

Diseases associated with ulcerative colitis and Crohn's disease

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The causes of both ulcerative colitis and Crohn's disease remain unknown, but a number of clues point towards a relationship between these two diseases and a possible genetic background for both. The studies of Evans and Acheson (1965) and of Wigley and Maclaurin (1962), preceded by those of Houghton and Naish (1958), indicate that the prevalence of ulcerative colitis in people of predominantly British stock is approximately 1 per 1,000 population, whereas the prevalence of Crohn's disease is approximately 1 per 8,000. The evidence from the North Island of New Zealand (Wigley and Maclaurin, 1962) is that those of Maori stock who are living the same urban or rural life as those of European stock have a very much decreased risk of contracting ulcerative colitis. In fact, the disease in Maoris is excessively rare. It is almost certain that the disease is equally rare amongst the Chinese and Japanese, but in countries where the chronic dysenteries are the commonest inflammatory bowel disorder it will probably be some years before reliable epidemiological studies can be made of the prevalence of such diseases as colitis and Crohn's disease.

In the meantime the epidemiological evidence from Britain (Evans and Acheson, 1965) and from the U.S.A. points to a definite genetic susceptibility to both ulcerative colitis and Crohn's disease (Kirsner and Spencer, 1963; Sherlock, Bell, Steinberg, and Almy, 1963). In various studies of populations culled through hospital records, the most informative of which is that of Evans and Acheson (1965) in which the hospital statistics were related to the population at risk (Oxfordshire, England), it has been shown that some 5% of colitics and 8% of sufferers from Crohn's disease have a first-degree relative suffering from the same disease. Furthermore, a significant number of colitics have near relatives suffering from Crohn's disease and vice versa. The increased liability of the Jewish population to contract colitis and Crohn's disease has been noted in many publications (Acheson, 1960; Birnbaum, Groen, and Kallner, 1960).

There are other interesting links between ulcerative colitis and Crohn's disease on the one hand and ankylosing spondylitis (Acheson, 1960; McBride, King, Baikie, Crean, and Sircus, 1963) and autoimmune hepatitis (Holdsworth, Hall, Dawson, and Sherlock, 1965) on the other. Since either disease may precede the development of the other, and since the prevalence of the linked disease is often higher than can be accounted for by chance in the first degree relatives of *propositi*, it is reasonable to assume that there may be a weak genetic predisposition to the development of one or more of these diseases with environmental stress determining the onset and expression.

In an attempt to find out more about the question of familial susceptibility we have ascertained the prevalence of certain diseases, some of which are thought to be of an allergic or autoclastic nature, in a group of patients suffering from ulcerative colitis, a group of patients suffering from Crohn's disease, and in their first degree relatives.

METHODS AND MATERIAL

The case records of 242 patients suffering from ulcerative colitis and 45 patients suffering from Crohn's disease were first scrutinized. All these patients had been under the care of one of us (J.M.N.) at Frenchay Hospital or Southmead Hospital, Bristol, during the years 1952 to 1965 inclusive. All of the patients with Crohn's disease were interviewed and the criteria of diagnosis critically reviewed. Diagnosis was based on histological data in all but a few of these cases and in these few the radiological and clinical findings were unequivocally those of Crohn's disease. Cases of Crohn's disease of the colon were included. Of the 242 patients with ulcerative colitis, 48 were rejected either because they were dead, because the criteria for diagnosis (radiological, sigmoidoscopic, histological, and haematological) were incomplete, or because they could not be traced. This left 198 patients available for analysis. Of these 97 were interviewed and 101 replied to a postal questionnaire. The questions put to these patients were as follows: any personal history of constitutional eczema (not dermatitis), psoriasis, hay fever, asthma, polyarthritis, any thyroid disease? Any

history of these diseases in the first-degree relatives of the patients (father, mother, siblings, and children)?

Polyarthritis was only recorded when there was a definite history of multiple joint pains and/or swellings causing a disability of more than three months' duration. It was not possible to define the type of polyarthritis from this kind of enquiry, but in many instances rheumatoid arthritis was stated to be the diagnosis. Eczema was recorded when there was a history of recurrent skin lesions in the typical sites not apparently caused by exposure to specific allergens.

A control group numbering 319 taken at random from the population in hospital attending for treatment of surgical conditions such as appendicitis, peptic ulcer, uterine prolapse, and other gynaecological abnormalities was interviewed and questioned in a similar way. Originally a control group of 197 patients matched for age and sex with the colitis group was mustered, but because the numbers of relatives with index diseases appeared to be rather small for purposes of analysis, the group was enlarged by the addition of 122 control patients with the correct age and sex distribution. Not surprisingly the colitic patients who were questioned by post recorded a

lower prevalence of the diseases under investigation than did those who were interviewed. Consequently it was decided to use information from the interviewed colitis group (97 patients) and compare this with that from the control group who had been interviewed in exactly the same way. The 101 colitic patients not interviewed did not differ as regards severity or extent of disease from those who were interviewed, and selection was based on availability for interview, geographical considerations, etc. Interviews were conducted by B.H. for colitic and most of the control group, and by P.A. for the Crohn's disease group and some of the control group.

RESULTS

Table I gives data on the prevalence of the index diseases in the colitic, Crohn, and control populations, and Table II similar data for the first-degree relatives of the propositi.

The differences between the prevalence shown have been tested by the χ^2 procedure with Yeates' modification, and the probability of the observed

TABLE I
PREVALENCE OF INDEX DISEASES IN SUFFERERS FROM ULCERATIVE COLITIS AND CROHN'S DISEASE COMPARED WITH A CONTROL GROUP

| Group | Numbers | Eczema | Psoriasis | Hay Fever | Asthma | Polyarthritis | Thyroid Diseases |
|-----------------------------|---------|-----------------------|-----------|-----------|--------|---------------|------------------|
| Crohn's disease | 45 | 15 (33%) ¹ | 2 | 8 (18%) | 2 (4%) | 10 (22%) | 0 |
| Colitis | 198 | 26 | 3 | 16 | 7 | 22 | 13 |
| Colitics (interviewed only) | 97 | 22 (23%) | 0 | 12 (12%) | 5 (5%) | 12 (12%) | 8 (8%) |
| Controls | 319 | 21 (7%) | 10 | 18 (6%) | 9 (3%) | 6 (2%) | 12 (4%) |

¹Percentages rounded off.

TABLE II
PREVALENCE OF INDEX DISEASES IN FIRST-DEGREE RELATIVES OF SUFFERERS FROM ULCERATIVE COLITIS AND CROHN'S DISEASE COMPARED WITH A CONTROL GROUP

| Group | Number of Propositi | No. of Relatives at Risk | Eczema | Psoriasis | Hay Fever | Asthma | Polyarthritis | Thyroid Diseases | Ulcerative Colitis | Crohn's Disease |
|-----------------------------|---------------------|--------------------------|-----------|-----------|-----------|-----------|---------------|------------------|--------------------|-----------------|
| Crohn's disease | 45 | 256 | 15 (5.9%) | 6 (2.3%) | 9 (3.5%) | 10 (3.9%) | 10 (3.9%) | 4 (1.5%) | 2 (0.8%) | 2 (0.8%) |
| Colitis | 198 | 1,376 | 32 | 9 (0.7%) | 31 | 39 | 27 | 16 | 8 (0.6%) | 2 (0.2%) |
| Colitics (interviewed only) | 97 | 623 | 18 (2.9%) | | 16 (2.6%) | 20 (3.2%) | 14 (2.2%) | 11 (1.8%) | 7 | 2 |
| Controls | 319 | 2,426 | 28 (1.2%) | 8 (0.3%) | 32 (1.3%) | 53 (2.2%) | 26 (1.1%) | 17 (0.7%) | 0 | 0 |

TABLE III
SIGNIFICANCE OF OBSERVED DIFFERENCES IN PREVALENCE OF ECZEMA, POLYARTHRITIS, AND HAY FEVER BETWEEN THE COLITIC AND CROHN'S DISEASE POPULATIONS AND THE CONTROL GROUP

| | Control Group | Colitics (Interviewed) | Value of P | Crohn's Disease | Value of P |
|---|---------------|------------------------|------------|-----------------|------------|
| Numbers | 319 | 97 | | 45 | |
| Percentage prevalence of eczema in propositi | 7 | 23 | <0.01 | 33 | <0.01 |
| Percentage prevalence of eczema in relatives | 1 | 3 | <0.01 | 6 | <0.01 |
| Percentage prevalence of polyarthritis in propositi | 2 | 12 | <0.01 | 22 | <0.01 |
| Percentage prevalence of polyarthritis in relatives | 1 | 2 | >0.02 | 4 | <0.01 |
| | | | <0.05 | | |
| Percentage prevalence of hay fever in propositi | 6 | 12 | >0.02 | 18 | <0.01 |
| | | | <0.05 | | |
| Percentage prevalence of hay fever in relatives | 1 | 3 | >0.02 | 4 | <0.01 |
| | | | <0.05 | | |

differences being significant is shown in Table III.

ECZEMA The observed prevalence in those with colitis (interviewed alone or whole group) is significantly higher than in the controls. The same applies to the prevalence of eczema in the first-degree relatives of patients with colitis and with Crohn's disease.

POLYARTHRITIS The high incidence of polyarthritis in *propositi* with colitis and Crohn's disease accords well with published data on this subject, but the reporting of a greater than expected prevalence of polyarthritis in the first-degree relatives of those with Crohn's disease and of those with ulcerative colitis is unlikely to be due to chance (P 0.02 (0.05).

HAY FEVER The other finding of significance is the higher than expected prevalence of hay fever in patients with Crohn's disease and colitis *propositi* and their first-degree relatives. Asthma is found to be commoner in the patients with Crohn's disease and their relatives, and slightly commoner in the patients with colitis and their relatives than in controls and their relatives, but the differences are not statistically significant.

THYROID DISEASES There was a slight excess of thyroid disease amongst the relatives of those with colitis and Crohn's disease, but as the significance of this finding was doubtful, the types of thyroid disease recorded have not been analysed. It was, in any case, difficult to ascertain for what disease a patient or his relatives had had a partial thyroidectomy.

PSORIASIS The numbers in the control and patient groups were too small to have any significance and no trend was apparent. In the families, the high prevalence of psoriasis amongst the Crohn's disease relatives, 2.3% of 256 compared with 0.3% of 2,426 relatives at risk, was noticeable, and the difference is significant ($P < 0.001$).

OTHER DISEASES Cases of erythema nodosum and of iritis were noted both in patients with Crohn's disease and with ulcerative colitis. Four patients of the 242 with ulcerative colitis had liver disease. One had portal triaditis (Stauffer, Sauer, Dearing, and Baggenstoss, 1965) as a complication of colitis and survives. Three more, part of the 44 colitic patients not included in the main survey, died. One had lupoid hepatitis for two years before developing colitis, and finally died of cirrhosis. The other two had portal cirrhosis, one dying as a result of the colitis.

ULCERATIVE COLITIS AND CROHN'S DISEASE We confirm that both diseases occur with significant frequency in the families of sufferers. In the 1,376 relatives of the 198 colitics there were eight confirmed cases of ulcerative colitis and two of Crohn's disease. Our records show that there were additional cases of colitis and Crohn's disease in the families of those colitics who had died or who could not be contacted for the full survey (44 cases), but since the family data are not complete they are not included. In the 198 colitics completely surveyed, 3.5% had a first-degree relative with the same disease: if uncles, aunts, and grandparents had been included the figure would have been higher.

DISCUSSION

The investigation showed that in this particular series of patients with ulcerative colitis all of British stock there was a high incidence of polyarthritis, of eczema, and of the seasonal allergic rhinitis usually known as hay fever. In patients with Crohn's disease the association with these allergic diseases and with polyarthritis was even stronger.

The tendency of colitic patients to develop polyarthritis is well known, and recent studies by Wright and Watkinson (1965) and Wright, Lumsden, Luntz, Sevel, and Truelove (1965) tend to show that this polyarthritis follows a pattern, which is in most respects, different from that of either rheumatoid arthritis or of an ankylosing spondylitis. However, it is also established that cases of 'true' rheumatoid arthritis and spondylitis coexisting with ulcerative colitis are not uncommon.

The finding in this investigation that the prevalence of polyarthritic diseases amongst the close relatives of patients with ulcerative colitis, and to an even larger extent amongst the relatives of those with Crohn's disease, is significantly greater than that in a control group is one which has not previously been reported, although Binder, Weeke, Olsen, Anthonisen, and Riis (1966) in a comparable study of ulcerative colitis in Denmark, found 11 cases of rheumatoid arthritis out of 884 relatives at risk (1.2%) compared with four out of 939 (0.4%) in a control group. The difference was significant to a level of less than 0.1 and more than 0.05. The actual number of polyarthritic relatives of their colitic patients (11/884 = 1.2%) is less than the numbers in our interviewed colitic relatives group (14/623 = 2.2%), and the prevalence they found in their control group (0.4%) is considerably less than that in our control group (1.1%). This suggests either that polyarthritis is commoner in England than in Denmark or that the criteria we adopted for the presumptive diagnosis of polyarthritis in a

relative was wider than that adopted by Binder *et al.* It is our experience that patients with mild rheumatoid arthritis are often not told the diagnosis, which to a lay mind is an alarming one, and for this reason we did not only include as polyarthritic those relatives in whom a positive diagnosis of rheumatoid arthritis had been made. Any relative who had suffered for more than three months from pain and swelling in more than one joint was classed as polyarthritic. As the same criteria were applied to the control group as to the test groups the observed differences must be significant. Thayer and Spiro (1963) found 10% of 98 relatives of 36 patients with ulcerative colitis had a rheumatoid factor (positive Rose Waaler test) in their serum. This compares with 0.74% positive tests in 5,086 normal subjects found by Edwards, Murphy, Osborne, Calabro, and Nosenzo (1961).

With regard to eczema, the prevalences we recorded in the relatives of Crohn's (5.8%) and colitic patients (2.9%) were very much higher than Binder *et al.* recorded for atopic dermatitis (0.7%) which is presumably synonymous. But both we and Binder *et al.* found a prevalence of 1.2% in our control groups, which suggests that this disease is as common in Denmark as it is in England. It is impossible to explain the difference between our experience and that of Binder *et al.* with regard to the relatives of those with ulcerative colitis. Their cases were not interviewed but interrogated by postal questionnaire, and in this connexion it is interesting to look at our figures for the prevalence of eczema amongst the relatives of colitic patients who were only interrogated by postal questionnaire. One hundred and one patients were questioned in this way, and of 753 relatives at risk 14 cases of eczema were recorded (1.9%). That this should be a lower figure than in those interviewed is as would be expected, but the prevalence is still a good deal higher than in the control group.

We have confirmed Binder's finding that there is a higher than expected prevalence of hay fever (allergic rhinitis) in the relatives of colitic patients, but in this instance their prevalence figures) 3.6% for colitic relatives and 1.7% for control relatives, are higher than ours, namely, 2.6% for colitic relatives and 1.3% for control relatives. This is probably due to our criteria of selection being narrower; we only recorded hay fever if the bouts of allergic rhinitis occurred in the early summer months.

Binder *et al.* also found a higher than expected prevalence of urticaria in the relatives of colitics. We purposely did not include urticaria in our survey as we thought that there would be too many difficulties in arriving at a correct assessment of the prevalence owing to the evanescent nature of the condition and the wide variety of stimuli which can provoke it.

However, it is certainly possible that there could be some overlap between a 'patient diagnosis' of urticaria and that of eczema in some of their relatives.

Apart from this one major dissonance on the subject of eczema (atopic dermatitis) and differences due to diagnostic criteria, our main conclusions accord well with those of Binder *et al.* We would not, however, wish to draw any inference from our findings that ulcerative colitis is genetically linked only with diseases of 'immediate allergic' type. The proven link, personal and familial, between ulcerative colitis, Crohn's disease, ankylosing spondylitis, and lupoid hepatitis argues against such an hypothesis.

With regard to the prevalence of eczema in sufferers from ulcerative colitis and Crohn's disease, we have found this to be high, and in most cases it has preceded the onset of the intestinal disease. In many patients the eczema is not widespread but confined to the flexures, behind the ears, on the shins, or around the perineum. In some patients the skin condition may flare up at the same time as a minor relapse of colitis; in others the skin condition does not worsen during a relapse of colitis. Some patients give a history only of eczema in infancy.

We conclude that in the families of those with ulcerative colitis, there is an increased liability not only to ulcerative colitis itself, but also to Crohn's disease, to polyarthritis (atypical or of rheumatoid pattern), to ankylosing spondylitis, to eczema, and to hay fever. In the families of those with Crohn's disease these family links are even more striking. It is not likely that these associations are due to a common environment, for many of the family members have split up and are living in different circumstances and different places. Nor is it likely that psychological factors are important. Only just over a third of the patients with ulcerative colitis, and less than a quarter of the patients with Crohn's disease, were thought to have 'odd' personalities, and these had no greater tendency to suffer from, or to have a relative suffering from, any of the associated disease than did those who were arbitrarily classed as 'normal' by one of us (J.N.).

The evidence in the present study, and the data on the prevalence of ulcerative colitis in the two racial groups on the North Island of New Zealand, suggests that there is a genetic predisposition to this disease. Crohn's disease, though less common generally, occurs more frequently in the relatives of those with the disease. The strong link between this disease and colitis, ankylosing spondylitis, polyarthritis, and eczema in certain families can best be explained on a genetic basis.

Although the search for trigger factors and the important intermediary mechanisms between the

constitutional predisposition and the eventual development of pathological changes in the target organs is undoubtedly the most difficult and the most important task ahead, it is important to appreciate that both Crohn's disease and ulcerative colitis have some genetic background.

SUMMARY

Using a series of patients suffering from ulcerative colitis and from Crohn's disease, an enquiry was made as to the prevalence of polyarthritis, eczema, psoriasis, asthma, hay fever, and thyroid disease both in the propoiti and their first-degree relatives, a control group of hospital patients being similarly questioned. Polyarthritis, eczema, and hay fever were particularly common in those suffering from Crohn's disease and their first degree relatives, and a similar, though less marked association with these diseases, was noted in those with ulcerative colitis.

This evidence, taken together with the already known associations between colitis, Crohn's disease, and ankylosing spondylitis in family groups, supports the concept of a genetic predisposition to these diseases.

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