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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 25-1990

PRESENTATION OF CASE

First admission. A 63-year-old man was admitted to the hospital because of recurrent diarrhea.

The patient stated that he became malnourished as a prisoner of war during World War II, with a decrease in his weight from 90 to 74 kg and symptoms of peripheral neuropathy. During the next 41 years he was well except for the passage of loose stools once or twice a week without associated abdominal pain, nausea, or vomiting. The stools were not malodorous and did not contain recognizable blood. Twenty-two months before admission the patient had a 9-kg loss in weight over a six-week period associated with the onset of the passage of three to eight loose, yellow, malodorous stools per day. The stools floated on water and did not contain oily droplets. The passage of stools was not related to food intake but was accompanied by gaseousness. Occasionally, bright-red blood was observed on the toilet paper. Twenty months before admission the patient was admitted to another hospital, where an increased fat content was noted in a 72-hour stool specimen. An iron-deficiency anemia and a slight decrease in the plasma level of calcium were observed. An esophagogastroduodenal endoscopic examination was negative. An upper gastrointestinal series was normal except for several large diverticula observed on small-bowel follow-through study. A barium-enema examination was negative. Colonoscopic study disclosed a prominent venous pattern. Aluminum hydroxide (Amphojel) and diphenoxylate were administered, with a reduction in the number of stools to two per day. Three months before admission increased frequency of stools recurred. The patient had vague arthralgia and experienced occasional symptoms consistent with peripheral neuropathy. He was admitted to this hospital.

The patient was a government worker and the father of three children. He admitted a moderate intake of alcoholic beverages. He had smoked two packs of cigarettes per day for 20 to 25 years but discontinued smoking 5 years before admission. There was no history of nausea, vomiting, abdominal pain, melena, jaundice, pruritus, fever, chills, or night sweats. He had not traveled recently in foreign countries. There was a family history of cancer of unknown type in two grandparents, but there was no history of gastrointestinal, hepatic, or pancreatic disease or sprue.

The temperature was 36.4°C, the pulse was 84, and the respirations were 20; the blood pressure was 130/90 mm Hg. The weight was 83 kg, and the height 188 cm.

Physical examination revealed that the patient appeared slightly older than his stated age; he was in no distress. Examination of the head and neck was negative. No cutaneous rash or signs of chronic hepatic disease were observed. The lungs were clear, and the heart was normal. Hyperactive bowel sounds were audible in all four quadrants of the abdomen. The liver span was percussed at 7 cm; its edge was palpated 2 cm below the right costal margin and was firm. There was no splenomegaly, abdominal mass, or tenderness. Rectal examination revealed palpable internal hemorrhoids and tan, foul-smelling stool, which gave a + test for occult blood. Neurologic examination was negative.

The urine had a specific gravity of 1.011; the sediment contained rare squamous cells, white cells, and red cells. No Bence Jones protein was detected in a 50-fold–concentrated specimen of urine. The hematocrit was 35.7 percent; the white-cell count was 7700, with 75 percent neutrophils, 17 percent lymphocytes, and 8 percent monocytes. The mean corpuscular volume (MCV) was 82 μm^3 per cell. The prothrombin time

was 13.6 seconds, with a control of 10.9 seconds; the partial thromboplastin time was 40.7 seconds. The urea nitrogen was 4.3 mmol per liter (12 mg per 100 ml), the creatinine 88 μmol per liter (1 mg per 100 ml), and the protein 66 g (the albumin 34 g and the globulin 32 g) per liter (6.6 g [3.4 g and 3.2 g] per 100 ml). The sodium was 139 mmol, the potassium 4.3 mmol, the chloride 104 mmol, and the carbon dioxide 27 mmol per liter, and the calcium 2.1 mmol per liter (8.6 mg per 100 ml). The magnesium was 0.8 mmol per liter (1.6 meq per liter), the iron 11 μmol per liter (60 μg per 100 ml), and the iron-binding capacity 48 μmol per liter (268 μg per 100 ml). The direct bilirubin was 2 μmol per liter (0.1 mg per 100 ml), and the total bilirubin 7 μmol per liter (0.4 mg per 100 ml). The alkaline phosphatase was 27 U, the amylase 71 U, and the 5′-nucleotidase 2 U per liter. Examination of a duodenal aspirate revealed no parasites. A culture of stool was negative for enteric pathogens, and a *Clostridium difficile* toxin assay of the stool was negative. The serum ferritin was 54 μg per liter. An x-ray film of the chest revealed elevation of the left hemidiaphragm, with increased markings at the left-lung base and slight hyperinflation of the lungs consistent with chronic obstructive pulmonary disease.

The patient received 25 g of D-xylose in 250 ml of water. At two hours the blood level was 21.1 mg per 100 ml (normal, >40) and the five-hour total urinary output was 4 g in 410 ml (normal, >5). An esophagogastroduodenoscopic examination was negative except for the presence of minimal duodenal edema. Multiple biopsies of the duodenum revealed total villous atrophy, marked crypt hyperplasia, interstitial inflammation, and surface epithelial injury in one of four fragments; numerous plasma cells were present in the lamina propria. Periodic acid–Schiff stains did not reveal the characteristic macrophages of Whipple's disease. No parasites were identified. The features suggested a patchy rather than a diffuse process such as celiac sprue. Colonoscopic examination revealed a redundant colon, which limited the passage of the colonoscope to the mid-ascending colon. The findings included sigmoid diverticulosis with a prominent venous pattern in the descending colon, especially in the sigmoid portion. No polyp could be identified. Internal hemorrhoids were noted.

The patient was discharged on a gluten-free diet on the seventh hospital day.

Second admission (one year later). After discharge the patient's condition stabilized with improvement of the diarrhea for 10½ months, and he gained 5 kg in weight. Two months before admission abdominal pain accompanied by diarrhea recurred during a trip to Mexico. On his return to the United States he was seen at another hospital, where a small-intestine-biopsy specimen was found to be "consistent with the diagnosis of sprue." Bacteria were identified and were observed to be adherent to the biopsy specimen. Tetracycline was administered for a month, without improvement of the symptoms. Ten days before admission the patient began to experience abdominal cramps and diarrhea three to four times a day. The symptoms were accompanied by a decrease in appetite and a low-grade fever, with the temperature ranging up to 38.3°C; during the two days before admission nausea and vomiting also occurred. He had lost 7 kg in weight during the month before admission.

The temperature was 36.9°C, the pulse was 88, and the respirations were 20. The blood pressure was 128/70 mm Hg.

Examination of the head and neck was negative. The lungs were clear, and the heart was normal. There was mild tenderness to deep palpation in the left upper quadrant of the abdomen. The splenic tip was palpable 6 cm below the left costal margin. The liver was not felt, and there was no mass or rebound tenderness. A stool test for occult blood was negative.

The urine was normal except for the presence of ++ albumin, mucin, 10 to 20 red cells, and rare hyaline and red-cell casts per high-power field in the sediment. The hematocrit was 30.8 percent; the white-cell count was 8100, with 78 percent neutrophils, 9 percent lymphocytes, and 13 percent monocytes. The MCV was 76 μm^3 per cell, and the platelet count 62,600. Examination of a blood smear revealed 52 percent neutrophils, 32 percent band forms, 8 percent lymphocytes, and 8 percent monocytes. The red cells were ++ hypochromic; occasional schistocytes were present; the platelets were ++ increased. The vitamin B_{12} was 550 pmol per liter (741 pg per milliliter), the folic acid over 45 nmol per liter (20 ng per milliliter), and the serum ferritin 211 μg per liter. The iron was

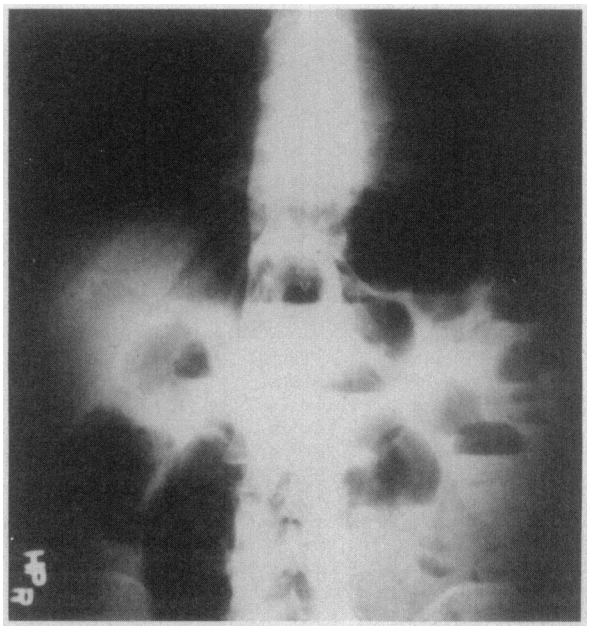

Figure 1. Film of the Abdomen with the Patient Erect, Disclosing Multiple Air–Fluid Levels within Dilated Loops of Small Bowel or Small-Bowel Diverticula, or Both.

4 μmol per liter (24 μg per 100 ml), and the iron-binding capacity 32 μmol per liter (180 μg per 100 ml). The urea nitrogen was 3.9 mmol per liter (11 mg per 100 ml), the creatinine 110 μmol per liter (1.2 mg per 100 ml), the fasting glucose 4.8 mmol per liter (87 mg per 100 ml), the protein 68 g (the albumin 22 g and the globulin 46 g) per liter (6.8 g [2.2 g and 4.6 g] per 100 ml), and the uric acid 0.1 mmol per liter (2.4 mg per 100 ml). The total bilirubin was 7 μmol per liter (0.4 mg per 100 ml). The alkaline phosphatase was 100 U, the amylase 36 U, the serum aspartate aminotransferase (ASAT) 25 U, the lactic dehydrogenase (LDH) 208 U, and the creatine kinase (CK) 40 U per liter. The sodium was 143 mmol, the potassium 4.8 mmol, the chloride 106 mmol, and the carbon dioxide 25 mmol per liter. The calcium was 2.10 mmol per liter (8.4 mg per 100 ml), and the phosphorus 1.07 mmol per liter (3.3 mg per 100 ml); the magnesium was 0.6 mmol per liter (1.2 meq per liter). A culture of stool was negative for enteric pathogens.

On the second hospital day the temperature was 37.8°C. The patient was placed on a liquid diet. A film of the abdomen (Fig. 1) with the patient upright revealed multiple air–fluid levels in the small bowel, which was slightly dilated; there was no evidence of pneumoperitoneum; on a film with the patient supine there was evidence of gas mixed with stool in the colon. On the following day the dilatation of the small bowel and large bowel appeared diminished, but multiple air–fluid levels persisted on the upright view. The findings suggested an adynamic ileus. A computed tomographic (CT) scan of the abdomen (Fig. 2) disclosed a soft-tissue mass, 8 to 10 cm, in the left mid-abdomen with scattered central air collections; there was no ascites, lymphadenopathy, or mass lesion in the liver or spleen. On the fourth hospital day an upper gastrointestinal series with a small-bowel follow-through study (Fig. 3) revealed a normal appearance of the esophagus and stomach; the duodenum was slightly dilated, with normal folds; the small bowel was slightly distended and was draped over a 12-cm mass in the left side of the abdomen; there was a scalloped appearance of the margins of the mass, suggesting tethering of the bowel. Two and a half hours after the examination barium was seen within the cecum and terminal ileum, which appeared normal; multiple diverticula were seen throughout the bowel.

An operation was performed on the fifth hospital day.

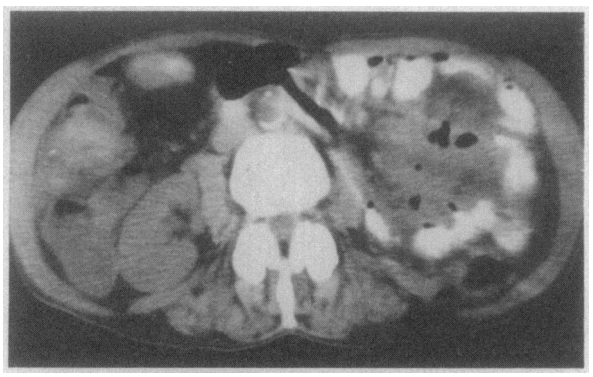

Figure 2. Computed Tomographic Scan of the Lower Abdomen, Revealing a Soft-Tissue Mass, 8 to 10 cm, with Several Central Gas Collections.

Small-bowel loops filled with contrast material surround the mass.

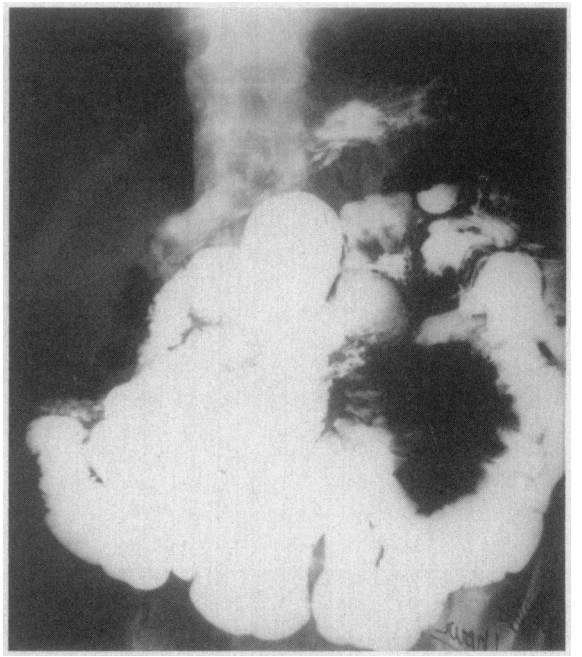

Figure 3. Film from a Small-Bowel Follow-through Examination, Demonstrating Diffuse Dilatation of the Small Bowel, Several Large Jejunal Diverticula, and a Large Mass in the Left Lower Quadrant Displacing the Adjacent Small Bowel.

A tethered, fixed-appearing segment of bowel is visible adjacent to the lateral aspect of the mass.

Differential Diagnosis

Dr. Raj K. Goyal*: May we begin with a review of the biopsy findings and radiologic studies?

Dr. Carolyn C. Compton: Four endoscopic biopsy specimens were received, and blunting of villi, superficial epithelial injury, elongation of crypts, and inflammation in the lamina propria were observed in three of them. One of the specimens appeared normal, suggesting a patchy process rather than a diffuse process, such as one would expect in sprue, which was the working clinical diagnosis at the time.

Dr. Joseph T. Ferrucci, Jr.: A radiograph of the chest obtained on the first admission demonstrates clear, slightly hyperinflated lungs, with no evidence of lymphadenopathy or pleural disease. Dilated bowel is visible beneath a slightly elevated left hemidiaphragm. At the time of the recent admission a repre-

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sentative film of the abdomen taken with the patient supine shows considerable gaseous distention of loops of small bowel and probably also gaseous distention of the colon. A radiograph taken with the patient erect demonstrates numerous air–fluid levels (Fig. 1). In view of the multiple small-bowel diverticula that had been seen on the films from the upper gastrointestinal series during the first admission it is possible that some of these air–fluid levels represented small-bowel diverticula. A computed tomographic scan of the abdomen (Fig. 2) discloses a large left-lower-quadrant soft-tissue mass with indistinct margins surrounded by loops of small bowel filled with contrast material. In the center of this mass are numerous scattered small collections of gas. No lymphadenopathy or evidence of ascites is seen. The spleen does not appear unusually prominent despite palpation of the splenic tip on physical examination, a finding that may have been related to the hyperinflation of the lungs. The small-bowel follow-through examination (Fig. 3) demonstrates multiple large jejunal diverticula, some of them 6 to 8 cm in diameter. There is moderate, diffuse dilatation of all the loops of small bowel extending into the pelvis. The overall appearance is that of a motility disorder. In the left lower quadrant there is evidence of an extraluminal soft-tissue mass, with the small bowel draped around it and with tethering and fixation of the bowel wall along the lateral margin of the mass.

DR. GOYAL: The four major features of this case that require explanation are the diverticula associated with the "ileus" and a long history of diarrhea dating back to the patient's days as a prisoner of war in World War II, the steatorrhea with microcytic hypochromic anemia, the hematuria, and the mass in the left side of the abdomen.

Multiple small-bowel diverticula are generally acquired rather than congenital.[1] They are rare in childhood, and 80 to 90 percent of them occur after the age of 40 years.[1,2] They recur in previously uninvolved regions of small bowel after the resection of a diverticulum-bearing segment.[3] They occur in patients with diseases that produce the intestinal pseudoobstruction syndrome, and they are frequently associated with neuromuscular disorders of the small bowel.[4]

The mesenteric border of the small bowel is potentially the weakest border because it is not supported by a peritoneal covering and is the site of entry of blood vessels into the bowel wall, rendering it particularly vulnerable to diverticulum formation. Indeed, the vast majority of small-bowel diverticula are on the mesenteric border.[1,2] The diverticula may result from herniation of mucosal sacs through weak spots in the underlying normal or even hypertrophied circular muscle, or they may reflect saccular dilatation of the bowel due to atrophy of the muscle layer. Increased intraluminal pressure, caused particularly by simultaneous contractions involving large segments of the small bowel, has an important role in the pathogenesis of both forms of diverticula. Such motor abnormalities are usually secondary to lesions in the intrinsic nerves of the gut.[4]

Multiple small-bowel diverticula have been described in association with progressive systemic sclerosis,[5] familial longitudinal-muscle myopathy with ophthalmoplegia,[6] hollow-viscera myopathy,[4] the Cronkhite–Canada syndrome,[7,8] the syndrome of hereditary nerve deafness, progressive sensory neuropathy, and small-bowel diverticulosis,[9] familial immune-mechanism–related jejunal diverticulosis,[10] and familial visceral neuropathy with eosinophilic neuronal inclusions.[11] All those possibilities can be excluded in this case because of the absence of a characteristic family history and other manifestations of those disorders.

Small-bowel diverticula also may occur in Fabry's disease[12,13] as a result of the accumulation of glycolipid ceramide trihexoside in the enteric neurons, nerve fibers, and smooth-muscle cells.[14] The glycolipid deposition occurs because of an X-linked hereditary lack of the lysosomal enzyme, ceramide trihexoside (α-galactosidase A).[14] This patient did not have the typical cutaneous angiokeratomas of Fabry's disease, but skin lesions may be absent. Also, there was no evidence of cardiac disease or hypohidrosis, he had no conjunctival venous dilatation, and the neuropathy was mild. Celiac disease may be associated with jejunal diverticulosis, but a cause-and-effect relation between the two disorders has not been established[15] and celiac disease is only a remote possibility in this patient. It is more likely that he had neuromyopathic or small-bowel lesions of undefined cause.

Many patients with jejunal diverticulosis have clinical features of acute and recurrent intestinal obstruction.[16] Some of these patients have mechanical obstruction due to associated volvulus or intussusception, but many of them have symptoms of obstruction without mechanical cause.[16] The frequency of acute "pseudoobstruction" in patients with jejunal diverticulosis varies from 10 to 25 percent in different series.[17] There is evidence to suggest that intestinal bacterial overgrowth can lead to an intestinal motor abnormality or worsen an existing one.[18] In most cases the disorder of the intestinal motility and transit leads to intestinal bacterial stasis and overgrowth, and in some cases it results in diverticulosis. This patient had generalized slight dilatation of the small bowel with normal mucosal folds. Some of the air–fluid levels may have been related to the diverticula, but others may have reflected the dilatation and lack of propulsion of the small bowel. These findings suggest a generalized motor disorder of the gut. Amyloidosis may be associated with small-bowel motor abnormalities, but it has not been reported to cause small-bowel diverticulosis, dilatation is usually absent, and the mucosal folds are thickened.

The long history of recurrent episodes of diarrhea in this patient may have been related to a longstand-

ing bowel-motility abnormality similar to the irritable-bowel syndrome or associated with luminal bacterial overgrowth.[17-19] Luminal bacterial overgrowth may cause diarrhea because products of bacterial metabolism, such as deconjugated bile salts, hydroxylated fatty acids, and organic acids, may induce fluid and electrolyte secretion from the gut. The history of diarrhea dating back to the patient's time as a prisoner in World War II also raises the possibility of parasitic infestation, such as giardiasis, strongyloidiasis, and amebiasis, as well as the possibility of tropical sprue.[19] However, the subsequent course and investigations do not support either of those diagnoses.

This patient's steatorrhea may have been due to multiple small-bowel diverticula[20] or may have been the result of the small-bowel bacterial-overgrowth syndrome. Steatorrhea is present in approximately a third of patients with small-bowel diverticula. Intestinal bacterial overgrowth is a constant feature of jejunal diverticulosis because the diverticula provide an environment conducive to bacterial proliferation, and the underlying problem with small-bowel motility leads to defective luminal clearance and bacterial stasis and overgrowth.[21] The bacterial population may resemble that usually found in colonic contents and feces, with 10^8 to 10^{10} viable organisms per gram of small-bowel content. Ten to 20 bacterial species may be found, and among these bacteroides, anaerobic lactobacilli, enterobacteria, enterococci, clostridia, and diphtheroids predominate.[22] Although small-bowel bacterial overgrowth was not documented by culture of the small-bowel aspirate in this patient, there is enough indirect evidence to suggest its occurrence.

Apart from steatorrhea, patients with bacterial overgrowth have malabsorption of vitamin B_{12},[21] elevated levels of folic acid,[23] and an abnormal result of the D-xylose test.[22] Steatorrhea is mainly due to bacterial deconjugation of bile salts, and the unconjugated bile salts, unlike conjugated bile salts, are rapidly absorbed by the jejunal mucosa, lowering the luminal bile-salt concentration for micelle formation and fat digestion and absorption.[22] Intestinal bacteria synthesize vitamin B_{12} as well as folic acid. The synthesized folic acid is released into the lumen, whereas the vitamin B_{12} is not. Moreover, ingested vitamin B_{12} is bound to the bacteria. Thus, high levels of both vitamin B_{12} and folic acid are present in the bowel lumen in these patients, but there are reduced vitamin B_{12} levels and elevated folic acid levels in the serum. Although vitamin B_{12} malabsorption is an invariable feature of small-intestine bacterial overgrowth, vitamin B_{12} deficiency may not occur because of large body stores of this vitamin.[21] Ingested xylose is metabolized by the bacteria and is hence not absorbed, leading to low serum and urinary levels. This patient had an elevated serum level of folic acid and an abnormal result of the D-xylose test consistent with the bacterial-overgrowth syndrome.[22,23]

Some features of this case are not typical of malabsorption due to simple intraluminal bacterial overgrowth. They are the microcytic hypochromic anemia with a low level of iron in the serum, the lack of response to tetracycline, the symptomatic response to a gluten-free diet, and the extensive changes seen in the biopsy specimens of the duodenal mucosa. These atypical features raise the possibility of an associated disease of the small-bowel mucosa. The mucosal-biopsy findings are helpful in excluding certain diagnoses.[24] The absence of a diffuse mucosal lesion and of PAS-positive macrophages excludes Whipple's disease, the presence of plasma cells excludes agammaglobulinemia, and the absence of lipid-laden vacuolated absorptive cells eliminates abetalipoproteinemia. Certain other diseases that may produce patchy lesions can also be ruled out because of the findings in the biopsy specimens. These diseases are lymphoma, in which there are malignant-tumor cells in the lamina propria, eosinophilic enteritis, which is characterized by eosinophilic infiltration, mastocytosis, in which there is infiltration by mast cells, and amyloidosis, in which amyloid deposits are present in the lamina propria. There was no evidence of giardia or coccidioidal forms on the mucosal surface or organisms within the absorptive cells, excluding giardiasis, cryptosporidiosis, and isosporiasis. The presence of hyperplastic rather than hypoplastic crypts is also against changes secondary to vitamin B_{12} deficiency or chronic intestinal ischemia.

In view of the biopsy findings the diagnoses of tropical sprue, celiac sprue, and intraluminal bacterial overgrowth are the major considerations in this case. However, tropical sprue is unlikely in this patient despite his having been a prisoner in World War II and perhaps his visits to the tropics, because patients with this disease have folic acid deficiency and respond to folate or antibiotic therapy. A coexistence of celiac sprue and jejunal diverticulosis should be considered seriously in the presence of iron-deficiency anemia and hypocalcemia.[15] However, several points are against the diagnosis of celiac disease in this case. The first is that the microcytic hypochromic anemia with a low serum iron level was not of the iron-deficiency type. The decreased iron-binding capacity and the normal or slightly elevated serum ferritin level are consistent with the microcytic hypochromic anemia associated with chronic disease including chronic infection rather than iron deficiency. Secondly, mucosal biopsies in patients with celiac sprue usually show more diffuse epithelial abnormalities.[24] Thirdly, although the symptoms apparently responded to a gluten-free diet for a limited period this response was not documented by improvement in the appearance of the biopsy specimens, and therefore a remission in the undulating clinical course of the bacterial-overgrowth syndrome cannot be excluded.[25]

The intestinal mucosal lesions seen in this patient

could have been due to luminal bacterial overgrowth. Originally, intestinal malabsorption of this cause was believed to be mainly the result of changes in the intraluminal environment, but the presence of associated mild to severe mucosal changes due to bacterial overgrowth have been well documented.[26,27] These changes are patchy, as in this case. However, certain features of the small-bowel bacterial-overgrowth syndrome, such as megaloblastic anemia, were absent. Iron deficiency may occur in the bacterial-overgrowth syndrome because of impaired iron absorption or increased intraluminal blood loss.[28,29] It is also possible that the severe persistent mucosal inflammation in this case was responsible for hypochromic anemia as a result of defective iron utilization. Typically, intraluminal small-bowel bacterial overgrowth responds promptly to treatment with antibiotics. This patient had no symptomatic improvement during a four-week course of tetracycline,[30] possibly because of resistance of the bacteria to this antibiotic. Recent reports suggest that up to 50 percent of patients with the luminal bacterial-overgrowth syndrome do not respond to tetracycline and may require the administration of metronidazole.[31]

Multiple jejunal diverticula, bacterial overgrowth, and microcytic hypochromic anemia may occur in Fabry's disease,[14,32-34] which can be diagnosed on biopsy of the small bowel. It reveals glycolipid deposits appearing as PAS-positive and Sudan-black–positive vacuoles in the venous endothelium, smooth-muscle cells, and submucous neurons.[33-36] These characteristic lesions can be missed if the biopsies are superficial or if specimens are not scrutinized carefully. I believe that the malabsorption in this patient was due to bacterial overgrowth associated with jejunal diverticula and that the associated low-iron, microcytic hypochromic anemia was secondary to severe inflammation of the small-bowel mucosa.

The microscopic hematuria in this case was not associated with hypertension or elevation of the blood urea nitrogen or serum creatinine level. The presence of red-cell casts indicates renal glomerular damage and narrows the differential diagnosis to conditions that produce glomerular damage. Asymptomatic glomerular damage in this patient could have been due to celiac disease,[37,38] Fabry's disease,[39] or an abdominal abscess[40,41] associated with ruptured diverticula. Glomerular lesions can occur in celiac disease as a result of IgA deposits, presumably in relation to circulating gluten-derived antigen absorbed from the gut.[37,38] The glomerular lesion in Fabry's disease is due to the deposition of glycolipid.[29] Intestinal bacterial overgrowth or an abdominal abscess resulting from perforation of diverticula can be associated with circulating immune complexes.[40,41] Circulating immune complexes and associated arthritis and even dermal vasculitis have been described in patients with intestinal bacterial overgrowth associated with intestinal bypass as well as other disorders, including intestinal diverticulosis.[42-45] To my knowledge, however, glomerulonephritis has not been described with these conditions. The explanation may be that glomerular damage occurs when circulating immune complexes are smallest, as in the presence of persistent antigen excess, whereas antigen excess may not be maintained with bacterial overgrowth in the intestinal lumen. However, visceral sepsis can produce a variety of glomerular lesions associated with circulating immune complexes, including acute glomerulonephritis and rapidly progressive extracapillary crescentic glomerulonephritis.[40,41] Some patients with these disorders are asymptomatic, as this patient was. In such patients depression of complement components (C1q, C3, and C4) is inconsistent, as is elevation of blood levels of rheumatoid factor (autoimmune globulin) and circulating cryoimmune globulins. Nevertheless, circulating immune complexes can be detected with proper studies.

The abdominal mass and questionable splenomegaly in this patient raise three diagnostic possibilities. One is abdominal lymphoma. If this patient had celiac disease associated with multiple jejunal diverticula the celiac disease may have been complicated by lymphoma.[46] The development of lymphoma could also explain the lack of a lasting response to the gluten-free diet. The presence of splenomegaly would also be consistent with lymphoma. However, the abdominal CT scan did not show splenomegaly or any lymph-node enlargement. Moreover, the presence of air in the mass and the small-bowel tethering do not support the diagnosis of lymphoma. The second diagnostic possibility is an intraabdominal abscess due to perforation of a diverticulum. The finding of extraluminal scattered air in the mass on the CT scan is highly characteristic of an abscess associated with gas-forming organisms.[47,48] The gastrointestinal series that showed small-bowel loops draping the mass and tethering of the bowel suggests a fibrotic process anchoring the small-bowel loops.[49] Retroperitoneal or mesenteric inflammatory processes can produce such a radiologic picture. The absence of more obvious clinical findings of an abscess in this case is not entirely surprising. Retroperitoneal, mesenteric, and intraperitoneal abscesses or masses that do not involve the anterior peritoneum may be clinically occult.[50,51] In patients with occult lesions superficial tenderness and rebound tenderness are lacking. Palpation of the mass is difficult because of the interposition of the bowel loops between the mass and the anterior abdominal wall. Fever and leukocytosis may be absent in patients with intraabdominal abscesses. This patient had 32 percent band forms, which are consistent with an infectious process. Small-bowel diverticula can rupture into the peritoneal cavity, causing diffuse or localized peritonitis. In this patient localized peritonitis did not appear to involve the anterior peritoneal wall. The spread of infection might have occurred between the

two leaves of the small-bowel mesentery to involve the anterior pararenal space. Rupture of a diverticulum can occur because of diverticulitis, a foreign-body impaction, an ulcer, or a tumor associated with a diverticulum.[52-54] In Fabry's disease perforation can occur because of vascular ischemia.[55] The third diagnostic possibility is a sarcoma or a similar tumor associated with small-bowel diverticula.[56] The extraluminal air that is sometimes seen in a mass of the type that was present in this patient may represent air that has leaked through the bowel wall and become trapped in a necrotic tumor.[48,49]

The possible splenomegaly in a patient with an abscess in or near the left anterior pararenal space may be due to thrombosis of the splenic vein. A diverticular abscess may also be complicated by pyelophlebitis.[57,58] However, patients with that complication have episodes of shaking chills and liver-function abnormalities, which were absent in this patient. Dilated colonic mucosal veins and varices may occur in association with portal hypertension secondary to portal-vein thrombosis, but prominent mucosal veins in the sigmoid colon may be seen normally. Rarely, splenomegaly also occurs in Fabry's disease.[59]

In conclusion, the best unifying, single diagnosis in this case would have been Fabry's disease, with a small-intestine motility disorder, the development of small-bowel diverticulosis, intraluminal bacterial overgrowth causing steatorrhea, and diverticular perforation leading to an intraabdominal abscess. The microcytic hypochromic anemia, neuropathy, dilated mucosal veins, and splenomegaly could also be attributed to Fabry's disease. These are unusual manifestations of an uncommon disease, however, and many characteristic features of Fabry's disease are lacking in this case. A statistically more likely underlying diagnosis is an intestinal motor disorder due to a neuromyopathy of unknown cause, with multiple jejunal diverticula and intraluminal bacterial overgrowth leading to steatorrhea, severe mucosal inflammation, and diverticular perforation, and an intraabdominal abscess complicated by immune-complex–related glomerular lesions and possible splenomegaly due to splenic-vein thrombosis.

DR. ROBERT E. SCULLY: May we have the medical students' diagnoses, Dr. Weinstein?

DR. DEBRA F. WEINSTEIN: The students thought that this patient's findings can be explained by either of two sequences. The first possibility is that the malabsorption was due to bacterial overgrowth associated with small-bowel diverticula, and the mass was caused by obstruction of a diverticulum or was a walled-off abscess. An alternative diagnosis that they favored slightly was celiac sprue with a small-bowel lymphoma.

DR. SCULLY: Dr. Rustgi and Dr. Katkov, will you tell us your diagnostic impressions before the procedure?

DR. ANIL K. RUSTGI: My care of the patient was limited to his first admission. We concluded then that he had celiac sprue coexisting with jejunal diverticulosis. Although bacterial overgrowth in the setting of jejunal diverticulosis could have accounted for the chronic intermittent diarrhea, he had failed to respond to trials of antibiotics in the past. We therefore instituted a gluten-free diet, with which he was meticulously compliant. Resolution of the diarrhea occurred over the ensuing 10 months.

DR. WILLIAM N. KATKOV: The differential diagnosis on the second admission focused on the presence of cachexia, weight loss, and a low-grade fever, with an abdominal mass. The impression on the way to the operating room was that we would find either a tumor or an abscess.

CLINICAL DIAGNOSES

Small-bowel diverticulosis.
Bacterial-overgrowth syndrome.
? Celiac sprue.
Lymphoma or intraabdominal abscess due to perforation of diverticulum.

DR. RAJ K. GOYAL'S DIAGNOSES

Small-bowel diverticulosis.
Intraluminal bacterial overgrowth causing steatorrhea.
Diverticular perforation, with intraabdominal abscess.
? Splenic-vein thrombosis.
Immune-complex-related glomerulitis.
? Fabry's disease.

PATHOLOGICAL DISCUSSION

DR. COMPTON: At operation the small bowel was involved by diverticulosis that was too extensive to permit resection of the entire affected portion, but a large inflammatory mass about 10 cm in diameter was removed, along with about 50 cm of adherent small bowel. Thickening of the ileum with adherent "creeping" fat was also observed intraoperatively and suggested a diagnosis of Crohn's disease as well.

The specimen consisted of a 50-cm segment of jejunum, with the loops matted together by fibrinous serosal adhesions. The small intestine surrounded a firm inflammatory mass in the mesentery, 9.0 cm in greatest dimension. Along the mesenteric border of the bowel multiple diverticula, most of which were 0.5 to 1.5 cm in length, were seen. The mucosa lining the diverticula and their orifices appeared congested and inflamed. Many diverticula were surrounded by adherent fibrofatty tissue. One of them communicated with a 5-cm abscess cavity in the center of the mesenteric mass. Another diverticulum, 4.5 by 3.5 by 3.5 cm, was inflamed but did not appear to have perforated.

Microscopical examination revealed that all the di-

verticula examined lacked a muscular coat and were lined only by mucosa and submucosa, as is characteristic of acquired rather than congenital diverticula of the small bowel (Fig. 4). The base of the diverticulum communicating with the abscess cavity was obliterated, and the surrounding mesenteric tissue was extensively inflamed, focally hemorrhagic, and fibrosed. The mucosa lining the perforated diverticulum and several others was markedly inflamed and focally eroded. In the mucosa adjacent to the diverticula there were inflammatory changes identical to those seen in the previous biopsy specimens. Antral metaplasia of the mucosa, a feature consistent with longstanding inflammation, was present in several diverticula. The mucosa distant from the diverticular openings was more normal in appearance, explaining the patchy nature of the mucosal inflammation seen in the earlier biopsy specimens. The muscularis propria throughout the affected bowel segment was moderately to markedly hypertrophied, and slight hypertrophy of the intermyenteric plexus was evident. No atrophy of the longitudinal layer, intermyenteric fibrosis, or ganglion-cell abnormalities were seen. The vasculature appeared normal except for acute congestion. The diagnosis was jejunal diverticulosis with both acute and chronic inflammation of several diverticula and subacute perforation with the formation of a large, walled-off mesenteric abscess.

Jejunal diverticulosis was first described over 180 years ago, but a century passed before it was recognized during life, at an operation for intestinal obstruction.[4] The frequency of jejunal diverticula in autopsy series varies from 0.06 to 1.3 percent and in radiologic studies of the small bowel from 0.02 to 0.42 percent. These diverticula are frequently associated with diverticula elsewhere in the gastrointestinal tract, especially in the ileum and colon, where synchronous diverticula are seen in 30 percent and 30 to 50 percent of the cases, respectively.[60] Diffuse small-bowel diverticulosis was demonstrable radiologically in this case, and sigmoid diverticulosis was seen on colonoscopic examination. The most likely explanation of the inflammatory changes resembling Crohn's disease of the ileum seen at the surgical procedure is chronic diverticular disease in the involved segment.

In the past the medical literature had suggested that jejunal diverticulosis is symptomatic in only 10 to 40 percent of the cases, but more recent reports have suggested that the frequency of symptoms may have been underestimated.[4,61] In fact, metabolic abnormalities attributable to bacterial overgrowth in diverticula are believed to be relatively common in this condition,[4] and a "blind-loop" syndrome was the most likely cause of this patient's malabsorption. Chronic but intermittent gastrointestinal symptoms occurring with variable periodicity and severity, as occurred in this case, are typical. Broad-spectrum antibiotics usually produce considerable relief, but their administration

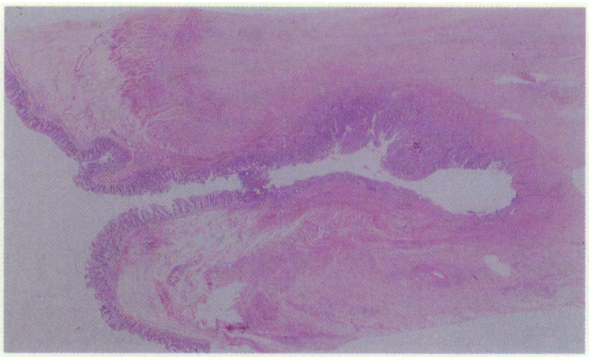

Figure 4. Diverticulum Characterized by Mucosal Herniation through the Muscularis Propria of the Jejunum (×3).

may have to be continued for long periods. Tetracycline is ineffective in some patients who subsequently respond to erythromycin. Repeated courses of treatment may be required since the length of remission after the antibiotic therapy is discontinued varies greatly.[62]

Diverticulitis with perforation is a well-documented complication of jejunal diverticulosis,[62-65] but it is seldom diagnosed preoperatively. It has been associated with a mortality rate of about 20 percent,[64] probably related both to a delay in the diagnosis and to its occurrence mostly in patients over 60 years of age. Other surgical complications of jejunal diverticulosis include pseudoobstruction, true mechanical obstruction due to inflammation or rarely enterolith impaction, hemorrhage, and pneumoperitoneum without demonstrable perforation.

The cause and pathogenesis of jejunal diverticulosis remain obscure. In a review of 10 cases in 1983 Krishnamurthy et al.[4] noted symptoms of pseudoobstruction in 9 of them and observed patchy smooth-muscle abnormalities and intermyenteric fibrosis or abnormalities of the intermyenteric nerve plexus on histopathological examination. Those authors suggested that the disease might result from a variety of primary abnormalities of the smooth muscle or myenteric plexus. No such abnormalities were observed on microscopical examination in this case.

DR. SCULLY: Dr. Wands, do you have a follow-up report on this patient?

DR. JACK R. WANDS: He has been well since the operation and has regained weight. He is being maintained on a gluten-free diet.

DR. GOYAL: A better understanding of the pathophysiology of small-bowel diverticulosis requires immunocytochemical study of the nerves in the involved small bowel. Also, manometric studies can characterize motility abnormalities, which may underlie jejunal diverticulosis. Only a few such motility studies have been done.[6,66]

Normally, the small-bowel motility pattern in the interdigestive (fasting) state is cyclical, with each cy-

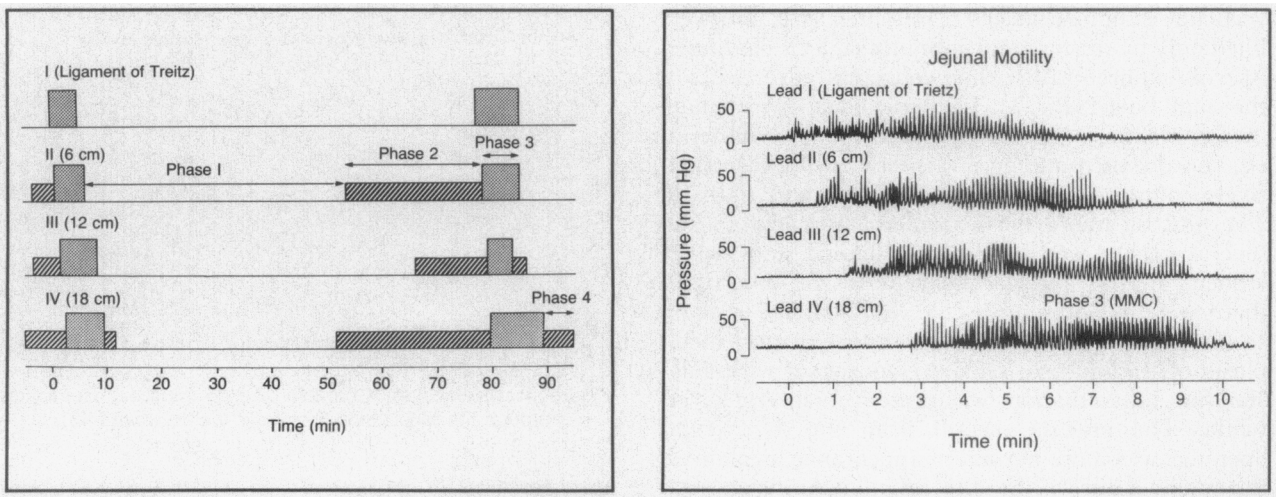

Figure 5. Small-Bowel Motility Study in a Normal Subject.
The left panel is a schematic diagram of various phases of cyclical motor activity, and the right panel shows a pressure tracing of the migrating activity front.

cle consisting of several phases — namely, a period of no activity (phase 1), a period of irregular contractions (phase 2), and a period of regularly occurring contractions called the "activity front" (phase 3). Each cycle lasts 1.5 to 3 hours. The cyclical activity migrates down the small bowel at 5 to 15 cm per minute and is therefore called the "migrating motor complex" (MMC). The propagation of the activity front is associated with propulsion of food residues. Many patients with small-bowel bacterial overgrowth have poorly developed or poorly propagated activity fronts.[66] Figure 5 shows a small-bowel motility tracing in a normal subject. The left panel is a schematic diagram of small-bowel motility. The four pressure-sensing leads recorded intraluminal pressures from four sites in the upper jejunum, which were 6 cm apart. The catheter assembly was passed through the mouth, and the most proximal lead was fluoroscopically located to the region of the ligament of Treitz. Phase 4, a period of irregular contractions, sometimes follows phase 3. Phases 2 and 4 are inconsistently present. In this example Lead I shows no phase 2 or 4, and Lead II shows no phase 4. The cyclical activity resumes about every 90 minutes and migrates down the small bowel. The right panel of Figure 5 is a tracing of phase 3 activity, with regularly occurring contractions at a rate of around 12 per minute; there is distal propagation of the activity front.

Some patients with multiple jejunal diverticula have spasm-like contractions of the small bowel leading to excessive and sustained increases in intraluminal pressure, which may result in the formation of the diverticula and the intestinal pseudoobstruction syndrome.[67] Figure 6 shows a small-bowel motility tracing in a patient with jejunal diverticulosis and the intestinal pseudoobstruction syndrome. The upper panel is a schematic diagram of small-bowel motility.

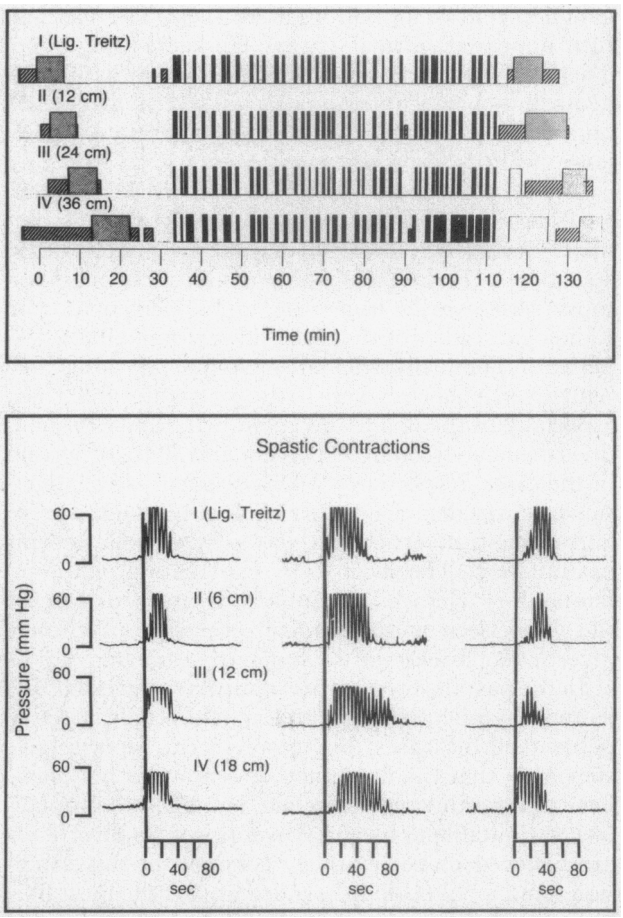

Figure 6. Small-Bowel Motility Study in a Patient with Multiple Jejunal Diverticula and the Intestinal Pseudoobstruction Syndrome.
The upper panel is a schematic diagram of one cycle of motor activity, and the lower panel is an actual tracing of spastic complexes.

The period of phase 1 activity is occupied by spastic contractions (solid bars) occurring nearly simultaneously at all the sites, which are 12 cm apart. Different phases of cyclical activity are present, as in normal persons. The lower panel of Figure 6 is a tracing of spastic complex contractions. These are complexes of repetitive contractions occurring nearly simultaneously at all the recording sites, which were 6 cm apart. Sometimes these complexes show retrograde propagation, and at other times they are simultaneous at some sites and propagated at other sites.

Anatomical Diagnosis

Small-intestine diverticulosis, with diverticulitis, perforation, and abscess in mesentery.

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