Crohn's disease of the appendix

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Summary: Granulomatous inflammation typifying Crohn's disease was centred within or confined to appendices in six patients, two of whom developed lesions attributable to Crohn's disease elsewhere in the gut. The remaining four patients have remained symptom-free for periods varying from two to six years. Histological evidence of Crohn's disease was also present in five of 46 appendices available for re-examination in a survey of 63 cases of Crohn's enterocolitis. It is adduced that appendiceal involvement in Crohn's disease is not uncommon.

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That Crohn's disease may co-exist in the appendix and other sites in the gastrointestinal tract is by now well recognized; that the appendix alone may be the initial target of Crohn's disease is less commonly appreciated but important if the risks of subsequent involvement elsewhere in the gut are to be weighed and the sequela anticipated or prevented.[1]

Materials and methods

Sixty-three cases of Crohn's disease were collected from the surgical pathology files of the Department of Laboratory Medicine, Ottawa General Hospital; the Department of Pathology, Ottawa Civic Hospital; and the Department of Pathology, Sacré Coeur Hospital, Hull. From one hospital to another, the survey periods varied from five to 15 years. The material reviewed included medical records and histopathological slides.

Gross and microscopic criteria for diagnoses of Crohn's disease are listed in Table I.[2] When surgical-pathology reports dealing with extra-appendiceal lesions left the diagnosis of Crohn's disease in some doubt or when atypical sites of involvement including the appendix were described, all of the available histopathologic slides were re-examined. Microscopic re-examination was waived, however, where histological reports included unequivocal evidence of Crohn's disease in a typical site. In 17 cases appendices had been removed prior to gut resection; histological material from these appendices remains unavailable and the diagnoses unknown.

Forty-six appendices were among the tissues resected. At least three sections of each appendix were available and in several cases the tissue blocks had been examined by multiple sections at several levels. All tissues had been fixed in 10% buffered formalin and embedded in paraffin. Five-micron sections routinely stained by hematoxylin, phloxine and saffron were re-examined by light microscopy.

Results

The lesions in the tissues resected in cases of Crohn's disease surveyed here and the histological findings in the 46 appendices available for re-examination are summarized in Tables II, III and IV. These lesions were morphologically similar irrespective of the level of gut affected. Unusual sites for Crohn's disease were combined in one patient, in whom

Meckel's diverticulum[3] and the appendix were involved; in another patient the duodenum was affected.[4]

Eleven appendices re-examined histologically in this survey exhibited granulomatous appendicitis (Figs. 1 and 2). In five patients granulomatous inflammation typifying Crohn's disease in an appendiceal site was accompanied by lesions of Crohn's disease elsewhere in the gut.

Granulomatous inflammation having the characteristics of Crohn's disease was initially deemed to have been confined to appendices from six patients who, at the time of appendectomy, exhibited no overt manifestations of Crohn's disease (Table IV). In one of these patients, however, abdominal pain with diarrhea ensued six weeks following appendectomy; identified roentgenologically, an ileal lesion was interpreted as Crohn's disease. Symp-

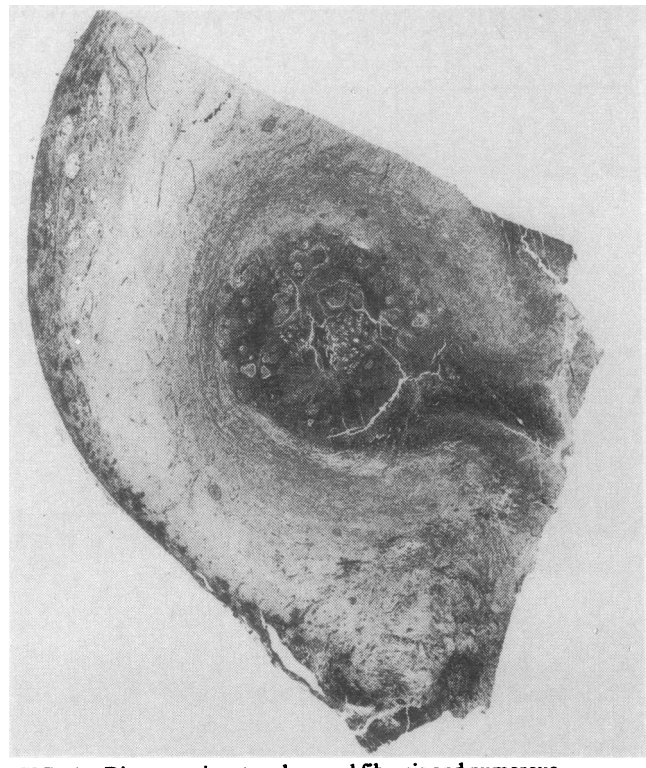

FIG. 1—Disproportionate subserosal fibrosis and numerous sarcoid-like granulomas characterize this focal granulomatous appendicitis. The patient had no other features of sarcoid or Crohn's disease and is well six years after appendectomy. Hemotoxylin, phloxine and saffron, x 5.1.

Table I
Morphological findings in Crohn's disease[12]

Gross	Microscopic
Thick wall	Mucosal ulcers
Strictures	Submucosal edema
Ulcerations	Transmural inflammation
Cobblestone appearance	Non-caseating granulomas
Fissures	Lymphangiectasia
	Myenteric plexus hyperplasia

Table II
Sites of gastrointestinal lesions in 63 patients with Crohn's disease

	No. of specimens examined	Specimens showing Crohn's disease
Terminal ileum	63	62
Colon	44	32
Appendix	46	5
Duodenum	1	1
Meckel's diverticulum	1	1

Table III
Anatomical findings in appendices in the patients with Crohn's disease

Acute appendicitis	17
Granulomatous appendicitis	5
Mucocele	2
Normal	22
No record	17

Table IV
Clinical findings associated with granulomatous appendicitis in 11 patients in this study

Crohn's disease of ileum or colon	5
Granulomatous appendicitis followed by Crohn's disease of ileum	2
Granulomatous appendicitis not followed by Crohn's disease elsewhere in gastrointestinal tract	4

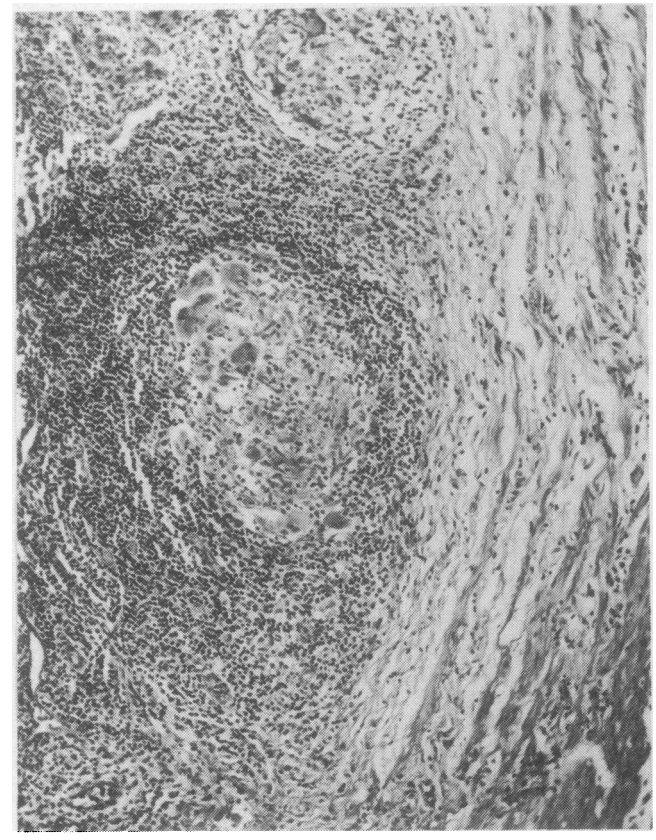

FIG. 2—Appendiceal lamina propria with one of the many sarcoid-like granulomas in a patient with typical Crohn's disease of appendix and ileum. Hematoxylin, phloxine and saffron, x 100.

toms subsided during short-term steroid therapy. In another patient, the ileum was thought during laparotomy to be "thickened"; following examination of the appendix, the ileal thickening was attributed to Crohn's disease but the patient has become lost to follow-up. The remaining four patients, although they had histopathologically identical appendiceal lesions, remained well.

No tubercle bacilli or fungi appeared in lesions stained by the Ziehl-Neelsen and Grocott techniques. None of the appendices contained parasites.

Discussion

The significance, the incidence, even the reality of Crohn's disease of the appendix have been subjects of controversy.[5-14] Histological evidence for appendiceal Crohn's disease has been recognized frequently only in recent years.

Rappaport, Burgoyne and Smetana found 12 "granulomas" in 35 appendices from 100 cases of Crohn's disease.[15] Lockhart-Mummery and Morson described Crohn's disease of the appendix in five patients, two with cecal involvement, three with Crohn's disease of the distal colon.[16] In 1969 Lennard-Jones and Morson estimated that one in four of all specimens including the appendix removed for Crohn's disease of the terminal ileum would exhibit appendiceal involvement.[1] Larson, Axelsson and Johansen in 1970 reported appendiceal involvement in more than 50% of such cases.[17]

What lesions should be considered in the differential diagnosis of granulomatous appendicitis? Present, Lindner and Janowitz list 19 causes for granulomatous inflammation involving the gastrointestinal tract.[18] In fact, however, Crohn's disease is the only common cause of granulomatous appendicitis once infectious processes such as tuberculosis and actinomycosis, lesions caused by common parasites, appendiceal diverticulitis,[19, 20] endometriosis, lesions due to foreign bodies[21] and previous surgery, and appendicitis caused by *Pasteurella pseudotuberculosis* are excluded.[22] None of these lesions is especially likely to be confused by the histopathologist with Crohn's disease.

Appendiceal granulomas attributed to Crohn's disease in six patients of our series were all of sarcoid type. Histopathological manifestations of Crohn's disease were found in the resected terminal ileum or elsewhere in segments of gut removed from these patients. Granulomas of Crohn's disease are indistinguishable from those of sarcoid. Indeed, if each of these processes represents, as it were, a special case in the story of tissue reactions to antigen, arguments over the differences between them are reduced in terms of pathogenesis to a quibble.[23-25] Accordingly, in these five patients the appendices were judged to exhibit stigmata of Crohn's disease.

When are signs of acute appendicitis related to Crohn's disease? In this series two patients in whom the initial diagnosis was acute appendicitis were treated for Crohn's disease first appreciated by histologic examination of appendices. In a 10-year survey reported from the University of California by Marx, acute appendicitis was the preoperative diagnosis in nine patients who were judged to have Crohn's disease at laparotomy.[26] The clinical pattern of an acute exacerbation of Crohn's disease, according to Bockus, cannot be distinguished from acute appendicitis.[27] However, acute appendicitis must be a concurrent lesion in some patients with Crohn's disease and an incidental finding in others.[28-30]

Leonard-Jones and Morson take the view that the appendix may in some patients be the only gastrointestinal organ ever to be afflicted by Crohn's disease.[10] The risk from assuming such a view to be true in all instances of Crohn's disease apparently confined to the appendix seems obvious. In this review the four patients whose Crohn's disease seems to have been confined to the appendix cannot—at least not by us—be written off as "cures", merely because after two to six years each of these patients remained symptom-free. These patients should, in our estimation, remain under close medical surveillance for about a decade; wariness in the face of an unpredictable disease of well-known chronicity but unknown pathogenesis seems more than justified.

The two patients reported here with appendiceal Crohn's disease and concurrent or sequential lesions of supposedly similar nature elsewhere in the gut may be suitable candidates for azathioprine therapy.[31, 32] Obviously, when drugs of such potency are employed, close and prolonged watch must be kept for drug adverse reactions even if dosages of azathioprine used in the treatment of Crohn's disease are small. Moreover, criteria for histologic diagnoses of Crohn's disease ought not, because straightforward, to be uncritically applied out of enthusiasm for trials of azathioprine lest granulomatous appendicitis due to worms, mycobacteria or actinomycosis be inappropriately treated. Also to be considered is the prospect that, as in four patients reported by us, the appendiceal lesions may represent a *forme fruste* of Crohn's disease for which, following appendectomy, no treatment is required. Until assessed by prolonged observations in many patients, however, such a prospect remains only a conjecture.

Résumé

Maladie de Crohn siégeant sur l'appendice

Une inflammation granulomateuse caractéristique de la maladie de Crohn était centrée dans l'appendice iléo-coecal ou limitée à cet organe, chez six malades, dont deux présentèrent des lésions attribuables à la maladie de Crohn ailleurs dans l'intestin. Les quatre malades restants sont demeurés asymptomatiques pendant des périodes variant de deux à six ans. Des signes histologiques de maladie de Crohn étaient également présents chez cinq des 46 appendices qui ont pu être ré-examinés, au cours d'une enquête portant sur 63 cas d'entérocolite de Crohn. On invoque que l'atteinte appendiculaire de la maladie de Crohn n'est pas une chose rare.

References

1. LEONARD-JONES JE and MORSON BC: Changing concepts in Crohn's disease. Disease a Month, August 1969. Year Book Medical Publishers Inc. Chicago
2. CROHN BB, YARNIS H: Regional Ileitis. 2nd revised edition, New York-London, Grune and Stratton, 1958, p. 22
3. WON KH: Endometriosis, Mucocele and Regional Enteritis of Meckel's Diverticulum. *Arch Surg* (Chicago) 98: 209, 1969
4. EDWARDS AM, MICHALYSHYN B, SHERBANIUK RW, et al: Regional enteritis of the duodenum. *Can Med Assoc J* 93: 1283, 1965
5. COLLINS DC: A study of 50,000 specimens of the human vermiform appendix. *Surg Gynecol Obstet* 101: 437, 1955
6. HALL JH, HELLIER MD: Crohn's disease of the appendix presenting as acute appendicitis. *Br J Surg* 56: 390, 1969
7. SHEINFELD WI, RUBINOW M: Noncaseating epithelioid granuloma of the appendix (Localized sarcoid disease). *J Int College Surgeons* 42: 1, 1964
8. FALLIS JC: Granulomatous appendicitis: a case report. *Can J Surg* 11: 449, 1968

9. HOLLINGS RM: Crohn's disease of the appendix. *M J Aust* 1: 639, 1964
10. LOWEN A: Uber Appendicitis Fibro-Plastica. *Deutsch Zuchr f Chir Leipzig* 129: 221, 1914
11. HOMANS I, HASS GM: Regional ileitis; A clinical not a pathological entity. *N Engl J Med* 209: 1315, 1933
12. ERB LH, FARMER AW: Ileo-colitis. *Surg Gynecol Obstet* 61: 6, 1935
13. WARREN S, SOMMERS SC: Cicatrizing enteritis (regional ileitis) as a pathologic entity. *Am J Pathol* 24: 475, 1948
14. SHNITKA TK: Current concepts of the pathogenesis and pathology of inflammatory lesions of the intestine. *Can Med Assoc J* 91: 7, 1964
15. RAPPAPORT H, BURGOYNE FH, SMETANA FA: The pathology of regional enteritis. *Milit Surg* 109: 463, 1951
16. LOCKHART-MUMMERY HE, MORSON BC: Crohn's disease of the large intestine. *Gut* 5: 493, 1964
17. LARSEN E, AXELSSON C, JOHANSEN A: The pathology of the appendix in Morbus Crohn and Ulcerative Colitis. *Acta Pathol Microbiol Scand* Section A Path Suppl No 112: 161, 1970
18. PRESENT DH, LINDNER AE, JANOWITZ HD: Granulomatous disease of the gastrointestinal tract. *Ann Rev Med* 17: 243, 1966
19. CLARK RM: Microdiverticula: A possible cause of granulomatous ileocolitis. *Can Med Assoc J* 100: 1025, 1969
20. CLARK RM: Microdiverticula and submucosal epithelial elements in ulcerative and granulomatous diseases of the ileum and colon. *Can Med Assoc J* 103: 24, 1970
21. BALCH CM, SILVER D: Foreign bodies in the appendix. *Arch Surg* (Chicago) 102: 14, 1971
22. MAIR NS, MAIR HJ, STIRK EM, et al: Three cases of acute lymphadenitis due to Pasteurella Pseudotuberculosis. *J Clin Pathol* 13: 432, 1960
23. MITCHELL DN, CANNON P, DYER NH, et al: The Kveim test in Crohn's disease. *Lancet* ii: 571, 1969
24. MITCHELL DN, CANNON P, DYER NH, et al: Further observations on Kveim test in Crohn's disease. *Lancet* ii: 496, 1970
25. KARLISH AJ, COX EV, HAMPSON F, et al: Kveim test in Crohn's disease. *Lancet* ii: 977, 1970
26. MARX FW JR: Incidental appendectomy with regional enteritis. *Arch Surg* (Chicago) 88: 546, 1964
27. BOCKUS HJ: Gastroenterology. Second edition Philadelphia and London Vol II, WB Saunders Co., 1964, p. 263
28. SCHENKEN JR, ANDERSON TR, COLEMAN FC: Acute focal appendicitis. *Am J Clin Pathol* 26: 352, 1956
29. CAMPBELL JS, FOURNIER P, DASILVA T: When is the appendix normal? A study of acute inflammation of the appendix apparent only upon histologic examination. *Can Med Assoc J* 85: 1155, 1961
30. CONWAY DJ, CAMPBELL JS: Acute focal appendicitis — Reality or Red Herring. *Med Serv J Can* 21: 177, 1965
31. BROOKE BN, HOFFMANN DC, SWARBRICK ET: Azathioprine for Crohn's disease. *Lancet* ii: 612, 1969
32. DRUCKER WR, JEEJEEBHOY KN: Azathioprine: an adjunct to surgical therapy of granulomatous enteritis. *Ann of Surg* 172: 618, 1970

Medical research began in Canada in 1921 with the work of Frederick Banting and Charles Best. Like all such dogmatic statements, this one must be qualified. Assuming the broadest latitude to investigation and experiment, one may cite the experience of Jacques Cartier, who on his second voyage of exploration in 1535 discovered and applied a remedy for scurvy which had decimated his crews. He learned from the native Indians that an infusion of spruce bark and leaves was a source of Vitamin C and his well-documented account of the cure antedates Lind's Treatise on the Scurvy *by 200 years.*

I'll admit that this is an example of opportunistic research, valuable but largely unplanned, until we come to the work of William Osler. Founded on systematic pathological and physiological studies, his contributions to knowledge were important if not brilliantly original. Maud Abbott's monumental studies in congenital cardiac abnormalities, J. B. McCallum's elucidation of the spiral nature of the heart musculature, his brother W. G.'s demonstration of the complete life cycle of the malarial parasite and his work on the parathyroid are a few examples. Despite the profession's prompt acceptance and application of the discoveries of Jenner, Pasteur, Semmelweis, and Lister, it was possible for a former C.M.A. President, Sir William Hingston, in the 1890s to declare forthrightly that Canadians had been too busy with practice to devote themselves to science and "if Canada has not done medicine any good, at least it hasn't done it any harm." — A. D. Kelly, "Personal View" from British Medical Journal, *18 December, 1971.*