

Progress report

Epidemiological aspects of Crohn's disease: a review of the literature

During the last 50 years, an apparently rare intestinal condition has become a common important clinical problem. Kennedy Dalziel,¹ while working in the Western Infirmary, Glasgow, described nine patients with an illness which is now known as Crohn's disease.² This disease became much more common in the 1950s and emerged as a major gastrointestinal problem with current estimates that as many as 20 000 people may be affected in Britain. As the disease often afflicts young people shortly after puberty and lasts throughout life, it has important implications for individual patients and those involved in their management. Treatment, which is empirical and not curative, is largely based on the use of steroids and surgical resections, both of which carry a significant morbidity and mortality. It is not surprising that there has been substantial research endeavour to identify the cause and although viruses, bacteria, and immunological abnormalities have all been implicated, direct evidence for the role of a major causative agent is lacking. It is therefore pertinent to review epidemiological data which may give some lead in the quest for such causative factors.

International differences in the occurrence of Crohn's disease

A review of current world literature suggests that Crohn's disease is most common in North America and northern Europe, emerging in southern Europe and least common in other areas of the world. Scandinavian studies have produced the highest prevalence figures (75 and 54/10⁵ of the population)^{22 23} while high British figures are between 26 and 56/10⁵^{6 12} (Table 1).

The type of health care available, particularly in Scandinavia and Great Britain may partly account for high figures from these countries. The health service is largely free and there are computerised records which would facilitate collection of epidemiological data. The type of health care cannot entirely explain the high prevalence figures, however, because comparable countries in the southern hemisphere, such as Australia,⁴⁰ apparently have low figures although good data to substantiate this is lacking. The incidence of Crohn's disease in New Zealand^{35 36} and South Africa^{32–34} is lower than in Europe despite the fact that many of their citizens are of European extraction, so that the major difference between countries is unlikely to be due to racial factors. Attempts to examine the disease in different racial groups within the same country do suggest that figures are higher in subjects of northern European origin.^{32–37} Prevalence figures for non-white people are less reliable for various reasons. Diarrhoea of uncertain aetiology and abdominal tuberculosis are common

Table 1 Studies of the incidence (cases/10⁵/year) and prevalence (cases/10⁵ of the population) with Crohn's disease

Place of study	Incidence	Prevalence	Place of study	Incidence	Prevalence
Great Britain			Denmark		
Oxford ³	0.8	9	Copenhagen ^{24 25}	2.7	32
London ⁴	—	13	Finland		
Gloucester ⁵	1.5	—	Turku ²⁶	0.27	
Nottingham ⁶	3.6	26.5	Europe		
North East Scotland ^{7 8}	2.1	32.5	Switzerland		
Clydesdale ⁹	1.5	—	Basle ²⁷	2.6	
Northern Ireland ¹⁰	1.3	—	Italy		
1 Belfast	3.5		Bologna ²⁸	0.8	
2 County Down	0.3		Spain		
North Tees ¹¹	5.3	35	Galicia ²⁹	0.14	1.22
Cardiff ¹²	4.8	56	Madrid ³⁰	0.7	
North America			Czechoslovakia		
Baltimore ¹³			Northern Bohemia ³¹	1.6-2.0	12
White male	2.5		South Africa		
White female	1.2		Western Cape ^{32 33}		
Standford University			Jewish	7.2	
Palo Alto, Calif ¹⁴	—	13	White	1.2	
USA - 15 towns study ¹⁵	2.4		Black	1.3	
Olmsted County, Minn ¹⁶	6.6	106	Pretoria ³⁴		
Sherbrooke, Quebec ¹⁷	0.7	6.3	White	1.1	
Scandinavia			Black	0.2	
Norway			New Zealand		
Norway ¹⁸	1.03	—	1 Whole country ³⁵	—	49
Bergen ¹⁹	3.5	—	2 Auckland ³⁶		
Sweden			Caucasians	1.8	
1 Uppsala and Vastmanland ²⁰	3	27	Polynesians	0	
2 Gothenburg ²¹	6.3		Israel		
3 Malmö ²²	6	75.2	Tel-Aviv ³⁷	1.3	12.3
4 Stockholm ²³	5	54.2	Beersheba ^{38 39}	1.8	12.3

among such populations and in areas with a limited medical service the true incidence of Crohn's disease would be masked. Additional factors include variations in diagnostic criteria used in different countries and it was with this in mind that guidelines for diagnosis were put forward by the Organisation Mondiale de Gastroenterologie.⁴¹

Few cases have been reported from Africa.⁴² Similarly, there is only a single series of 44 cases from India,⁴³ and small groups of cases have been reported from Chile.^{44 45} There appear to be relatively low incidence figures for the East Indian⁴⁶ and Asian populations⁴⁷ in Britain and further studies on different racial groups in Britain may be of value in establishing the role of racial origin in the cause of disease.

The highest figures for Crohn's disease come from northern Europe and North America where the highest current figures for prevalence are 75 and 56/10⁵ of the population from Malmö in Sweden and Cardiff.

Urban and rural Crohn's disease

Studies from different parts of the world support the view that Crohn's disease is more common in towns than country areas (Table 2). This has been shown in Wales where prevalence was examined throughout the country, involving 1100 patients;⁴⁸ similar findings were also made in

Table 2 *Urban-rural distribution of Crohn's disease*

<i>Place</i>	<i>Measurement</i>	<i>Urban</i>	<i>Rural</i>
Wales ⁴⁸	Period prevalence (cases/10 ⁵)	47.6	34
Northern Ireland ¹⁰			
Belfast/County Down	Incidence (cases/10 ⁵ /yr)	3.5	0.29
Aberdeen ⁷	Prevalence (cases/10 ⁵)	49	29
Olmsted County, USA ¹⁶	Prevalence (cases/10 ⁵)	116.7	84.2
New Zealand ³⁵	Mean rates/yr	119	59
Madrid Province ³⁰	Percentage composition	94.2	5.8
Bologna ²⁸	Percentage composition	77.8	22.2

Ireland,¹⁰ Scotland,⁷ New Zealand,³⁵ and the USA¹⁶ with some smaller studies in Madrid³⁰ and Bologna.²⁸ These differences, however, have not been observed in central Sweden where the incidence is particularly high.^{20, 23} The differences observed in Aberdeen⁷ and Olmsted County, Minnesota,¹⁶ were against the background of a marked rise in incidence during the last decade, which was most marked in urban areas. Recent figures from Aberdeen which suggest a fall in incidence no longer show a difference in prevalence between urban and rural communities.⁸ One interpretation of these findings is that environmental changes which may be responsible for Crohn's disease affect town dwellers first and their more conservative countrymen later.

Most studies show that Crohn's disease is more common in urban than rural areas.

Has the incidence of Crohn's disease changed?

Although there were early reports of the disease last century^{49, 50} it was not until the 1960s that attempts were made to quantify the size of the problem. Evans and Acheson³ in Oxford were among the first to review the disease in Britain and identified only 24 cases. During the subsequent 15 years studies of incidence and prevalence were reported in Britain from London,⁴ Gloucester,⁵ Cardiff,¹² Nottingham,⁶ Aberdeen,⁷ Clydesdale,⁹ and North Tees.¹¹ Similar techniques were used to identify patients in all centres although the studies were retrospective; prevalence ranged from 12 to as high as 55/10⁵.⁵¹

During the 1960s clinical impressions suggested that the disease was becoming more common and attempts were made to investigate this. Cardiff,¹² Nottingham,⁶ and Aberdeen⁷ all showed a rise in the incidence. Figures for quinquennia 1970–75 and 1975–80 were the same in Cardiff⁵² and may represent a plateau although one would like to see figures for a decade to give a reliable indication of the trend in view of the considerable variation which occurs from year to year. From Aberdeen⁸ the figures for 1962 and 1976 for North East Scotland suggest a fall in incidence from 2.6 to 2.1/10⁵/year but one would like to see figures for a longer period. There are many difficulties in retrospective studies because the definition of disease may change. In the last 20 years the recognition of Crohn's disease limited to the colon only has contributed to this difficulty.⁵³ In its early history, Crohn's disease was usually recognised by surgical intervention but more sophisticated radiology has made recognition of mild cases possible.

Retrospective studies are limited by the completeness with which cases are identified, particularly where outpatients are excluded and inadequate data from early series may give a false impression of change in incidence.

Although these considerations probably contribute to an apparent rise in incidence, they do not completely explain it. The Cardiff studies show that milder cases have not contributed to the increase in incidence.¹² There has been a steady rise in the number of cases recognised at surgery and mortality expressed as standardised mortality ratio for Crohn's disease has not fallen in the same period;⁵⁴ both these factors suggest that the increased incidence is not because of recognition of mild cases.

Changes in incidence may help to identify causative factors. The possible protective effect of breast milk has been considered; Heller's⁵⁵ work is of interest for bottle feeding has decreased in northern Europe but increased in developing countries⁵⁶ during the last decade. If breast feeding has a protective effect we might expect a decline in the incidence of Crohn's disease in northern Europe and the USA after a latent period of 20 years or so.

The incidence of Crohn's disease has risen during the last 25 years in northern Europe with high figures of 6/10⁵/year in Malmö, Southern Sweden.

Infectious aetiology

Considerable laboratory endeavours have been directed towards isolation of an infectious agent in Crohn's disease and these will not be discussed here. Although epidemiology has traditionally been concerned with the discovery of causes and modes of transmission of infection, it is incongruous that few studies have looked at this aspect of Crohn's disease.

There have been several studies from Nottingham.^{57 58} In the first the date and place of domicile and work at the time symptoms began was obtained for 260 patients in the city. There is no evidence of clustering of cases in time or space. These negative findings, however, do not completely rule out the possibility of an infectious agent with a long latent period, or an abnormal response to some childhood infection. In the second a different approach was used in which patients were compared with age and sex matched controls and the 'effective contact' between members of each group was measured. There was no greater contact between patients with Crohn's disease than between healthy controls. Neither study has given encouragement to the idea that Crohn's disease is infectious.

Three studies have sought evidence for a transmissible agent in Crohn's disease by looking at doctors and nurses who have frequent contact with affected patients.

In Goodman *et al's* study⁵⁹ 998 members of the American Gastroenterological Association had responded to a questionnaire distributed to 1755 doctors; eight had either ulcerative colitis or Crohn's disease (combined prevalence of 810/10⁵ population). This high prevalence was attributed to age structure and bias in returning the questionnaire, selection of career, and possibly an increased diagnostic accuracy.

Two antibodies which occur with high frequency in patients may be markers of infection and have been studied. No evidence was found for an

increased incidence of lymphocytotoxic antibody in American gastroenterologists,⁵⁹ and this is a similar finding to the absence of serum antibodies to anaerobic coccoid rods in British doctors.⁶⁰ Similarly there is no evidence that nurses have an increased risk of the disease.⁶¹

There is no evidence from epidemiological studies for transmission or spread of an infective agent in the causation of Crohn's disease.

Genetic factors in Crohn's disease

There are only two particular studies^{51 62} measuring the prevalence of Crohn's disease in first degree relatives of patients. In Cardiff,⁵¹ details of family structure were obtained from 139 of the surviving 147 patients in 1979. The prevalence of Crohn's disease in siblings was 1602/10⁵ (based on seven siblings with Crohn's disease disease in a population of 437), compared with a prevalence of 56/10⁵ for all residents in the city of Cardiff. No affected parents or children were reported in the group. A similar study in Leiden⁶² gave a prevalence of 1597/10⁵ in siblings. The studies were not strictly comparable for the Cardiff data were based on patients resident in the city rather than the hospital population as in Leiden. The studies show that Crohn's disease may be 30 times more common in siblings compared with the general population and 13 times more common in all first degree relatives (Table 3). This increased risk factor does not suggest inheritance by a simple Mendelian inheritance with high penetrance but suggests several factors may be involved.

Information from other areas suggest a genetic predisposition for Crohn's disease. The association between Crohn's disease and ankylosing spondylitis is one;⁶³ McBride *et al*⁶⁴ examined 560 patients with ankylosing spondylitis and a diagnosis of Crohn's disease was made in four cases (expected number, 0.3). Patients with Crohn's disease also appeared to have a greater occurrence of ankylosing spondylitis than would have appeared by chance. Some evidence comes from attempts to test an association with atopic disease;^{65 66} these have shown a significantly high prevalence of eczema among both patients and first degree relatives.

Family studies can be of particular value in the assessment of factors which may operate early in life and predispose to the disease. Twin studies are often valuable in this context, but to date less than 20 affected twins have been reported.⁶⁷ The number of twins in Britain⁶⁸ with at least one

Table 3 Prevalence of Crohn's disease in family members

	Cardiff			Leiden		
	Cases of Crohn's disease (no)	Population at risk	Prevalence (/10 ⁵)	Cases of Crohn's disease (no)	Population at risk	Prevalence (/10 ⁵)
Residents	156	280 100	56	—	—	—
Parents	0	278	0	4	758	528
Siblings	7	437	1602	20	1252	1597
Children	0	152	0	3	—	—

Reports of Crohn's disease in first degree family members in studies reported from Cardiff⁵¹ and Leiden.⁶²

affected member may be as high as 350 and the discrepancy between the two figures is not easily explained. HLA studies are in progress in several centres.^{69 70} There is no evidence for a particular genetic marker predisposing to Crohn's disease, but 80% of patients lack DR2 compared with only 64% of healthy controls. Individuals possessing DR2 had a 40% less chance of developing inflammatory disease.

There is a small genetic predisposition to Crohn's disease which increases the risk by 30 in siblings and only by 13 in all first degree relatives.

Incidence in Jews

In 1960 Acheson⁷¹ showed that Crohn's disease was particularly common in Jewish American veterans but recognised that this may reflect different social attitudes to hospital admission rather than a real difference in incidence. Subsequent clinical series reported a high frequency among Jews, especially in South America where Crohn's disease is rare.^{44 45 72} High prevalence figures have been reported uniformly from western Europe and South Africa but these are not supported by studies in Tel Aviv and Beersheba (Table 4).

The view that Crohn's disease is more common among Jews than other groups is based on small numbers and may not be true.

Diet and Crohn's disease

Dietary studies are fraught with difficulties and cannot reflect pre-illness diet. Patients' attempts to record eating habits before diagnosis are

Table 4 Crohn's disease in Jewish populations

Centre	Crohn's disease		
	Cases (no)	Incidence (cases/10 ⁵ /yr)	Prevalence (cases/10 ⁵)
Baltimore ^{13*}	28	3.5	14
Western Cape			
1970-74 ³²	24	2.8	200
1975-79 ³³	20	7.2	—
Basle ²⁷	1	3.6	35.7
Nottingham ⁷⁴	2	—	100
Malmö ²²	5	25	400
Stockholm ⁷³	24	10	200
Tel-Aviv ³⁷	44	1.3	12.3
Born in Europe and America	26	—	20.6
Israeli born	12	—	7.9
Born in Asia and Africa	5	—	8.2
Ashkenazim	37	—	16.7
Sephardim	5	—	4.2
Beersheba ³⁹	—	—	12.3
Immigrants†	—	—	22.75
Israeli born†	—	—	16.43

The incidence and prevalence of Crohn's disease in Jewish populations reported from various centres. The figures have been calculated from published data and are in some cases estimates.

* Figures based on hospital admissions.

† Age adjusted prevalence figures.

unreliable and their motivation will differ from controls. Studies which involve patients recording and weighing food for several days often produce changes and such studies are probably no more accurate than those dependent on a simple questionnaire.

The relationship between diet and Crohn's disease is one which has aroused interest since earliest descriptions of the condition. The possibility that a dietary antigen provokes a granulomatous reaction is attractive and an early suggestion was silica which produces a granulomatous reaction in dogs.⁷⁵ The association between milk consumption and ulcerative colitis in some patients was first reported by Wright and Truelove⁷⁶ but Warthin⁷⁷ later reported that American troops with Crohn's disease had a remission from their symptoms while taking combat rations which excluded milk products. This report, however, was anecdotal and no attempt was made to validate the findings.

After a decade of silence, James⁷⁸ reawakened interest when he reported an association between the disease and cornflakes. Studies from Oxford,⁷⁹ Bristol,⁸⁰ and Cardiff⁸¹ failed to confirm the high intake of cornflakes but drew attention to several German studies^{82 83} which recorded sugar and fibre consumption.

SUGAR

In 1976 two German studies from Marburg⁸² and Düsseldorf⁸³ reported an increased sugar consumption by patients with Crohn's disease. Martini and Brandes⁸² studied 63 patients and controls; patients ate 116 g/day refined sugar at the time of study and 177 g/day before the condition was diagnosed, compared with 74 g/day by controls. Miller *et al*⁸³ reported similar findings from Düsseldorf. The main criticism of these and other dietary studies is the inaccuracy of information related to the time of diagnosis. The findings, however, have been confirmed from Cardiff,^{81 84 85} Bristol,⁸⁶ Tel Aviv,⁸⁷ and Orebro, Sweden,⁸⁸ although their significance remains obscure. In Cardiff and Bristol the high sugar consumption cannot be attributed to the effect of longstanding illness with diarrhoea, for it was not seen in patients with ulcerative colitis.^{84 89} Recent work in Orebro,⁸⁸ however, may not support this. All other studies suggest that sugar consumption is high initially and falls subsequently (Table 5). A combined study of newly diagnosed cases from Cardiff and Birmingham⁸⁵ also showed that patients had a high sugar consumption at the time of interview.

The increased consumption of sugar is independent of cultural differences and has been described in various Anglo Saxon and Nordic groups together with Ashkenazi and Sephardic Jews.⁸⁷ In the Israeli groups the difference was independent of immigration status. The significance of dietary studies, however, remains uncertain. Three recent attempts to relate the increased consumption to differences in taste sensitivity have failed to explain these findings.⁹¹⁻⁹³

Patients may need more sugar than healthy people but two preliminary reports suggest that patients actually benefit from a low sugar intake.^{94 95}

DIETARY FIBRE

The association between fibre consumption and Crohn's disease is uncertain. There have been three main assessments from Wurzburg,⁹⁰

Table 5 Consumption of sugar by patients with Crohn's disease

Study centre	Consumption of sugar (g)		
	Patients		Controls
	At diagnosis	At time of interview	
Marburg ⁸²	177	116	74
Düsseldorf ⁸³	150	115	55
Wurzburg ⁹⁰	—	156	91
Orebro ⁸⁸	—	89	64
Cardiff ⁸⁴	60	52	29
Bristol ⁸⁶	—	122	65
Tel-Aviv ⁸⁷	314	269	200

The consumption of sugar was assessed by different techniques and using different analytical tables in the various centres. The definition of refined sugar is also variable from study to study. The consumption of sugar was significantly different between patients and controls at the time of diagnosis and at the time of interview.

Bristol,⁸⁶ and Cardiff⁸⁵ respectively. The outcome of these could not be more dissimilar; in Wurzburg⁹⁰ patients ate more, in Bristol⁸⁶ less, and in Cardiff⁸⁵ they ate the same quantity of fibre. It therefore seems unlikely that fibre plays an important role in the development of Crohn's disease.

Breast and bottle feeding in childhood

Epidemiological studies on breast feeding have come from Stockholm²³ and show that patients with Crohn's disease were breast fed for shorter periods than healthy controls but the difference was only 1.17 months. Whorwell *et al*⁹⁶ were unable to show such an association in a considerably smaller study. It is possible that pathogenic infections in infancy may become manifest later in life as Crohn's disease; if this were true then breast feeding could give passive protection.

The only consistent and rather surprising finding from dietary studies is the high sugar consumption in patients compared with healthy controls; this is probably a secondary factor rather than one of primary significance.

Mortality

Mortality figures reflect the severity of disease in different groups of patients. Longitudinal studies from Cardiff⁵⁴ and Stockholm²³ have shown no change in survival during the last 30 years although surgical and medical treatment has probably made life more tolerable. In most centres mortality is twice the expected figure for the general populations, but international comparisons⁴⁰ of such data are of limited value because of differences in patient identification.

Several centres have reported their experience with Crohn's disease over many years and assessed the mortality of their patients. Standardised mortality rates allow comparisons to be made between such centres (Table 6). Studies based on hospital series are from centres with a special interest in Crohn's disease which often attract ill patients who may contribute to a higher mortality;⁹⁷ groups who appear at particular risk in these centres

Table 6 *Mortality in Crohn's disease*

Centre	Period of study	Patients (no)	Deaths (no)	Standardised mortality rates
Tubingen ⁹⁹	1972-78	256	12	3.8
Leiden ¹⁰⁰	1934-72	226	21	3.5
Stockholm ^{2,3}	1955-74	826	65	1.9
Copenhagen ^{97*}	1964-76	297	36	5.6
Oxford ^{101*}	1938-70	221	31	2.2
Cardiff ^{5,4†}	1934-76	218	40	2.2
Birmingham ¹⁰²	1941-76	513	102	2
Bridgend ^{98†}	1961-80	79	5	1.3
Olmsted County (USA) ^{16†}	1935-75	103	13	1.7

Mortality rates reported in various centres.

* Mortality rates were significantly increased at these centres by referral of ill patients.

† Studies at these centres were based on population data.

may reflect this bias. Population based studies such as the one from Cardiff,^{5,4} Stockholm,^{2,3} Bridgend,⁹⁸ and Olmsted County¹⁶ identify the patients at greatest risk without prior selection. Groups with a high mortality include young patients under 20 years of age at the time of diagnosis, those with extensive disease, particularly affecting small bowel, and newly diagnosed patients. If mortality figures are to improve, then treatment in these particular groups should be more effective.

In Birmingham the effect of treatment on mortality has been examined where the standardised mortality rate was found to be 2.4.¹⁰³ When the effect of steroids was considered, the standardised mortality rate in that groups of patients increased to 3.6 compared with 1.8 among patients not receiving steroids, although this effect may have been because of severity of the disease.

The standardised mortality ratio is twice normal in most series but is especially high in young patients or those with extensive disease.

Crohn's disease and cancer

Patients with Crohn's disease have an increased risk of developing carcinoma of the gastrointestinal tract. Weedon *et al*¹⁰⁴ has reviewed 449 patients with Crohn's disease who were treated at the Mayo Clinic. Twelve developed cancer; in seven cases the colon was affected and in one the rectum; the probability of developing colorectal cancer over 20 years was estimated at 2.8%. Although this appears to be small, the number of cases was 20 times greater than would have been expected in an age and sex matched population from Connecticut. The group of patients considered, however, came from all over North America. A recent study of 513 patients from Birmingham¹⁰² reported only nine deaths (expected, 4) and suggested that the risk was much less, although it probably increases with longstanding disease which may be particularly relevant after bypass surgery. There is no support for an extensive programme of routine screening for carcinoma of the colon in patient with Crohn's disease.

There is a slightly greater risk of the patient with Crohn's disease developing carcinoma.

Crohn's disease has remained an enigma since its earliest description and despite 50 years of intensive investigation it is still unclear whether autoimmunity, infection, or toxic environmental agents are the major causative factors; even the role of genetic susceptibility is uncertain. Diet and events in childhood may both be important in the aetiology of the condition. Simply to assume that all of these factors play a role is to avoid the issue and withdraw from attempting to establish the cause.

After 70 years of endeavour in many different fields we can only echo the words of Kennedy Dalziel¹ when he wrote, 'I can only regret that the aetiology of the condition remains in obscurity, but I trust that 'ere long further consideration will clear up the difficulty'.

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References

- 1 Dalziel TK. Chronic interstitial enteritis. *Br Med J* 1913; **2**: 1068-70.
- 2 Crohn BB, Ginsburg L, Oppenheimer GD. Regional ileitis. A pathologic and clinical entity. *JAMA* 1932; **99**: 1323-9.
- 3 Evans JG, Acheson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. *Gut* 1965; **6**: 311-24.
- 4 Wright JT. The prevalence of Crohn's disease in an East London Borough. 4th World Congress of Gastroenterology. Advance Abstracts p 389, 1970.
- 5 Tresadern JC, Gear MWL, Nicol A. An epidemiological study of regional enteritis in the Gloucester area. *Br J Surg* 1973; **60**: 366-8.
- 6 Miller DS, Keighley AC, Langman MJS. Changing patterns in epidemiology of Crohn's disease. *Lancet* 1974; **2**: 691-3.
- 7 Kyle J. An epidemiological study of Crohn's disease in North East Scotland. *Gastroenterology* 1971; **61**: 826-33.
- 8 Kyle J, Stark G. Fall in the incidence of Crohn's disease. *Gut* 1980; **21**: 340-3.
- 9 Smith IS, Young S, Gillespie G, O'Connor J, Bell JR. Epidemiological aspects of Crohn's disease in Clydesdale, 1961-1970. *Gut* 1975; **16**: 62-7.
- 10 Humphreys WG, Parks TG. Crohn's disease in Northern Ireland - a retrospective study of 159 cases. *Irish J Med Sci* 1975; **144**: 437-46.
- 11 Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. *World J Surg* 1980; **4**: 183-93.
- 12 Mayberry JF, Rhodes J, Hughes LE. Incidence of Crohn's disease in Cardiff between 1934 and 1977. *Gut* 1979; **20**: 602-8.
- 13 Monk M, Mendeloff AI, Siegel CI, Lilienfeld A. An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore. 1. Hospital incidence and prevalence, 1960 to 1963. *Gastroenterology* 1967; **53**: 198-210.
- 14 Gelpi A. Inflammatory bowel disease among college students. *Western J Med* 1978; **129**: 369-73.
- 15 Garland CF, Lilienfeld AM, Mendeloff AI, Markowitz JA, Terrell KB, Garland FC. Incidence rates of ulcerative colitis and Crohn's disease in fifteen areas of the United States. *Gastroenterology* 1981; **81**: 1115-24.
- 16 Sedlack RE, Whisnant J, Elveback LR, Kurland LT. Incidence of Crohn's disease in Olmsted County, Minnesota, 1935-1975. *Am J Epidemiol* 1980; **112**: 759-63.
- 17 Nootens J, Devroede G. Fréquence de l'enterite regionale dans les cantons de l'Est. *Union Med Can* 1972; **101**: 1138-40.
- 18 Myren J, Gjone E, Hertzberg JN, Rygvold O, Semb LS, Fretheim B. Epidemiology of ulcerative colitis and regional enterocolitis (Crohn's disease) in Norway. *Scand J Gastroenterol* 1971; **6**: 511-4.

- 19 Skarstein A, Arnesjö B, Burhol P *et al.* The incidence of ulcerative colitis and Crohn's disease in an urban population. *Scand J Gastroenterol* 1982; **17**: 349.
- 20 Norlen BJ, Krause U, Bergman L. An epidemiological study of Crohn's disease. *Scand J Gastroenterol* 1970; **5**: 385-90.
- 21 Kewenter J, Hulten L, Kock NG. The relationship and epidemiology of acute terminal ileitis and Crohn's disease. *Gut* 1974; **15**: 801-4.
- 22 Brahme F, Lindstrom C, Wenckert A. Crohn's disease in a defined population. An epidemiological study of incidence, prevalence, mortality and secular trends in the city of Malmö, Sweden. *Gastroenterology* 1975; **69**: 342-51.
- 23 Hellers G. Crohn's disease in Stockholm County 1955-1974. A study of epidemiology, results of surgical treatment and long-term prognosis. *Acta Chir Scand* 1979; suppl 490.
- 24 Hoj L, Brix Jensen P, Bonnevie O, Riis P. An epidemiological study of regional enteritis and acute ileitis in Copenhagen County. *Scand J Gastroenterol* 1973; **8**: 381-4.
- 25 Binder V, Both H, Hansen PK, Hendriksen C, Kreiner S, Torp-Pedersen K. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen 1962-1978. *Gastroenterology* 1982; **83**: 563-8.
- 26 Havia T, Thomasson B. Crohn's disease. A follow-up study. *Acta Chir Scand* 1972; **138**: 844-7.
- 27 Fahrlander H, Baerlocher Ch. Clinical features and epidemiological data on Crohn's disease in the Basle area. *Scand J Gastroenterol* 1971; **6**: 657-62.
- 28 Lanfranchi GA, Michelini A, Brignola C, Campieri M, Cortini C, Marzio L. Uno studio epidemiologico sulle malattie infiammatorie intestinali nella provincia di Bologna. *G Clin Med* 1976; **57**: 235-45.
- 29 Ochoa R. Epidemiologia. In: 'Simposio sobre La enfermedad de Crohn en Galicia' by Fiol M, Ochoa R, Perez P, Albrades, G, Lesquereux P, Villaneuva P. *Rev Esp Enferm Apar Dig* 1977; **50**: 469-82.
- 30 Paredes JG, Garcia JMP. Crohn's disease in the central area of Spain. In: Peña AS, Weterman IT, Booth CC, Strober W, eds. *Developments in gastroenterology. 1. Recent advances in Crohn's disease*. The Hague: Martinus Nijhoff, 1981: 168-73.
- 31 Bitter J, Zuvacova J. Crohnova choroba v severoceskem kraji. *Cesk Gastroenterol Vyz* 1981; **35**: 137-44.
- 32 Novis BH, Marks IN, Bank S, Louw JH. Incidence of Crohn's disease at Groote Schuur Hospital during 1970-1974. *S Afr Med J* 1975; **49**: 693-7.
- 33 Wright JP, Marks IN, Jameson C, Garisch JAM, Burns DG, Kottler BR. The Cape Town experience of Crohn's disease. In: Lee ECG, ed. *Crohn's workshop. A global assessment of Crohn's disease*. London: H M & M Heyden, 1981: 95-100.
- 34 Miény CJ, Laage NJ, Simson IW. Crohn's disease in Pretoria. In: Lee ECG, ed. *Crohn's workshop. A global assessment of Crohn's disease*. London: H M & M Heyden, 1981: 101-6.
- 35 Couchman KG, Wigley RD. The distribution of the systemic connective tissue diseases; ulcerative colitis and Crohn's disease in New Zealand: an analysis of hospital admission statistics. *N Z Med J* 1971; **74**: 231-3.
- 36 Tasman-Jones C, Eason R, Lee SP. Inflammatory bowel disease - ethnic variations in Auckland, New Zealand. *Scand J Gastroenterol* 1982; **17**: 350.
- 37 Rozen P, Zonis J, Yekutiél P, Gilat T. Crohn's disease in the Jewish population of Tel-Aviv-Yafo. *Gastroenterology* 1979; **76**: 25-30.
- 38 Krawiec J, Odes HS, Lasry Y, Weitzman S. *Crohn's disease in Beer-Sheba, Israel: demographic and clinical aspects*. [Abstracts.] *International Symposium on Inflammatory Bowel Diseases*. Jerusalem: Hebrew University and Israeli Gastroenterological Society, 1981: 37.
- 39 Odes HS, Krawiec J, Weitzman S. Prevalence of Crohn's disease in Israel. *N Engl J Med* 1982; **306**: 750-1.
- 40 Newcombe RG, Mayberry JF, Rhodes J. An international study of mortality from inflammatory bowel disease. *Digestion* 1983; **24**: 73-8.
- 41 Myren J, Bouchier IAD, Watkinson G, De Dombal FT. Inflammatory bowel disease, an OMGE Survey. In Studies co-ordinated by the Research Committee of the Organisation Mondiale de Gastroenterologie. *Scand J Gastroenterol* 1979; **14**: 1-29.
- 42 Segal I, Oufimov L, Hamilton DG, Mannella A. The Baragwanath experience of Crohn's disease and intestinal tuberculosis in the Black population. Lee ECG, ed. *Crohn's workshop. A global assessment of Crohn's disease*. London: H M & M Heyden, 1981: 107-15.
- 43 Gupta RS, Chatterjee AK, Roy R, Ghosh BN. A review of the results of treatment of 44

- cases of Crohn's disease. *Indian J Surg* 1962; **24**: 797-805.
- 44 Castillo HC. Enteritis regional (enfermedad de Crohn). *Arch Soc Ciruj Hosp Santiago de Chile* 1959; **11**: 751-61.
 - 45 Quintana C, Diaz F, Croxatto H, Montero E. Crohn's disease in a Chilean University Hospital. *Gastroenterology* 1978; **74**: 1141.
 - 46 O'Donoghue DP, Clark ML. Inflammatory bowel disease in West Indians. *Br Med J* 1976; **2**: 796.
 - 47 Burke GJ, Zafar SA. Problems in distinguishing tuberculosis of bowel from Crohn's disease in Asians. *Br Med J* 1975; **4**: 395-7.
 - 48 Mayberry JF, Rhodes J, Newcombe RG. Crohn's disease in Wales, 1967-76; an epidemiological survey based on hospital admissions. *Postgrad Med J* 1980; **56**: 336-41.
 - 49 Fielding JF. Dalziel's (Crohn's) disease. An historical review. *History Med* 1972; **4**: 20-3.
 - 50 Kyle J. *Crohn's disease*. London: Heinemann, 1972.
 - 51 Mayberry JF, Rhodes J, Newcombe RG. Familial prevalence of inflammatory bowel disease in relatives of patients with Crohn's disease. *Br Med J* 1980; **1**: 84.
 - 52 Harries AD, Baird A, Rhodes J, Mayberry JF. Has the rising incidence of Crohn's disease reached a plateau? *Br Med J* 1982; **284**: 235.
 - 53 Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut* 1960; **1**: 87-105.
 - 54 Mayberry JF, Newcombe RG, Rhodes J. Mortality in Crohn's disease. *Q J Med* 1980; **49**: 63-8.
 - 55 Hellers G. Some epidemiological aspects of Crohn's disease in Stockholm County, 1955-1979. In: Peña AS, Weterman IT, Booth CC, Strober W, eds. *Developments in gastroenterology. 1. Recent advances in Crohn's disease*. The Hague: Martinus Nijhoff, 1981: 158-62.
 - 56 McCann M, Liskin LS, Piotrow PT, Rinehart W, Fox G. Breast-feeding, fertility and family planning. *Population Rep* 1981; **9**: 525-75.
 - 57 Miller DS, Keighley AC, Smith PG, Hughes AD, Langman MJS. Crohn's disease in Nottingham: a search for time-space clustering. *Gut* 1975; **16**: 454-7.
 - 58 Miller DS, Keighley AC, Smith PG, Hughes AO, Langman MJS. A case control method for seeking evidence of contagion in Crohn's disease. *Gastroenterology* 1976; **71**: 385-7.
 - 59 Goodman MJ, Strickland RG, Kirsner JB. Inflammatory bowel disease and lymphocytotoxic antibody in members of the American Gastroenterological Association. *Gastroenterology* 1979; **76**: 1140.
 - 60 Mayberry J, Rhodes J, Matthews N, Wensinck F. Serum antibodies to anaerobic coccoid rods in patients with Crohn's disease or ulcerative colitis, and in medical and nursing staff. *Br Med J* 1981; **282**: 108.
 - 61 Mayberry JF, Newcombe RG. Are nurses at an increased risk of developing inflammatory bowel disease? *Digestion* 1981; **22**: 150-4.
 - 62 Weterman IT, Peña AS. Family occurrences in Dutch patients with Crohn's disease. *Scand J Gastroenterol* 1982; **17**: 354.
 - 63 McConnell RB. Genetics of Crohn's disease. *Clin Gastroenterol* 1972; **1**: 321-34.
 - 64 McBride JA, King MJ, Baikie AG, Crean GP, Sircus W. Ankylosing spondylitis and chronic inflammatory diseases of the intestines. *Br Med J* 1963; **2**: 483-6.
 - 65 Hammer B, Ashurst P, Naish J. Diseases associated with ulcerative colitis and Crohn's disease. *Gut* 1968; **9**: 17-21.
 - 66 Pugh SM, Rhodes J, Mayberry JF, Roberts DL, Heatley RV, Newcombe RG. Atopic disease in ulcerative colitis and Crohn's disease. *Clin Allergy* 1979; **9**: 221-3.
 - 67 Klein GL, Ament ME, Sparkes RS. Monozygotic twins with Crohn's disease: a case report. *Gastroenterology* 1980; **79**: 931-3.
 - 68 Mayberry JF, Dew MJ, Morris JS. Monozygotic twins with ulcerative colitis. *Postgrad Med J* 1982; **58**: 112-6.
 - 69 Burnham WR, Gelsthorpe K, Langman MJS. HLA-D related antigens in inflammatory bowel disease. In: Peña AS, Weterman IT, Booth CC, Strober W, eds. *Developments in gastroenterology. 1. Recent advances in Crohn's disease*. The Hague: Martinus Nijhoff, 1981: 192-6.
 - 70 Biemond I, Weterman IT, Van Rood JJ, Klasen EC, Meera Khan P, Peña S. Search for genetic markers associated with Crohn's disease in the Netherlands. In: Peña AS, Weterman IT, Booth CC, Strober W, eds. *Developments in gastroenterology. 1. Recent advances in Crohn's disease*. The Hague: Martinus Nijhoff, 1981: 197-203.
 - 71 Acheson ED. The distribution of ulcerative colitis and regional enteritis in United States Veterans with particular reference to the Jewish religion. *Gut* 1960; **1**: 291-3.

- 72 Faustino-Porto JA. Crohn's disease in Brazil: a newcomer in a parasitic field. In: Lee ECG, ed. *Crohn's workshop. A global assessment of Crohn's disease*. London: H M & M Heyden, 1981: 127-35.
- 73 Hellers G. Crohn's disease in Stockholm County. In: Lee ECG, ed. *Crohn's workshop. A global assessment of Crohn's disease*. London: H M & M Heyden, 1981: 85-91.
- 74 Keighley AC, Miller DS, Hughes AO, Langman MJS. The demographic and social characteristics of patients with Crohn's disease in the Nottingham area. *Scand J Gastroenterol* 1976; **11**: 293-6.
- 75 Chess S, Chess D, Olander G, Benner W, Cole WH. Production of chronic enteritis and other systemic lesions by ingestion of finely divided foreign material. *Surgery* 1950; **27**: 221-34.
- 76 Wright R, Truelove SC. A controlled therapeutic trial of various diets in ulcerative colitis. *Br Med J* 1965; **2**: 138-41.
- 77 Warthin TA. Some epidemiological observations on the aetiology of regional enteritis. *Trans Am Clin Climatol Assoc* 1969; **80**: 116-24.
- 78 James AH. Breakfast and Crohn's disease. *Br Med J* 1977; **1**: 943-5.
- 79 Rawcliffe PM, Truelove SC. Breakfast and Crohn's disease - I. *Br Med J* 1978; **2**: 539-40.
- 80 Archer LNJ, Harvey RF. Breakfast and Crohn's disease - II. *Br Med J* 1978; **2**: 540.
- 81 Mayberry JF, Rhodes J, Newcombe RG. Breakfast and dietary aspects of Crohn's disease. *Br Med J* 1978; **2**: 1401.
- 81 Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. *Klin Wochenschr* 1976; **54**: 367-71.
- 83 Miller B, Fervers F, Rohbeck R, Strohmeyer G. Zuckerkonsum bei patienten mit morbus Crohn. *Verh Dtsch Ges Inn Med* 1976; **82**: 922-4.
- 84 Mayberry JF, Rhodes J, Newcombe RG. Increased sugar consumption in Crohn's disease. *Digestion* 1980; **20**: 323-6.
- 85 Mayberry JF, Rhodes J, Allen R *et al*. Diet in Crohn's disease: two studies of current and previous habits in newly diagnosed patients. *Dig Dis Sci* 1981; **26**: 444-8.
- 86 Thornton JR, Emmett PM, Heaton KW. Diet and Crohn's disease: characteristics of the pre-illness habit. *Br Med J* 1979; **2**: 762-4.
- 87 Silkoff K, Hallak A, Yegena L *et al*. Consumption of refined carbohydrate by patients with Crohn's disease in Tel-Aviv-Yafo. *Postgrad Med J* 1980; **56**: 842-6.
- 88 Jarnerot G, Jarnmark I, Nilsson K. Sugar consumption in Crohn's disease, ulcerative colitis and irritable bowel syndrome. *Scand J Gastroenterol* 1982; **17**: 352.
- 89 Thornton JR, Emmett PM, Heaton KW. Diet and ulcerative colitis. *Br Med J* 1980; **1**: 293-4.
- 90 Kasper H, Sommer H. Dietary fiber and nutrient intake in Crohn's disease. *Am J Clin Nutr* 1979; **32**: 1898-1901.
- 91 Penny WJ, Mayberry JF, Aggett PJ, Gilbert JO, Newcombe RG, Rhodes J. Relationship between trace elements, sugar consumption and taste in Crohn's disease. *Gut* 1983; **24**: 288-92.
- 92 Tiomny E, Horwitz C, Graff E, Rozen P, Gilat T. Serum zinc and taste acuity in Tel-Aviv patients with inflammatory bowel disease. *Am J Gastroenterol* 1982; **77**: 101-4.
- 93 Kasper H, Sommer H. Taste thresholds in patients with Crohn's disease. *J Hum Nutr* 1980; **34**: 455-6.
- 94 Heaton KW, Thornton JR, Emmett PM. Treatment of Crohn's disease with an unrefined carbohydrate, fibre rich diet. *Br Med J* 1979; **2**: 764-6.
- 95 Brandes JW, Lorenz-Meyer H. Zuckergefreie Diat: Eine neue Perspektive zur Behandlung des Morbus Crohn? Eine randomisierte, Kontrollierte Studie. *Z Gastroenterol* 1981; **19**: 1-12.
- 96 Whorwell PJ, Holdstock G, Whorwell GM, Wright R. Bottle feeding, early gastroenteritis and inflammatory bowel disease. *Br Med J* 1979; **1**: 382.
- 97 Storgaard L, Bischoff N, Henriksen FW, Fischerman K, Jarnum S. Survival rate in Crohn's disease and ulcerative colitis. *Scand J Gastroenterol* 1979; **14**: 225-30.
- 98 Mayberry JF, Dew MJ, Morris JS, Powell DB. An audit of Crohn's disease in a defined population. *J R Coll Physicians Lond* 1983; **17**: 196-8.
- 99 Malchow H, Riker U, Dietz K. Lebenserwartung bei Morbus Crohn. *Lebensversicherungsmedizin* 1981; **33**: 27-30.
- 100 Weterman IT. *Course and long-term prognosis of Crohn's disease*. Leiden: MD Thesis.
- 101 Truelove SC, Peña AS. Course and prognosis of Crohn's disease. *Gut* 1976; **17**: 192-201.
- 102 Prior P, Gyde S, Cooke WT, Waterhouse JAH, Allan RN. Mortality in Crohn's disease.

- Gastroenterology* 1981; **80**: 307–12.
- 103 Prior P, Fielding JF, Waterhouse JA, Cooke WT. Mortality in Crohn's disease. *Lancet* 1970; **1**: 1135–7.
- 104 Weedon DD, Shorter RG, Ilstrup DM, Huizenga KA, Taylor WF. Crohn's disease and cancer. *N Engl J Med* 1973; **289**: 1099–103.