THE PATHOGENESIS OF ULCERATIVE COLITIS; APPARENT PRECIPITATION OF ACUTE EPISODES BY STANDARD ENEMAS

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FOR many years there has been no agreement as to the pathogenesis of ulcerative colitis. In the numerous published studies on the subject the theory that infection is the cause has predominated. Bargen and Buie[1] believed that a *Diplococcus* was the specific etiologic agent, and treated patients with a vaccine prepared from this *Enterococcus*. Felsen,[2] among others, believed that ulcerative colitis resulted from bacillary dysentery, and reported that positive cultures were obtained from 17.7 percent of his patients. He also reported high agglutination titers from blood specimens of his patients, an observation not confirmed by others. Brown,[3] on the other hand, observed that in 650 cases of proved bacillary dysentery, ulcerative colitis did not develop. In addition, Brown and Bargen[4] stated that after a severe epidemic of bacillary dysentery that required hospitalization of 140 patients and resulted in 15 deaths, chronic ulcerative colitis was seen in only one patient. After World War II, during which our soldiers were stationed throughout the world and lived in many areas where amebiasis is endemic, a number of patients were seen with the typical proctoscopic and roentgenographic evidence of ulcerative colitis, but with amebas in the feces. Specific antiamebic therapy was effective in nearly 50 percent of these patients; the remainder continued to have signs and symptoms of ulcerative colitis. Other clinicians[5] have observed the same relationship of ulcerative colitis to amebiasis.

The possibility remains that a specific virus or as yet unknown bacteria or other organisms may be the etiologic factor, but studies on the culture of feces, and immunologic tests[6] have not been promising. Ulcerative colitis develops in a sufficient number of patients after a specific infection, such as amebiasis, to suggest that the infection may have so sensitized the colonic mucosa, in a susceptible individual, as to set the stage for chronic nonspecific ulcerative colitis.

Rider and Moeller[7] have found that a large proportion of patients with ulcerative colitis exhibit a positive reaction to milk, egg, and other protein, when these substances are injected submucosally into the rectum. Subsequent proctoscopic examination and biopsy specimens have yielded evidence of an allergic type of reaction. Rider and Moeller[7] have successfully treated patients with diets that omit these protein substances. The standard type of skin test for food allergies seldom causes a reaction in these patients. However, on careful inquiry, a significant number have reported that they do not tolerate milk and dairy products; that the ingestion of such products results in gaseous distention and an increase of diarrhea. Others

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have not been able to corroborate the good results obtained by Rowe and Rowe[8] with the use of elimination diets. If allergy were the only factor, it should be obvious that the pathogenesis and treatment of ulcerative colitis would not still be a problem.

We recently examined a patient who had chronic diarrhea of several years' duration. For three years, extensive annual studies at another institution had shown no abnormality, and the diagnosis was said to be chronic irritable colon. Results of our studies, including proctoscopic, fecal, and barium enema examinations, were also within normal limits; however, of the submucosal injections of three proteins into the rectum, only milk protein caused an erythematous reaction. Omission of milk and dairy products from the patient's diet relieved the diarrhea promptly within 24 hours, and in the next three months, while avoiding milk, he had no recurrence of diarrhea. Although this patient did not have ulcerative colitis, the chronic diarrhea apparently was an allergic reaction from a sensitivity to milk protein. We wonder whether or not the diarrhea may have been similarly caused in other patients who have had positive mucosal skin tests without their having true ulcerative colitis. The inflammation of the rectal mucosa in most patients with ulcerative colitis limits the use of the mucosal allergic test to those with atypical involvement (not including the rectum).

Recently autoimmunity (reaction of the body to some of its own cells and protein) has been cited in a number of conditions including some hemolytic anemias, Hashimoto's disease, postnecrotic cirrhosis, Hodgkin's disease, and possibly some types of carcinoma. Some of these conditions may be directly or indirectly related to an autoimmune mechanism without being caused by it; this mechanism may result in the persistence of a pathologic process previously initiated by another agent. A possible example might be the development of postnecrotic cirrhosis as an autoimmune reaction after an original specific injury to the liver by viral hepatitis. There is some evidence that autoimmunity may also play a role in the pathogenesis of ulcerative colitis. Many patients, with any one of the above-named conditions, have changes in their electrophoretic protein patterns, including increase in the gamma-globulin concentration, consistent with such a reaction.

Kirsner and associates[9, 10] have shown that hypersensitivity in the rabbit, including the Arthus, Shwartzman, and Auer reactions, can cause injury to the colonic mucosa and produce findings similar to those of ulcerative colitis in humans.

Rheumatoid arthritis may be a serious complication of ulcerative colitis, but also there are similarities in the two conditions. The association of ulcerative colitis and lupus erythematosus appears to be more than coincidental.[11] Arterial changes have been observed in patients having ulcerative colitis which are somewhat suggestive of periarteritis nodosa, but these vascular changes may be secondary to infection and the basic pathologic lesions of ulcerative colitis. Therapy for rheumatoid arthritis and the collagen diseases frequently is effective in the patient with ulcerative colitis (agents such as steroids, amino-oxidase inhibitors, phenylbutazone, and possibly nitrogen mustard and antimalarial drugs). Similarities between

the two conditions raise the question of a possible common etiologic factor in these diseases.

Psychogenic factors have been repeatedly studied since Murray's[12] report of personality reviews in 12 patients in 1930. Since then, others[13-20] have extensively studied emotional factors in ulcerative colitis, and have noted a frequent association of emotional trauma and the onset of ulcerative colitis. The emotional aspects in the pathogenesis of ulcerative colitis are reviewed in another report,[21] and six cases are cited in which dramatic and shocking emotional stress precipitated ulcerative colitis, and a seventh case in which the stress initiated a flare-up of the disease. The immediate onset of ulcerative colitis after such severe emotional trauma strongly suggests that psychogenic factors may be etiologic in some patients.

Chemical or traumatic irritations seldom have been cited as causes of ulcerative colitis. Sheehan and Brynjolfsson[22] reported a case in which ulcerative colitis developed after treatment with an enema containing hydrogen peroxide. They also experimentally produced similar findings in rats by administering such enemas. Frequently an acute flare-up of ulcerative colitis will follow proctoscopic or barium enema examination; however, there is a lack of reports of ulcerative colitis after standard cleansing enemas. Because of the rarity of the association, the development of a condition simulating ulcerative colitis clinically in three patients after standard cleansing enemas were given, in preparation for ophthalmologic surgical procedures in two of the patients and for prostatic surgery in the other patient, merits reporting.

Report of Cases

Case 1. A 69-year-old man was admitted to the hospital on September 6, 1962, for an elective intracapsular cataract extraction and complete iridectomy of the left eye. Five years previously he was treated for recurrent nosebleed, and had been under treatment (with steroids) for emphysema since that time. He had an episode of intermittent diarrhea in 1957, lasting three or four weeks. Results of the proctoscopic examination were essentially normal at that time, and studies after a barium enema were negative except for evidence of diverticulosis of the sigmoid colon. His history was otherwise negative. There was some question of penicillin allergy. The patient underwent preoperative preparation. After the administration of an enema consisting of milk of magnesia, glycerine, and water, the patient immediately passed numerous bloody, diarrheal feces. Proctoscopic examination the next morning showed an edematous, friable, bleeding, and inflamed rectal mucosa. The patient received vigorous medical treatment that included: adrenocorticotropin (ACTH), 40 units per day; prednisone, 5 mg. daily; Sulfathalidine,* four 1-gm. doses daily; Lomotil,† four 5-mg. doses daily; neomycin, four 0.5-gm. doses daily; and at bedtime, 40 mg. of Depo-Medrol‡ in 100 ml. of water as a retention enema. The first night, he did not retain the enema, having six bloody bowel movements. However, after two days of treatment there were formed feces without bleeding. The blood hemoglobin content decreased from 16.5 gm. per 100 ml. on September 6, 1962 (the day of admission), to 13.9 gm. per 100 ml. on September 12, 1962. Other laboratory findings, including fecal studies

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for parasites, were normal. Proctoscopic examination five days later showed a somewhat erythematous mucosa with some edema, but there was no friability and no evidence of bleeding.

On September 14, eight days after the onset of the bloody diarrhea, the patient underwent the surgical procedure on the left eye. There was no diarrhea postoperatively, only mild mid-abdominal cramping for two days. He was discharged from the hospital on September 23, nine days after the operation, and was advised to follow a graded residue diet; to take Sulfathalidine, four 1-gm. doses daily; prednisone, 5 mg. daily; supplemental vitamins; and at bedtime to use rectal suppositories containing 15 mg. of neomycin and 50 mg. of hydrocortisone. On examination four months later he reported that he had been entirely free of diarrhea, bleeding, and gastrointestinal symptoms.

Case 2. A 60-year-old man was admitted to the hospital on December 29, 1961, for a lamellar scleral resection (for a left retinal detachment). On examination he had a temperature of 100 F., minimal abdominal discomfort, and reported having constipation of two days' duration. His history was essentially noncontributory, with no previous episode of diarrhea to suggest ulcerative colitis, allergy, or other disease. Physical examination disclosed no abnormality, and the patient underwent preparation for the surgical procedure.

Following a milk of magnesia, glycerine, and water enema, the patient began to have bloody, watery feces, and the abdomen became distended. Proctoscopic examination revealed bleeding and bullous edema with narrowing of the lumen at 15 cm., which prevented further introduction of the proctoscope. A moderate amount of pus was present. A plain roentgenogram of the abdomen showed evidence of a dilated transverse and ascending colon, and portions of dilated small bowel, thought to be compatible with obstruction of the left half of the colon. Because of increasing distention, and the roentgen evidence suggesting obstruction, the patient underwent laparotomy. At operation, the left colon was firm, edematous, contracted, and the serosal surface appeared to be injected for a distance from the sigmoid to the splenic flexure. The cecum and transverse colon appeared to be dilated, but showed no evidence of inflammation. A skin-level transverse colostomy was performed, and the mucosa in the transverse colon appeared to be normal.

Immediately after the operation, a vigorous medical program of treatment was instituted, including intramuscular administration of 40 units of ACTH daily; 40 mg. of Depo-Medrol as a retention enema[23] at bedtime; Sulfathalidine, four 1-gm. doses daily; and vitamins.

The postoperative course was uncomplicated, and the response to the colostomy and the medical program was dramatic. On the eighth postoperative day, proctoscopic examination showed evidence of erythema of the mucosa, with no edema, friability, or bleeding. On January 12 (the tenth postoperative day) the operation on the eye was performed. The same medical program for the colitis was continued after this operation, and the postoperative course again was uneventful.

During his illness, the blood hemoglobin decreased from 15.3 gm. (at the time of admission) to 11.2 gm. Results of fecal examinations were negative for parasites, but positive for blood and pus. The electrophoretic protein pattern showed slight changes, with a decrease in albumin to 2.97 gm. per 100 ml., and an increase in beta-globulin (0.90), gamma-globulin (1.35), and alpha-globulin (0.85). A barium enema examination on January 29, 1962, to the height of the transverse colostomy showed only slight coarsening of the folds in the evacuation films.

On January 30, a surgical proctoscopic examination showed a normal mucosa, with no ulceration, inflammation, or pus, and consequently the transverse loop colostomy was closed the same day. The patient was asymptomatic and was discharged from the hospital on February 9, 1962. One year later he had remained asymptomatic.

Case 3. A 65-year-old man was examined on January 4, 1963, and diagnoses were made of hiatus hernia, diverticulosis of the colon, emphysema, and symptomatic benign prostatic

hypertrophy with urinary retention. Results of physical examination were normal except for evidence of emphysema with an increase in the anteroposterior thoracic diameter, prolongation of expiration, and moderate enlargement of the prostate gland. Residual urine was 6 ounces. Proctoscopic examination revealed normal structures except for minimal melanosis coli. Results of laboratory studies and an electrocardiogram were normal. A roentgenogram demonstrated a normal chest, while one of the stomach showed a moderate-sized hiatus hernia, and a barium enema study showed diverticulosis of the colon.

The patient was admitted to the hospital for prostatic surgery on February 24, 1963. After the administration of a milk of magnesia, glycerine, and water enema, diarrhea developed, and rather severe rectal bleeding. Proctoscopic examination revealed a friable mucosa that bled easily and diffusely on swabbing, in addition to the minimal melanosis coli observed one month previously. A rectal biopsy specimen showed moderate hemorrhage in the lamina propria, and melanosis coli, but there were no crypt abscesses. His history was entirely negative regarding any symptoms suggestive of ulcerative colitis, since he had not had diarrhea, and proctoscopic examinations one month, and four and one-half years, previously showed no evidence of ulcerative colitis.

The patient was treated with Depo-Medrol retention enemas,[23] Azulfidine,* and Lomotil.[24] The diarrhea and bleeding ceased within a few days, and the transurethral resection was done on March 5, eight days later, without complications. He was discharged from the hospital on March 11, 1963. At a progress examination on March 26, 1963, the patient was entirely asymptomatic, and the proctoscopic examination showed only minimal melanosis coli, with no evidence of ulcerative colitis.

Comment. The outstanding features of these three cases are the sudden first (only) onset of a condition simulating acute ulcerative colitis after a simple milk of magnesia, glycerine, and water enema, and the prompt response to treatment. The appearance of the rectal mucosa proctoscopically was typical of acute ulcerative colitis with edema, hemorrhage, friability, and bleeding. The edema of the sigmoid was so great in one patient (case 2) that all of the symptoms and signs of colonic obstruction developed, and a temporary loop colostomy was performed. None of the three patients had a history suggestive of previous episodes of ulcerative colitis.

Microscopic examination of a rectal biopsy specimen from one patient (case 3) showed submucosal hemorrhage, but did not show the crypt abscesses typical of ulcerative colitis—an absence that we believe does not exclude the probability that the patient had acute ulcerative colitis or a similar reaction. We have observed an absence of crypt abscesses on rectal biopsy specimens from a number of patients with typical *chronic* ulcerative colitis; a positive biopsy specimen is pathognomonic, but a negative biopsy specimen does not exclude the disease. The reaction in the rectal mucosa may have been too sudden and too acute for the development of the crypt abscesses characteristic of ulcerative colitis.

It is a well-known fact that an acute flare-up of chronic ulcerative colitis may occasionally follow a sigmoidoscopic examination or a barium enema.

In these three patients the colonic mucosa apparently reacted vigorously to the standard enema, which must have been noxious. Careful inquiry may reveal other instances of enema-precipitated acute ulcerative colitis.

Discussion

The number of theories regarding the pathogenesis of ulcerative colitis makes one suspect that not one current theory is the final answer. Just as in the field of surgery, when several or a great number of operations are proposed for a specific

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condition, such as pancreatitis, one can be certain that no one procedure is completely satisfactory for every case; similarly the number of theories regarding ulcerative colitis suggests that none is completely applicable, but that in each there may be some truth; furthermore, there is experimental evidence in support of each theory.

In the 1920s, bacterial infection was considered the cause of most disease. In the '30s, allergy became popular, and in the '40s, viruses were the cause of all diseases we did not understand. In the '50s, psychosomatic factors exerted their force, and at present autoimmunity is in vogue. With the evidence that lends some support to each of these theories, perhaps the final answer will be that there are multiple factors in the pathogenesis of ulcerative colitis.

The final explanation may be that any insult to the colonic mucosa, whether the result of infection with bacillary dysentery or amebiasis, a severe allergic reaction, emotional crisis causing motility and vascular changes, or chemical irritants, may sensitize it. The secondary, and the most important factor, may be biologic predisposition, an autoimmune mechanism that follows any type of injury to the colonic mucosa. In support of this, we have seen apparently typical ulcerative colitis follow the standard enema comprising milk of magnesia, glycerine, and water, given in preparation for elective operations, such as procedures for glaucoma, cataracts, and hernias. Despite the removal of the initiating cause, the secondary reaction may continue. This reaction may be analogous to the match that lights a dynamite fuse or starts a forest fire; the explosion and forest fire continue long after the initiating stimulus (the match) has been extinguished.

Summary

Theories regarding the pathogenesis of ulcerative colitis are discussed briefly, and it is suggested that multiple factors, all causing injury to the colonic mucosa, may initiate ulcerative colitis, in the susceptible individual. Among these precipitating factors are: specific infection with bacillary or amebic dysentery, allergic reactions, trauma from enemas, possibly virus infections, and other as yet unknown agents. Following such a nonspecific injury to the colonic mucosa, other mechanisms, such as autoimmunity, may perpetuate the reaction.

A condition simulating typical acute episodes of ulcerative colitis developed in three patients after standard enemas of milk of magnesia, glycerine, and water; there had been no previous history of similar difficulty. The severity of the colitis was sufficient to require colostomy in one patient; however, all three patients responded to medical treatment.

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