THE NATURAL HISTORY AND TREATMENT OF CROHN'S DISEASE

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by

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INTRODUCTION

I SHOULD LIKE to thank the Council of the Royal College for granting me the honour of delivering a lecture to commemorate John Hunter, whose collection and written works demonstrate an interest in inflammatory disorders of the bowel. Two centuries later there are still many unresolved problems in this field. It was the protean manifestations of non-specific granulomata of the alimentary tract which led to this study, and the major part of this lecture will be devoted to the wide range of natural history seen in these conditions and its relationship to their treatment.

The first description of a non-specific granuloma of the bowel was that by Hunter's contemporary Morgagni, who, in 1761, recorded a case of inflammatory thickening of the terminal ileum. In this country, the first report was presented early in the last century by Saunders (Combe and Saunders, 1813), and later Abercrombie (1828) described a patient with ileitis who showed skip lesions in the small bowel and a localized segmental colitis.

Non-specific granulomata of the alimentary tract aroused little interest for almost a century until Moynihan (1907) reported two cases in which the colon was involved. Dalziel (1913) described non-specific jejunitis, ileitis and colitis, and Moschcowitz and Wilensky (1923) described four cases of non-specific granulomata of the ileo-caecal region and colon.

In 1932, Crohn, Ginzburg and Oppenheimer presented their classical work, in which they showed that regional ileitis was a definite clinical and pathological entity. This aroused such widespread interest that very soon many cases were reported and it was realized that lesions with similar histology could affect any part of the alimentary tract. Harris *et al.* (1933) described jejunal involvement, in the following year Colp (1934) described colonic involvement and similar changes have been recorded in the duodenum by Shapiro (1939) and in the stomach by Ross (1949).

PATHOLOGY

Many terms have been used to describe the disease process which has the characteristic histology described by Hadfield (1939). Despite the valid argument against the use of eponyms, I feel that this confusion in terminology is best overcome by referring simply to Crohn's disease, whatever part of the gut is involved.

The bowel affected by Crohn's disease presents a striking appearance as it is red, thickened and oedematous with a greatly thickened mesentery containing many enlarged lymph nodes. The microscopic appearance is of massive oedema of the bowel wall, especially the sub-mucosa, with hyperaemia and lymphangiectasia, blunting of the villae and ulceration of the mucosa. Inflammatory cells and fibrosis are present in the sub-mucosa, going on to cicatrization in this layer with hypertrophy of the muscularis mucosae and lymphoid tissue. There is endarteritis with increasing ulceration and formation of non-caseating, tuberculoid granulation tissue in the sub-mucosa and sub-serosa (Meadows and Batsakis, 1963). Because of these appearances, it has been suggested that the condition might be either an atypical form of tuberculosis or sarcoidosis. There were repeated unsuccessful attempts to isolate mycobacterium tuberculosis from the lesion and it is now generally accepted that this disease is not of tuberculous origin (Van Patter *et al.*, 1954). That Crohn's disease is a manifestation of sarcoidosis seems very unlikely since it has been established that the alimentary tract is rarely involved in generalized sarcoidosis (Longcope and Freeman, 1952). A Kviem test was found to be negative in all 15 patients in whom it was carried out in this series.

The aetiology of Crohn's disease remains obscure despite the fact that similar lesions can be produced in the experimental animal by obstruction of the lymphatics (Reichert and Mathes, 1936) or by an immune reaction (Slaney, 1962). In man the multiplicity of suggested causes, which range from auto-immune disease to the ingestion of toothpaste (Edwards, 1958), shows how far we are from the solution.

Pemberton and Brown (1937) divided the disease into two categories, localized and that with sub-mucosal spread (diffuse). They record that the localized lesion is single and proceeds to cicatrization forming a stricture and intestinal obstruction. The diffuse process shows a tendency to progressive extension involving large segments with spread not necessarily in continuity and produces much more systemic upset and malabsorption.

CLINICAL MATERIAL

This series consists of a retrospective study of 156 patients seen at Manchester Royal Infirmary from 1949 to 1962. Of these cases 121 were classified as Crohn's disease, 111 of them on histological criteria and 10 on clinical and radiological grounds. In addition, cases of acute ileitis and solitary caecal granuloma, both of which may be confused with Crohn's disease, have been included in this series (Table I).

TABLE I

TOTAL SERIES (156 PATIENTS) SEEN 1949 TO 1962

Acute ileitis		25
Solitary caecal granuloma		10
Crohn's disease		121
Jejunum	6	
Ileum	87	
Ileum and colon	12	
Colon	16	

ACUTE ILEITIS

All the 25 cases were between the ages of 15 and 35 years. Reports of this disease stress the frequency of its occurrence in children (Stores and Hoekeiman, 1953), but the absence from this series merely reflects the fact that the Manchester Royal Infirmary does not admit children. The sexes were affected in approximately equal numbers (13 male; 12 female). The history was from one to three days and simulated appendicitis, as did the findings on examination. The only differentiating feature was the frequent occurrence of diarrhoea, which was noted in 12 cases. The importance of this symptom in diagnosis has been stressed by Crohn and Yarnis (1958). All our cases had emergency operations at which the typical red and oedematous terminal ileum with thickened mesentery was seen.

TABLE II

TREATMENT OF ACUTE ILEITIS (25 CASES)

Laparotomy	12
Appendicectomy	8
Bypass	4
Resection	1

There have been several lines of surgical management (Table II), but most often the surgeon has deemed it wise simply to close the abdomen with or without appendicectomy; however, 5 out of 25 had a definitive procedure.

There were several ways in which this group appeared to differ from Crohn's disease of the ileum. Firstly, the histology of the one resected specimen showed changes which, whilst situated principally in the submucosa, were those of acute inflammation. Secondly, only two patients progressed to typical Crohn's disease, two other patients had persisting symptoms for two and three months, respectively, but then settled completely; however, most of the patients had no further symptoms after their laparotomy. Eight of the patients whose symptoms settled immediately after operation had normal barium follow-through examinations within six weeks of the attack. Two patients had further operations 12 and 18 months later, respectively, and in both the ileum was perfectly normal. Finally, there was no example of post-operative fistula even after appendicectomy.

As long ago as 1937 Strombeck noted acute ileitis associated with enlarged mesenteric nodes, and indeed a slight reddening of the ileum is not a rare finding in the mesenteric lymphadenitis so commonly seen in children. It seems possible that mesenteric lymphadenitis and acute ileitis are but different facets of the same disease. Certainly acute ileitis rarely goes on to Crohn's disease, in fact its tendency to spontaneous resolution is so great that if the lesion is discovered at laparotomy no definitive procedure should be undertaken.

GRANULOMA OF THE CAECUM

In addition to 29 cases in which the caecum was involved by direct spread from Crohn's disease of the ileum, there was an interesting group of 10 patients in which the caecum was involved alone—the solitary caecal granuloma—which provide a separate clinical entity. Nine of the 10 patients were women, aged 37 to 88 years, who presented in a manner simulating carcinoma of the caecum.

Case report

Mrs. C. B., aged 88, was admitted with a three-month history of weight loss, having had attacks of central abdominal pain associated with attacks of diarrhoea, and just before admission she passed a large amount of fresh blood per rectum. She was found to be an ill old lady who was shocked, and on abdominal examination a mass was found in the right iliac fossa. After resuscitation, investigation and preparation for surgery, she had a right hemicolectomy at which the diagnosis was still felt to be carcinoma of the caecum but it was noted that the lesion was rather softer than usual. She progressed poorly after the operation and died on the eighth post-operative day. Histology of the lesion was typical of tuberculosis with caseation, and acid-fast organisms were found on Ziehl-Neelsen staining of the caecal wall, but post-mortem examination showed no evidence of tuberculosis in the other organs.

On histological grounds, 8 of these 10 cases of solitary caecal granuloma were of tuberculous origin for they showed caseation in the centre of tuberculoid follicles, the only examples of caseation in the whole series. Of the other two cases, one had open pulmonary tuberculosis, but the histology of the caecal lesion was compatible with Crohn's disease; the other case showed an atypical histological picture with fibrosis and oedema in the sub-mucosa and scanty chronic inflammatory cells.

Seven of the eight patients whose lesions showed caseation had a normal chest X-ray and no acid-fast organisms were isolated from the sputum or faeces of any of these patients. Hypertrophic ileo-caecal tuberculosis is usually a solitary phenomenon without any other evidence of tuberculosis. Anand (1956) showed that caseation may not be present in a lesion from which mycobacterium tuberculosis can be isolated, thus the differentiation from Crohn's disease may prove difficult. Although in this country the disease is uncommon, tuberculosis should be considered in all cases of granulomata which principally involve the caecum and careful screening of the lesion and the regional nodes for mycobacterium tuberculosis should be undertaken.

In this series, nine of the cases of solitary caecal granuloma were treated by right hemicolectomy. There were two post-operative deaths, but the other seven patients have survived from 2 to 12 years and are apparently well without further treatment. The other patient in this group died after a simple laparotomy.

CROHN'S DISEASE

Crohn's disease may involve any part of the alimentary tract (Table III). Ninety-nine (80.5 per cent) of the 121 cases of Crohn's disease affected the ileum either alone or together with the colon, and of these 99 ileal cases there was spread to the caecum in 29 and there were " skip " lesions in the small gut in 24 cases.

TABLE III

CROHN'S DISEASE (121 CASES)

Site of involvement	
Jejunum	6
Ileum	87
Ileum and colon ..	12
Colon and/or rectum	16

Age (Fig. 1)

The maximum age incidence in the patients with Crohn's disease occurred in the third decade, indeed in 57 per cent the onset was before the age of 30 and in 84 per cent before the age of 40. The maximum incidence in Crohn's disease of the large bowel was in the fifth decade and 67 per cent occurred after the age of 40. These findings agree well with those previously reported (Crohn and Yarnis, 1958; Van Patter *et al.*, 1954; Colcock and Vansant, 1960; Edwards, 1964).

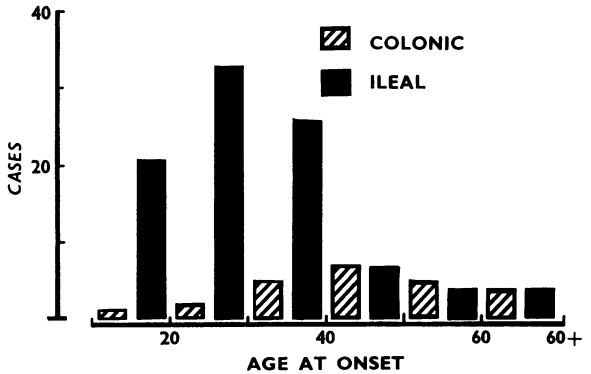

Fig. 1. The age at onset in Crohn's disease of the ileum and of the colon is compared. The maximum incidence in Crohn's disease of the ileum is in the third decade, whilst that in Crohn's disease of the colon is in the fifth decade.

Sex

Crohn and Yarnis (1958), in a review of the world literature, state that there is a slight male predominance, but many British workers (Cooke, 1955; Pollock, 1958; Edwards, 1964) have found a slight predominance of females. In the present series the female predominance was even more marked, for 76 (63 per cent) of the patients were female.

Race

In this series there were British, Irish, Indian and Pakistani patients but no West Indian or African, despite the fact that the hospital draws on a fairly large West Indian community. There were eight persons of Jewish origin, which is little more than one would expect to find by chance.

Family

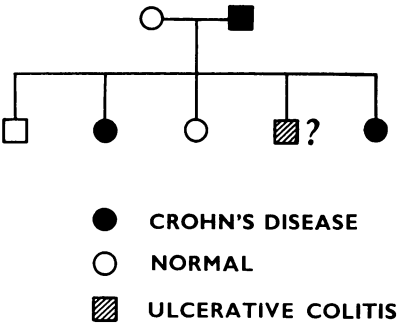

Fig. 2. A family in which the father and two daughters have proven Crohn's disease is shown in diagrammatic form. One son had ulcerative colitis diagnosed in his youth, but this diagnosis is doubtful.

We have seen three examples of familial Crohn's disease, one brother and sister, two cousins and a family in which several members had the disease (Fig. 2). In this family the father had Crohn's disease, two of the five children were affected and another of the children was diagnosed on clinical grounds as having ulcerative colitis in his youth, but this must be considered doubtful as he is now symptom-free with little active treatment.

ASSOCIATED DISEASE (TABLE IV)

In the patients with Crohn's disease, there was no active pulmonary tuberculosis, but six had evidence of old pulmonary tuberculosis. A few

TABLE IV
ASSOCIATED DISEASES (121 CASES)

	Cases
Old tuberculosis ..	6
Erythema nodosa ..	5
" Arthritis " ..	7
Ca colon	2
Gall stones ..	11
Pancreatitis ..	3

patients had erythema nodosa or joint swelling and pain and three had manifest ankylosing spondylitis. Of particular interest is the unusual association, not previously noted, with gall stones. Dreiling (1953) observed that 5 of 22 patients with Crohn's disease in whom he carried out pancreatic function studies had pancreatic or biliary dysfunction.

CROHN'S DISEASE OF THE ILEUM

The symptoms of typical Crohn's disease are well known. In the earliest stage, it has been repeatedly stressed that diagnosis is extremely difficult and success is attendant upon constant awareness of the condition. I wish to draw particular attention to the fact that the patient

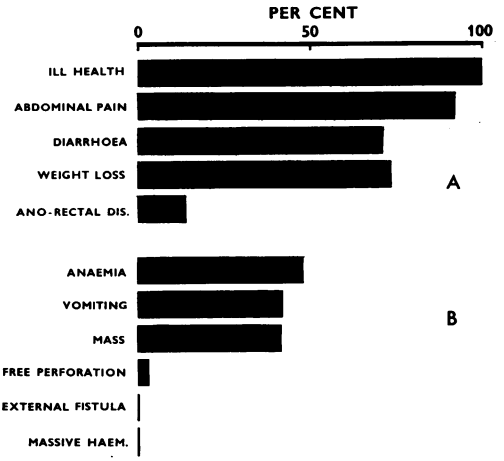

Fig. 3. The signs and symptoms present in this group of patients with Crohn's disease of the ileum are represented. Those in group A were usually present in the stage of diagnostic difficulty. Those in group B were present when the disease was manifest.

may present with a fissure or fistula-in-ano which may have either the typical or an atypical appearance (Morson and Lockhart-Mummery, 1959). The presence of minor ano-rectal disease in a young person who has a little diarrhoea, especially if the lesion is of unusual appearance, should make one suspect the presence of Crohn's disease.

The signs and symptoms of our patients with Crohn's disease of the ileum when they presented before operation had been undertaken are shown in Figure 3. A rare presentation seen in this series was free perforation (two cases), but massive haemorrhage and external fistula without operation were never seen. It was equally common for the history to be continuous or remitting, and though the history was of variable length (Fig. 4) it was of less than two years duration in 60 per cent of the patients.

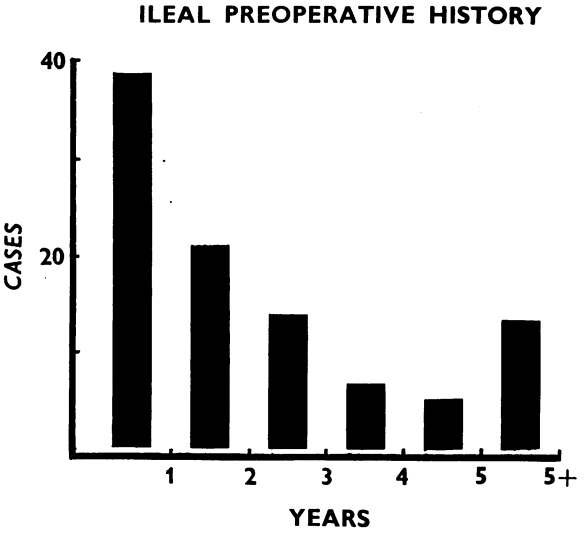

Fig. 4. The length of history before operation in the patients with Crohn's disease affecting the ileum is illustrated.

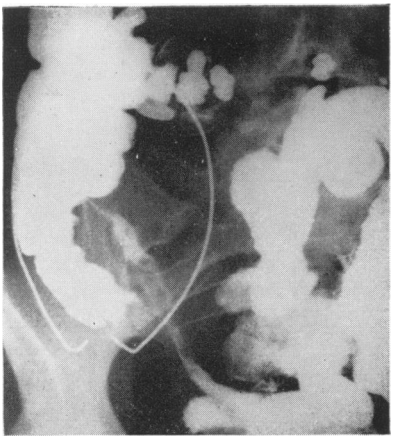

Fig. 5. Barium study. Note the terminal ileum, which shows narrowing and an abnormal mucosal pattern.

In diagnosis it is important to assess whether the disease is of the localized or the rarer diffuse type, since this has an important bearing on treatment. Diffuse disease has a much shorter history, which is continuous, with more constitutional upset, fever, gross weight loss, steatorrhoea and possibly splenomegaly and clubbing of the fingers. Localized disease has a longer history, which frequently shows remissions and often symptoms suggestive of intestinal obstruction.

An assessment of the daily output of fat in the faeces should be made in all patients under investigation for Crohn's disease, for it has been shown (Cooke, 1958) that, even with the patient on an ordinary ward diet, a good indication of steatorrhoea can be obtained. The presence of steatorrhoea is suggestive of the diffuse type of disease, but this finding alone is not diagnostic, for steatorrhoea also occurs in the presence of an internal fistula and occasionally in a patient with a localized stricture without a fistula.

Barium follow-through examination is useful for demonstrating the terminal ileum, when " cobblestoning " of the mucosa or the string sign of Kantor (1934) may help to confirm the diagnosis (Fig. 5). It is much more difficult to obtain good visualization of the rest of the small bowel so that it may be impossible to demonstrate the extent of the disease radiologically.

TREATMENT

The treatment of Crohn's disease may be conservative or operative. Since the aetiology is unknown, medical treatment tends to be empirical, consisting of rest, a diet of high nutrition with vitamin supplements, the correction of anaemia and occasionally antibiotics and steroids.

TABLE V

INITIAL SURGERY (121 CASES)

Right hemicolectomy	69
Partial or total colectomy	18
Bypass	18
Local resection	8
None	8

The results of the medical regime and steroids (prednisone 15–30 mg. per day in divided doses) were reviewed in 22 patients. Of these, seven were categorized as worse, three improved and 12 unchanged. Within a year, 16 of these 22 patients came to operation; the other six have remained on medical treatment for more than two years; three are improved; three are unchanged. It would seem that medical treatment has little to offer in cure of localized Crohn's disease in most patients (Stahlgren and Ferguson, 1961), but it may be that this therapy has a part to play in the management of the diffuse type of disease.

Two types of operation may be used, either a resection of the diseased bowel and as much of the diseased mesentery and glands as is possible or a bypass procedure. Most of the 121 patients with Crohn's disease have been treated medically initially, but all except eight have come to operation (Table V).

At operation, the typical findings are a thickened segment of dark red, soggy bowel, usually the terminal ileum extending to the ileo-caecal valve and possibly involving the caecum or even more of the large gut, with a thick mesentery containing large glands which may have broken down to form abscesses. There may be skip lesions in the ileum or even the jejunum and " kissing " lesions in the sigmoid colon. Internal fistulae may be

TABLE VI

INTERNAL FISTULAE (14 CASES)

Ileo-ileal	6
Ileo-sigmoid ..	3
Ileo-vesical ..	4
Ileo-uterine ..	1

present (Table VI) which can be between loops of gut, between the ileum and the bladder or between the ileum and vagina or uterus. It should be stressed that almost certainly the incidence of ileo-ileal fistulae has been underestimated since they can be easily overlooked at operation.

Forty-nine patients had a right hemicolectomy performed more than five years ago. There was an operative death in two patients (4.1 per cent); nine (18.4 per cent) had a recurrence and 33 (67.3 per cent) had no further trouble. The present status of these patients after further treatment is that: 37 (75.5 per cent) are now well after one or more operation; five (10.2 per cent) are dead, due to the disease or its treatment; five (10.2 per cent) died of other causes or cannot be traced, and two (4.1 per cent) are alive though they have recurrent disease.

More than five years ago, 18 patients had a bypass procedure in continuity. Twelve had to be converted to a right hemicolectomy due to persisting pain and general ill health within a year and 16 patients had to be converted within five years. In the last two years, i.e. after the period of this study, 12 defunctioning bypasses have been made as suggested by Garlock and Crohn (1945); three have had more trouble within this period, two due to persisting pain and ill health and one due to recurrence in the new distal ileum. Two of these patients have already come to re-operation and the other is to do so.

COMPLICATIONS OF SURGERY

The main problems after excision are:

(1) external fistulae,
(2) recurrence,
(3) malabsorption.

External fistulae

Many of the patients in this series presented having had some form of surgery since the onset of the disease. External fistulae have only been seen after operation and have been found most frequently in patients who have undergone non-definitive surgery.

The danger of appendicectomy or drainage of an abscess must be stressed, for 10 out of 23 patients who had these operations developed a faecal fistula. After definitive operation there were eight early fistulae (within two weeks of the operation); of these, four healed spontaneously and can be considered to be due to a defect in technique, but the other four were due to residual disease and persisted until further resection was done or the patient died. There were five late fistulae occurring from 18 months to four years after operation, which were all due to recurrence.

Recurrence

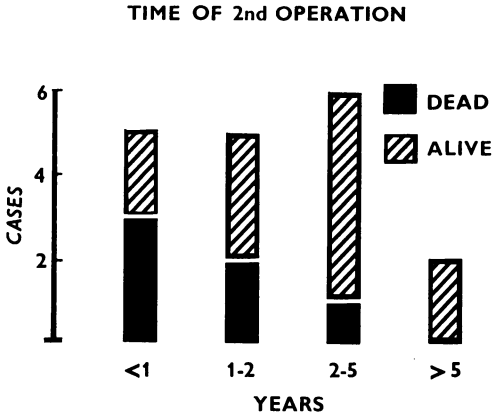

Fig. 6. If a second operation had to be undertaken early, then the prognosis was poor.

The recurrence rate five years after right hemicolectomy was 18.4 per cent in this series, which is similar to that reported in the series of Barber *et al.* (1962), 19.1 per cent, and Edwards (1964), 11 per cent, but much less than that reported in many other series, e.g. Brown and Daffner (1958) reported 54 per cent and Jackson (1958*a*) 55 per cent.

In the time under consideration, 18 recurrences have been seen after right hemicolectomy performed at Manchester Royal Infirmary or elsewhere. In our own cases, two factors seem to have been important in assessing the possibility of a recurrence: (1) the length of the involved segment—only two of those that recurred had less than one foot noted to be involved at the original operation; (2) the average length of history before operation—if this was short, the disease was more likely to recur and then the whole tempo and severity seemed greater.

Site of recurrence. The recurrence was almost invariably proximal to the anastomosis (16 cases). It was in a localized segment in nine cases, but diffuse involvement of the small gut had occurred in seven. Rectal involvement occurred later in the disease in six cases. There were two cases of diffuse colonic involvement which proved on histology to be ulcerative colitis.

Results of re-operation. If the recurrence occurred early after definitive operation then a further operation gave less chance of success, indeed 50 per cent of the patients who developed a recurrence within two years are dead (Fig. 6). A second or third resection cured nine of the 18 recurrences, but no further cure occurred with further operation (Fig. 7).

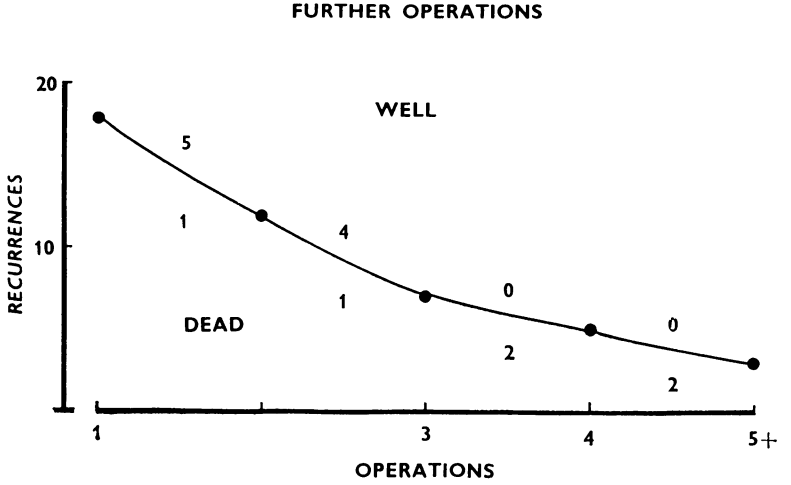

Fig. 7. There were 18 recurrences after excision. Above the line are shown the patients " cured " by a subsequent operation. Note that no cures occurred in the patients who had more than three operations.

Malabsorption

There are three possible causes of malabsorption in Crohn's disease:

(1) resection,

(2) active disease,

(3) blind loop.

The third of these causes, blind loop, has not been important in this series. The disease itself certainly may produce some degree of malabsorption, as is seen by the fact that steatorrhoea may occur preoperatively (Cooke, 1955). Resection, producing loss of intestinal length, especially in the presence of recurrent disease, often causes steatorrhoea.

Malabsorption may produce various deficiency states (Table VII), either separately or in combination, which have been well described by Kiefer (1955) and by Cooke (1955) in a Hunterian oration. I shall concentrate my remarks on one aspect of this problem, namely the malabsorption of vitamin B_{12} which I have specially studied.

TABLE VII

DEFICIENCY STATES

Gross hypoproteinaemia	Oedema
Hypokalaemia	Muscle weakness
Hypocalcaemia	Tetany
Vitamin D deficient	Osteomalacia
Vitamin K deficient	Bleeding
Vitamin B_{12} deficient	Megaloblastic anaemia

Absorption of vitamin B_{12}. The site of absorption of vitamin B_{12} has been the subject of speculation, but there appear to be two main mechanisms, one for a small amount (1 μg.) which needs intrinsic factor for its mediation and one for a large amount (1,000 μg.) which may be absorbed from any part of the alimentary tract by diffusion (Ross *et al.*, 1954). It is only the former of these two methods of absorption which has physiological importance. Wallerstein *et al.* (1953) suggested that absorption of vitamin B_{12} occurred in the upper jejunum, but Rosenthal and Hampton (1955) felt the main site was the duodenum. In physiological quantities, Citrin *et al.* (1957) showed that no absorption took place in the colon, but suggested that it could occur at any level in the small bowel. Experimental work in the dog (Baker *et al.*, 1958) suggested that the absorption of physiological amounts of vitamin B_{12} occurred in the ileum, and Booth and Mollin (1959) presented some evidence suggesting that this was so in man. Drapanas *et al.* (1963) investigated the problem extensively in the dog and showed conclusively that the ileum is the site of absorption of physiological amounts of vitamin B_{12} in this animal.

The development of megaloblastic anaemia in man after resection of the ileum (Cooke *et al.*, 1957; Kalsar *et al.*, 1960; Allcock, 1961) has lent support to the idea that this is the site of absorption of vitamin B_{12} in man. Even more suggestive evidence was supplied by Sherman and May (1963), who excluded the whole ileum of a woman by jejuno-transverse colostomy for the treatment of obesity. After this procedure she was incapable of absorbing vitamin B_{12}. They re-operated and implanted the jejunum into the terminal ileum, after which absorption of vitamin B_{12} was restored to normal.

After radioactively labelled vitamin B_{12} is ingested, measurement of blood radioactivity gives an index of its absorption (Booth and Mollin, 1956; Doscherholmen and Hagen, 1957). The typical absorption pattern was confirmed in the present studies (Fig. 8). The radioactivity does not

start to rise for three hours, but then increases for a further nine hours. It would seem that from three to 12 hours after its ingestion vitamin B_{12} is being absorbed, and during this time the part of the gut responsible for its absorption should have the substance in its wall.

The following procedure was undertaken in 16 patients who were to have an intestinal resection but who showed no evidence of intestinal obstruction. Between six and nine hours before resection, 1 μg. of vitamin B_{12} labelled with 1 μc. of ^{58}Co was ingested by each patient. A careful note of the level of the resection with reference to the ileo-caecal valve was made, and after resection an area of normal mucosa was dissected free from the specimen and its radioactivity and weight measured. It was found that there was negligible radioactivity in the stomach, duodenum, jejunum and right and left colon, but there was a high level of radio-

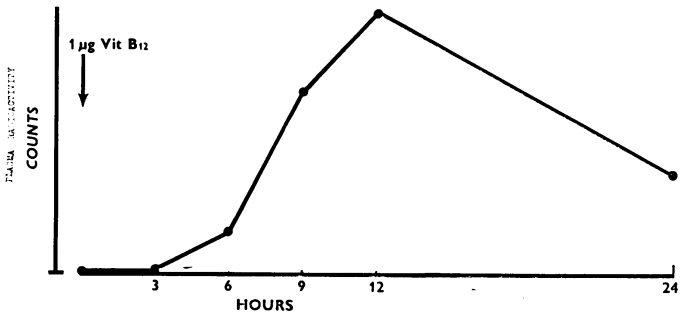

Fig. 8. Shows the plasma radioactivity assessed after the ingestion of a physiological amount of radioactively labelled vitamin B_{12}.

activity in the mucosa of the last three feet of the ileum; this high level was found constantly in the eight patients in whom observations on this part of the gut were possible. Due to lack of material I have not been able to make any observations between three and eight feet from the ileo-caecal junction, but I have shown, on one occasion, a large amount of radioactivity in the mucosa three feet from the ileo-caecal valve but a negligible amount eight feet from the ileo-caecal valve. It seems that physiological absorption of vitamin B_{12} occurs in the last three feet or more of the ileum, but does not occur eight feet from the ileo-caecal junction. The exact upper limit of this absorptive area has not yet been located.

Malabsorption of vitamin B_{12}. It seemed of interest to assess the relative importance of the part played in malabsorption of vitamin B_{12} by resection of the ileum and by potential reduction of the absorptive surface by active Crohn's disease. In order to do this, the serum vitamin B_{12} levels were estimated in several groups of patients:

(1) Crohn's disease before operation.

(2) Five years after right hemicolectomy for carcinoma of the colon.

(3) Five years after right hemicolectomy for Crohn's disease, at which operation less than one foot of ileum was resected.

(4) Five years after right hemicolectomy for Crohn's disease, at which operation more than three feet of ileum was resected.

(5) Gross Crohn's disease of many years' duration showing malabsorption of substances other than vitamin B_{12} but with minimal resection of ileum.

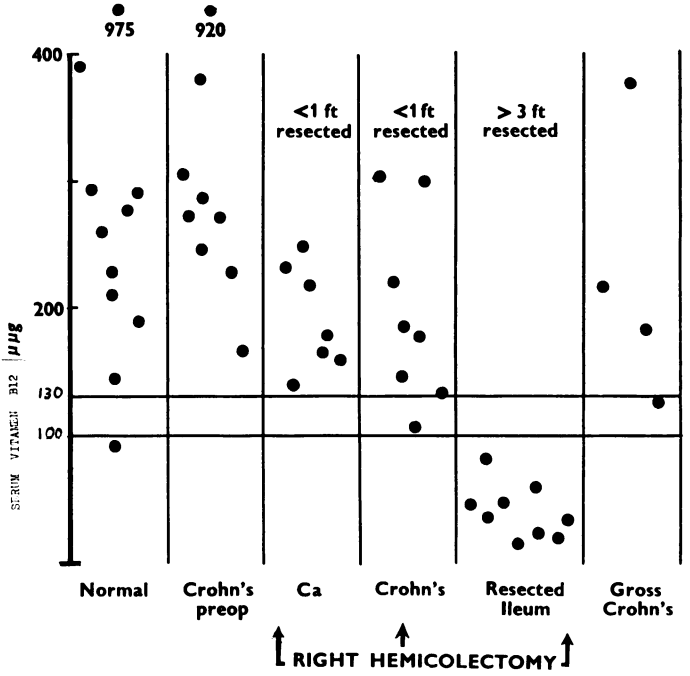

Fig. 9. Scattergram shows serum vitamin B_{12} in various groups of patients.

(6) Normal controls—a group of fit subjects aged between 20 and 40 years, half male and half female, so that this group was of similar age and sex distribution to the patients with Crohn's disease.

The results of these observations are shown in full in Figure 9.

The normal serum vitamin B_{12} level has a wide range (900–130 μμg.) (Watson-Williams, 1964), but values below 100 μμg. are usually considered to be diagnostic in pernicious anaemia. There were nine patients who had three or more feet of terminal ileum resected and they all had vitamin B_{12} levels below 100 μμg. Of these nine patients, five were not anaemic but four had manifest megaloblastic anaemia with marrow changes, peripheral

blood changes and an inability to absorb vitamin B_{12} as indicated by balance studies. Two further subjects who had five and eight feet of terminal ileum resected, respectively, developed megaloblastic anaemia, but were undergoing treatment before the present investigation. All the other subjects, except one of the controls, had levels above 100 μμg. and this abnormal control has been found to have changes in her blood count compatible with early pernicious anaemia and is, at present, undergoing further investigation. Even in the presence of gross Crohn's disease the serum vitamin B_{12} levels were within the normal range, though all these subjects showed gross malabsorption of other substances. The patients who developed megaloblastic anaemia did so between three and eight years after their last resection, the delay being due to the considerable hepatic stores of vitamin B_{12} (Glass, 1959).

On both experimental and clinical grounds, malabsorption of vitamin B_{12} with the development of megaloblastic anaemia must be expected if three or more feet of the terminal ileum have been resected. Defective absorption of vitamin B_{12} has been reported after even shorter resections (Fone *et al.*, 1961), but most of the reported cases of megaloblastic anaemia have had quite extensive resections of the ileum (MacIntyre *et al.*, 1956; Mollin *et al.*, 1957; Kalsar *et al.*, 1960; Allcock, 1961; Booth *et al.*, 1964). The anaemia of these patients responds well to parenteral vitamin B_{12}.

CROHN'S DISEASE OF THE JEJUNUM

The jejunum was more rarely involved by Crohn's disease than the ileum, and the disease was either localized or diffuse. There were six cases of localized jejunal involvement by Crohn's disease and three in which the jejunum was involved as a massive skip lesion associated with typical ileitis. In the localized form the history was relatively short, often only a few weeks, and the patient presented as a sub-acute obstruction due to a short cicatrized segment which on histology showed the typical changes of Crohn's disease. Localized jejunal Crohn's disease had to be distinguished from a solitary ulcer of the jejunum (Watson, 1963) and the recently described stricture ascribed to thiazide derivatives (Lindholmer *et al.*, 1964). Treatment was in all cases by resection and the lesion recurred in only one of these six cases.

There were 11 diffuse cases of ileo-jejunitis (Crohn and Yunich, 1941), of these only four were identified at the first operation when they were treated by massive resection and bypass. The other seven were recognized at their second operation, when recurrence had occurred within 18 months and usually within 12 months. In two of these cases the duodenum was involved, causing obstruction. This type of disease had the usual signs and symptoms of Crohn's disease, but the patients tended to be younger, to have a shorter history with much more systemic upset, steatorrhoea and gross weight loss. The results of surgical treatment in this group of 11

patients were appalling: three are dead, eight had massive recurrences, and seven show gross malabsorption.

It seems that one of the most difficult problems in management is to avoid surgical treatment in this group.

CROHN'S DISEASE OF THE COLON AND RECTUM

Non-specific inflammation of the ileum and of the colon may be either granulomatous (Crohn's disease) or ulcerative. The combination of ulcerative colitis with ulcerative ileitis is well known; the co-existence of Crohn's disease of the ileum and Crohn's disease of the colon is well recognized, though the incidence is in dispute, but the possibility of the existence of Crohn's disease of the ileum in combination with ulcerative colitis is of interest. Otani (1955) stated that these diseases co-exist as often as one would expect by chance. Whilst Crohn and Yarnis (1958)

TABLE VIII

PERIANAL FISTULA

Associated with

	per cent
Ileal Crohn's ..	14.3
Colonic Crohn's ..	43.7

found 60 cases of this combination and Jackson (1958*b*) found that 11 per cent of his patients with Crohn's disease had also ulcerative colitis, Lockhart-Mummery and Morson (1960) state that they have never seen Crohn's disease of the ileum and ulcerative colitis in the same patient. In our series, the combination has never been seen at the same time in any one patient, but two patients who had a resection for Crohn's disease of the ileum subsequently developed ulcerative colitis necessitating a panproctocolectomy three and four years later, respectively. It is not always appreciated that Crohn's disease can affect the colon without affecting the ileum, but attention has been drawn to this by Wells (1952) and more recently by Brooke (1959), by Lockhart-Mummery and Morson (1960) and by Nevin (1961).

The patient was older in Crohn's disease of the colon than in either ileal Crohn's disease or ulcerative colitis (Fig. 1) and the history tended to be without remission and of only a few months' duration before operation became necessary. The characteristic features were persistent diarrhoea, weight loss and abdominal pain of colicky type, and when the lesion was on the left side of the colon there was often bleeding per rectum. There was a high incidence of peri-anal fistulae (Table VIII), often of a complex nature, which sometimes showed giant cell systems on histology (Morson and Lockhart-Mummery, 1959); an even higher incidence has been reported (Cornes and Stecher, 1961).

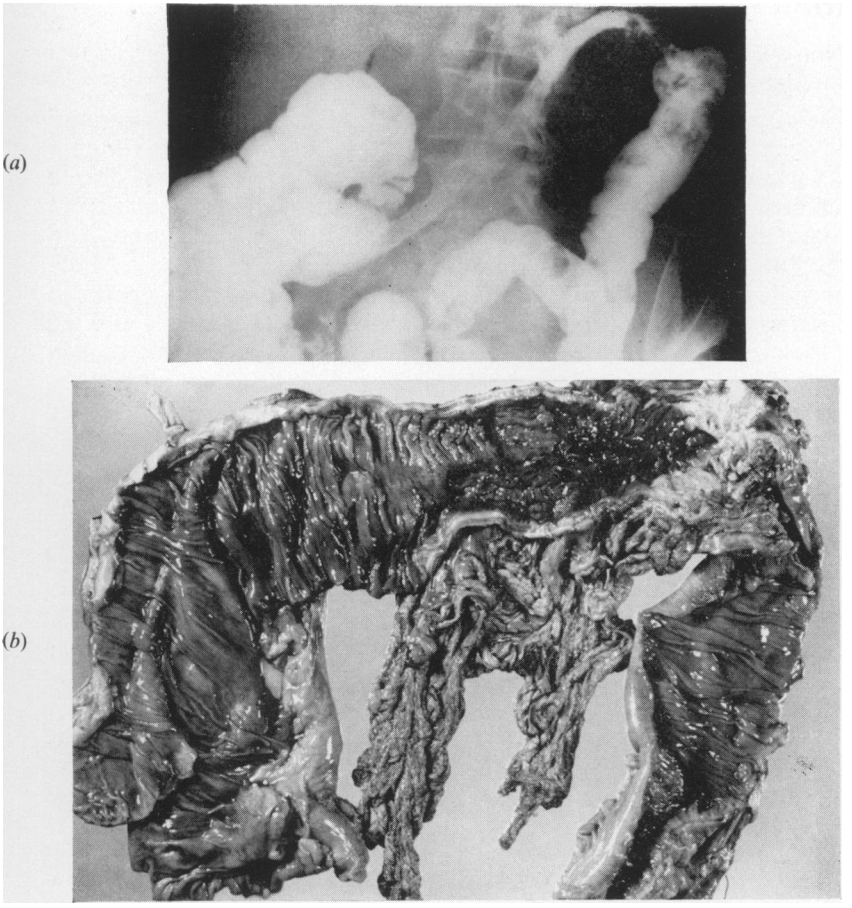

Fig. 10. (*a*) Barium enema showing the narrowed transverse colon with gross effacement of the mucosa and the normal mucosa in the ascending and descending colon. (*b*) The operation specimen from the same patient.

TABLE IX

CROHN'S DISEASE OF THE COLON (28 CASES)

With ileal involvement (12 cases)	
Spread in continuity	
to transverse colon	5
to rectum	2
" Kissing " sigmoid ..	5
Without ileal involvement (16 cases)	
Segmental colitis ..	12
Diffuse colitis	4

The differentiation between Crohn's disease of the colon and ulcerative colitis can be made with certainty only on histological grounds (Warren and Summers, 1954), but one can suspect the diagnosis of Crohn's disease on clinical grounds in view of the continuous history with abdominal pain and the high incidence of peri-anal fistulae. Barium enema may help in the differentiation because areas of normal mucosa can be seen beside segments of affected bowel (Fig. 10*a*). The affected colon was thickened and narrow (Fig. 10*b*) with often more than one area apparently affected and the mesentery thickened, with enlarged regional lymph nodes, though this latter was not as constant a finding as in ileal Crohn's disease.

Crohn's disease affecting the colon can be divided into two large subgroups, namely those with ileal changes and those without (Table IX). In the former group, there was spread from the ileum in continuity to involve the ascending and transverse colon or more rarely the whole colon, but occasionally only the sigmoid colon was affected—the " kissing " sigmoid lesion. When the colon alone was affected by Crohn's disease,

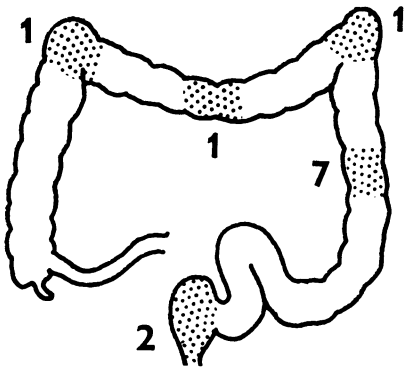

Fig. 11. A diagram showing the site of maximum involvement in the twelve localized cases of Crohn's disease of the colon. The extent of the disease was usually greater than is indicated by the diagram.

the lesion most often was a segmental colitis (Fig. 11), but occasionally generalized involvement of the whole colon was seen; even in these cases the disease tended to show areas which were more severely affected interspersed with those less severely affected.

Treatment of Crohn's disease of the colon or rectum was by appropriate excision [extended right hemicolectomy (10 cases), other partial colectomy (9 cases), total colectomy (7 cases) or abdomino-perineal excision of the rectum (2 cases)]. The results of treating the five patients with the " kissing " sigmoid lesion were not good, for there were two recurrences and one operative death, but in the rest of the patients with Crohn's disease of the colon or rectum the general results were excellent since, apart from two post-operative deaths after total colectomy, there was no recurrence in the rest of this group.

CONCLUSIONS

In Crohn's disease of the small gut, the policy depends upon whether the disease is of the localized or diffuse type. If the history is a long one with little constitutional upset and apparently a short segment involved on radiological examination, then an appropriate excision is the treatment of choice. When this is in the common situation, the terminal ileum, then right hemicolectomy has been shown to produce good results. I feel that much of the ascending colon can be retained when this area is apparently normal, for there have been no examples of a local recurrence on the colonic side of the anastomosis. If the lesion has progressed to localized perforation and is very adherent, so that one deems that excision would be hazardous, then a bypass is an acceptable alternative, provided it is performed with exclusion. Though Crohn advocates exclusion bypass as the treatment of choice, on the grounds that its results are similar to right hemicolectomy and it carries a lower operative mortality (Crohn and Yarnis, 1958), others (Barber *et al.*, 1962; Colcock and Vansant, 1960) do not share his opinion and prefer excision. In this series there were insufficient cases to give a dogmatic opinion, but our preliminary assessment suggests that exclusion bypass will not be as satisfactory as excision for routine use.

The diffuse disease is characterized by its shorter natural history with more constitutional symptoms and evidence of malabsorption before operation. The surgeon should delay as long as possible, using a supportive regime as suggested by Edwards (1964), probably including the exhibition of steroids. In this group, operation should be reserved for intestinal obstruction or fistulae, but occasionally may be forced onto a surgeon in the case of a patient deteriorating on the medical regime. The best treatment is minimal excision or bypass to overcome any obstruction, leaving active disease still present, for massive excision leads to gross malnutrition and there is evidence that the disease may burn itself out pro-

ducing multiple fibrous strictures which are much more amenable to surgery.

In recurrent disease, more emphasis has been laid on medical management (Kiefer, 1955; Pollock, 1958), since a larger proportion of these patients have diffuse disease. However, some do have recurrent localized disease and these will be cured by a second or third excision, but since further intervention has never produced a cure in our series I agree with the view expressed by Kiefer (1955) that a fourth resection is not justified.

When the large bowel is involved, whether alone or in combination with an ileal lesion, then the best policy is complete excision of the affected gut, preferably in continuity, with anastomosis if this is possible; but if the rectum is severely diseased it should be removed together with any affected colon.

Finally, I would like to stress that excision has produced an apparently permanent restoration to good health in two-thirds of the cases of Crohn's disease of the ileum and almost all of the cases of Crohn's disease of the colon. Yet in this disease more than many others one should perhaps remember the words of John Hunter, who said: " No surgeon should approach the victim of his operation without a sacred dread and reluctance. . . . "

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