have carcinoma of the colon, the same surgical approach should be taken since these cancers are often multifocal or cover very extensive areas. The only exception to this is the patient who is found at laparotomy to have metastatic disease. This patient's cancer should be treated palliatively, usually by simple resection without total proctocolectomy (see Case Report 2).

[+] A similar "pull-through" operation has been used by Soave since 1964 for the treatment of Hirshsprung's disease (Surgery 56:1007-1014, 1964).

References

Aylett, S. Cancer and ulcerative colitis. Brit. Med. J. 2:203-205, 1971.

Bacon, H.E., Bralow, S.P., and Berkley, J.L. Rehabilitation and long-term survival after colectomy for ulcerative colitis. JAMA 172:324-328, 1960.

Beahrs, O.H. Use of ileal reservoir following proctocolectomy. Surg. Gyn. Obst. 141:363-366, 1975.

Beart, R.W., Jr., McIlrath, D.C., Kelly, K.A., van Heerden, J.A., Mucha, P., Jr., Dozois, R.R., Adson, M.A., and Culp, C.E. Surgical management of inflammatory bowel disease. In: Current Problems in Surgery, Volume 17, Ravitch, M.M., and Steichen, F.M. (eds.)., Year Book Medical Publishers, Inc., Chicago, 1980, pp. 534-584.

Cattell, R.B. The surgical treatment of ulcerative colitis. Gastroenterology 10:63-80, 1948.

Dennis, C., and Karlson, K.E. Surgical measures as supplements to the management of idiopathic ulcerative colitis: Cancer, cirrhosis, and arthritis as frequent complications. Surg. 32:892-912, 1952.

Farnell, M.B., van Heerden, J.A., Beart, R.W., and Weiland, L.H. Rectal preservation in nonspecific inflammatory disease of the colon. Ann. Surg. 192: 249-253, 1980.

Fonkalsrud, E.W., Ament, M.E., and Byrne, W.J. Clinical experience with total colectomy and endorectal mucosal resection for inflammatory bowel disease. Gastroenterology 77:156-160, 1979.

Fonkalsrud, E.W. Total colectomy and endorectal ileal pull-through with internal ileal reservoir for ulcerative colitis. Surg. Gyn. Obst. 150:1-8, 1980.

Goligher, J.C. The quest for continence in the surgical treatment of ulcerative colitis. In: Ulcerative Colitis: Postsurgical Continence, Year Book Medical Publishers, 1980, 53-83.

Grundfest, S.F., Fazio, V., Weiss, R.A., Jagelman, D., Lavery, I., Weakley, F.L., and Turnbull, R.B. The risk of cancer following colectomy and ileorectal anastomosis for extensive mucosal ulcerative colitis. Ann. Surg. 193:9-14, 1981.

Hulten, L., Kewenter, L., and Kock, N.G. The long-term results of partial resection of the large bowel for intestinal carcinomas complicating ulcerative colitis. Scand. J. Gastroent. 6:601-604, 1971.

Kurtz, L.M., Flint, G.W., Platt, N., and Wise, L. Carcinoma in the retained rectum after colectomy for ulcerative colitis. Dis. Col. Rect. 23:346-350, 1980.

Martin, L.W., LeCoultre, C., and Schubert, W.K. Total colectomy and mucosal proctectomy with preservation of continence in ulcerative colitis. Ann. Surg. 186:477-480, 1977.

May, R.E. Sexual dysfunction following rectal excision for ulcerative colitis. Brit. J. Surg. 53:29-30, 1966.

Burnham, W.R., Lennard-Jones, J.E., and Brooke, B.N. Sexual problems among married ileostomists. Gut 18:673-677, 1977.

Mayo, C.W., Fly, O.A., Jr., and Connelly, M.E. Fate of the remaining rectal segment after subtotal colectomy for ulcerative colitis. Ann. Surg. 144: 753-757, 1956.

Parks, A.G., and Nicholls, R.J. Proctocolectomy without ileostomy for ulcerative colitis. Brit. Med. J. 2:85-88, 1978.

Parks, A.G., Nicholls, R.J., and Belliveau, P. Proctocolectomy with ileal reservoir and anal anastomosis. Brit. J. Surg. 67:533-538, 1980.

Peck, D.A. Rectal mucosal replacement. Ann. Surg. 191:294-303, 1980.

Johnston, D., Williams, N.S., Neal, D.E., and Axon, A.T.R. The value of preserving the anal sphincter in operations for ulcerative colitis and polyposis: A review of 22 mucosal proctectomies. Brit. J. Surg. 68:874-878, 1981.

Ravitch, M.M., and Sabiston, D.C. Anal ileostomy with preservation of the sphincter. A proposed operation in patients requiring total colectomy for benign lesions. Surg. Gyn. Obst. 84:1095-1099, 1947.

Ritchie, J.K. Ileostomy and excisional surgery for chronic inflammatory disease of the colon: A survey of one hospital region. Gut 12:528-540, 1971.

Ritchie, J.K. Ulcerative colitis treated by ileostomy and excisional surgery. Fifteen years' experience at St. Mark's Hospital. Brit. J. Surg. 59:345-351, 1972.

Saegesser, F., and Waridel, D. Does the frequency of canceration in ulcerative colitis justify a prophylactic proctocolectomy? Am. J. Proctology 20:33-44, 1969.

Scoma, J.A. Current concepts of rectum and sphincter preservation in inflammatory bowel disease. Dis. Colon. Rectum 24:370-372, 1981.

Telander, R.L., and Perrault, J. Total colectomy with rectal mucosectomy and ileoanal anastomosis for chronic ulcerative colitis in children and young adults. Mayo Clin. Proc. 55:420-424, 1980.

Watts, J.M., de Dombal, F.T., and Goligher, J.C. Early results of surgery for ulcerative colitis. Brit. J. Surg. 53:65-1005-1015, 1966.

Williams, J.T., and Slack, W.W. A prospective study of sexual function after major colorectal surgery. Brit. J. Surg. 67:772-774, 1980.

CONCLUDING COMMENTS

Ulcerative colitis is a serious condition. Those few patients whose disease cannot be controlled with medical therapy should be subjected to surgery. Patients whose disease can be controlled medically (even those in apparent remission) are nevertheless at high risk for developing cancer, especially those with pancolitis of more than 10 years duration. The optimal approach to the follow-up and treatment of these latter patients has not been determined. Choices include (a) an intensive and periodic endoscopic, histologic, and radiologic search for precancer (or early cancer) or (b) elective proctocolectomy (ideally with an operation that allows fecal continence without an ileostomy). Additional prospective studies of the significance of dysplasia (precancer) on a colonic biopsy specimen are necessary to facilitate clinical decision making in the care of these patients.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to Dr. Ed Lee (Pathology Dept.), Dr. Herb Smith (Radiology Dept.) and Ms. Pat Ladd (Medical Media Section) for their invaluable assistance and also to Ms. Vicky Usry for preparing the text.