

Granulomatous (Crohn's) appendicitis

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H BINDER, HJ FREEMAN. Granulomatous (Crohn's) appendicitis. *Can J Gastroenterol* 1991;5(3):112-117. Four patients with Crohn's disease limited initially to the appendix, treated by appendectomy and seen at the University of British Columbia Hospital, Vancouver, during 1980-90 are described. In all patients the initial diagnosis was based on the presence of an appendiceal granulomatous inflammatory process, while other causes such as sarcoidosis, tuberculosis and bacterial gut pathogens were excluded. While post appendectomy complications, including enterocutaneous fistula, did not occur, symptomatic recurrence was later observed in three patients four to 24 months following appendiceal resection. This recurrence was associated with a diagnosis of recurrent Crohn's disease and histological findings of granulomas elsewhere in the gastrointestinal tract. In conclusion, a 'reagent grade' population of patients with Crohn's disease limited to the appendix was seen. A high frequency of recurrent disease was defined, indicating that isolated granulomatous appendicitis may be the initial and sole presenting feature of Crohn's disease.

Key Words: *Appendiceal granulomas, Crohn's disease of the appendix, Granulomatous appendicitis, Inflammatory bowel disease, Yersinia enterocolitica*

Appendicite granulomateuse (de Crohn)

RESUME: On rapporte le cas de quatre patients porteurs d'une maladie de Crohn initialement limitée à l'appendice et traités par appendicectomie au University of British Columbia Hospital, à Vancouver, de 1980 à 1990. Chez tous les patients, le diagnostic initial s'appuyait sur la présence d'un processus inflammatoire granulomateux intéressant l'appendice, et qui ne pouvait être attribué ni à une sarcoïdose, ni à une tuberculose, ni à des bactéries intestinales. Bien que des complications post-opératoires, une fistule entérocutanée par exemple, ne soient pas survenues, le retour des symptômes a été observé chez trois patients, dans les quatre à 24 mois qui suivaient l'intervention. Il a été associé au diagnostic d'une maladie de Crohn récidivante et à des trouvailles histologiques de granulomes ailleurs dans les voies gastro-intestinales. En conclusion, on a constaté l'existence d'une population de patients chez qui la maladie de Crohn se limitait à l'appendice. On a noté la fréquence élevée des récurrences, signalant qu'une granulomatose intestinale intéressant isolément l'appendice pourrait être le seul élément révélateur initial de la maladie de Crohn.

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IN 1932, CROHN ET AL (1) EMPHASIZED in their first description of regional ileitis that "the process never transcends the limits of Bauhin's valve, and the appendix is always free from guilt and changes". Since that time, it has become increasingly recognized that Crohn's disease may involve any site within the gastrointestinal tract from the mouth to the anus. Although contiguous involvement of the appendix vermiformis occurs, isolated Crohn's disease of the appendix appears to be rare.

During the course of a retrospective review of patient files for the 10 year period from 1980 to 1990, four patients with features typical of Crohn's disease initially limited to the appendix and characterized by granulomatous inflammation were found. In this report, the presentation and subsequent clinical course following appendectomy of these four are detailed, and the literature experience on this uncommon condition is reviewed.

PATIENTS AND METHODS

The records of Crohn's disease patients seen during the 10 year period from 1980 to 1990 at the authors' hospital were reviewed. All patients were seen and followed by a single gastroenterologist (HF). In an effort to describe a 'reagent grade' population with Crohn's disease for this report, only patients with granulomatous inflammation initially confined to the appendix were included. Because of a clinical diagnosis of appendicitis, all

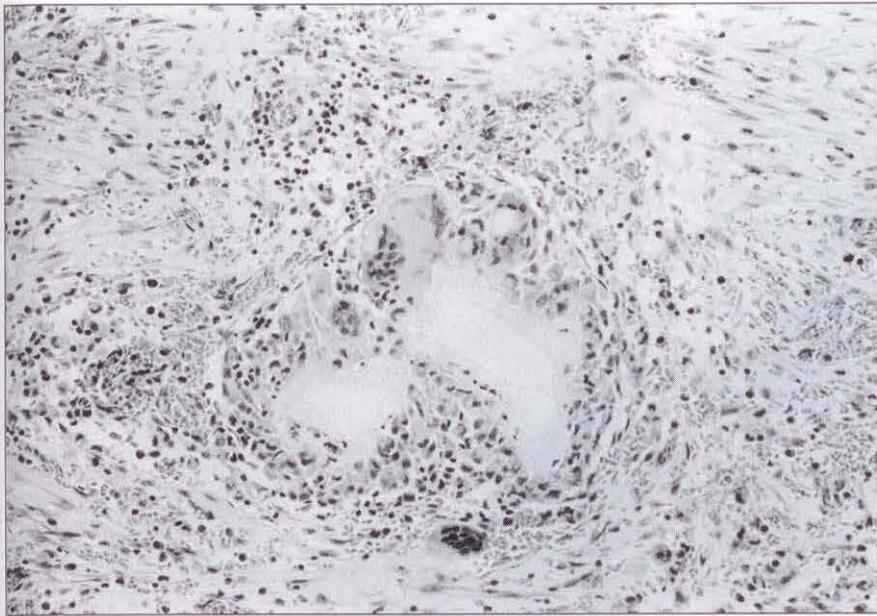


Figure 1) Appendiceal granuloma with multinucleated giant cell (case 1)

had undergone laparotomy and appendectomy. For each patient, microscopic sections of the appendix were re-examined (by HF), and the pathologist's diagnosis of granulomatous appendicitis was confirmed in three patients; for one patient (case 3), the finding of granulomatous inflammation was only recognized on review of surgical sections during the present study. In each case, definition of discrete noncaseating appendiceal granulomas containing multinucleated giant cells was required. For each specimen, 5 μ m sections were examined with hematoxylin and eosin; no parasites, foreign bodies or obstructive lesions were evident, and stains for acid-fast bacilli and fungi were negative. Patients were excluded if Crohn's disease was evident elsewhere in the gastrointestinal tract at initial presentation, or if another cause for granulomatous appendicitis was evident on clinical, histological or microbiological review.

CASE PRESENTATIONS

Case 1: A 25-year-old female was initially admitted November 1986 with a two month history of malaise and lower abdominal pain. A gynecological disorder was suspected, but laparoscopy was normal. Dilation and curettage failed to relieve symptoms and showed normal secretory endometrium. During the

next two months, the pain became constant, more severe and localized to the right lower quadrant. There was no diarrhea or weight loss. In January 1987 the patient was readmitted; appendicitis was suspected. Laparotomy revealed a firm enlarged appendix; the small and large bowel were normal. Appendectomy was performed, and the patient's postoperative course was uncomplicated. Histology study revealed an acute-on-chronic process with epithelial ulceration and transmural inflammation. Several discrete noncaseating granulomas with multinucleated giant cells were present (Figure 1). Most were localized in the deep submucosa and in the junction between the muscle coat and serosa, although isolated epithelioid cell clusters were also present in the mucosa (Figure 2). No parasites, foreign bodies or obstructing lesions were seen. Further investigations were done to determine if Crohn's disease was present elsewhere. Sigmoidoscopy, abdominal ultrasound, indium-labelled abdominal white cell scan and barium radiographic studies of the upper and lower gastrointestinal tract were normal. Fecal specimens for bacterial cultures (including *Yersinia* species) (2) and parasitology were negative. Chest x-ray was normal.

Four months later, the abdominal

pain recurred with diarrhea. Examination revealed right lower quadrant tenderness. Fiberoptic colonoscopy and rectal biopsy were normal, and stool studies for parasites and bacterial cultures were negative. Ultrasound and computed tomography scan of the abdomen and pelvis were normal, but barium radiographic studies of the small bowel showed rigidity, cobblestoning and linear ulceration in the distal 7 to 8 cm of the terminal ileum (Figure 3). The patient was treated with oral metronidazole 250 mg qid for three months. Symptoms resolved and she has remained well with annual follow-up for the past three years.

Case 2: A 28-year-old female was admitted in December 1989 with fever and severe lower abdominal pain for less than 12 h. During the previous month, the patient had noticed vague abdominal discomfort, malaise and intermittent constipation. Examination suggested an acute abdomen and laboratory investigations revealed a white blood cell count of $23.0 \times 10^9/L$. Chest and abdominal x-rays were normal. Laparotomy showed a perforated thickened appendix with peritonitis.

Appendectomy was done; histological features similar to those in case 1 were present, with acute-on-chronic granulomatous inflammation and multinucleated giant cells (Figure 4).

Following surgery, the patient developed recurrent lower abdominal pain. Additional studies were normal, including abdominal and pelvic ultrasound, barium radiographic investigation of the small intestine and serological studies for *Yersinia* species. Colonoscopy and colorectal mucosal biopsies were normal. Fecal studies for parasites and bacterial cultures were negative. The patient's abdominal pain resolved spontaneously and no treatment was prescribed. One year later, she remains free from symptoms.

Case 3: A 22-year-old female was admitted in August 1981 to the gynecological service of another teaching hospital with fever and right lower quadrant abdominal pain for 10 days. Chest and abdominal x-rays as well as cervical, fecal, urine and blood cultures were negative. Pelvic inflammatory dis-

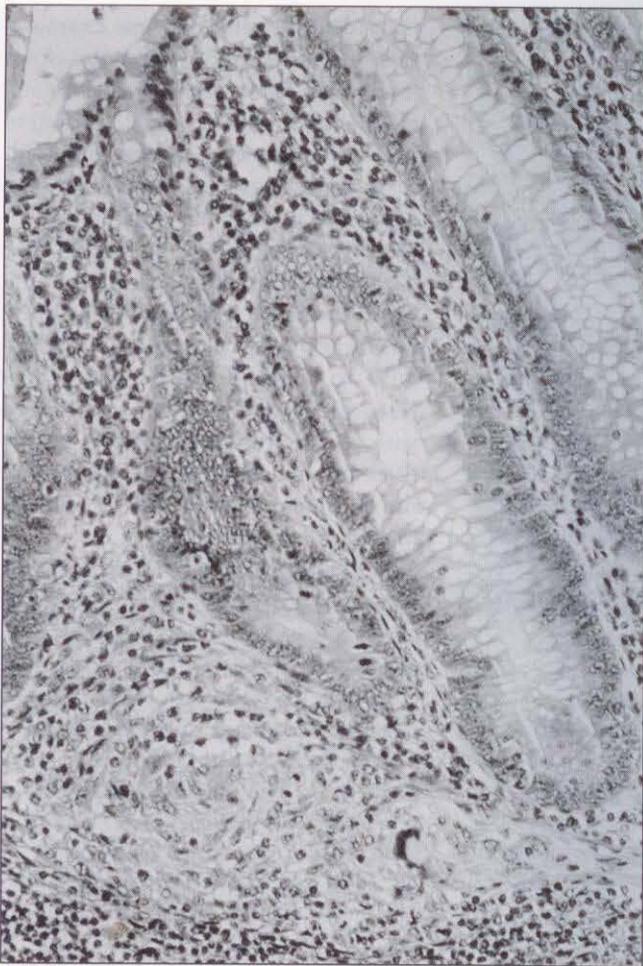


Figure 2) Appendiceal mucosal clusters of epithelioid cells (case 1)

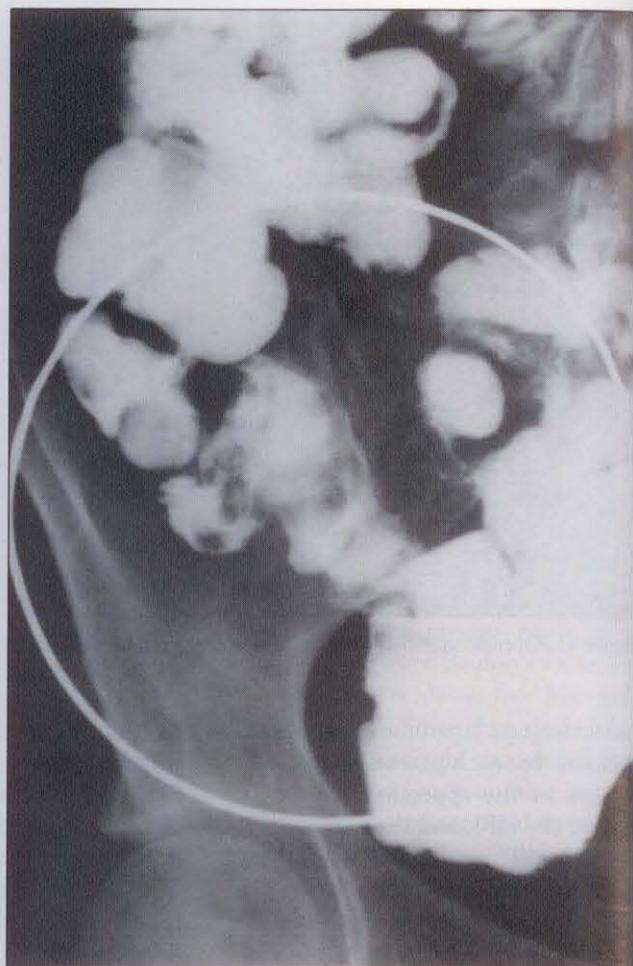


Figure 3) Small bowel barium radiograph with ileal narrowing and ulceration (case 1)

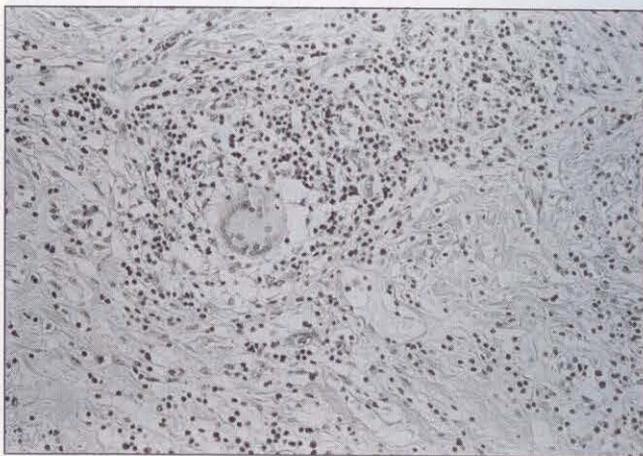


Figure 4) Appendiceal granulomatous inflammation with multinucleated giant cell (case 2)

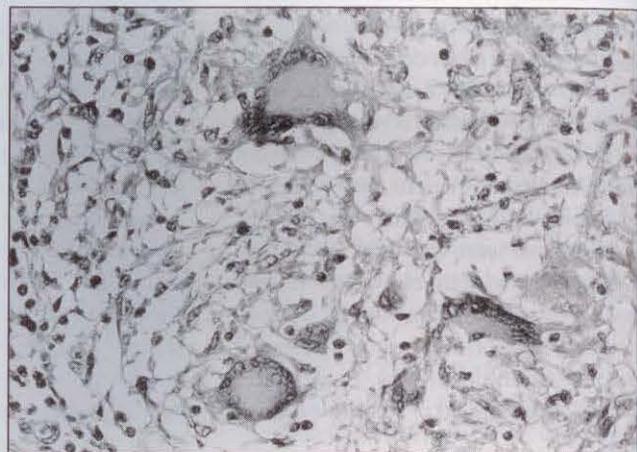


Figure 5) Appendiceal granulomatous inflammation with several multinucleated giant cells (case 3)

ease was suspected and treatment with intravenous cefoxitin commenced; the fever recurred, however, and laparotomy 12 days later detected appendicitis with a localized appendiceal abscess. The small intestine and colon were nor-

mal. Following appendectomy, the patient's postoperative course was uncomplicated; pathological studies reported acute appendicitis with peri-appendicitis. In March 1982 lower abdominal pain and fever recurred; pelvic

inflammatory disease was again diagnosed. Because of continued symptoms despite intravenous cefoxitin, a pelvic abscess was suspected and a second laparotomy was done.

The terminal 30 cm of the ileum was

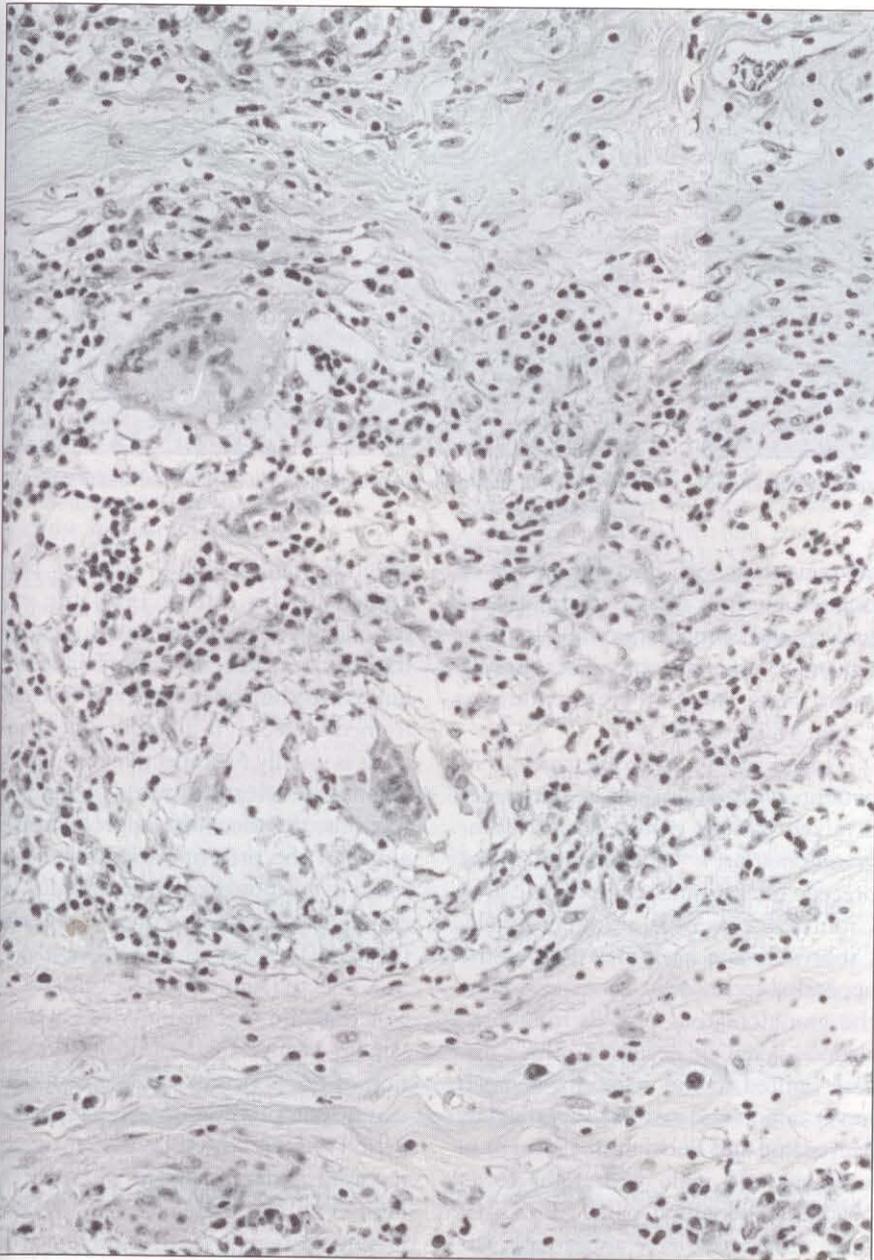


Figure 6) Appendiceal granulomatous inflammation with two multinucleated giant cells (case 4)

inflamed and strictured; the distal ileum and proximal cecum were removed. The resected ileum was thickened and ulcerated with scattered granulomas containing multinucleated giant cells. Following surgery, the patient remained completely well until 1985; at that time, an anal fissure was diagnosed and treated conservatively with sitz baths. No other gastrointestinal symptoms were present, but sigmoidoscopy, rectal biopsy and barium enema were normal.

The patient was first seen in August 1990 because of lower abdominal dis-

comfort, intermittent diarrhea and constipation for two weeks. Except for surgical scars, examination was normal. Fecal studies for parasites and bacterial cultures were negative. Flexible sigmoidoscopy and rectal biopsy were normal. Barium radiographic studies of the upper gastrointestinal tract, including the remaining small bowel, were normal. The symptoms resolved completely with added dietary fibre. As the histological findings in the resected ileum from 1982 were typical for Crohn's disease, the previous appendectomy sections from 1981 were also

reviewed; granulomas with multinucleated giant cells were detected that had not previously been reported (Figure 5).

Case 4: A 22-year-old male was admitted in November 1984 with a one month history of worsening right lower quadrant abdominal pain. There was no diarrhea or weight loss. Laboratory investigations revealed a white cell count of $13.0 \times 10^9/L$. Chest and abdominal x-rays were normal. Because appendicitis was suspected, laparotomy was done, and an enlarged, inflamed appendix was resected. Although the surgeon suspected that Crohn's disease involving the appendix alone might be present, examination of the small and large intestine was normal. Microscopic examination of the appendix revealed a marked acute and chronic inflammatory cell reaction, with multiple noncaseating granulomas containing multinucleated giant cells (Figure 6). The patient's postoperative course was uncomplicated and he remained free from symptoms for two years.

In 1986, fatigue, abdominal pain and diarrhea (up to three to four non-bloody stools daily for two months) developed. Fecal cultures were negative. Barium radiographs of the upper and lower gastrointestinal tracts were normal. Sigmoidoscopy was normal, but a rectal biopsy revealed focal granulomatous inflammation. The patient was treated with sulphasalazine 0.5 g qid for six months; symptoms resolved and the patient ceased pharmacological therapy. In July 1988, abdominal pain, diarrhea and fatigue recurred with a weight loss of 10 kg. Examination revealed oral aphthous ulcers. Fecal studies for parasites and bacterial cultures as well as *Clostridium difficile* cytotoxin were negative. Upper gastrointestinal tract fiberoptic endoscopy revealed a single focal gastric mucosal erosion in the prepyloric antrum, while flexible sigmoidoscopy showed patchy mucosal hyperemia. Gastric, duodenal and colonic mucosal biopsies confirmed the presence of inflammatory changes in the gastric antrum and colon, with scattered mucosal granulomas containing multinucleated giant cells (Figures 7,8). A

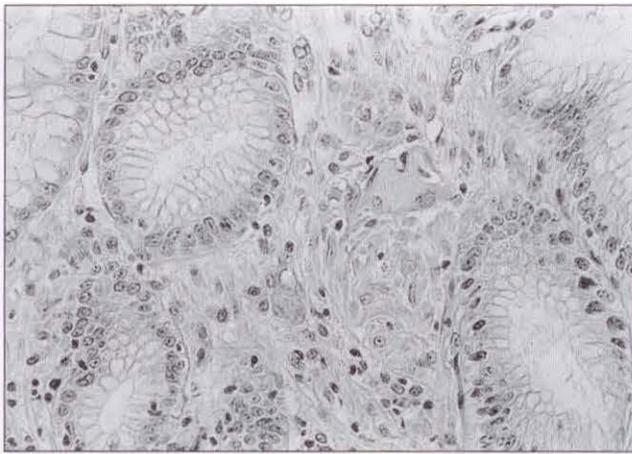


Figure 7) Endoscopic gastric biopsy with mucosal epithelioid cell microgranuloma (case 4)

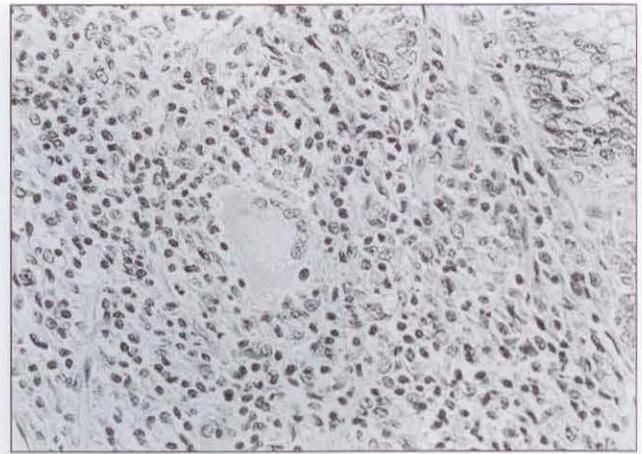


Figure 8) Endoscopic colorectal biopsy with mucosal multinucleated giant cell (case 4)

lactose-free diet was recommended with oral 5-aminosalicylate 800 mg bid. Symptoms resolved within two weeks, and the patient has remained free from symptoms for the past 10 months.

DISCUSSION

Granulomatous appendicitis is a distinct but rare clinicopathological entity characterized by a granulomatous inflammatory process localized solely to the appendix vermiformis. When fungi, parasites, foreign bodies and obstruction secondary to fecalith, mucocele or tumour have been eliminated histologically as causes, fewer than 100 cases have been reported. Various diseases may be responsible, including sarcoidosis (3) and specific infections, ie, tuberculosis (4) and yersiniosis (5,6). In addition, isolated Crohn's disease initially limited to the appendix and causing granulomas solely at this site has been well described (7-36). The present report details the authors' accumulated experience (over 10 years) with Crohn's disease initially limited to the appendix and treated with appendectomy. A 'reagent grade' population was defined based on the presence of an appendiceal granulomatous process and the exclusion of other known causes, including infectious agents such as *Yersinia enterocolitica* (2). The present report indicates that recurrent symptoms and subsequent detection of Crohn's disease elsewhere in the gastrointestinal tract, including stomach, small bowel and colorectum, may be frequent. These observations

are consistent with previous reports of isolated Crohn's disease at other sites such as the oropharynx, and the subsequent observation, occasionally many years later, of more extensive Crohn's disease (37-39).

Appendiceal involvement in patients with Crohn's disease includes a mixed patient group. Acute ('non-granulomatous') appendicitis may precede establishment of a diagnosis of Crohn's disease (40) or, alternatively, Crohn's disease itself may involve the appendix secondarily by extension of the granulomatous process from contiguous ileum or cecum. Crohn's disease limited to the appendix is much less common and was first described by Meyerding and Bertram in 1953 (7) in a 21-year-old male with right lower quadrant abdominal pain. Since that time, other cases have appeared in the literature (8-36); patients are usually in the second to third decade of life, tend to be male, and present with right lower quadrant abdominal pain and, occasionally, a palpable mass. The uncharacteristically long duration of symptoms of acute appendicitis noted elsewhere (28), and the difficult separation from more indolent gynecological causes of inflammatory disease, were underlined in the present series of patients.

Previous recommendations for more extensive surgical resection, including ileocelectomy (28), may be based largely on the fear of complications in the postoperative period, including fistulization. Despite the suggestion that

appendectomy should not be performed in this setting (41), the experience in the present report suggests that recognition of Crohn's disease limited to the appendix, even for well trained surgeons, is difficult. The diagnosis is usually retrospective, established after histological review of surgical sections. Significantly, appendectomy alone in the present patients did not result in any postoperative morbidity or complication such as enterocutaneous fistula (40).

Collected surgical series of cases suggest that the vast majority of patients remain asymptomatic following resection of the appendix. This conclusion may be potentially misleading since the period of long term follow-up for most reported patients appears often to be limited to less than one year. In the present patients, as in patients with Crohn's disease at other sites 'treated surgically', recurrent symptoms and histological evidence of Crohn's disease were frequent. Accordingly, close follow-up on a regular basis seems appropriate and, if symptoms recur, further evaluation may be warranted.

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