

Crohn's disease in childhood

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SUMMARY In 32 patients with Crohn's disease which started in childhood, abdominal pain, diarrhoea, and weight loss were the common presenting symptoms, but unexplained fever and failure to grow were also prominent. Stunted growth was the most frequent physical abnormality when first seen in hospital. The mean delay in diagnosis was almost 3 years and the principal contributing factor here was failure to consider the diagnosis and thus perform a barium follow-through examination. The cumulative relapse rate after medical therapy or surgical resection was disappointingly high, but because the median relapse time is much longer for surgically treated patients, surgery is recommended at an early stage, especially in those patients who are growth-retarded or whose education is suffering because of time lost from school.

Crohn's disease was until recently a rare condition for the paediatrician to meet. Its mode of presentation and various manifestations may not be appreciated, and the disease therefore not considered in the differential diagnosis of children with gastrointestinal and other upsets.

There is now good evidence that the incidence of Crohn's disease is increasing both in Great Britain and Europe (Miller *et al.*, 1974) so that one can expect that the condition will be seen more frequently in childhood. We therefore decided to review our experience of this condition in childhood with special reference to problems in diagnosis, its response to treatment, and its effect on the education and early social life of these young people. We studied patients who had presented to this hospital over a 10-year period whose disease started before their 16th birthday.

Methods

Thirty-two patients referred for the first time to this hospital between the years 1965 and 1975 were diagnosed or had definite symptoms of Crohn's disease before their 16th birthday, and 21 of these had in fact been diagnosed before then (Fig. 1). There was an equal sex ratio. All the children were born in Britain; 30 were Caucasian and the remaining 2 were Negro children of West Indian extraction.

All cases of acute ileitis were excluded as were 16 patients with Crohn's disease whose only childhood symptom was abdominal pain. The 32 patients discussed here form part of a larger group of 246

new patients with Crohn's disease seen at this hospital over the same interval of time. With the exception of 3 patients who had undergone surgical resection of diseased bowel before presentation to us, all previous illnesses were ignored when calculating relapse rates. Clinical and surgical relapses have been combined. A clinical relapse was defined as a recurrence of symptoms requiring admission to hospital and/or a change in treatment, while surgical relapse was defined as a laparotomy with resection. Laparotomies, fistula operations, and drainage of abscesses have not been included. Medical treatment in the first half of the study invariably meant corticosteroids plus symptomatic relief of pain and diarrhoea, while in the latter part of the study azathioprine was added.

To ascertain the effect of the disease on education, social and family life, the patients (with one exception) were interviewed. Participation in physical recreation was said to be severely restricted when children who had previously enjoyed such activities

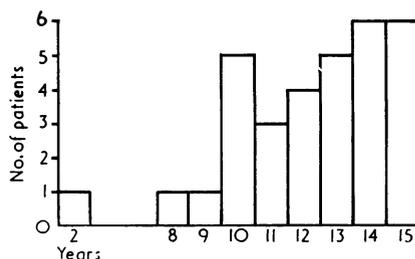


Fig. 1 Age at onset of symptoms in 32 children with Crohn's disease.

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were unable because of their disease to take part in school games for one year or more. Questions were also asked concerning group outings, parties, scouting, etc., in a subjective attempt to outline the effect of the disease on their social lives. Growth retardation was defined as height below the 3rd centile.

Statistical analysis

Recurrence rates were calculated by actuarial methods. This is an adaptation of the concept of life tables and was first used by Berkson and Gage (1950) when evaluating the survival of patients with cancer. The number of patient 'years at risk' for any particular period of time is set out and the proportion of patients suffering a recurrence during that period is then calculated. The probability of suffering a relapse over a given number of years is obtained from the product of proportions experiencing a relapse in the intervening years. An excellent account of this method as applied to Crohn's disease is given by Lennard-Jones and Stalder (1967). That period of time in which 50% of a group of patients experience a relapse is known as the *median relapse time*.

Results

Clinical features. Abdominal pain, diarrhoea, and weight loss were the most frequent presenting symptoms. These and other presenting symptoms are listed in Table 1, along with the dominant symptom in each patient. Fever occurred in nearly one-quarter and was predominant in 2 children. This led to diagnostic difficulties (see below). Erythema nodosum, seen at presentation in 4 patients, occurred at some period in the illness in 9.

Table 1 Symptoms in 32 patients with childhood Crohn's disease

Symptom	Presenting	Dominant
Pain	21	12
Diarrhoea	18	8
Weight loss	13	0
Lassitude	9	1
Anorexia	9	1
Fever	7	2
Nausea/vomiting	6	1
Growth retardation	6	2
Erythema nodosum	4	2
Arthritis	3	2
Miscellaneous		
Oedema (2)		
Perineal ulceration (1)		
Uveitis (1)		
Perianal abscess (1)		
Rectal haemorrhage (1)		
Fissure-in-ano (1)		
	7	1

Growth retardation, a presenting symptom in 6 children, was found in 9 patients. Table 2 gives the principal abnormal physical signs at presentation to hospital. Only 2 of the 9 patients observed to have stunting of growth had previously received corticosteroids. The site of the disease involvement in these patients was as follows: small bowel alone 4, large bowel alone 4, and 1 with ileocaecal disease.

Table 2 Main physical findings in 32 patients with childhood Crohn's disease

Growth retardation	9
No abnormality	8
Anal/perineal lesion	7
Abdominal mass	6

The earlier the onset of the disease the more likely was the child to display problems of growth; 8 of the 20 patients whose disease started before the age of 14 fell into this category. No physical abnormality was found in one-quarter of the group at presentation. One young girl presented with spreading perineal ulceration, her colonic Crohn's being virtually asymptomatic. Finger clubbing was not seen.

Diagnosis. Only 6 patients were correctly diagnosed after the initial series of investigations. Apart from failure to attempt a diagnosis the commonest misdiagnosis was that of a febrile illness (Table 3). Not

Table 3 Initial diagnosis in 32 patients with childhood Crohn's disease

Correct	6
No diagnosis made	7
Incorrect	
Febrile illness	
Glandular fever	2
Rheumatic fever	1
Brucellosis	1
Still's disease	1
Toxoplasmosis	1
Pyrexia of unknown origin	1
Ulcerative colitis	6
Psychiatric/functional bowel disorder	4
Appendicitis	3
Pancreatic insufficiency	2
Tuberculosis	1
Coeliac disease	1
Abdominal reticulosis	1
Peptic ulcer	1
Chronic pelvic infection	1

surprisingly, 6 patients initially diagnosed as ulcerative colitis were later found to have Crohn's disease. Functional bowel disorders were mainly diagnoses of 'school phobias', though in one case overt psychiatric disease was diagnosed. Many other

gastrointestinal disorders were considered and in some cases more than one incorrect diagnosis was made.

Delay in diagnosis. The mean delay in diagnosis was 2.9 years from the onset of symptoms (range 3 months–11 years). This delay was greater than 1 year in 20 children, the principal causes being inadequate investigations (7), failure to refer (5), and absence of gastrointestinal symptoms (4). Inadequate investigations invariably meant failure to perform a barium follow-through examination.

Site of disease (Table 4). 13 of the 32 patients had diffuse disease by which is meant combined discontinuous small and large bowel involvement.

Table 4 Site involved in 32 patients with childhood Crohn's disease

Diffuse	13
Large bowel alone	7
Ileocaecal	6
Small bowel alone	4
Anorectal	2

Almost one-quarter of the patients had large bowel involvement alone, but in contrast to this only 4 children had isolated small bowel disease.

Life style. 10 of the 32 children lost one-quarter or more of their schooling and a similar number felt that their illness seriously impaired their choice of career. 8 children felt that their illness had a marked effect on their 'way of life'. Failure to grow and develop at the same rate as their school mates rather than continued ill health was the commonest reason given by these children for this disturbance of their early social life.

Relapse rate. Fig. 2 shows the cumulative recurrence rates for those experiencing a first and a subsequent second relapse after presentation to this hospital. Thus we see that by 6 years 81% had experienced a primary relapse (median relapse time (MRT) 17 months), and of these patients 73% experienced a further recurrence at 6 years with MRT 27 months.

Fig. 3 shows the relapse rates separated for medically and surgically induced remissions. The recurrence rates at 6 years are 85% and 61%, with MRT 16 months and 48 months respectively.

Current state of health. Twenty-one patients are at this time 'well' (symptom-free for at least one year); 8 are 'fair' (recurring symptoms controlled by medication); 2 are disabled and 1 has died. The death occurred in a young girl whose diffuse disease

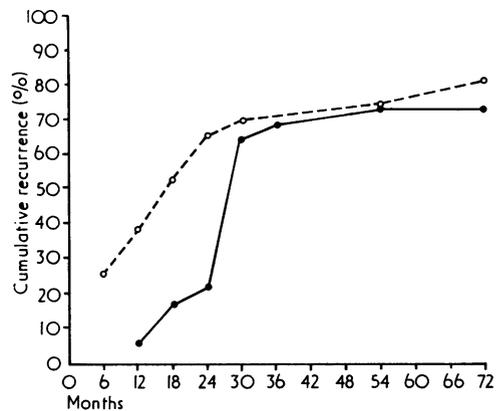


Fig. 2 Relapse rate after presentation to hospital. ○ = 1st relapse, median relapse time (MRT) 17 months; ● = 2nd relapse, MRT 27 months.

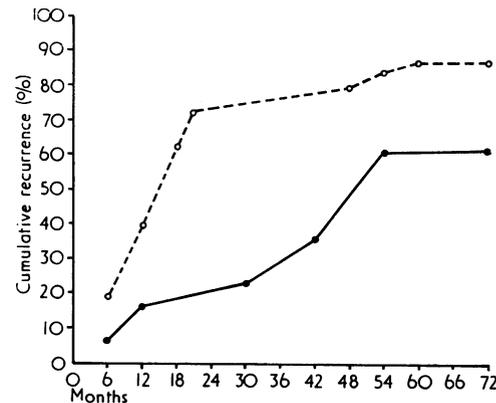


Fig. 3 Relapse rate after medical treatment. MRT 16 months (○); relapse rate after surgery, MRT 48 months (●).

required emergency surgery—previous medical therapy having failed (Appendix: Case 2). One of the disabled patients is suffering from the short bowel syndrome following multiple resections (Appendix: Case 3), while the second experiences severe recurrent disease despite multiple resections and immunosuppressive therapy.

Ten of the 21 patients described as 'well' are on no treatment; 5 take azathioprine, 2 are on low dose prednisone, and 4 take both azathioprine and prednisone.

Discussion

This is the first detailed study in this country of Crohn's disease in childhood and it is of interest to

note that the proportion of patients seen by us whose disease started before the age of 16 (13%) is very similar to that reported by American authors (Van Patter *et al.*, 1954; Burbige *et al.*, 1975). Yet this chronic disease rarely presents to paediatricians in this country, a point well illustrated by Raine (1975), who found only 6 definite cases of Crohn's disease in children presenting to a large paediatric hospital in Glasgow over an 18-year period, and this despite the fact that the incidence of the disease in the same region has been increasing in the period of time under question. This anomaly is probably explained by the delay in diagnosis, seen in this study to be almost 3 years, which means that many of these young people are no longer in the paediatric age range by the time the disease is diagnosed. A greater awareness of how early the disease may begin and its various manifestations will, we hope, lead to earlier diagnosis.

The fact that 2 of the children reported are 'West Indians' born in Britain is of interest in that until very recently inflammatory bowel disease was not known to occur in these people (O'Donoghue and Clark, 1976).

We have excluded from our study those patients whose only complaint during childhood was recurrent abdominal pain but who were subsequently found to have Crohn's disease. Abdominal pain is a common problem presenting to paediatricians and such children rarely develop serious organic disease in later life (Christensen and Mortensen, 1975). We have no proof that in our patients it was an early symptom of their Crohn's disease.

The triad of pain, diarrhoea, and weight loss appears to dominate all clinical reports of Crohn's disease and this one is no exception. However, fever, often a presenting symptom, occurs more frequently in children than adults, a point noted by Burbige and his colleagues (1975) who record pyrexia as a manifestation of Crohn's disease in 83% of children reported by them. Similarly, Guttman (1974) noted fever as an initial symptom in 27 of 52 children and young adolescents with the disease. Why fever should occur predominantly in the younger age group is a mystery; in this series the presence of unexplained pyrexia led to 7 incorrect diagnoses. This is in contrast to an earlier survey from this hospital that included all age groups when only 2% of the patients were misdiagnosed as suffering from a febrile illness (Dyer and Dawson, 1970). Crohn's disease should clearly be excluded in children suffering fevers of unknown origin.

In only 4 of the 32 children we report here was the disease confined to the small bowel. This contrasts sharply with large studies encompassing all age groups where isolated small bowel involvement

varies from 28.6% (Farmer *et al.*, 1975) to 54% (Smith *et al.*, 1975).

Although Crohn's disease has long been recognized as a cause of delayed growth and sexual maturation (Logan and Brown, 1938; Tanner, 1939), to date there is no satisfactory single explanation for its occurrence. The site of disease involvement is irrelevant as growth stunting is seen with equal frequency in Crohn's disease whether the small bowel or large bowel is affected (Farmer *et al.*, 1975). McCaffery and colleagues (1970) showed that 11 of 13 patients with inflammatory bowel disease and growth retardation had inadequate growth hormone responses to a hypoglycaemic stimulus but a further study by the same group (McCaffery *et al.*, 1974) showed no benefit to such children from the administration of human growth hormone.

The mean delay in diagnosis in this study was almost 3 years. In trying to improve on this figure it is worth remembering that failure to consider the diagnosis and thus perform a barium follow-through examination was the most common cause of this delay. Those cases presenting without gastrointestinal symptoms pose a very difficult problem requiring a high index of suspicion.

Although Ehrenpreis *et al.* (1971) in Sweden record a crude relapse rate of more than 50% after 2 years following primary surgery for childhood Crohn's disease, the work of Greenstein *et al.* (1975) emphasizes the importance of applying actuarial analysis which they have done in a series of adult patients. Their data show how different are the results that can be obtained using each type of analysis. For example, crude data implied that the reoperation rate diminished with each succeeding operation from 58% after the first operation to 47% after the fourth, whereas actuarial analysis showed that at the 3-year follow-up point the cumulative chance of reoperation increased from 37% after the first surgical procedure to 60% after the fourth. The fact that 61% of children reported here had relapsed at 6 years after surgery was disappointing, but what did offer encouragement was the greatly prolonged median relapse time when compared to medically induced remissions. This has important implications when managing children with Crohn's disease, for we have shown the serious effect this chronic disease has on physical development, education, and lifestyle. The increased time 'bought' by surgery will get many of these young people through the growth spurt of puberty and the formative years of their education. Drugs currently used in the treatment of Crohn's disease, though often beneficial in the short term are clearly disappointing in the long term and should not be allowed to delay surgery in those patients in whom it is feasible. Unfortunately, as we

have shown in this series, the extent of the disease often precludes radical surgery and this plus the fact that surprises do occur (Appendix: Case 1) leads to a conservative approach initially.

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Appendix

Case 1. This patient illustrates one of the unusual ways in which Crohn's disease may present, the difficulty in reaching a diagnosis, and the unpredictable course of the disease. A 14-year-old boy presented to hospital with a 6-month history of facial oedema and weight loss and a 3-month history of abdominal pain and diarrhoea. In addition he complained of itching, fevers, and night sweats. Examination showed a small ill-looking boy (height and weight <3rd centile). Apart from a palpable liver edge there were no other abnormal findings. The most striking biochemical abnormality was a low serum albumin. A barium follow-through examination showed widespread changes throughout the small bowel with thickening and irregularity of the folds. In some areas nodular filling defects were visible. The provisional diagnosis was an abdominal lymphosarcoma. Histology of a peroral jejunal biopsy showed a marked inflammatory cell infiltration suggestive but not diagnostic of Crohn's disease. There was no evidence of lymphoma.

Because of the diagnostic dilemma a laparotomy was performed at which gross hyperaemia of the jejunum and proximal ileum was seen. Large fleshy lymph nodes were present in the small bowel mesentery. Histology of one of these nodes and a full thickness jejunal biopsy confirmed Crohn's disease with granuloma formation. No bowel was resected. Postoperatively his symptoms disappeared without specific medical therapy. 4 years later he was well, had had no recurrence of disease, and his height approached the 25th centile.

Case 2. This patient contrasts with the previous one, as the disease process was virtually continuous for 5 years and ultimately fatal. She was 12 years old when Crohn's disease presented as pyrexia of unknown origin. Diagnosis was made at laparotomy which was performed because radiology was inconclusive. Over the next 5 years the disease process flared on several occasions requiring high dose steroids to obtain a remission. The ileum and colon were affected.

At the age of 17 her symptoms worsened despite maintenance low dose steroids and azathioprine. She developed splenomegaly and an erythematous rash, and despite negative blood cultures was treated for septicaemia. She failed to improve and because of continuing pyrexia, sudden abdominal pain, and a palpable mass in the right iliac fossa surgery was

performed. The terminal ileum was diseased and very oedematous. An ileal intussusception was noted and the colon was distended containing altered blood. A large abscess was present in the lateral wall of the abdomen communicating via openings into the 2nd part of the duodenum and the caecum. The holes in the duodenum were closed and a right hemicolectomy performed. An ileostomy and a relieving colostomy were raised. Postoperatively she developed severe respiratory distress and septicaemia and died on the fifth postoperative day.

Case 3. This case history again shows the difficulty that may be encountered in making a diagnosis and the 'crippling' complications that may ensue. When 12 years old his disease began with abdominal pain, diarrhoea, and weight loss. No diagnosis was made but at a laparotomy performed for an acute abdomen 12 months later the small intestine was congested and enlarged mesenteric nodes were present. Histology of a lymph node suggested toxoplasmosis; there was no evidence of Crohn's disease.

Two years later there was a recurrence of his symptoms and diseased proximal ileum with a surrounding 'inflammatory' mass was noted on a barium follow-through examination. This was confirmed at a laparotomy where two-thirds of the small bowel, excluding the terminal ileum, required resection. Histology was that of Crohn's disease.

Since that time the disease has spread to involve the colon, requiring initially a left hemicolectomy and proctectomy, and subsequently, with further spread of the disease, a right hemicolectomy. At this latter operation because of an anomalous blood supply the terminal ileum had also to be removed. He is now left with the 'short bowel syndrome', the main features of which are excessive fluid and electrolyte loss via his ileostomy. He has been given an A-V fistula so that he can self-administer intravenous saline at night in the hope of alleviating his symptoms and returning him to useful employment.

Case 4. This patient's story illustrates how problems of growth and development can precede gastrointestinal symptoms. She was first investigated at the age of 15½ years for failure of secondary sexual development. Height and weight were below the 3rd centile. She gave no history referable to the gastrointestinal tract but when in hospital developed abdominal pain and vomiting for the first time. A barium follow-through examination showed a stricture of the jejunum and at laparotomy 20 cm small bowel was resected. Histology showed Crohn's disease.

Postoperatively she gained in height and weight but within 12 months her symptoms returned and

there was radiological evidence of further small bowel disease. A further resection of 75 cm jejunum and proximal ileum on either side of the original anastomosis was performed. She was symptom free 2 years later, had crossed the 25th centile for height, and has regular menstrual periods.

Case 5. This case history illustrates how readily Crohn's disease can mimic a rheumatoid condition. Her symptoms started at the age of 8 with pyrexia and intermittent swelling of several joints. The initial diagnosis was rheumatic fever and later the possibility of Still's disease was considered. She responded well to salicylates. 2 years later polyarthritis recurred and in addition she complained of vomiting, lower abdominal pain, and diarrhoea. Barium enema examination showed a right-sided colonic lesion suggestive of Crohn's disease. Oral corticosteroids and sulphasalazine were given and symptoms again remitted.

She remained intermittently unwell over the next 3 years requiring occasional steroid therapy. By the age of 15, it was obvious she was not growing. Her height was below the 3rd centile and periods had not started. Because of this and continuing poor health a right hemicolectomy was performed. The resected specimen confirmed Crohn's disease. Postoperatively she was well, with height between the 10th and 25th centiles, and she had started menstruating. Arthritis recurred in one knee joint 5 months after operation but settled rapidly on azathioprine 2.2 mg/kg. She remains on this drug.

Case 6. Failure to consider the diagnosis and perform barium studies contributed to the false diagnosis of psychiatric disease in this patient. She first complained of abdominal pain and vomiting at the age of 9. For the previous 3 years she had unexplained iron deficiency anaemia and a tendency to constipation. No organic cause was found for her complaints (barium studies not performed) and as her symptoms finally led to school refusal she was referred to a child psychiatrist. She remained unwell over the next 3 years during which time she complained of intermittent diarrhoea.

At the age of 13 she was finally referred to a physician as she had a swinging pyrexia, severe diarrhoea, and erythema nodosum. She was anaemic and had severe stunting of growth. Barium studies showed changes suggestive of Crohn's disease affecting the right side of the colon. Colonoscopy confirmed this diagnosis. She was given corticosteroids and azathioprine and made a good recovery. One year later she was symptom free on azathioprine alone.