Patterns of Ileal Recurrence in Crohn's Disease

A Prospective Randomized Study

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To gain information on the pathogenesis of ileal recurrence, 86 patients with Crohn's disease undergoing their first ileocolic resection were randomized to receive either an end-to-end (n = 47) or side-to-end (n = 39) anastomosis. The demographic and clinical characteristics of both groups were similar. There were no statistically significant differences between the two groups in postoperative complications or in the subsequent development of symptomatic or documented recurrences. Among the 43 patients with follow-up in the end-to-end anastomosis group, there were 10 documented ileal recurrences (23%), and all involved distal ileum in the characteristic preanastomotic location. Among the 35 patients with follow-up in the side-to-end anastomosis group, there were 11 documented recurrences (31%, not significant). The ileal recurrence pattern could be determined accurately in five of these 11 patients and involved the ileum adjacent to the colon, but spared the distal ileum in the blind pouch. This study suggests that the fecal stream and reflux of colonic contents are important factors in determining the pattern of ileal recurrence after ileocolectomy for Crohn's disease.

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RECURRENCE OF CROHN'S disease after resection of distal small bowel and proximal colon characteristically involves the small bowel just proximal to the anastomosis.[1,2] This typical recurrence pattern was noted by Crohn in his original article published in 1932.[3] He attributed preanastomotic recurrence to inadequate resection, assuming that residual disease had been left in the distal ileum. A variety of other explanations have been offered for the pattern of recurrence after resection.[4] These include passage of an agent from mesenteric lymph nodes to the resection margin; the presence of the suture line itself, which could induce local ischemia or local immunologic changes; or reflux of colonic contents into the ileum.[2,4] Restoration of enteric continuity by side-to-end anastomosis allows assessment of some of these explanations. With this type of anastomosis, a small blind pouch of ileum is exposed to mesenteric lymph nodes and contains a suture line, but is not directly in the fecal stream and should not be exposed to reflux of colonic contents. Therefore, a prospective randomized study was carried out to compare similarities and differences in the recurrence pattern after end-to-end and side-to-end anastomosis (Fig. 1).

Clinical Material

Between April of 1983 and February of 1991, 92 patients undergoing first-time resection of terminal ileum and proximal right colon for Crohn's disease were randomized to receive either an end-to-end or side-to-end anastomosis. Randomization was performed at the beginning of the operative procedure by picking from an envelope a card on which was written either end-to-end or side-to-end. Six patients were subsequently excluded from analysis. In two patients the pathology of the resected specimen did not confirm the preoperative diagnosis of Crohn's disease. In one patient, an end-to-side anastomosis was performed in error instead of a side-to-end ileocolostomy. An additional patient underwent a side-to-side anastomosis for technical reasons. A decision was made in a fifth patient, after randomization, not to perform a resection. The final patient had only small bowel resected, and therefore was excluded. This left 86 patients in the study.

All patients underwent resection of all gross disease in the terminal ileum, or terminal ileum and proximal colon,

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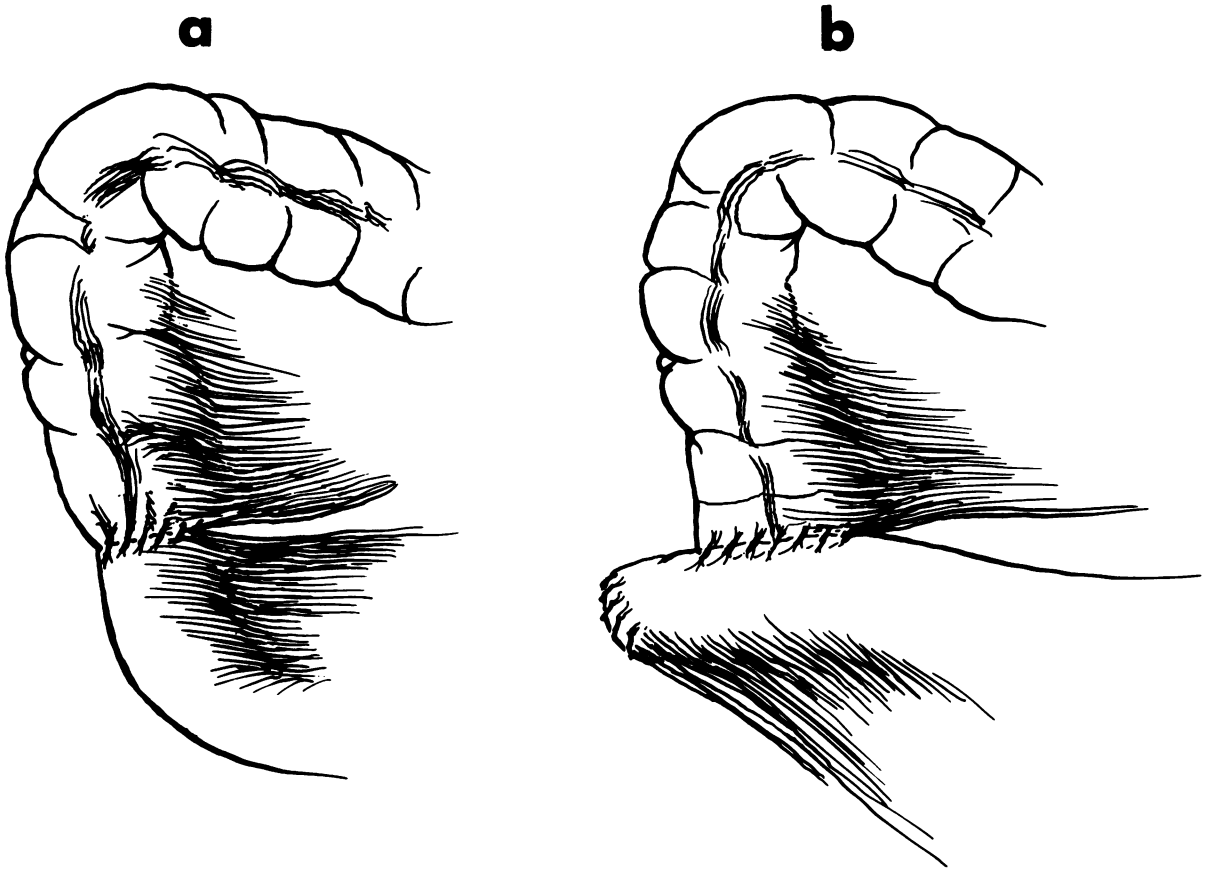

FIG. 1. After ileocolic resection, the ileocolostomy was performed in either (A) an end-to-end or (B) a side-to-end fashion on a random basis.

taking approximately a 5-cm margin of normal bowel both proximally and distally. End-to-end anastomoses were performed in a standard fashion with an inner continuous layer of absorbable synthetic suture material, and an outer layer of interrupted silk. Side-to-end ileocolostomies were performed with a similar technique, after closing the end of the ileum with an inner continuous layer of absorbable synthetic suture material, and an outer layer of interrupted silk. The blind pouch of ileum in the side-to-end group was approximately 1 inch in length.

Age of the 86 patients ranged from 12 to 68 years, with a mean of 31 years. Thirty-nine patients were men, and 47 were women. Disease duration before surgery ranged from 0.2 to 25 years, with a mean duration of 6.4 years. Body weight ranged from 34 to 99 kg, with a mean weight of 60 kg. Preoperative hematocrit varied from 28% to 49%, with a mean of 37%. White blood count ranged from 3.1 to 21 thousand, with a mean of 9.8 thousand. Serum albumin levels ranged from 2.3 to 5 g/dL, with a mean of 3.9 g/dL (Table 1).

The most common indications for surgical intervention were partial intestinal obstruction with crampy abdominal pain and diarrhea, fistula formation, or intra-abdominal abscess (Table 2). Before surgery, all patients had received drugs in an attempt to ameliorate their symptoms, and to control their inflammatory bowel disease. The medications used and the length of time administered were extremely variable. At surgery, all patients underwent resection of the terminal ileum and proximal colon for ileal or ileocolic Crohn's disease. In addition, eight patients had resection of another segment of small bowel (1) or large bowel (7), one had a stricturoplasty performed, 31 had division of one or more entero-enteric, enterovesical,

TABLE 1. *Patient Demographics*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Age (yr)	31 (12–60)	31 (14–68)	31 (12–68)
M/F	19/28	20/19	39/47
Disease duration (yr)	6.3 (0.2–20)	6.6 (0.5–25)	6.4 (0.2–25)
Weight (kg)	60 (34–94)	61 (34–99)	60 (34–99)
Hematocrit (%)	37 (28–43)	38 (30–49)	37 (28–49)
White blood count (1000)	9.7 (3.1–21)	9.9 (5.0–16.1)	9.8 (3.1–21.0)
Albumin (g/dL)	3.8 (2.3–5.1)	4.0 (2.9–5.0)	3.9 (2.3–5.1)

TABLE 2. *Indications for Surgery*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Surgical indications			
Total obstruction	0	1	1
Partial obstruction	41	33	74
Bleeding	0	1	1
Perforation	1	0	1
Fistula	16	15	31
Abscess	6	4	10

Some patients had more than one indication for surgery.

TABLE 3. *Operative Management and Postoperative Course*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Length of resection			
Small bowel (cm)	28 (1–90)	29 (6–120)	28 (1–120)
Large bowel (cm)	9 (1–39)	10 (3–40)	9 (1–40)
Pathology			
Active	44	39	83
Inactive	3	0	3
Other operative procedures			
Small bowel resection	1	0	1
Large bowel resection	2	5	7
Stricturoplasty	1	0	1
Division of enterofistula into			
Bowel	9	10	19
Bladder	5	8	13
Vagina	2	1	3
Drainage of intra-abdominal abscess	6	4	10
Postoperative complications			
Urinary tract infection	1	0	1
Small bowel obstruction	0	2	2
Wound infection	0	1	1
Fever	0	1	1
Total	1	4	5
Postoperative mortality rate	0	0	0
Postoperative days	8 (5–12)	9 (6–16)	8 (5–16)

or enterovaginal fistulas, and 10 had drainage of an intra-abdominal abscess.

Forty-seven patients were randomized to receive an end-to-end ileocolostomy, and 39 patients were randomized to receive a side-to-end ileocolostomy. The demographics and clinical characteristics of these two groups did not differ significantly one from the other, or from the group as a whole (Table 1). A mean of 28 cm of small bowel and 9 cm of large bowel were resected in those patients undergoing an end-to-end anastomosis, as compared with a mean of 29 cm of small bowel and 10 cm of large bowel in those undergoing a side-to-end anastomosis. A total of 26 other operative procedures were performed at the same time in those patients undergoing an end-to-end anastomosis, as compared with 24 other procedures performed in the group undergoing a side-to-end anastomosis. These differences were not statistically significant (Table 3). The pathology specimens demonstrated active disease in 44 of the 47 patients undergoing resection and end-to-end anastomosis, as compared with all 39 patients in the side-to-end anastomosis group.

There were no hospital deaths. After surgery there was one postoperative complication in the end-to-end group, and mean postoperative hospital stay was 8 days. In the side-to-end group, there were four postoperative complications, with a mean stay of 9 days. These differences were not statistically significant (Table 3). In addition, one patient in the side-to-end group developed symptoms 5 months after surgery, and a barium study demonstrated a small fistula leading from the end of the blind pouch. The patient was explored, the anastomosis resected, and an end-to-end ileocolostomy performed. Histopathologically there was no evidence of Crohn's disease in the specimen.

Clinical Course

Patients followed at The Johns Hopkins Hospital were seen periodically during the course of the study. These patients, and patients not followed at The Johns Hopkins Hospital, were contacted annually by questionnaire. Each patient's physician also was contacted annually. Follow-up information was available for 78 of the 86 patients. Follow-up ranged from 5 to 94 months, with a mean of 47 months. There was no statistical difference in length of follow-up in the end-to-end and side-to-end groups (Table 4).

A symptomatic recurrence was defined as abdominal pain or diarrhea that occurred at least once a week during follow-up. Forty of the 78 patients (51%) developed symptomatic recurrences. The prevalence was identical for both anastomotic groups (Table 4). Recurrence at the ileocolic anastomosis was documented in 10 of the 43 patients undergoing end-to-end anastomosis (23%), and

TABLE 4. *Clinical Course*

	Type of Anastomosis		
	End to End	Side to End	Total
Patients	47	39	86
Patients with follow-up	43	35	78
Duration (mo)	49 (6–94)	45 (5–91)	47 (5–94)
Symptomatic recurrence	22 (51%)	18 (51%)	40 (51%)
Documented recurrence at anastomosis	10 (23%)	11 (31%)	21 (27%)

TABLE 5. *Ileal Recurrences*

	Type of Anastomosis		
	End to End	Side to End	Total
Documented	10	11	21
Documented by			
Surgery	3	6	9
Barium studies	5	3	8
Endoscopy	2	2	4

in 11 of the 35 patients undergoing side-to-end anastomosis (31%). This difference was not statistically significant. In the end-to-end group, the recurrences were documented by surgery (n = 3), barium studies (n = 5), and endoscopy (n = 2). In all 10 patients developing a recurrence in the end-to-end group, the recurrence involved the distal ileum just proximal to the anastomosis. In the side-to-end group, the recurrences were documented by surgery (n = 6), barium studies (n = 3), and endoscopy (n = 2) (Table 5). In 5 of the 11 patients with a recurrence at the anastomosis in the side-to-end group, the anatomy of the recurrence could be accurately determined. Four of these patients were operated on, and one underwent colonoscopy. In each of the five patients whose recurrence could be documented, the recurrence was in the ileum adjacent to the colon at the anastomosis. Of particular note, the 1 inch of distal blind ileum in the side-to-end anastomosis was grossly normal (Fig. 2). In two of the patients in the side-to-end group requiring resection, the surgery was performed elsewhere and the exact pattern of recurrence could not be determined. In addition, in three patients in whom the recurrence was documented radiographically, and in one determined by endoscopy, the recurrence pattern at the anastomosis could not be determined accurately.

As was the case before operation, most patients received a wide variety of medications after operation to control or prevent symptoms or recurrence of their inflammatory bowel disease. These medications were administered for variable lengths of time. There were no discernible patterns in either group.

Discussion

The preanastomotic recurrence pattern after resection has fascinated physicians since Crohn's initial report,[3] but very little information explaining this phenomenon has evolved. The current study was carried out primarily to gain information as to factors that might influence this characteristic recurrence pattern. In addition, little information is available concerning the influence of the type of anastomosis on the subsequent course of Crohn's disease. Over the years, surgeons have treated Crohn's disease by surgical bypass, surgical exclusion, and surgical resection with end-to-end, side-to-end, end-to-side, or side-to-side anastomosis. There are virtually no controlled studies to support one anastomotic procedure over another. This study therefore also served as a basis to compare two different types of surgical anastomoses after resection for Crohn's disease.

The randomization process resulted in two groups of patients that were similar demographically. For age, sex, body weight, and disease duration, there were no statistically significant differences between the two groups. In addition, when hematocrit, white blood count, and serum albumin are used as criteria, both groups were healthy and comparable. In terms of indications for surgery, the amount of bowel resected at surgery, and the number of patients with active disease, both groups were also comparable. Thus the only clear difference between the two groups was the means by which enteric continuity was re-established after resection of the terminal ileum and proximal colon. In one group, an end-to-end anastomosis was performed. This is perhaps the anastomosis that is now most commonly used after resection of terminal ileum and proximal colon in patients with Crohn's disease. The second group received a side-to-end ileocolostomy. Although end-to-side and side-to-side anastomoses are more commonly used, a side-to-end anastomosis was chosen for the second group so that a segment of distal ileum extended beyond the anastomosis to test the possible explanations of preanastomotic recurrence.

Both groups of patients had similar courses after surgery. Length of follow-up was similar for both groups, an identical number of symptomatic recurrences developed in each group, and there was no statistically significant difference between the groups in the incidence of documented recurrence at the anastomosis. Thus, there was no clear advantage of one type of anastomosis over the other, and the clinical course of both groups was comparable. However, one patient in the side-to-end group developed a small fistula from the blind pouch 5 months after surgery and required re-exploration. Because there was no evidence of Crohn's disease in the specimen, this complication could be attributed to the side-to-end anastomosis.

The main purpose of the study was to compare the pattern of recurrence in each of these two types of anastomosis. As was expected, the recurrence pattern in those patients who had undergone an end-to-end anastomosis assumed the characteristic pattern of disease in the preanastomotic distal ileum, generally stopping at the suture line. By contrast, the five patients in the side-to-end anastomosis group in whom the anatomy of the recurrence could be adequately determined showed sparing of the distal portion of the ileum contained in the blind pouch. Rather, the recurrent disease developed in the ileum immediately adjacent to the ileocolostomy.

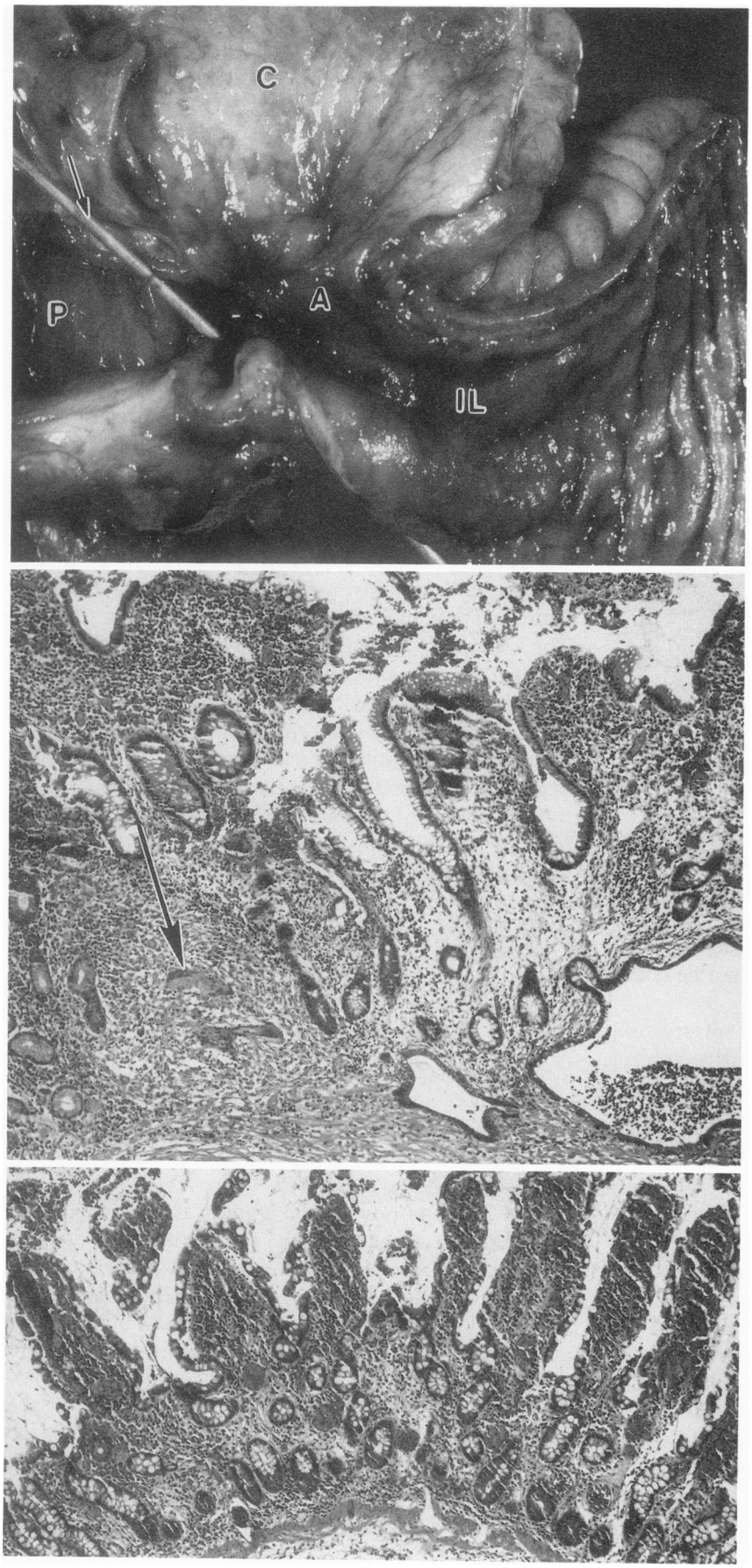

FIG. 2. Resected specimen of side-to-end ileocolonic anastomotic site with recurrent Crohn's disease. (A, top) In the gross specimen, the recurrence involves the ileum (IL) at the anastomotic site (A) with the colon (C). At this site, the ileum is strictured and gives rise to a fistula tract (containing probe indicated by arrow). By contrast, the blind pouch (P) of ileum distal to the anastomotic site is spared by recurrent Crohn's disease (×1.1). (B, center) Histopathologic features of preanastomotic ileum. Active Crohn's disease is manifested by a crypt abscess, noncaseating epithelioid cell granuloma (arrow) with pyloric metaplasia of adjoining ileal glands, villous blunting, chronic inflammation of the lamina propria, and fibromuscular proliferation of the subjacent muscularis mucosae (H&E, ×70). (C, bottom) Histopathologic features of blind ileal pouch distal to anastomotic site. Only mild villous blunting and chronic inflammation of the lamina propria are present, and there is no evidence of active Crohn's disease (H&E, ×70).

Even though the recurrence pattern seen in Crohn's disease has been recognized since Crohn's initial report, a logical explanation of this characteristic pattern has not been forthcoming. Initially, as Crohn suggested,[3] it was thought that inadequate resection left residual disease in the distal ileum. Because microscopic disease is often present throughout the entire small and large bowel,[5] and is no more likely at the resection margin than elsewhere, this explanation now seems untenable. Others have suggested that if the surgeon leaves hypertrophied lymph nodes behind in the root of the small bowel mesentery, some residual agent subsequently passes up to the ileal margin and is responsible for the recurrence. Although this theory has received support for many years, surgeons have been reluctant to perform the radical resections that would be required if one were to try to remove all of the enlarged lymph nodes in the root of the mesentery. The current study would appear to eliminate both of these explanations as possibilities. First, the recurrence pattern in patients who underwent a side-to-end anastomosis did not involve the distalmost portion of the ileum. If leaving residual disease behind at the resection margin, or leaving hypertrophied lymph nodes behind that contained an agent that would pass up to the resection margin of the distal ileum were important, the recurrence would have involved the distal ileum in the blind pouch. That was not the case, and in fact the blind pouch was spared grossly in all five instances in which the recurrence pattern could be determined. Furthermore, the pouch was spared histopathologically in all but one of the specimens resected at Hopkins. Finally, the suture line itself did not appear to be an important factor in determining recurrence because there was a suture line in the end of the blind pouch.

The recurrence pattern that was seen in the patients who developed recurrence after a side-to-end anastomosis suggests that the fecal stream and reflux of colonic contents into the ileum are important factors. Supporting evidence for this includes a unique patient recently seen at Hopkins who underwent resection of the terminal ileum for Crohn's disease. In the middle of the diseased bowel there was a narrow mouthed diverticulum, presumably relatively isolated from the fecal stream. The diverticulum was spared by the inflammatory process, and its mucosa was histopathologically uninflamed. In addition, Rutgeerts et al[6] have recently reported five patients who underwent ileocolectomy for Crohn's disease. All five patients underwent an ileocolostomy anastomosis, but were diverted proximally by an ileostomy. Six months later, endoscopy with biopsy showed no gross or microscopic disease in the neoterminal ileum. The ileostomies were then taken down and the fecal stream re-established over the neoterminal ileum. Six months after ileostomy takedown, endoscopy and biopsy demonstrated gross and microscopic Crohn's disease in the neoterminal ileum in all five patients. This study provides additional strong support for our evidence that the fecal stream and reflux of colonic contents into the ileum are important factors in determining the site of recurrence in Crohn's disease. This characteristic recurrence pattern in Crohn's disease undoubtedly contains important clues to the pathogenesis of this disease.

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Discussion

DR. GEORGE BLOCK (Chicago, Illinois): President Ochsner, Dr. Jones, Fellows of the Association, I wish to express my pleasure and my appreciation for your generosity and forbearance in electing me to membership in this distinguished group. I look forward to participation for many years and not only thank you but specifically thank my sponsors, Dr. Harrington, Dr. Sawyers, and Dr. Cohn.

Dr. Cameron's presentations are always provocative, sometimes perplexing. Today's are both provocative and perplexing. They are provocative because Dr. Cameron espouses the conventional wisdom. This is an unusual role for Dr. Cameron; he usually challenges conventional wisdom such as the anastomotic recurrence. It is perplexing because it is at variance with some of our own observations. Obviously, we use different methods of achieving our conclusions. His was a prospective study; ours was retrospective. He has relied on operative specimens, endoscopy, and radiographs; we believed and do believe that radiographic and endoscopic determinations of the exact pattern of recurrence are not reliable and look only to the examination of the resected specimens. We looked at several hundred of our patients who had recurrences. And they followed conventional wisdom for a segment of population. Fewer than one third had preanastomotic recurrences in the ileocolic group of Crohn's disease. Some of them or a good number of them were postanastomotic, and many of them were far distant from the anastomosis. This is not explainable by the thesis that Dr. Cameron has elaborated today, that the recurrence of Crohn's disease in the ileal segment is due to colonic reflux; I would caution against making this conclusion on the basis of five patients. This is almost anecdotal evidence. But if this thesis is correct, then we should perhaps vary our approach to this disease by trying to design some operation that would prevent colonic reflux, such as no anastomosis at all, and a stoma in all patients. Yet we know that patients who do have stomas and, for one reason or another, do not have anastomosis at the primary operation, are heir to recurrence usually below the fascial line of the stoma. We could, perhaps, do a total colectomy and abrogate the colon completely. Dr. Cameron's observations give some credence to the observation that in those patients in whom