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TREATMENT OF DIVERSION COLITIS WITH SHORT-CHAIN–FATTY ACID IRRIGATION

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Abstract A condition known as diversion colitis frequently develops in segments of the colorectum after surgical diversion of the fecal stream; it persists indefinitely unless the excluded segment is reanastomosed. The disease is characterized by bleeding from inflamed colonic mucosa that mimics the bleeding of idiopathic inflammatory bowel disease, and it may culminate in stricture formation. We hypothesized that this condition is caused by the absence of luminal short-chain fatty acids, the preferred metabolic substrates of colonic epithelium.

We studied four patients with diversion colitis, none of whom had evidence of Crohn's, idiopathic ulcerative, or infectious colitis. The excluded segment of the rectosigmoid contained negligible concentrations of short-chain fatty acids. When D-glucose was instilled, it did not undergo appreciable anaerobic fermentation. Instillation of a solution containing short-chain fatty acids twice daily resulted in the disappearance of symptoms and the inflammatory changes observed at endoscopy, over a period of four to six weeks. Remission has been maintained for up to 14 months (in one patient) by instillation daily to twice weekly. Administering enemas containing isotonic saline, or omitting treatment for periods of two to four weeks during the regimen, by contrast, did not produce any improvement or rapid relapse of the colitis. Histologic observation revealed a distinctive type of mucosal inflammation that resolved more slowly and less completely than the gross appearance of the inflamed mucosa.

From these preliminary studies we infer that diversion colitis may represent an inflammatory state resulting from a nutritional deficiency in the lumen of the colonic epithelium, which is effectively treated by local application of short-chain fatty acids, the missing nutrients. (N Engl J Med 1989; 320:23-8.)

DIVERSION colitis is an inflammatory process that occurs in segments of the colorectum after surgical diversion of the fecal stream. The condition is usually asymptomatic, but it may be manifested by drainage of bloody fluid and cramping pains.[1] Its incidence may be as high as 100 percent when it is observed prospectively, with the onset occurring between 3 and 36 months after operation.[2] The endoscopic characteristics of diversion colitis include erythema, friability, edema, nodularity, aphthous ulcerations, exudates, and frank bleeding — features similar to those of active idiopathic ulcerative and granulomatous colitis. The histologic changes may include crypt abscesses,[2] mucin granulomas, and lymphoid follicular hyperplasia.[3] The inflammation uniformly disappears after surgical reanastomosis; therapy with topical corticosteroids is rarely effective.[1-3] The natural history of this condition consists of unremitting inflammation that may progress to formation of strictures and a loss of function of the colonic segment.[2] The current inability to distinguish reliably between diversion colitis and active inflammatory bowel disease presents clinical problems when reanastomosis of an inflamed segment of the distal colorectum is contemplated. The cause of this condition is not known, but several mechanisms have been postulated — i.e., bacterial overgrowth of normal colonic flora, invasion of the bypassed segment by pathogenic organisms, or a nutritional deficiency of the colonic epithelium, specifically due to the absence of short-chain fatty acids (SCFAs) normally present in colonic contents. In this study we tested these three hypotheses, and we conclude that diversion colitis may be caused by a lack of SCFAs and can be brought into remission by replenishing them by intermittent irrigation with SCFA solution.

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METHODS

We studied four patients in whom inflammation of the bypassed rectosigmoid had been observed during fiberoptic endoscopy. Three patients had been referred for evaluation of bloody discharge from the diverted bowel segment. The characteristics of all four patients are shown in Table 1. Patients 1 through 3 underwent the entire series of studies; Patient 4 was available only for a two-week therapeutic trial (see below). All were ambulatory and had not taken any

immunosuppressive or antibiotic medications for at least four weeks before study. Colonoscopy with biopsy of specimens obtained through the colostomy stoma, radiographic study of the small intestine, medical history, and physical examination revealed no evidence of inflammatory bowel disease. (This study was approved by the Human Research Review Committee of the Medical College of Wisconsin.)

The patients underwent fiberoptic flexible-instrument sigmoidoscopy, without preparatory cleansing through the mucous fistula or the anal canal. The endoscopic appearance of mucosa was noted, and numerous photographs were taken. Each of five abnormalities — erythema, edema, friability, granularity, and erosions — was scored as absent (grade 0), mild (1), or severe (2). The sum of the scores was considered to be an endoscopic index, with a range of 0 to 10. The endoscopist was blinded (because of serial examinations) to the patients' treatments. However, the endoscopic index calculated at the time of the procedure was compared with an index based on a review of endoscopic photographs by another endoscopist. The two values were in agreement within 1 point. Small amounts of blood-tinged intraluminal fluid were aspirated, with or without prior instillation of 5 ml of nonbacteriostatic normal saline solution. Three or four specimens of the most inflamed areas were obtained by forceps biopsy, oriented on nylon mesh, and fixed in Bouin's solution. The specimens were cut into stage sections 4 μm thick and stained with hematoxylin and eosin. The changes evaluated as present or absent were surface erosions and exudate, inflammation and edema of the lamina propria, crypt morphology, lymph follicles, and mucin granulomas. Overall inflammatory change was graded from 0 (absence) to 4 (extensive confluent inflammation in all biopsy particles submitted). All biopsy specimens, including those obtained during treatment, were interpreted in a random and blinded manner by a single pathologist.

After these studies, the patients underwent two successive breath hydrogen tests. One hundred milliliters of 10 percent D-glucose in water was instilled into the bypassed segment, and then 250 ml of the same solution was instilled into the proximal colon through the colostomy, after breath hydrogen values were determined at base-line levels. Breath samples of end-expiratory air were collected at −10, −5, 5, 10, and 15 minutes and at 15-minute intervals thereafter until 90 minutes after instillation. The breath hydrogen concentration was determined with a model 12 Microlyzer (Quintron Instrument, Milwaukee). A breath hydrogen test was considered positive for bacterial carbohydrate fermentation if the hydrogen concentration rose by 10 ppm or more above the base-line level in two successive samples.

Part of the luminal aspirate was sent to the clinical microbiology laboratory for culture for enteric pathogens, including shigella, salmonella, campylobacter, and yersinia. The remaining part was analyzed for two-carbon to five-carbon SCFAs on a gas chromatograph (Perkin–Elmer, Model 8500).[4] The lower limit of detection of this method is 0.5 mM.

Treatment Protocol

The SCFA solution instilled consisted of sodium acetate (60 mM), sodium propionate (30 mM), and sodium n-butyrate (40 mM), plus sufficient sodium chloride (about 22 mM) to produce an osmolality of 280 to 290 mOsm per liter; the pH was adjusted to 7.0 by titration with 1 *N* sodium hydroxide. This solution is stable for up to four months at 4°C. The concentrations of the three SCFAs present in this solution were the same as or lower than those in normal stool water but represented an increase in the molar percentage of n-butyrate.[5] Each patient was instructed on how to instill the solution; 60 ml was to be instilled twice daily through an inflated Foley catheter in the mucous fistula or through a soft enema tip into the anus, and the patient was to remain supine for 30 minutes thereafter. None reported major leakage of the instillate. Flexible-instrument sigmoidoscopy (with endoscopic photography and biopsies) was repeated every two or three weeks by the same endoscopist until healing was noted at endoscopy. Afterward, the frequency of instillations was reduced in two patients in order to determine the minimum of treatment required for maintaining remission. For periods of two to four weeks during the regimen the patients received either no therapy (two patients) or irrigation with isotonic saline in a single-blind manner (three patients) in order to determine the cause of any improvement observed during treatment with the SCFA solution.

Table 1. Clinical Characteristics of Four Patients with Diversion Colitis.

Patient No.	Age/Sex	Reason for Diversion	Type of Diversion	Months to Symptoms*	Months to Study†
1	63/M	Neurogenic fecal incontinence	Mucous fistula	13	14
2	63/F	Irradiation of rectum‡	Mucous fistula	0.5	1
3	54/M	Perianal fistulas	Rectosigmoid pouch	35	54
4	56/M	Diverticulitis	Mucous fistula	§	2

*Interval between bypass operation and the onset of bloody discharge with or without cramps.

†Interval between bypass operation and study entry.

‡Diversion colitis was present up to the midtransverse colon, which was well out of the radiation field. (Irradiation was given 23 years before the creation of the colostomy.)

§Noted to have colitis at sigmoidoscopy before planned resection and reanastomosis.

Results

In the three patients tested, the breath hydrogen test was negative after instillation of glucose into the excluded rectosigmoid but became positive within 5 to 10 minutes after instillation through the colostomy stoma. These results suggest that the normal carbohydrate-fermenting anaerobic bacterial flora was absent from the bypassed segment but present as expected in the colon, remaining in continuity with the fecal stream. Cultures of luminal contents obtained from the bypassed part of the rectosigmoid of these same three patients revealed no enteric pathogenic bacteria. The total SCFA concentration in these aspirates (corrected for dilution) was 0, 4.0, and 0.8 mM for acetic, propionic, and n-butyric acid, respectively. These findings confirm the absence of any notable bacterial fermentation producing SCFAs.

Endoscopic Observations

Before treatment, the lumen contained a few milliliters of bloody fluid mixed with cellular debris and mucous strands. The mucosa was erythematous and friable and appeared to be swollen. Epithelial defects, ranging from 1 to 5 mm in diameter and numbering up to 12, were grouped in one or two clusters. These erosions frequently had a hyperemic margin and were covered by a whitish exudate (Fig. 1A). Coarse granularity or nodularity was noted in three of the four patients, in whom the erosions generally were located on top of these small mucosal elevations, appearing as aphthous ulcers. The intensity of these changes varied unpredictably along the bypassed segment. Luminal strictures[2] were not observed. Treatment with SCFA instillation twice daily for two to three weeks markedly improved the endoscopic appearance of the segment (Table 2); the endoscopic index decreased by a mean of 5.5 points, from a mean pretreatment value of 9.0.

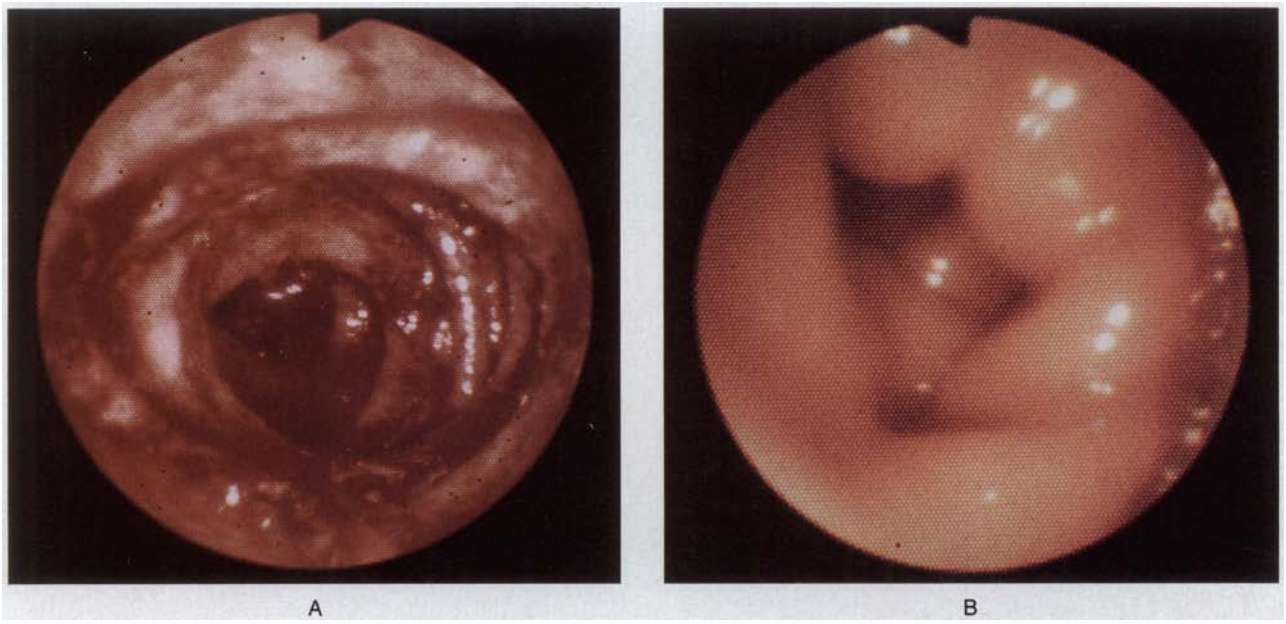

Figure 1. Diverted Segment of the Descending Colon of Patient 2 before (A) and after (B) Daily Instillation of SCFA Solution for Two to Three Weeks.

The endoscopic photograph in Panel A shows severe diversion colitis with severely inflamed, friable mucosa; blood was present before the endoscope was inserted (endoscopic score, 10; see text). Panel B shows improvement of the segment (endoscopic score, 1).

Spontaneous passage of the bloody discharge ceased. Continued treatment resulted in further improvement, with endoscopic scores of 0 and 2 after four weeks and a score of 1 after six weeks of instillations given twice daily. The residual abnormalities were limited to mild edema or erythema (Fig. 1B). Interruption of treatment for two weeks resulted in definite worsening; the endoscopic scores increased by 4 points in each of the two patients tested (Table 2). In striking contrast to the effects of the SCFA solution, the effect of enemas containing physiologic saline, given twice daily for two to four weeks, was only a small decrease in the endoscopic score (1 point) for each of three patients.

Maintenance therapy was instituted in two patients. Patient 1 remains in complete remission (endoscopic score of 0) at 14 months, receiving one instillation of 60 ml twice weekly. Patient 2 had slight worsening after six weeks of the same regimen; her treatment was then changed to instillation once daily, which induced and maintained remission, as of the last follow-up examination at six months.

Histologic Observations

Specimens of mucosa obtained before therapy had similar morphologic features. The majority of specimens had at least one fragment bearing a superficial erosion that extended to a depth not greater than half the diameter of a colonic crypt. Exudates were present that consisted of a leukocyte-rich coagulum near epithelial defects in the intercrypt area (Fig. 2). The lamina propria underlying these areas was markedly edematous. The overall morphology of the crypts was generally normal. Crypt abscesses (Fig. 2) were common in specimens with marked inflammation, with collections of neutrophils in the crypt lumens and between the epithelial cells lining the crypt walls. The decrease in mucin secretion paralleled the degree of inflammation — i.e., the greater the inflammation, the greater the loss of mucin secretion by crypt and sur-

Table 2. Endoscopic Evaluation of Effect of SCFA Irrigation on Diversion Colitis.

Patient No.	Type of Treatment*	Weeks of Treatment	Endoscopic Score†
1	Entry		10
	SCFA twice daily	2	5
	None	2	9
	Isotonic saline twice daily	4	8
	SCFA twice daily	4	0
	SCFA twice weekly	60	0
2	Entry		10
	Isotonic saline twice daily	2	9
	SCFA twice daily	2	3
	SCFA twice daily	4	2
	SCFA twice weekly	6	4
	SCFA once daily	7	2
	SCFA once daily	14	1
	SCFA once daily	21	1
3	Entry		9
	SCFA twice daily	3	4
	None	2	8
	Isotonic saline twice daily	3	7
	SCFA twice daily	6	1
4	Entry		8
	SCFA twice daily	2	2

*Each treatment consisted of a 60-ml retention enema.

†Scores for bypassed segment of rectosigmoid, obtained during sequential endoscopic examinations (see text).

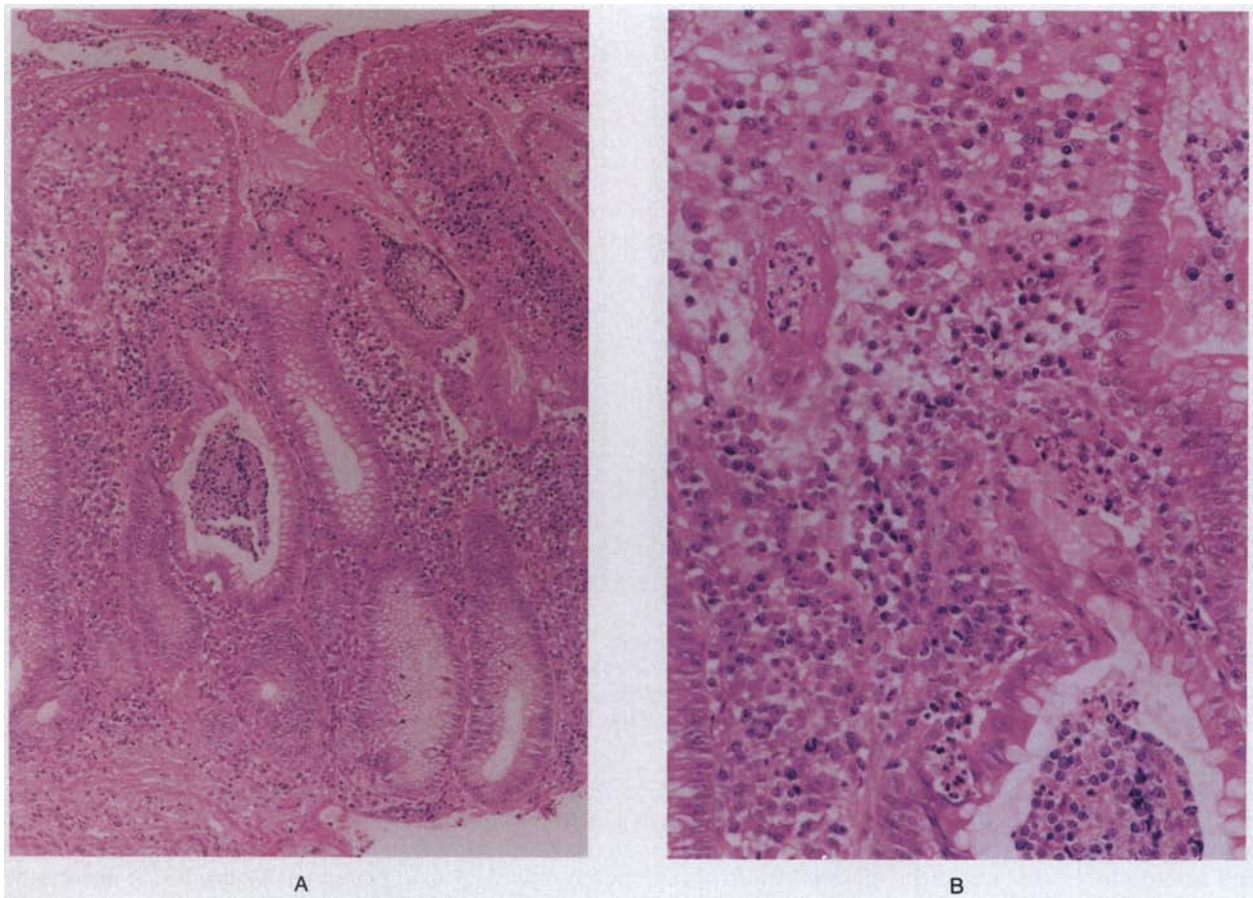

Figure 2. Colonic Mucosa before SCFA Treatment in Patient 1 (Hematoxylin and Eosin).
The endoscopic biopsy specimen in Panel A (×100) shows marked edema of the mucosa, which is more than twice its normal thickness. Note the crypt abscess in the center of the photograph.
At a higher magnification, Panel B (×200) shows an inflammatory infiltrate of both acute and chronic cells in the lamina propria and the crypt abscess. Lining epithelial cells show decreased mucin secretion.

face columnar epithelium. Paneth-cell metaplasia was found in only a single case. The most striking finding was an intense infiltration of the lamina propria by plasma cells, which filled every available space of this layer. In addition, smaller numbers of acute inflammatory cells and eosinophils and occasional mucin granulomas were observed. Acute inflammatory cells were also found in the lamina propria in areas not involved by crypt abscesses. Lymphoid follicles, both with and without germinal centers, were prominent in these specimens.

With therapy, the superficial erosions, exudates, and edema of the lamina propria disappeared. The number of acute inflammatory cells in the lamina propria decreased (Fig. 3). Much more persistent were the infiltration by plasma cells and the increase in the number of lymphoid follicles. When endoscopy demonstrated a remission, the biopsies showed an intact mucosa with a return of adequate mucin secretion and the absence of crypt abscesses and acute inflammation of the lamina propria. Persistent changes included the increase in the numbers of plasma cells and lymphocytes and prominence of the lymphoid follicles (Fig. 3) (Table 3).

Discussion

The development of inflammation in diverted segments of colon and rectum was described as a specific entity in 1981 by Glotzer et al.[1] It was soon recognized that this condition may persist indefinitely but remit after surgical reanastomosis,[1,2] in contrast to the inflammatory changes of idiopathic ulcerative and granulomatous colitis. Diversion colitis appears to occur nearly universally within months of the operation for diversion,[2] but its incidence tends to be clinically underestimated because the majority of patients remain asymptomatic. However, severe bleeding,[3] stricture formation,[2] and chronic diarrhea[6] may occur. The diagnosis is made by endoscopic observation. Histologic examination of mucosal specimens usually supports the diagnosis by endoscopy, but the differentiation between diversion colitis and active idiopathic inflam-

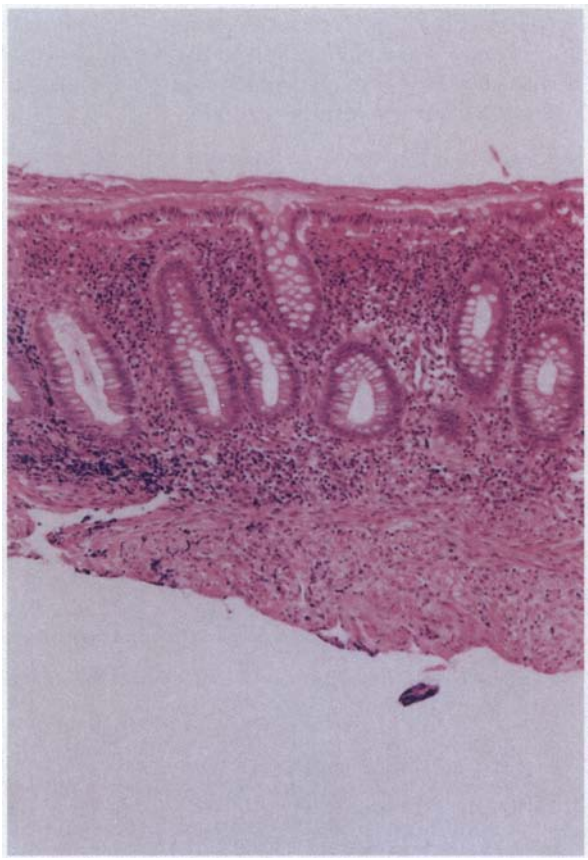

Figure 3. Colonic Mucosa after SCFA Treatment in Patient 1 (Hematoxylin and Eosin, ×100).
The edema has resolved, the lining mucin-secreting cells are intact, and the inflammatory cells in the lamina propria are decreased.

matory bowel disease remains problematic in many instances and rests largely on the difference between the responses to surgical diversion and reanastomosis. The enteritis that follows jejunoileal bypass for obesity[7] is an entirely different and a clinically more severe disorder and is associated with overgrowth of anaerobic bacteria in nonexcluded segments of small intestine.

The current study provides evidence against a role of bacterial pathogens and of overgrowth of anaerobic bacteria in the pathogenesis of this condition. The absence or near absence of SCFAs from the excluded rectosigmoid and the reversal of the disease after surgical reanastomosis or topical application of an SCFA mixture point to these acids as the key to the understanding of diversion colitis.

SCFAs are the predominant solutes in the aqueous phase of colonic contents and stool, with a total concentration of 100 to 240 mM. About 90 percent of the total SCFA content is accounted for by acetic, propionic, and n-butyric acids, which are present in a molar ratio of 57:26:17.[5] These acids are produced by anaerobic bacterial fermentation of carbohydrate, a process of which mammalian cells are incapable.[8] SCFAs are readily absorbed by the colon in humans and animals in exchange for bicarbonate and with simultaneous stimulation of water and sodium absorption.[9] Roediger demonstrated that SCFAs are the major and preferred energy source for human colonic epithelium, and that this dependence on metabolic substrates is greater in the distal than in the proximal colon.[8] The colonocyte must assimilate these SCFAs from the lumen because plasma concentrations are negligible.[10] Among the SCFAs normally present in colonic contents, n-butyric acid is most avidly metabolized.[8] This observation led us to prepare an SCFA solution in which n-butyric acid was in excess as compared with its physiologic concentration in molar ratio to other SCFAs.[5] Rolandelli et al. demonstrated in rats that the instillation of SCFAs or pectin (a substrate for bacterial production of SCFAs) accelerates the healing of colonic anastomoses,[11,12] and that oral administration of pectin leads to healing of experimentally induced colitis.[13] In dogs, luminal perfusion of the colon with SCFAs increases regional blood flow and oxygen uptake.[14] Although instillation of acetate, propionate, or n-butyrate into the ileum elicits bursts of contractions,[15] it is unlikely that SCFAs have similar motor effects in the colon, where they normally are present. In rats, luminal SCFAs have a trophic effect on the ileal and colonic epithelium in vivo, and this action appears to be mediated systemically rather than exerted directly on the epithelial cells.[16] By contrast, exposure of rat colonic epithelium[16] and a human colonic-carcinoma cell line[17] to SCFAs in vitro results in decreased cell multiplication and increased cellular differentiation. In patients, rectal biopsy specimens obtained serially after diversion of the fecal stream showed a decrease in the in vitro production rate of crypt cells 2 weeks after operation, with a return to normal rates of proliferation 12 weeks postoperatively.[18] These data are difficult to interpret because the investigators did not provide estimates of

Table 3. Histologic Evaluation of Biopsy Specimens from Three Patients.*

	Before Treatment	During Remission
	no. of patients with lesion	
Erosions	2	0
Surface exudate	2	0
Lymph follicles	3	2
Crypt abscesses	2	0
Edema	2	0
Mucin granuloma	1	0
Inflammation grade (0 to 4+)	4+, 4+, 2+	2+, 4+, 1+

*Histologic lesions were graded as present or absent (except for the grade of inflammation). "During remission" denotes the time of the last sigmoidoscopic examination, when the endoscopic scores in the patients were 0, 1, and 1, respectively (see Table 2).

the total epithelial-cell population or its turnover rate, or use SCFAs in the incubation medium.

Our clinical results suggest that a local nutritional deficiency leads to an inflammatory state. It is interesting to note that Roediger observed that the utilization of n-butyrate by colonocytes was decreased in patients with active ulcerative colitis and that this led to cellular energy deficiency. He postulated that this metabolic defect is due to a reduction in coenzyme A, a nucleotide required for oxidation of fatty acids.[19] Indeed, decreases in SCFAs (especially n-butyrate) were recently observed in patients with severe ulcerative colitis.[20] The possible role of the suppression of the colonic flora, with a concomitant reduction in the fecal concentration of SCFAs, in the pathogenesis of antibiotic-associated diarrhea needs to be evaluated.[21]

In summary, we have shown that diversion colitis can be clinically ameliorated and histologically improved by intermittent exposure of the inflamed mucosa to a mixture of acetate, propionate, and n-butyrate. Whether this therapeutic response is sufficiently specific to this type of proctocolitis so that this disorder can be differentiated from active inflammatory bowel disease in a bypassed segment of colorectum remains to be determined. Similarly, identifying the mediators of mucosal inflammation initiated by nutritional deficiency of the epithelium remains a challenge for further investigations.

Addendum

Since the submission of our manuscript, we have studied another patient with diversion colitis. A 45-year-old woman with histologically confirmed Crohn's colitis extending from the rectum to the transverse colon underwent resection of the sigmoid colon because of perforation. Six months later she presented with greenish, bloody rectal discharge. Proctosigmoidoscopy revealed an ileorectal fistula and diffuse inflammation (endoscopic score, 10). SCFAs were absent from the rectal contents. The endoscopic score decreased to 2 after four weeks of SCFA treatment (given as an enema twice daily); it rose to 5 after six weeks of saline enemas and dropped to 1 after reinstitution of SCFA enemas for four weeks. Rectal biopsy specimens had an appearance typical of active diversion colitis, which resolved after treatment. These specimens also contained giant-cell granulomas, as did specimens of the descending colon. The patient's response to SCFA enemas allowed the classification of her disorder as inactive Crohn's colitis with concurrent active diversion colitis.

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