

Arthritis and Crohn's disease

A family study

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The association of arthritis with intestinal disease has been recognized since White (1895) described arthritis in association with ulcerative colitis. This arthritis has now been well characterized (Wright and Watkinson, 1959) and the familial aspects have been explored (Macrae and Wright, 1973). The association of arthritis with Crohn's disease is, however, less well documented, the generally accepted incidence of polyarthritis being the 15.4 per cent. described by Ansell and Wigley (1964). These authors specifically excluded primary colonic Crohn's disease from their series, whereas this is now an accepted part of Crohn's disease. This could have important implications from the point of view of polyarthritis, since it has been suggested (Cornes and Stecher, 1961) that this complication arises preferentially in patients with colonic involvement rather than in those with small intestinal disease only.

The present investigation was designed to examine the incidence of articular complications of Crohn's disease throughout the whole spectrum of the disorder and to study the families of patients with Crohn's disease with respect to articular involvement.

Material and methods

The patients selected had been diagnosed as having Crohn's disease at the General Infirmary at Leeds. They were invited to attend a special evening clinic at which a questionnaire concerning both their gastrointestinal tract and their joints was completed. Chest expansion and flexion of the lumbar spine were measured by the methods previously described from this unit (Macrae and Wright, 1969; Moll and Wright, 1972). The joints were examined clinically and radiologically, using the radiographic technique recommended by the New York C.I.O.M.S. Conference (Bennett and Burch, 1968), and blood was taken for estimation of rheumatoid factor. All radiographs were read by two observers, using the criteria for sacroiliitis previously evaluated in this unit (Macrae,

Haslock, and Wright, 1971) and the criteria for rheumatoid arthritis and osteoarthritis of the Rome C.I.O.M.S. Conference (Kellgren, Jeffrey, and Ball, 1963).

The patients were asked to fill in a list of the members of their family comprising all first-degree relatives over the age of 15 years and their parents' siblings as a group of second-degree relatives. These relatives were subsequently invited to attend the same clinic and to be subjected to the same questionnaire and examination techniques. Patients living more than 20 miles from the centre of Leeds were invited to attend their local hospital, where the hospital was willing to co-operate, for radiographic examination only. The patients' spouses were used as a control group drawn from the same immediate environment as the patients.

Results

(1) Ascertainment

One hundred and twenty-two patients were approached directly or sent a standard letter of invitation to attend the research clinic. Of these, 116 (95 per cent.) attended for examination. The initial aim was to study 100 families. When 116 probands had been interviewed, 102 had given permission for their family members to be contacted and ascertainment was accordingly terminated. Two of the probands subsequently withdrew consent for involving their families. Of the 100 remaining probands, two died in the interval between being seen in the clinic and the time when their relatives would have been asked to attend. It was considered inappropriate to ask the help of their family members so soon after bereavement. The final study was, therefore, carried out on 116 patients with Crohn's disease and the families of 98 of them.

(2) Age and sex distribution

Exactly half the proband group (58 patients) was male and half female. The age distribution at the time of the examination is shown in Fig. 1 (overleaf).

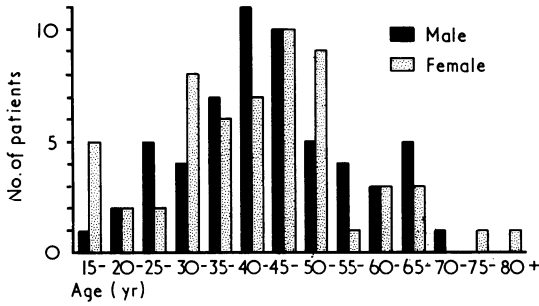


FIG. 1 Age distribution of patients

The mean age of the proband group was 46 yrs (range 16 to 74) for males and 43 yrs (range 15 to 83) for females.

(3) *Crohn's disease*

The age at onset of Crohn's disease is shown in Fig. 2, the age used being that at which the presenting symptom occurred. The duration of the disease at the time of examination is shown in Fig. 3.

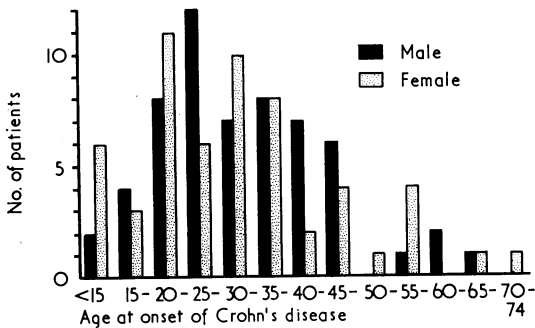


FIG. 2 Age at onset of Crohn's disease

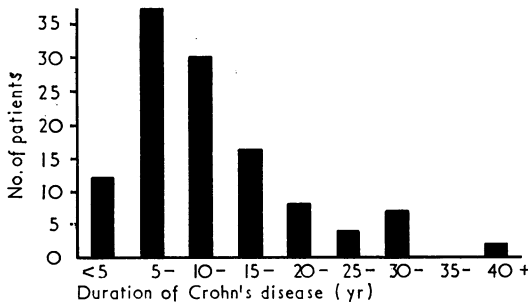


FIG. 3 Duration of Crohn's disease

The diagnostic criteria for Crohn's disease are shown in Table I. The cumulative pathological criteria of Schachter, Goldstein, Rappaport, Fennesy, and Kirsner (1970) were used. Any case in which the histological report was equivocal, irrespective of a confirmatory subsequent course of the disease, is tabulated in the next appropriate diagnostic group. Despite this, an unequivocal tissue diagnosis was obtained in 50 per cent. of the patients, and in only 11.2 per cent. was the diagnosis made on clinical or incompletely documented grounds.

Surgery had been undertaken in 99 patients, one third of these (13 males and 20 females) having had total procto-colectomy and ileostomy.

The incidence of the major complications of Crohn's disease is shown in Table II. Malabsorption was only diagnosed where definite fat malabsorption had been demonstrated by metabolic investigation.

(4) *Enteropathic synovitis*

This was diagnosed if the patient had a past or present history of one or more episodes of acute synovitis for which no other cause could be found.

Two patients with seropositive rheumatoid arthritis and sixteen with symptoms arising from radiologically confirmed osteoarthritis were, therefore, excluded from this group.

Twenty-four patients (20.7 per cent.) fulfilled these criteria, ten showing signs of an acute synovitis at the time of examination. Five male and five female patients gave a clear history of synchronous exacerbation of the gastrointestinal disease and the synovitis (Table III, opposite).

The joints involved are shown in Table IV. All were radiologically normal and all the affected probands had negative sheep cell agglutination tests for rheumatoid factor.

Table IV Joints involved in probands with enteropathic synovitis, by sex

Joints	Males (10)	Females (14)
Knee	7	11
Ankle	2	7
Shoulder	2	2
Wrist	3	0
Elbow	2	1
Metacarpophalangeal	2	0

Table I *Diagnosis of Crohn's disease, by sex*

Sex		Male		Female		Total	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Diagnosis	Clinical	5	9	5	9	10	9
	Radiological	5	9	5	9	10	9
	Laparotomy	21	36	14	24	35	30
	Histological	24	41	34	59	58	50
	Not known	3	5	0		3	3
Total		58		58		116	

Table II *Incidence of complications of Crohn's disease, by sex*

Sex		Male		Female		Total	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Internal fistulae		15	26	14	24	29	25
External fistulae		13	22	9	15	22	19
Malabsorption		4	7	4	7	8	7
Total cases		58		58		116	

Table III *Probands with enteropathic synovitis, by sex*

Sex	Male	Female	All
With enteropathic synovitis	10	14	24
Active synovitis at time of examination	4	6	10
Synchronous activity of gut and joints	5	5	10

The relationship of the time of onset of the gut and joint symptoms is shown in Fig. 4.

In only two patients were the joint symptoms thought to ante-date the intestinal disease.

There was no significant association of enteropathic synovitis with the major complications of Crohn's disease, fistula formation and malabsorption (Table V).

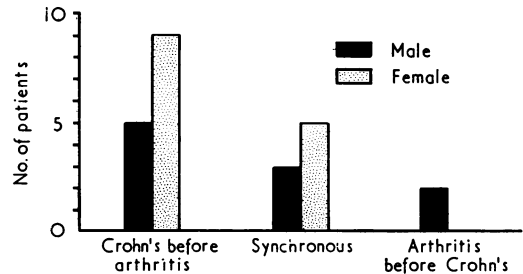


FIG. 4 *Onset of Crohn's disease related to enteropathic synovitis*

Table V *Numbers of probands with major complications of Crohn's disease, i.e. internal or external fistulae or proved malabsorption*

Enteropathic synovitis	Present (24)			Absent (92)		
	Male (10)	Female (14)	All (24)	Male (48)	Female (44)	All (92)
No.	3	7	10	21	15	36
Per cent.	50	42	44	34	34	39

The effect of surgery is shown in Table VI.

Table VI *Effect of surgery on enteropathic synovitis, by sex*

<i>Effect of surgery</i>	<i>Male (10)</i>	<i>Female (14)</i>	<i>All (24)</i>
Exacerbation	0	0	0
Remission	4	4	8
No effect	5	9	14
Post-operative onset	1	1	2

An attempt was made to delineate the area of gut affected by the Crohn's disease in patients with and without enteropathic synovitis (Fig. 5). These data were based on the available evidence of observation at laparotomy, histology, and radiology. Although a trend is observed towards a higher incidence of large intestinal disease in patients with synovitis, no support is lent to the theory that such involvement is an essential associate of the articular disorder.

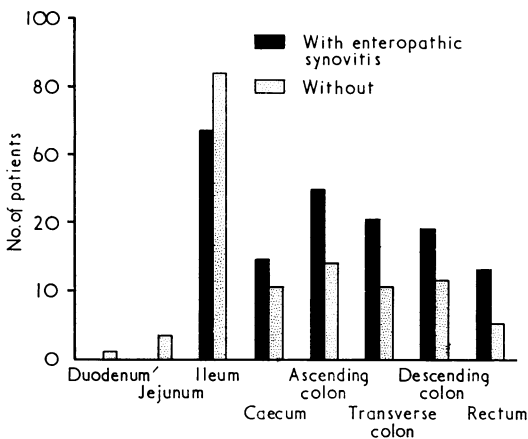


FIG. 5 *Area of gut known to be involved in probands with and without enteropathic synovitis*

(5) Sacroiliitis and ankylosing spondylitis

Radiological sacroiliitis was found in nineteen patients, of whom eight had the clinical criteria of definite ankylosing spondylitis (Table VII).

Table VII *Incidence of sacroiliitis and ankylosing spondylitis*

<i>Sex</i>	<i>Male (58)</i>		<i>Female (58)</i>		<i>All (116)</i>	
	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>	<i>No.</i>	<i>Per cent.</i>
Ankylosing spondylitis	4	7	4	7	8	7
Asymptomatic sacroiliitis	7	12	4	7	11	9
Total sacroiliitis	11	19	8	14	19	16

In five of the patients with clinical ankylosing spondylitis, the peripheral joints, in addition to the spine, were involved. The onset of symptoms from the gut disease and arthritis is shown in Fig. 6, which contrasts with the finding in intestinal synovitis (Fig. 4) in that the majority of the patients developed articular symptoms before gastrointestinal ones. None of the patients had observed synchronous activity of their gut and joint disease and surgery made no difference to the progression of their arthritis.

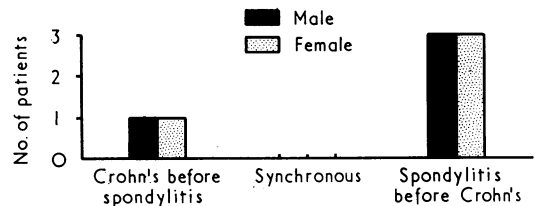


FIG. 6 *Onset of Crohn's disease related to ankylosing spondylitis*

(6) The relatives

Three hundred and forty-two blood relatives and spouses were available to the study and of these 253 were seen, giving a completion rate of 73.9 per cent. These comprised 146 first-degree relatives, 53 second-degree relatives, and 54 spouses. Of these, 198 relatives and spouses were seen personally and 55 had radiography only at another hospital. No seronegative polyarthritis was seen, although one spouse had seropositive rheumatoid arthritis.

None of the relatives or spouses showed clinical ankylosing spondylitis, but sacroiliitis was found in 8.3 per cent. of first-degree and 1.9 per cent. of second-degree relatives (Fig. 7, opposite). No spouse showed evidence of sacroiliitis.

Neither Crohn's disease nor ulcerative colitis had been diagnosed in any relative or spouse, but there were two inter-relationships in the probands of whom two were sisters and two were mother and daughter.

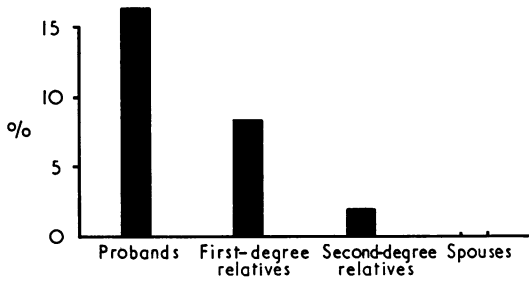


FIG. 7 Comparative incidence of sacroiliitis in probands, relatives, and spouses

Discussion

Although large series of patients with Crohn's disease are occasionally reported in which arthritis is not found (Kiefer and Ross, 1945), this complication has been recognized for many years. Polyarthritides of 'rheumatoid type' was found in 4.5 per cent. of the 600 cases reported from the Mayo Clinic (Van Patter, Borgen, Dockerty, Feldman, Mayo, and Waugh, 1954). It was noted in this series that the severity of the arthritis reflected the activity of the intestinal disease, that control of the intestinal portion of the disease resulted in the remission of the arthritis, and that exacerbation of joint symptoms subsequently almost invariably heralded recurrence of the intestinal lesion. Of Crohn's personal series of 674 patients, 2.3 per cent. had arthritis, predominantly affecting large joints (Crohn and Yarnis, 1958). Increasing interest in this aspect of Crohn's disease, allied to increasing participation in the investigations by rheumatologists, has led to a rise in the recognized incidence of enteropathic synovitis (Table VIII).

The clinical aspects have also been studied in greater detail, particularly by Ansell and Wigley (1964). They reviewed 91 patients with regional

enteritis and found six with polyarthritides at the time of survey and a further eight with a past history of polyarthritides. The most commonly involved joint was the knee, followed by the proximal interphalangeal joints, and less frequently the wrists, ankles, and hips. There were neither clinical nor radiological residual signs in those joints which had been reported as being involved in the past. Relationship of the arthritis to the bowel symptomatology was variable, but in only one case had the arthritis ante-dated any bowel symptoms. A similar pattern of joint involvement was seen in the five patients described by Soren (1966).

Wagner (1969) described five cases of arthritis associated with Crohn's disease, a complication which he described as uncommon. One patient appeared to have ankylosing spondylitis with peripheral joint involvement, one had possible ankylosing spondylitis, and the other three had peripheral joint involvement typical of enteropathic synovitis. There was no temporal relationship between the joint and gut disease in any of Wagner's patients and in fact one patient expressed the opinion that her joint and gut symptoms alternated.

The suggestion that the incidence of polyarthritides in Crohn's disease is less than that associated with ulcerative colitis has recently been challenged by Hammer, Ashurst, and Naish (1968). They found an incidence of polyarthritides in patients with Crohn's disease of 22 per cent., compared with a 12 per cent. incidence in those with ulcerative colitis. The incidence of polyarthritides described by these authors is extremely close to the 20.7 per cent. incidence in the present series. In a family study of ulcerative colitis carried out in Leeds, using identical methods to the present survey, an incidence of polyarthritides of 12.1 per cent. was found (Macrae and Wright, 1973). Previous comparisons of the incidence of enteropathic synovitis in the two diseases have been made on the basis of series conducted at different times in different countries by authors of varying disciplines

Table VIII Incidence of enteropathic synovitis in Crohn's disease

Authors	Number of patients	With arthritis	
		Number	Per cent.
Van Patter and others (1954)*	600	27	4.5
Crohn and Yarnis (1958)*	674	15	2.2
Daffner and Brown (1958)*	100	6	6.0
Cornes and Stecher (1961)	131	14	10.7
Ansell and Wigley (1964)	91	14	15.4
Hammer, Ashurst, and Naish (1968)	45	10	22.2
Haslock (1973)	116	24	20.4

* Described as 'rheumatoid polyarthritides'.

using varying criteria for their diagnosis. It is considered significant that the only studies of the incidence of polyarthritis in ulcerative colitis and Crohn's disease which are truly comparable show a higher incidence of enteropathic synovitis associated with Crohn's disease than ulcerative colitis (Table IX).

Table IX *Percentage of patients with enteropathic synovitis*

<i>Diagnosis</i>	<i>Ulcerative colitis</i>	<i>Crohn's disease</i>
Cornes and Stecher (1961)	9.5	10.7
Hammer, Ashurst, and Naish (1968)	12.4	22.2
Haslock and Macrae (1973) in preparation	12.1	20.7

Such a higher incidence is to be expected. The temporal association of both onset and exacerbations of the gut and articular aspects of the disease, the extreme rarity of joint disease occurring before gut disease, and the frequent remission of the joint lesions after surgery all point to some factor in the diseased gut initiating the production of the enteropathic synovitis. The association with surgery is of particular interest in this respect, in that total proctocolectomy in ulcerative colitis, which removes all the gut potentially affected by this disease, invariably abolishes enteropathic synovitis (Wright and Watkinson, 1965). However radical the surgery in Crohn's disease, it is impossible to remove all the potentially diseased areas of gut. The potential for triggering the enteropathic arthritis, therefore, is not only found in a greater proportion of the gut but is also retained after surgery.

The pattern of joint involvement in all the major series has been similar. The present study confirms the preponderance of large over small and of lower limb over upper limb joints. It also confirms the absence of radiological damage to the affected joints and the dissimilarity of the disease in its distribution, course, serology, and radiology from rheumatoid arthritis.

The association between ankylosing spondylitis and Crohn's disease has been studied in somewhat more detail than the peripheral arthritis, both from the point of view of the incidence of joint disease in patients with intestinal disease and *vice versa*. The two major series of patients with Crohn's disease (Van Patter and others, 1954; Crohn and Yarnis, 1968) included only passing reference to spinal involvement, and Daffner and Brown (1958) classified their cases of ankylosing spondylitis in the then

customary American fashion as part of rheumatoid arthritis. Cases of Crohn's disease were, however, included in series of patients with inflammatory bowel disease and ankylosing spondylitis both in Britain (Steinberg and Storey, 1957) and Canada (Ford and Vallis, 1959).

Powerful statistical support for a preferential association between Crohn's disease and ankylosing spondylitis was provided by Acheson (1960), who found that, of 742 male patients discharged from Veterans Administration Hospitals, seventeen (2.3 per cent.) had also been diagnosed as having ankylosing spondylitis. In Edinburgh it was found that the incidence of Crohn's disease in patients attending for radiotherapy for ankylosing spondylitis was 4.58 per thousand compared with the population incidence of 0.14 per thousand (McBride, King, Baikie, Crean, and Sircus, 1963). It was noted that there was a higher proportion of females among patients with ankylosing spondylitis complicating intestinal disease than among patients with uncomplicated spondylitis.

Two cases of Crohn's disease and ankylosing spondylitis were described in detail by Stewart and Ansell (1963). The careful study from the same unit published a year later (Ansell and Wigley, 1964), in which 91 patients with Crohn's disease were surveyed, described ankylosing spondylitis in one female and four male patients, with possible spondylitis in one further male. Of the five confirmed cases, the articular symptoms ante-dated the intestinal symptoms in two and post-dated them in three. Three patients had an associated peripheral arthritis. One of the patients with arthritis and Crohn's disease reported by Wagner (1969) was originally described as having ankylosing spondylitis. Although the author later discarded this diagnosis, the combination of back pain, positive Schober's test, and sacroiliac sclerosis would fit the generally accepted criteria for ankylosing spondylitis.

All the clinical series mentioned so far have dealt with the occurrence of arthritis in patients with intestinal disease. The only systematic studies of the reverse relationship have been those of Jayson and his colleagues (Jayson and Bouchier, 1968; Jayson, Salmon, and Harrison, 1970). They found inflammatory bowel disease in six of 33 and eight of 47 patients with ankylosing spondylitis. At least one of these patients had Crohn's disease.

The present study is only the second in which the sacroiliac joints have been examined in asymptomatic patients. The results of the two surveys are strikingly similar. Ansell and Wigley (1964) found eighteen cases of sacroiliitis in their patients and two cases in their controls, an excess incidence in the patients of 17.6 per cent. This compares with the 16.4

per cent. incidence in probands, with none in the controls, described in this paper. The numbers of patients with clinical ankylosing spondylitis were also similar—five (5.5 per cent.) and eight (6.9 per cent.) respectively. The increased incidence of sacroiliitis in the first-degree relatives affords good support for the suggestion that sacroiliitis and ankylosing spondylitis are genetic accompaniments of Crohn's disease in a similar manner to their association with ulcerative colitis (Macrae and Wright, 1973).

Summary

A study was undertaken of the articular diseases of 116 patients with Crohn's disease and the families of 98 of them. Of the probands 24 (20.7 per cent.) were diagnosed as having enteropathic synovitis. This was an episodic polysynovitis affecting large rather than small joints and lower limb rather than upper limb joints. The synovitis almost invariably accompanied or followed the onset of intestinal symptoms and showed a tendency to be associated with exacerbations of the disease and to be ameliorated by surgery.

Radiological sacroiliitis was found in nineteen patients, of whom eight (6.9 per cent.) had clinical ankylosing spondylitis. Five of these had an associated peripheral arthritis. In contrast to the enteropathic synovitis, neither the onset nor the course of the spondylitis had any relationship to the onset and course of the intestinal disease.

Radiological sacroiliitis was found in 8.3 per cent. of the first-degree and 1.9 per cent. of the second-degree relatives.

The articular complications of Crohn's disease are common, and are probably the commonest extra-intestinal manifestation of the disease. Enteropathic synovitis appears to be a complication of active gut disease, whereas ankylosing spondylitis appears to be an hereditary accompaniment.

I should like to thank Prof. V. Wright, under whose direction this work was undertaken, and the physicians and surgeons of the General Infirmary at Leeds, who allowed me to study their patients. Financial support was provided by the Board of Governors of the United Leeds Hospitals. This work forms part of an M.D. thesis of the University of Edinburgh.

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