

Lesions of the Gastrointestinal Tract Resembling Regional Enteritis—A Granulomatous Disease

A Report of Three Cases

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CROHN, Ginzburg and Oppenheimer in 1932¹ described a disease of the terminal ileum with rather typical pathological and roentgenological features which they termed regional ileitis. Since that time, vast experience with this condition has accumulated² and a number of different names have been given to the disease, including regional enteritis, regional ileitis, segmental enteritis and cicatrizing enteritis. Although in the great majority of cases it has been found that the terminal ileum is the region involved, a similar disease process may affect any segment of the gastrointestinal tract from the esophagus to the rectum.³⁻⁶ This may occur in association with involvement of the terminal ileum or as an independent lesion. It is the purpose of this paper to report three cases of regional enteritis-like lesions, involving areas other than or in addition to the terminal ileum.

CASE REPORTS

CASE 1.—A 30-year-old white woman was first admitted to hospital in 1959 because of abdominal cramps, pain in the periumbilical area and constipation alternating with diarrhea for a one-month period. Physical examination revealed tenderness in the suprapubic area and in both iliac regions, but no palpable masses or organs. Digital examination of the rectum revealed some external hemorrhoids and a moderate degree of tenderness.

Examination of the blood showed a hemoglobin of 12.4 g. % and a sedimentation rate of 101 mm./min. (Westergren). Sigmoidoscopic examination revealed only normal colonic mucosa. A gastrointestinal series showed no significant abnormalities; the terminal ileum was not visualized.

Barium enema (Fig. 1) disclosed a tubular recto-sigmoid and descending colon with a smooth contour devoid of haustrations. The mucosa of these segments showed destruction of the rugal pattern and spiky projections due to filling of minute ulcerations. The remainder of the colon appeared fairly normal. Ulcerative colitis was considered to be the most likely diagnosis and the patient was discharged on a medical regimen.

A second admission was necessary three months later because of persistence of the crampy abdominal pain, increasing constipation and weight loss. The patient was febrile and had anorexia. Examination of the abdomen revealed a firm tender mass in the right lower quadrant, measuring three inches in diameter. On pelvic examination, the mass was thought to be of ovarian origin. A laparotomy was performed and it was

ABSTRACT

Although regional enteritis classically involves the terminal ileum, lesions showing similar histology may involve other segments of the gastrointestinal tract, either independently or concomitantly with terminal ileum involvement. Histologically the basic reaction is non-specific chronic inflammation with a granulomatous component and a variable degree of fibrosis. Such lesions in the upper gastrointestinal tract resulted in nonspecific intestinal complaints and roentgenographically showed mucosal alterations and loss of normal motility. Those with colonic involvement were difficult to differentiate from ulcerative colitis, clinically and, in the early stages, roentgenographically. With more advanced involvement, roentgenographical diagnosis was possible.

Three patients with lesions illustrating the aforementioned features were diagnosed and treated. One had lesions in the colon and terminal ileum. In the others the terminal ileum was not involved; in the second the stomach, duodenum and upper jejunum were involved, and in the third the colon was involved.

found that the lesion was caused by regional ileitis. A right hemicolectomy was carried out, which included the terminal 45 cm. of ileum. This woman made an uneventful recovery and was discharged on the tenth postoperative day.

The resected specimen consisted of a 45-cm. segment of ileum and the cecum, ascending and transverse colon. The proximal one-third of the resected ileum was dilated and its wall was thin. The remainder revealed marked narrowing of the lumen and thickening of the wall. The mucosa showed superficial linear ulcerations. The mesentery was thickened and contained some enlarged firm lymph nodes. The cecum and colon were grossly normal.

Microscopically, the wall of the ileum was thickened by marked fibrosis of the submucosa and lesser fibrosis involving the muscle coats and serosa. Superficial acute erosions of the mucosa were surrounded by acute inflammation. There were lymphocytic and histiocytic infiltrations into the submucosa and subserosa. Small non-caseating granulomas were found in the mucosa, submucosa, subserosa and local lymph nodes.

This woman was admitted a third time, 27 months later, for a hemorrhoidectomy made necessary because of prolapsed, painful and bleeding hemorrhoids. In

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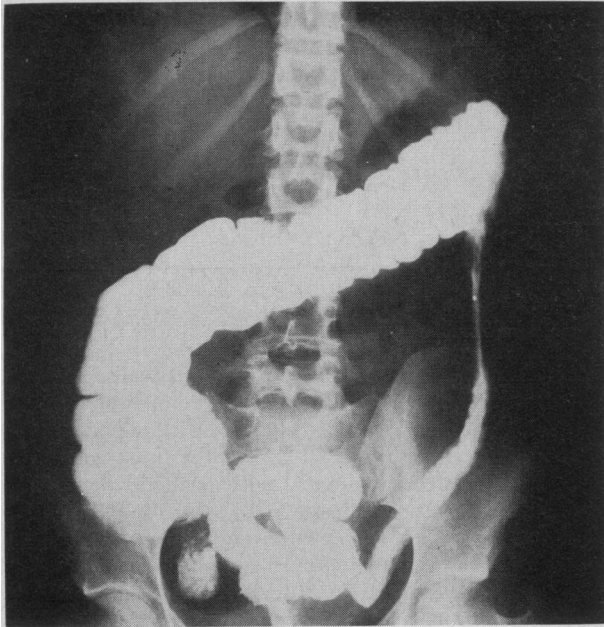


Fig. 1.—Case 1. The narrowed, rigid, tubular descending colon and sigmoid contrast with the normal-appearing ascending and transverse colon. The penumbra-effect along the sigmoid and the finely irregular contour of the involved segments due to mucosal edema and ulcerations are evident.

the interim she had continued to have some crampy abdominal pain and diarrhea. Barium enema examination showed a normal functioning ileocolostomy with progression of the lesions, involving the terminal colon. Because of the presence of regional ileitis, it was felt at that time that the changes in the large bowel were most likely due to non-specific granulomatous inflammation, rather than to chronic ulcerative colitis.

The fourth admission, four months later, was occasioned by continuing diarrhea (six to eight movements a day) and the appearance of a painful swelling in the anal region which periodically discharged foul-smelling material. The stools had often contained bright red blood. She had lost 20 lb. in four months. Rectal digital examination revealed a tender perianal swelling, surrounding a fistula-in-ano from which pus was easily expressed. Culture of this material showed a heavy growth of *Pseudomonas* and *Proteus mirabilis*. An incision of the abscess was done. Under anesthesia, an anoscope could not be advanced beyond 1" from the anus because of a stricture. Hyperemia and pseudopolypi were found at this level. The appearance on barium enema examination had not changed appreciably from that seen four months before.

At laparotomy, the descending colon was found to be rigid and narrowed from the splenic flexure to the anus. The transverse colon was markedly dilated. The regional lymph nodes were enlarged. A resection of the total remaining large bowel, including the rectum, was performed and an ileostomy was fashioned. Post-operatively, she made a steady improvement.

The resected specimen consisted of 80 cm. of bowel, including proximally a short segment of ileum, the ileocolic anastomosis and the remaining large intestine. The wall of the ileum was somewhat thickened. The ileocolic anastomosis was slightly thickened, but the remaining portion of the transverse colon was thin and markedly dilated. The distal colon from the splenic flexure downwards had a thickened fibrotic wall. The mucosa in this area was swollen and contained numer-

ous small mucosal ulcerations. A number of small lymph nodes were found in the pericolic tissue. Microscopic examination of the involved areas showed marked fibrosis of the submucosa and lesser fibrosis involving the muscle coats. There were superficial acute erosions of the mucosa surrounded by acute inflammatory cells. There were lymphocytic and histiocytic infiltrations of the submucosa and subserosa. Small non-caseating granulomas were found in the mucosa, submucosa, subserosa and lymph nodes. Sections of the ileum and proximal portions of the large intestine showed a milder involvement by the same type of reaction pattern. The diagnosis was: "Granulomatous enterocolitis involving the ileum; ileocolic anastomosis, descending colon and rectum".

By the time of her discharge from hospital the patient's weight had increased and her appetite had markedly improved. One year later her weight had increased by 29 lb. and she was feeling well.

CASE 2.—A 52-year-old white woman was first admitted in 1952 because of abdominal pain and vomiting. Attacks of periumbilical pain, most often nocturnal, first appeared at the age of 41. The pain was usually followed by vomiting of bile-containing material and, frequently, of undigested food. In the year prior to admission the pains had increased in intensity and the vomiting had become more frequent. The patient had suffered from episodic diarrhea and sustained a 25-lb. weight loss.

Physical examination revealed only normal findings. The hemoglobin was 12.2 g. %. A cholecystogram disclosed a well-functioning gallbladder, which, however, contained multiple small calculi. Cholecystectomy and appendectomy were performed; pathological examination revealed chronic cholecystitis and cholelithiasis, and fibrosis obliterans of the appendix.

This woman was admitted for a second time 15 months later. The previous operation had failed to relieve her symptoms. Physical examination again was non-contributory. A gastrointestinal series revealed partial duodenal obstruction located near Treitz' angle.

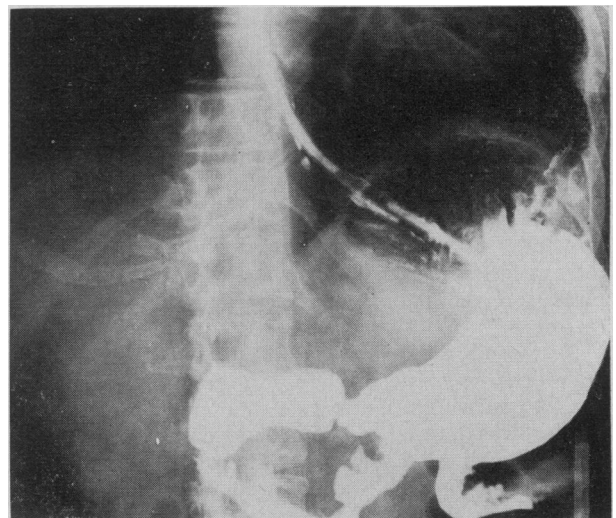


Fig. 2.—Case 2. Postero-anterior view of the stomach, duodenum and proximal jejunum obtained 20 minutes after ingestion of barium. The gastric curvatures and the outline of the duodenal cap are smooth and regular. The pylorus is patent. Only a minimal amount of barium had reached the proximal jejunum. The duodenal loop and first segment of jejunum have an irregular contour with absence of the usual feathery appearance of the mucosal relief.



Fig. 3.—Case 2. One hour after ingestion of the barium, the appearance of the stomach was unchanged. The duodenal and proximal jejunal loops show irregular rigid contours with abnormal mucosal pattern of the involved segments.

Gastric analysis showed normal free and total acidity. At laparotomy, adhesions were found in the gallbladder area and between the gallbladder, liver and first two parts of the duodenum; the common bile duct, pancreas and stomach were normal in appearance. The adhesions were freed. She made an uneventful recovery from the operation.

A third admission took place 10 months later, to permit radical mastectomy for breast carcinoma with metastatic involvement of the regional axillary nodes. The gastrointestinal symptoms were unchanged from her previous admissions.

The final admission occurred six months later at the age of 56 and was necessary because of persistence of periumbilical pains, belching, intractable vomiting and bouts of diarrhea. Because of these symptoms, she had restricted her diet to clear soups, tea and bread. Except for emaciation, physical examination was still essentially negative. Examination of the blood revealed a hemoglobin of 13.2 g. % and a white blood count of 7300 per c.mm. with a normal differential count. A fasting blood sugar was 78 mg. %. Following her normal breakfast, the blood sugar was 92 mg. %. The serum proteins were 6.4 g. %, with 3.4 g. albumin. Serum sodium was 137, serum potassium 5.1, chlorides 94.6 and carbon dioxide 29.0 mEq./l. Gastric analysis revealed normal free and total acidity and volume. Tests for occult blood in the stool were negative. Roentgenographic examination of the upper gastrointestinal tract disclosed a normal esophagus. The stomach showed a well-defined and flexible contour, but the tone of the gastric walls was decreased. The stomach was dilated and almost completely akinetic;

only occasional peristaltic activity was noted. Gastric evacuation was considerably delayed, so that barium was found in the stomach 24 hours later. The pylorus showed marked decrease of its rhythmic contractions. The duodenal cap filled fairly well, but failed to empty during long intervals. The small amount of opaque material that did pass showed that the duodenum and proximal jejunum were rigid and consistently deformed; areas of narrowing alternated with pseudodiverticular outpouchings on the concave side of the duodenal loop (Fig. 2). A mucosal pattern was not recognizable (Fig. 3). On intubation of the duodenum, the tip of the tube could not be advanced beyond the duodenal cap and the injected barium was dammed back into the stomach. The roentgenological diagnosis was segmental enteritis involving the duodenum.

At laparotomy, the stomach was grossly normal. The duodenum was partially mobilized by means of the Kocher maneuver, but no definite abnormality could be noted by inspection or palpation. A number of small subserosal air-filled cysts (*pneumatosis cystoides intestinorum hominis*) were present in the terminal ileum. A gastroenterostomy was performed. The post-operative course was uneventful until the fifth day, when the patient developed clinical signs of occlusion of the left femoral artery. An emergency embolectomy was performed but the patient died a few hours later.

Autopsy Findings

At postmortem examination, the esophagus was normal. The stomach showed a recent healing gastro-

jejunostomy closed with black silk sutures. The pylorus was slightly reduced in size and quite rigid, but easily admitted two fingers. There was a localized, bile-containing paraduodenal abscess, 8 x 5 x 1 cm. The duodenum and first two feet of the jejunum showed a smoothing-out of the mucosal folds. The wall was not remarkably thickened and the lumen was not narrowed. Along the concavity of the duodenum were several very shallow and very wide-mouthed out-pouchings. A 0.3 cm. perforation was found in the mucosa of one of these, communicating with the above-mentioned paraduodenal abscess. The remainder of the small intestine was essentially normal; the peritoneal pneumocysts could no longer be identified. The large intestine was unremarkable. Other findings were marked myocardial fibrosis of the left ventricle; coronary artery sclerosis, and recent occlusion of left femoral artery.

On microscopic examination, sections of the pylorus, duodenum and proximal jejunum showed an inflammatory process, patchy in distribution, normal areas alternating with involved areas. It was most marked in the duodenum, especially the first two portions. The inflammatory process was localized principally to the mucosa and submucosa, and consisted of a heavy cellular infiltration with lymphocytes, plasma cells and occasional eosinophils; this had flattened the normal structure of the mucosa. The reaction also contained histiocytes and multinucleated giant cells. Scattered fibrosis was found involving the submucosa and subserosa and to a lesser degree the muscle coats. An occasional superficial mucosal erosion was found. Normal myenteric plexus elements were found throughout. The antrum of the stomach showed some increase in thickness of the muscularis mucosae and some scarring and degeneration in the muscular layers. Multiple sections of the lower jejunum and ileum were normal. Sections of the pancreas showed a small islet cell adenoma; on special staining, the cells were not beta cells.

The anatomical diagnoses were: (1) Chronic granulomatous inflammation, non-specific of the pylorus, duodenum and jejunum. (2) Paraduodenal abscess, bile-containing, small, with fibrinopurulent peritonitis, localized; secondary to minute perforation of the duodenum. (3) Occlusion, recent, left femoral artery. (4) Myocardial fibrosis, marked.

CASE 3.—A 52-year-old woman was first admitted to hospital in 1955 because of episodic abdominal pain, constipation, diarrhea and bright-red bleeding on defecation during the previous month. Physical examination revealed only some tenderness on palpation in the left lower quadrant of the abdomen and the presence of an ill-defined mobile mass in this area. Her temperature was 100° F. Examination of the blood revealed a hemoglobin of 12.8 g. %, a white blood cell count of 13,300 per c.mm. and a sedimentation rate of 57 mm./minute (Westergren). Barium enema examination showed an abrupt change in the calibre of the splenic flexure, and the bowel proximal to this was moderately dilated (Fig. 4). The involved segment was rigid and its contour showed spiky projections (Fig. 5), indicating mucosal ulcerations. The calibre of the lumen did not exceed 0.5 cm. in diameter in the involved area. The mucosal relief was completely destroyed. The remainder of the large intestine appeared normal. The provisional radiologic diagnosis was "segmental colitis". Sigmoido-

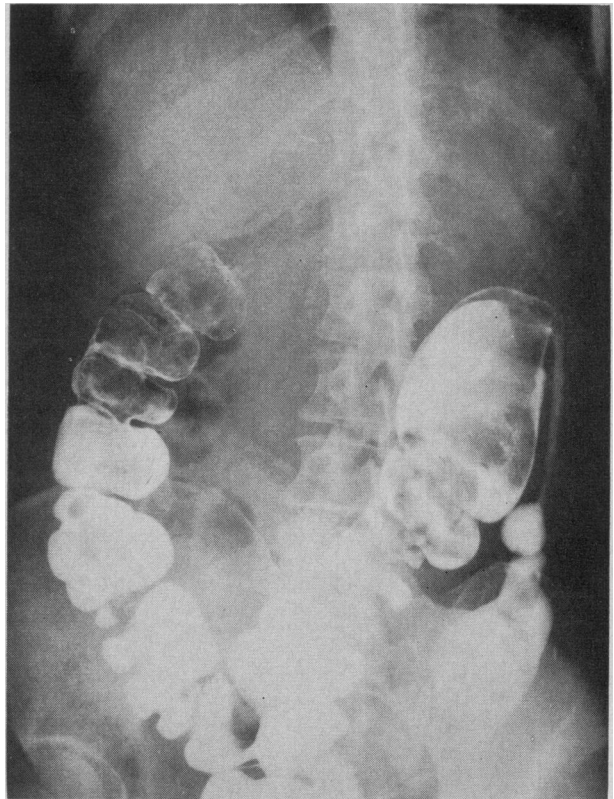


Fig. 4.—Case 3. Barium enema examination showing the "string sign" involving the proximal portion of the descending colon. The line of demarcation between the distended but otherwise normal transverse colon and distal descending and sigmoid segments is abrupt.

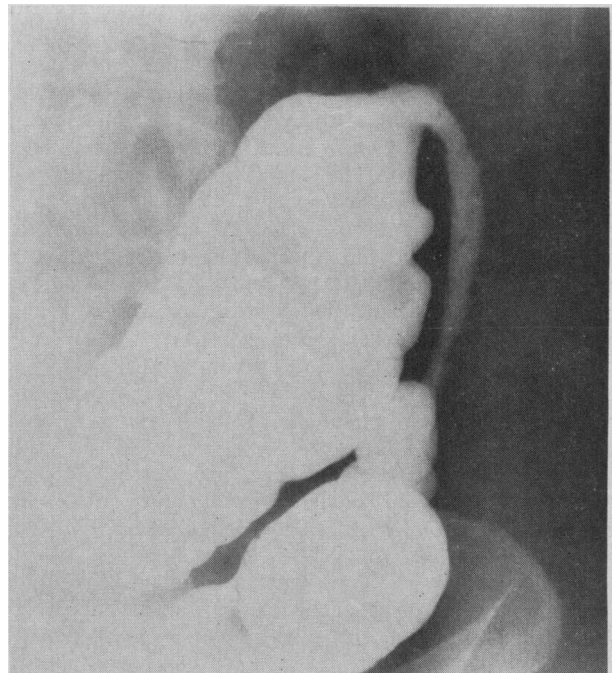


Fig. 5.—Case 3. Close-up of the involved segment of the descending colon showing rigidity and a fine spiky contour due to filling of ulcerations by the barium. There are small filling defects within the involved segments; these are due to islands of hyperplastic mucosa.

scopic examination was negative. She was placed on a trial medical regimen and discharged.

The second admission took place six weeks later because of increasing weakness, crampy abdominal

pain and diarrhea. Physical examination was essentially as described above. The hemoglobin was 11.5 g. %. The findings on barium enema examination were unchanged. Gastrointestinal series revealed no abnormality. At laparotomy the large bowel proximal to the splenic flexure was slightly dilated. The descending colon from just below the splenic flexure for a distance of about seven inches was generally narrowed, firm and rigid. A block resection of the involved colon was performed and continuity restored by an end-to-end anastomosis. The postoperative course was uneventful and she was discharged in good condition with satisfactory bowel function.

The resected specimen consisted of 18 cm. of colon. In the central portion there was a stenotic area 8 cm. in length. The bowel proximal to this was dilated. The mucosa of the stenotic area was dark brown in color, contained multiple small shallow erosions and a few minute polypoid projections, and was firmly bound to the underlying bowel wall, which was thickened and appeared fibrous. The serosa was also thickened and fibrous. Small, soft lymph nodes were present in the attached pericolic fat.

Microscopic examination of the central stenotic area showed many shallow mucosal ulcerations with an acute inflammatory reaction. The submucosa was greatly thickened by edema and fibrosis and was infiltrated by lymphocytes. The muscle layer was thickened and showed some fibrosis. There were no granulomas. Sections from the colon proximal and distal to the gross stenotic area showed mild submucosal edema and fibrosis. The lymph nodes showed lymphoreticular hyperplasia. The diagnosis was "segmental cicatrizing granulomatous colitis".

The patient has been followed up for a period of seven years. She has had no further gastrointestinal complaints and has gained 15 lb. in weight. Follow-up barium enema examinations have revealed no abnormal findings.

DISCUSSION

The foregoing cases are examples of non-specific granulomatous inflammation involving intestinal segments other than those found in classical regional ileitis. In Case 1, the descending colon, sigmoid and rectum were involved, in addition to the terminal ileum. In the other two instances, the terminal ileum was free of disease. In Case 2, the pylorus of the stomach, the duodenum and jejunum were the involved sites, while in Case 3, a short segment of the descending colon was affected.

Leichtling and Garlock⁵ have recently reviewed the literature on such lesions which involve the colon. They noted that a conflicting nomenclature has arisen concerning cases of this type because of a difficulty in classifying the histological lesion. The microscopic findings in the classical variety of regional ileitis vary with the stage of the disease, and the histological diagnosis is established by the total reaction pattern of the tissues, rather than by any single isolated feature. Although microscopic granulomas were once considered a necessary requisite, a diagnosis of regional ileitis can be made in the absence of these granulomas.⁵ The basic histological pattern in regional ileitis is that of a

non-specific chronic inflammation with a granulomatous component and a variable degree of fibrosis. The latter, especially, varies with the stage of the disease. Although identical pathological reaction patterns do not necessarily mean identical etiology, it would appear that until further knowledge is forthcoming, it is logical to consider as one group all of the non-specific idiopathic granulomatous enteropathies.

The histological reaction pattern in each of the three cases described in this report illustrates a stage of non-specific granulomatous inflammation. In Case 1, the resected ileum showed the typical gross and microscopic features of regional ileitis, including granulomas in the lymph nodes, and 31 months later a similar histological process, including granulomas, was found in the region of the ileocolic anastomosis and in the sigmoid colon and rectum. In Case 2, there was a patchy involvement extending from the pylorus to proximal jejunum; the prominent histological feature was heavy cellular infiltration of the mucosa and submucosa by lymphocytes, plasma cells, histiocytes and multinucleated giant cells, but there were no granulomas. In Case 3, a sharply demarcated segment of colon was involved; marked submucosal edema, lymphocytic infiltration and fibrosis of all coats resulted in reduction of the diameter of the bowel to 0.5 cm.

The clinical and roentgenographic features of granulomatous lesions in sites other than the terminal ileum vary with location. Durrance⁶ has recently presented a review of the literature concerning the clinical and roentgenographic features of involvement of the upper gastrointestinal tract by this process. In brief, as in our Case 2, upper gastrointestinal signs and symptoms dominate the clinical picture. Roentgenographically, mucosal alterations and loss of normal intestinal motility are the main findings. The only diseases likely to be confused with this lesion roentgenographically are lymphomas, scleroderma or amyloidosis. It is interesting that in our Case 2 there was marked gastric retention and yet no evidence of organic narrowing could be noted either at operation or a few days later at autopsy.

The clinical and roentgenographic features of granulomatous inflammation involving the colon have been well documented in recent reviews.^{4, 5, 7, 8} Clinically, it is usually difficult to differentiate this disease from ulcerative colitis. The development of internal fistula should alert one to the possibility of granulomatous colitis rather than ulcerative colitis.⁵ Roentgenographic examination should include both small-bowel series and barium enema, as the finding of a lesion in the terminal ileum would suggest that a process in the large bowel is similarly a granulomatous reaction; the co-existence of regional ileitis and classical ulcerative colitis in the same patient does not appear to be common.⁹ In the early stage of the disease, the roentgenographic findings in granulomatous colitis

may be difficult to differentiate from ulcerative colitis. However, in advanced stages, a roentgenographic diagnosis is possible, from the features recently described by Wolf and Marshak,⁷ such as skip areas, longitudinal ulcerations, transverse fissures, narrowing of the involved segment with rigidity of its wall and pseudopolypoidal cobblestone appearance of the inner relief of the bowel wall.

Laparotomy is usually indicated in cases with involvement of the upper gastrointestinal tract, because of the difficulty of establishing a diagnosis. A bypass procedure, combined with a vagotomy to minimize the possibility of stomal ulceration, appears to be the procedure of choice.¹⁰⁻¹² Excisional surgery would appear to be warranted only as a life-saving measure when there is massive hemorrhage, or when there is a localized lesion in an accessible and expendable region. Steroid therapy has been stated to be of value as a primary therapeutic measure,¹⁰ whereas others^{11, 13} feel that this form of therapy is best reserved for patients with recurrent and extensive disease.

Recently, Lockhart-Mummery and Morson,⁴ Sutcliffe,¹⁴ and Anton and Sutherland¹⁵ have reported their findings in patients with colonic lesions. From experience with 25 patients with colonic involvement, Lockhart-Mummery and Morson⁴ concluded that excisional therapy gives better results than does a bypass procedure. If excision was not possible, ileostomy or colostomy was performed. The authors noted that the incidence of recurrence after excisional therapy for granulomatous colitis has been lower than that occurring with classical regional ileitis. Longer follow-up of a larger number of cases will be necessary to establish this definitely. Two patients in this report are free from recurrence, one for one year following resection of the colonic lesions, and the other for seven years following excisional therapy.

SUMMARY

Although the terminal ileum is the region commonly involved by regional enteritis, a similar histological reaction may affect any segment of the gastrointestinal tract. The disease may occur concomitantly with involvement of the terminal ileum, or as an independent lesion. This course is exemplified by the three cases presented. In one case, the descending colon, sigmoid and rectum were involved, in addition to the terminal ileum; in the other two instances, the terminal ileum was free from disease.

From the pathological point of view, a conflicting nomenclature has arisen concerning cases of this type because of difficulties in histological classification. The tissue reaction patterns in these lesions are essentially similar and it is suggested these be considered as one group designated "non-specific granulomatous enteropathies".

The clinical and roentgenographic features are briefly described. From the cases reported in the literature it would appear that, when it is feasible, excisional therapy is preferable to by-pass procedures. Two of the patients described in this communication are free from recurrence, one for one year following resection and the other for seven years.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CONGENITAL CARDIAC DISEASE

The case is one of pulmonary hypoplasia, stenosis of the conus of the right ventricle with supplementary cusps, defect of the interventricular septum at the base with *Rechtslage* of the aorta, and patent foramen ovale . . .

The patient, E.H., aged sixteen years, was first seen on January 17th, 1913, when he was suffering from a typical attack of influenza; on that occasion the following history was obtained. He was born in Worcester, England, January, 1897, being a premature, eight months' child. The labour was normal, except that it was a breach presentation. When two months pregnant, the mother had a threatened abortion and had lost considerable blood. The day following his birth, he was noticed to be blue and has always since remained bluish, and has been subject from birth to dyspnoeic attacks and a spasmodic cough with glary tenacious sputum, often slightly blood-tinged. At ten months of age, he had a severe attack of *measles*, the rash of which was purplish in hue, and at three years of age is said to have

had a fall resulting in *complete paralysis* of the lower limbs for about one week. At the age of seven, he had *pertussis*, and at nine was in the contagious hospital with *diphtheria* followed by *scarlet fever* during his convalescence. Two years ago, he had a very severe attack of *pneumonia* accompanied by marked abdominal pain. He came to Canada one and one half years ago, and since that time his general health has been better. He has all his life been subject to bronchitis following the least exposure, while the dyspnoea has always been so great on exertion, that to walk three or four hundred yards was sufficient to exhaust him completely.

Clinically the interest of the case centres round the following features:

1. *The marked resistance shown to infectious diseases.* This is a characteristic feature of pulmonary stenosis cases. While there is an equal liability of infection, there seems to be an increased rather than a decreased resistance to all infections except pulmonary tuberculosis.

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