Regional Enteritis and Entero-Colitis:

A Study of 74 Patients over 15 Years

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SINCE the description of the clinical and pathological entities of regional enteritis by Crohn, Ginzburg, and Oppenheimer in 1932 [8] and of granulomatous enterocolitis by Colp in 1934,[7] these diseases have been of special interest to the staff of the Mount Sinai Hospital. Previous reports from this institution have involved mainly patients seen on the private service. This paper reviews the experience from 1950 to 1965 with 74 patients treated on the ward service of the hospital and subsequently followed in the outpatient department or in staff members offices. The purpose in presenting this group of ward patients is to emphasize the high rate of recurrence and the less than satisfactory long-term postoperative outlook.

Clinical Material

The records of all ward patients seen in the Mount Sinai Hospital with a diagnosis of regional enteritis were reviewed. Many had histories dating from the decade 1930–1939 and one from 1929. The patients under review had chronic or recurrent granulomatous disease of the small intestine proven radiologically or pathologically. Included are those initially operated upon at The Mount Sinai Hospital, others with a first operation elsewhere, and a small group not operated upon. All patients with postoperative clinical recurrences had radiographic confirmation. All patients with recurrent disease visible on x-rays ultimately developed further symptoms of the disease.

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Patients with granulomatous colitis without small bowel disease have not been included, nor those with chronic ulcerative colitis and "backwash" ileitis. Also excluded were patients with acute regional enteritis who did not progress clinically or radiologically.

Thirty-seven per cent (27/74) of the patients had granulomatous enterocolitis. Of these, in 11 onset was in the small intestine, with subsequent progression to the colon; in five initial manifestations were in the colon, and 11 had combined disease at the time of diagnosis. In 6 of the 27, the diagnosis was made after 1962, and the disease was called granulomatous ileo-colitis. In 9, cecal disease was found adjacent to involved ileum at operation or on x-rays. Since the other 12 patients also had small bowel disease, the diagnosis of granulomatous colitis was warranted from the clinical course, despite the difficulties of making this diagnosis retrospectively.[16]

1. Sex

Sex distribution of the group was almost equal consisting of 36 women and 38 men (Table 1). Men predominated in those with enteritis alone, but there were more women amongst those with enterocolitis.

2. Race

Although this hospital serves a large Negro and Puerto-Rican population, only two Negro patients were seen (both in 1966) and only three were Puerto-Rican.

3. Age

Half the patients (36/74) developed the disease before the age of twenty (Fig. 1). In most patients with enterocolitis (71%: 19/27) onset was prior to that age. Of those who died, 47% (7/15) developed the disease before age twenty.

4. Site

All levels of the gastrointestinal tract below the diaphragm were involved (Table 2). In 62% (46/74), the disease started in the distal ileum and in 63% of these (29/46) it remained confined to that area. Twenty-four per cent (18/74) had diffuse small bowel disease with "skip" areas involving the proximal ileum or jejunum. Three patients had gastric or duodenal involvement.

Analysis of the operative technics and results include only those procedures aimed at curing the disease by resection or bypass. Incision and drainage or abscesses, peri-anal operations, appendectomy, lysis of adhesions and repair of incisional hernia have not been included.

Follow-up has been undertaken by clinic attendance, letters to patients, and discussion with private physicians involved. Nine patients were lost to follow-up.

Recurrence is defined as symptomatic disease radiologically or surgically proven. Asymptomatic patients were not routinely x-rayed.

TABLE 1. *Distribution by Sex*

	Female	Male
Total number	36	38
Died	8	7
Enteritis	18	29
Enterocolitis	18	9

TABLE 2. *Location of Disease*

	Onset	Entire Course
Distal ileum	46	29
Colon, alone or with small intestine	16	27
Diffuse small intestine	12	18
Gastroduodenal	0	3*

* These three had involvement elsewhere and are included in one of the other groups.

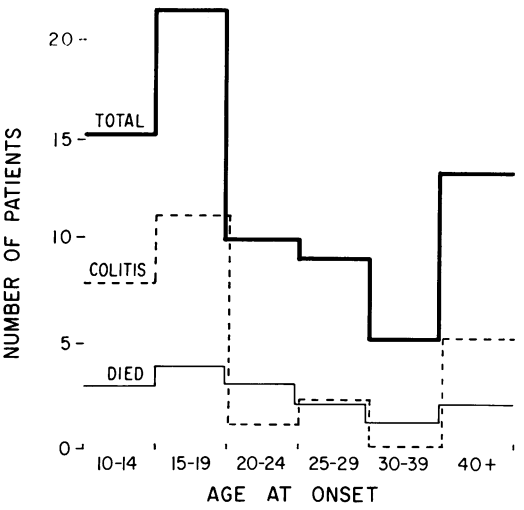

FIG. 1. Age distribution of 74 patients with regional enteritis and entero-colitis.

Results

Steroid Therapy. Thirty-three of the 76 patients (45%) were treated with ACTH gel, 40μ–80μ dosages, or cortisone derivatives, 60–80 mg. hydrocortisone/day dose ranges, at some time during the course of the disease. These dosages were ordered as clinical conditions warranted. Patients were usually given maintenance doses of steroids. Of this group, 13 (40%) required subsequent operation. The mortality rate of the steroid treated group was higher (24%) than that of the non-steroid treated group (17%) (Table 3), but the small numbers of patients and lack of a carefully designed prospective study of steroid treatment does not permit statistical validity.

Forty-six per cent (41/74) of the patients had bowel perforations and fistulas clinically and radiographically demonstrated. Perforation is defined as either free perforation of the bowel (which is rare) or localized perforation into the mesentery. The

TABLE 3. *Granulomatous Disease and Steroids*

	No Steroids			Steroids			Total		
	Number	Died	(%)	Number	Died	(%)	Number	Died	(%)
Enteritis	30	3	(10%)	17	3	(18%)	47	6	(13%)
Enterocolitis	11	4	(36%)	16	5	(31%)	27	9	(33%)
Total	41	7	(17%)	33	8	(24%)			

latter may go on to a walled-off intraperitoneal abscess, a retroperitoneal abscess, or a fistula into adjacent hollow viscus or to the skin. Fifty-five percent (18/33) of steroid treated patients had perforations at some time in the course of the disease. In 33% (11/33) of steroid treated patients, perforations occurred while the patients were taking these drugs (Table 4). Six of these 11 perforations occurred during the first year of steroid therapy, two in the second year, and the remaining three occurred up to 6 years after the start of steroid therapy.

Surgical Therapy. One hundred and thirty-four curative operations were undertaken on 61 patients: an average of 2.2 operations per patient (Table 5). Thirty-five patients had more than one operation; one patient had eight. Enterocolostomy with exclusion was more frequent as an initial operation (24), than resection (19) (Table 6).

Incidence of Recurrent Disease. All six patients who had bypass operations in continuity without total exclusion suffered progressive active disease. Of the 19 patients who had resections of the terminal ileum, either with or without adjacent color, 14 (74%) developed recurrent disease (Table 6). Of the 24 patients who had bypass operations with transection of the bowel, 16 (67%) had recurrences.

The average number of symptom-free years in 43 patients who had postoperative recurrences was 4.1 (Table 7). Seventy-nine per cent (34/43) of recurrences (almost invariably at the anastomotic site) occurred within five years of operation. Only five of these 43 patients were symptom free for 10 years or longer, the longest being 19 years. The period of remission was twice as long in those in whom resections were performed (5.3 years) as in the bypass group (2.7 years). Reoperations were done for recurrences. Few difficulties arose in or because of bypass segments.

Overall results of treatment are seen in Figures 2 and 3. Nine patients were lost in follow-up. Fifteen patients died (20%), 13 of these were operated upon and two were not. These will be discussed below. Twelve of the 15 who died had postoperative recurrences at the time of death (five with regional enteritis and seven with enterocolitis). Seven patients had no operation. Of the remaining 43 patients, in 27 recurrences occurred postoperatively and in 16 there were no recurrences. Of this latter group, seven have been followed less than 5 years. Since 79% of recurrences occurred in 5 years and since this survey includes some followed for shorter periods, the recurrence rate is probably artificially low at this time. In no instances of granulomatous colitis did proximal extension of disease to the small intestine occur without operative intervention.[3]

Fifteen Deaths

A) Nine patients died from the disease or from complications of treatment. Three deaths in the immediate postoperative period include one from peritonitis during steroid therapy, one following massive gastrointestinal hemorrhage which in turn followed serum hepatitis and steroid therapy, and one following deep venous thrombosis

TABLE 4. *Perforations and Steroids*

	No Steroids	Steroids	Perforation while Receiving Steroids
No perforation	18	15	
Perforation	23	18	11
Totals	41	33	

TABLE 5. *Number of Operations*

Number of Operations	Number of Patients
0	13
1	26
2	14
3	13
4	4
5	1
6	2
7	0
8	1
Total number of operations	134
Average number of operations/patient	2.2

of the leg and a subsequent stroke. The remaining six deaths resulted from a variety of complications months or years later (Table 8).

B) Two patients died from rectal carcinomas with metastases and both had granulomatous colitis with clinical rectal involvement. There were no instances of small intestinal carcinoma.

C) Four other patients died from unrelated or questionably related causes (Table 8).

All deaths fell into one of two groups: those who had the disease for less than 10 years and those who had it more than 20 years. Of seven patients who had the disease for 10 years or less, all except one died of causes related to regional enteritis. The exception died of malignant nephrosclerosis, although there was active enterocolitis at the time of death.

The other eight patients died 20 years or more after diagnosis. Only three died of

TABLE 6. *Type of First Operation*

	Total Number	MSH Number	Recurrence
Resection, ileocolic or small intestine	19	9	14
Entero-colostomy with exclusion	24	19	16
Entero-colostomy in continuity	6	3	6
Colectomy and ileostomy	6	6	4
Massive small bowel resection	2	2	1
Other	4	3	2

TABLE 7. *Analysis of Recurrence*

Number of recurrences	43
Range—symptom free years	0–19
Years:	
0	11
1–5	23
6–10	4
10–over	5
Average number symptom free years	4.1 (30)
Entero-colostomy with exclusion	2.7 (16)
Resection—ileocolic or small intestine	5.3 (14)

causes directly related to regional enteritis. The other five died of malignant tumors (Table 8).

Figures 1, 2, and 3 illustrate the clinical courses of the group. Of 40 patients with regional enteritis (Fig. 2), 35 (87%) were operated upon and 23/35 (66%) had postoperative recurrences. Five of those with recurrences died. The sixth death of a patient with regional enteritis occurred 2 months after operation following a central nervous system hemorrhage secondary to thrombocytopenic purpura of unknown cause. The five patients who were not operated upon are alive 3–11 years after onset of the disease.

Of the 25 patients with granulomatous enterocolitis who were followed (Fig. 3) 21 (84%) were operated upon and 17 (81%) had postoperative recurrences. Figures 4,

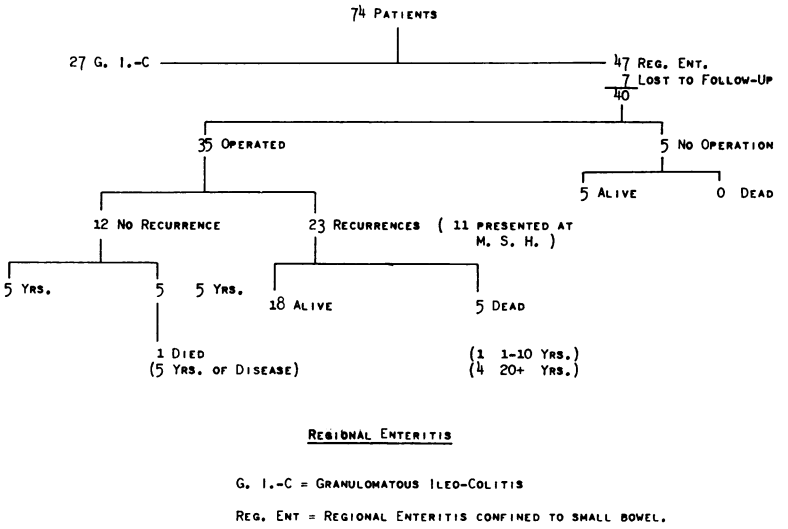

FIG. 2. Fate of 47 patients with regional enteritis.

5, 6, and 7 show the initial sites of disease and indicate operations performed as well as the sites of recurrence. Seven of these died. Of four patients not operated upon, one died of malignant nephrosclerosis, another of hemorrhage from colitis. The remaining two are well at the time of follow-up, but disease has been present for less than a year.

Discussion

When subdivided into varieties of the disease, this group of 74 patients is not large, and some categories have small numbers of cases. Statistical analysis is not possible, but the development of the disease and its response to medical or surgical treatment over many years shows clearly discernible trends.

It is difficult to assess the results of steroid treatment. It is the impression of the surgical staff that the use of steroids in regional enteritis has led to a higher rate of perforation of the bowel with fistulization into adjacent hollow viscera or skin. Forty per cent of patients who received steroids required subsequent operations; the average number of operations per patient in this group was 1.5, compared with 2.0 in the non-steroid treated group. This might support the view that steroid therapy obviates the need for operation in some patients. On the other hand, mortality in the steroid treated group was slightly higher (24%) than in the non-steroid group (17%). Sixty-four per cent of those who died with active disease were taking steroids at the time of death.

While many toxic patients become afebrile while taking these drugs, inflammatory processes often continue and are masked by the drugs. Several patients seemed to have a virtual "explosion" of fistulae as seen on the follow-up x-ray examination after steroids were started. Even if no gross fistulization is obvious, microabscesses and fistulae of the bowel wall are found in resected specimens. Thus, there seems to be a stronger argument for not administering steroids for patients known to have had perforations.

When steroids were first used between 1950 and 1953, perforation or hemorrhage from diseased sites in the gastrointestinal tract were reported in association with these drugs.[13, 19, 20] In 1959, Garlock[11] stated that the increased incidence of perforation seen in chronic ulcerative colitis was "undoubtedly due to the indiscriminate and prolonged use of steroids."

Jones and Lennard-Jones[17] recently reviewed their experience with regional en-

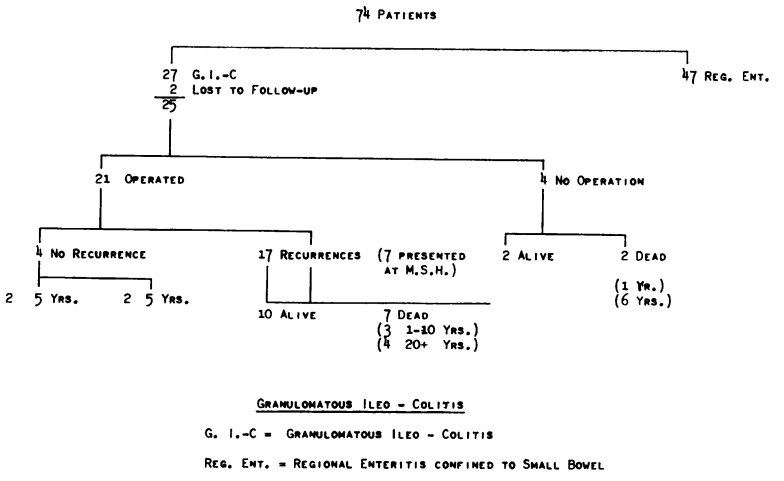

FIG. 3. Fate of 27 patients with granulomatous ileo-colitis.

teritis and steroids. Of 30 patients, three became worse, five showed no change, and 22 showed initial improvement. However, of these latter, four died, eight needed subsequent operations; and seven required long-term steroid therapy for continuing active disease. Recurrence occurred in one of three patients who had been weaned off steroids. Of 15 brief case histories, four patients developed perforations while taking steroids; in two others this possibility could not be ruled out from the information given. The authors concluded that the drugs were useful only to abort an acute attack and not for long-term management.

TABLE 8. *Causes of Death*

	Number
Died of disease:	9
Peritonitis	2
GI bleeding	3
Malabsorption	1
Deep venous thrombosis	1
CNS bleeding, ITP	1
Unknown	1
Died of cause questionably related to disease	3
Rectal carcinoma	2
Metastatic adeno carcinoma, primary site unknown	1
Died: Unrelated cause	3
Malignant nephrosclerosis	1
Metastatic adeno carcinoma, primary site unknown	1
Lymphosarcoma	1
Total	15

The present study could not demonstrate either long-term efficacy or harm from steroids. Nevertheless, the data suggest that these effects are harmful. There is need for operation in 40% of patients receiving steroids, an equal or slightly increased mortality rate, and a chance of abetting and masking fistulization. A long-term study is needed to define more clearly the role of steroids in granulomatous disease of the bowel.

Regardless of how unimpressive steroids seem to be, surgical results are also discouraging. The recurrence rate following either small bowel resection or bypass with exclusion is equally high, although those with resections had longer palliation. Since all patients who had bypass operations without exclusion had continuing active disease, this technic should be used only under most unusual circumstances.[14]

The overall recurrence rate in those operated upon was 71% (40/56)—66% in those with regional enteritis and 81% in those with granulomatous enterocolitis. Forty-five per cent (18/40) of patients with re-

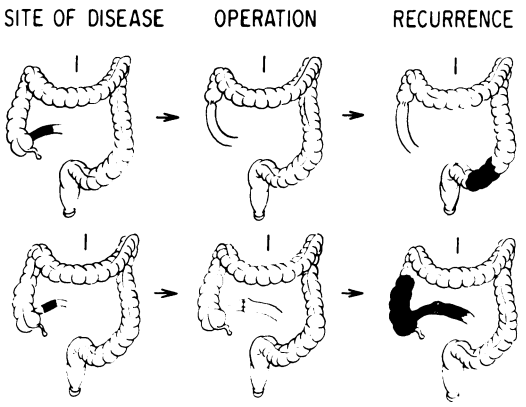

FIG. 4. Two instances of localized ileitis with postoperative large bowel recurrence.

currences were referred to the hospital after having been operated upon elsewhere. Since recurrence is characteristic of the disease, referred recurrent cases have been included in the series. Of patients originally operated upon at The Mount Sinai Hospital, 58% (22/40) developed recurrences.

There is considerable variation in other reports regarding results of surgical treatment of regional enteritis. The most gratifying figures are quoted by Barber *et al.*[3]: Nineteen per cent recurrences with an average follow-up of 10 years. Colcock and Vansant[6] reported a 37% recurrence rate. Garlock[10] in a series of private patients from The Mount Sinai Hospital reported a 23 to 46% recurrence rate, depending on the type of operation. In discussing this paper, Bockus[4] cited his recurrence rate as being greater than 50%. Sixty-three per cent of Brown and Baffner's patients[5] had postoperative recurrences. Jackson[5] reported a 55% overall recurrence rate in a series in which 93% of the patients were operated upon. He defined a good result as no recurrence within 4 years, implying that operation is, at best, only palliative.

Crohn[9] reported a recurrence rate of 14–20% in 1945—a figure revised to 22.5% in 1951 and to about 30% in 1957. Most recently Atwell *et al.*[1] reported a 62% recurrences and 15% mortality rate.

It is difficult to explain this wide variation. Since late recurrence is not uncommon, the incidence will tend to rise with increasing time of follow-up. Combined granulomatous disease of the small and large intestine tends to be more severe. Hence any series weighted with such patients will have higher recurrence and mortality rates.

Although this series consisted of ward service patients, malnutrition seemed to be more a result of the underlying disease than of socio-economic factors. Moreover, malnutrition, while it might explain a high mortality rate, probably does not account for recurrences.

Indications for operation and the technics employed were supervised by members of the Surgical Staff who had considerable experience in the field.

Apart from recurring morbidity affecting young people, 20% of the patients died in the course of the disease. Patients who died had the diseases for an average of 14.6 years, the range being 1 to 27 years. Those with regional enteritis had the disease for somewhat longer periods prior to death

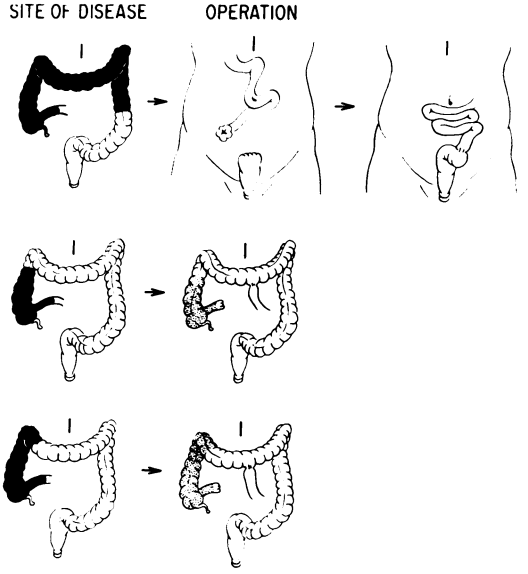

FIG. 5. Three instances of ileo-colitis with no recurrence after operation.

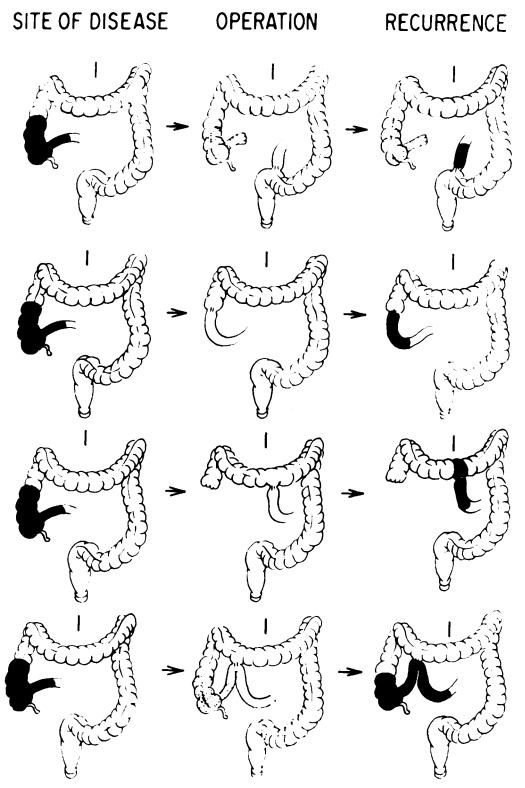

FIG. 6. Four cases of localized ileo-colitis. All developed postoperative recurrence in the proximal segment, two of which in addition involved adjacent large bowel.

(17.3 years) than did those with granulomatous enterocolitis (12.8 years). The mortality rate for GEC was 33%; for regional enteritis, 13%.

Nine patients died as a result of the disease, three died of unrelated causes. In three the relationship is questionable, in that two died of metastatic rectal adenocarcinoma. Both had granulomatous colitis with rectal involvement. They were 45 and 65 years old at the time of death and had granulomatous disease for 23 and 26 years, respectively. It is impossible to say whether carcinoma is related to prolonged inflammatory disease or not. The third patient died of metastatic adenocarcinoma, primary source unknown. At laparotomy he had general peritoneal carcinomatosis. He had regional jejunitis for 20 years. Jejunum is the site of origin of primary small bowel carcinomas reported associated with regional enteritis.[2, 12, 18]

As a result of experience with regional enteritis, present surgical judgment is that palliation is the best that can be offered these unhappy patients and thus, surgical procedures have become more conservative. If the patient can tolerate his symptoms, operation should be withheld. For example, a patient with cramps, diarrhea, and a fistula into an adjacent ilial loop or cecum is given a prolonged trial of medical therapy, bed rest, low residue diet, and nonabsorbable antibiotics. A short course of steroids may be used to control toxicity, but these drugs should be avoided, if possible, if there is a fistula or abscess. The same approach should be tried in a patient with a right lower quadrant mass, but in such instances fistulization and symptoms are likely to continue. Operation may be required at a later date. Intestinal obstruction usually responds to intestinal intubation, although a 2 to 3 weeks trial is sometimes necessary. Operation should be considered if this fails.

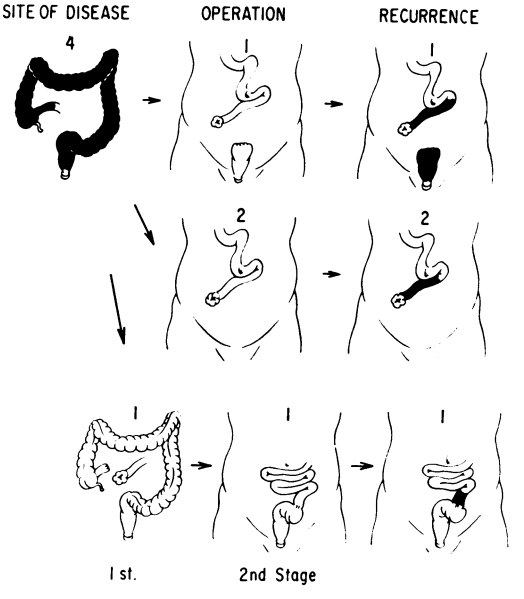

FIG. 7. Four cases of universal granulomatous ileo-colitis. All developed recurrence.

Clear surgical indications are: 1) vaginal or vesical fistulae, or sigmoid fistulae with diarrhea; 2) unrelenting or frequently recurring obstruction; 3) free perforation; 4) severe hemorrhage; 5) severe peri-anal suppuration, or 6) the combination of fever, weight loss, and debility unresponsive to intensive medical regimen.

That 20–25% of patients who began with localized ileitis progressed to colonic involvement (Table 2) further supports a conservative approach.

In general, the patients are young. To go to work or school, even with some symptoms, is not unsatisfactory in the light of present methods or treatment. Such a course is preferable to a short lived surgical success with the risk of recurrence within 5 years in not less than 2/3 of patients with enteritis and 4/5 of those with granulomatous enterocolitis.

Summary

1. Seventy-four patients with regional enteritis seen at The Mount Sinai Hospital since 1950 are reviewed. All levels of the gastrointestinal tract below the diaphragm were involved.

2. Results of steroid and surgical treatment are discussed. Forty per cent of those treated with steroids required subsequent operations. Nearly 1/4 of the steroid treated patients died. The postoperative recurrence rate was 70%, 4/5 of recurrences within five years. The mortality rate for the entire series was 20%.

3. Conservative treatment is urged for these patients. Both steroids and operative surgery should be withheld whenever possible. Clear indications for operation and steroid administration are presented.

References

1. Atwell, J. D., Duthie, H. L. and Goligher, J. C.: The Outcome of Crohn's Disease. Brit. J. Surg., 52:966, 1965.
2. Berman, L. G. and Prior, J. T.: Adenocarcinoma of the Small Intestine Occurring in a Case of Regional Enteritis. J. Mount Sinai Hosp., 31:30, 1964.
3. Barber, Jr., K. W., Waugh, J. M., Beahrs, O. H. and Sauer, W. G.: Indications for and the Results of the Surgical Treatment of Regional Enteritis. Ann. Surg., 156:472, 1962.
4. Bockus, H. L.: Discussion of Paper II. Gastroenterology, 19:421, 1951.
5. Brown, C. H. and Daffner, J. E.: Regional Enteritis II, Results of Medical and Surgical Treatment in 100 Patients. Ann. Int. Med., 49:595, 1958.
6. Colcock, B. P. and Vansant, J. H.: Surgical Treatment of Regional Enteritis. New Eng. J. Med., 262:435, 1960.
7. Colp, R.: A Case of Nonspecific Granuloma of the Terminal Ileum and Cecum. Surg. Clin. N. Amer., 14:443, 1934.
8. Crohn, B. G., Ginzburg, L. and Oppenheimer, G.: Regional Ileitis—A Pathological and Clinical Entity. JAMA, 99:1323, 1932.
9. Crohn, B. B. and Yarnis, H.: Regional Enteritis. New York, Grune and Stratton, 2nd Revised Edition, 1958, p. 140.
10. Garlock, J. H.: An Appraisal of the Long-Term Results of Surgical Treatment of Regional Enteritis. Gastroenterology, 19:414, 1951.
11. Garlock, J. H.: Surgical Treatment of Ulcerative Colitis. Dis. Colon, Rectum, 2:529, 1959.
12. Ginzburg, L., Schneider, K. M., Dreizen, D. H. and Levinson, C.: Carcinoma of the Jejunum Occurring in a Case of Regional Enteritis. Surgery, 39:347, 1956.
13. Habif, D. V., Hare, C. C. and Glaser, G. H.: Perforated Duodenal Ulcer after ACTH Therapy. JAMA, 144:996, 1950.
14. Heaton, L. D., Ravdin, I. S., Blades, B. and Whelan, J.: President Eisenhower's Operation for Regional Enteritis. Ann. Surg., 159:661, 1964.
15. Jackson, B. B.: Chronic Regional Enteritis. Ann. Surg., 148:81, 1958.
16. Janowitz, H. D.: Notes of the Panel of Granulomatous Colitis of the Annual Meeting of the American Gastroenterological Association. Gastroenterology, 51:588, 1966.
17. Jones, J. H. and Lennard-Jones, J. E.: Corticosteroids aind Corticotropin in the Treatment of Chronic Disease. Gut, 7:181, 1966.
18. Kornfeld, P., Ginzburg, L. and Aldersberg, D.: Adenocarcinoma Occurring in Regional Jejunitis. Amer. J. Med., 23:493, 1957.
19. Sauer, W. G., Brown, P. W. and Dearing, W. H.: Experience with the Use of Corticotropin in Regional Enteritis. Gastroenterology, 22: 550, 1952.
20. Sauer, W. G., Dearing, W. H. and Wollaeger. E. E.: Serious Untoward Gastrointestinal Manifestations Possibly Related to Administration of Cortisone and Corticotropin. Proc. Staff Meeting, Mayo Clinic, 28:641, 1953.