Progress report

Familial inflammatory bowel disease—heredity or environment?

Soon after ulcerative colitis was first recognized as a disease entity distinct from epidemic dysentery, occasional instances of familial cases were reported but, early in the twentieth century, these were regarded as being merely coincidental. Some years later, the man in whom Crohn made his initial observations of ileitis was found to have a sister similarly affected and Crohn suggested the name ‘familial ileitis’ for the condition. It has become generally accepted that both of these inflammatory bowel diseases (IBD) are sometimes familial.

When this subject was reviewed in the first volume of *Gut* the significance of familial cases was uncertain. Despite advances in the intervening years the cause, or causes, of IBD remains unknown, and the significance of familial involvement is still conjectural.

Epidemiology

Most of the population surveys of the incidence of IBD have been carried out in Western Europe and North America. The differences that have been found are not striking and may represent variations in ascertainment of cases and diagnostic standards rather than differing racial propensities or the differing local environment. Little is known of the incidence of IBD in other parts of the world, especially in those parts where ulcerative colitis and Crohn’s disease may be overshadowed by endemic dysenteries and intestinal tuberculosis. There have, for example, been few reports of IBD in Asians or Africans, a fact which has led to the suggestion that the low fibre content of the modern Western diet might be an important environmental factor in IBD.

In seeking for genetic influence, comparisons of ethnic subgroups in a locality are probably more valid than is the comparison of different races in different parts of the world. In New Zealand, ulcerative colitis is 16 times more common in European immigrants than in the Maoris. In a Baltimore study the incidence of ulcerative colitis was 0.45/10^5 for the black population, 3.5/10^5 for the white population, and 10/10^5 for the Jews. In Israel, IBD is more common among Ashkenazim Jews than in the Oriental Jews. However, the overall incidence of ulcerative colitis in Tel Aviv is estimated to be 3.6/10^5 population, which is considerably lower than the estimates of 6.5/10^5 in Oxford, 7.3/10^5 in Sweden, and 7.2/10^5 in Rochester, Minnesota.

Familial incidence of IBD

Assuming the prevalence figures for Crohn’s disease to be 20 cases per 10^5 population and for ulcerative colitis 100 cases per 10^5 population, the prob-
ability of encountering two affected siblings has been estimated as 0.0000004 and 0.0000001 respectively. The validity of these calculated risks has been questioned and it has been suggested that the expected familial incidence of ulcerative colitis is around 1%, whereas the observed figure is 5% to 10%. In fact, there have been numerous reports, fully reviewed by Kirsner, which have established that familial IBD is much more common than would be expected on the basis of random chance. Many investigations have also shown that both ulcerative colitis and Crohn's disease occur in the same families.

Table 1 summarizes the finding in a group of well-documented patients with IBD attending the Colon Clinic of the Liverpool Royal Infirmary. There were 19 cases with a positive family history of one or more affected relatives, out of a total of 142 patients investigated. There is considerable difficulty in defining a suitable control series for this type of investigation. In this relatively small survey, 200 blood donors were questioned, of whom one had a history of ulcerative colitis, and none gave any family history suggesting ulcerative colitis, Crohn's disease, or ankylosing spondylitis. In a series of 646 IBD patients in Chicago there were 78 instances of affected first-degree relatives; in 45 both patient and relative had ulcerative colitis, in 14 both had Crohn's disease, and in 19 relationships one had ulcerative colitis and the other had Crohn's. This large Chicago series included a high proportion of Jewish patients and the overall extent of familial involvement is lower in other published series. This variation may reflect patient selection, differing diagnostic criteria, or the authors' particular interests. Generally, the reported familial incidence is lower in retrospective studies of records than in planned family studies and in series in which the first author is a surgeon. The most common pattern of familial involvement is two or more affected siblings. The next most frequent relationship is parent and child familial cases, and affected second or third degree relatives are seen least often (Table 2). This dis-

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis (UC)</th>
<th>Crohn's disease (CD)</th>
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<tr>
<td>Propositi</td>
<td>103</td>
<td>39</td>
</tr>
<tr>
<td>First degree relatives with UC</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>First degree relatives with CD</td>
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<tr>
<td>Second degree relatives with CD</td>
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Table 1 Relationships in familial IBD cases in a series of Liverpool patients

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn's disease</th>
<th>Mixed ulcerative colitis and Crohn's disease</th>
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<tbody>
<tr>
<td>Parent-children</td>
<td>40</td>
<td>16</td>
<td>5</td>
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<tr>
<td>Siblings</td>
<td>48</td>
<td>24</td>
<td>6</td>
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<tr>
<td>Collateral relatives</td>
<td>13</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Monozygous twins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One affected</td>
<td>6</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Both affected</td>
<td>5</td>
<td>7</td>
<td>-</td>
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Table 2 Pattern of relationships in familial cases of IBD (Family data compiled by Almy and Sherlock and twin reports from Kirsner)
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The distribution of familial involvement—namely, the greatest risk being in those who share the most genes with the propositus—is what would be expected in a disease partly determined by polygenic inheritance.

It is notable that in the literature there has been only a very small number of affected spouses. These include a husband and wife with ulcerative colitis\textsuperscript{18}, a husband and wife with Crohn’s disease\textsuperscript{19}, and a wife and son with ulcerative colitis where the husband later developed Crohn’s disease\textsuperscript{8}. There is also a lack of reports of affected parents and adopted children. The paucity of reports of affected non-related members of families and households may well represent comparative under-reporting and poor ascertainment but, even taking this into account, the lack of such reports argues strongly that familial cases indicate genetic influence. A corollary to this argument is that geographical clustering of cases in unrelated individuals suggests the presence of important environmental influences. It is likely that such instances are rarely noted or thought to be other than a matter of chance. In our recent series (Table 1), there were three examples of environmental coincidence: (1) the mother of a patient with Crohn’s disease died of fulminating ulcerative colitis, and their next-door neighbour had Crohn’s disease; (2) a patient newly diagnosed as having ulcerative colitis had two contacts already attending the Colon Clinic, one was a colleague at work and the other was a young nephew related by marriage; (3) a young women with ulcerative colitis, whose uncle had Crohn’s disease, lived for several years in a house 100 metres away from a young man who later had a colectomy for ulcerative colitis.

Genetic associations

Clearly, the discovery of some mark of individual susceptibility would bring about an enormous advance in understanding familial IBD. True genetic markers for inherited human diseases are very rare. Of less genetic significance are the statistical associations such as that between blood group O and duodenal ulceration. While these associations are generally not of importance in any individual case, taken overall in a group of affected patients they indicate that heritable factors are contributing to the disease state. There have been many attempts to find blood group or similar associations with IBD but none has been substantiated. The distribution of the ABO blood groups does not differ from expectation in ulcerative colitis\textsuperscript{20,21,22} or Crohn’s disease\textsuperscript{23}. The ABO blood groups are examples of genetic polymorphism—that is, the existence in a population of differing inherited forms of a character. The most complex human genetic polymorphism is the HLA system of histocompatibility or transplantation antigens. The theoretical importance of the HLA system lies in the analogy with other mammalian histocompatibility systems in which, particularly in rodents, there are closely associated or linked genes which control specific immune responses\textsuperscript{24,25}. Reports of biased distribution of HLA antigens in some series of IBD patients\textsuperscript{26,27} have not been confirmed in other series\textsuperscript{28,29}. Certainly, there is no strong association of either ulcerative colitis or Crohn’s disease with any particular HLA antigen comparable, for example, with the association of HLA-B8 with coeliac disease\textsuperscript{30}. If there is a real, but weak, association with IBD, large numbers of patients will be necessary to establish the statistical validity of the association\textsuperscript{31,32}.

The most intriguing aspect of the familial nature of IBD is the association
with ankylosing spondylitis, a disorder which is markedly familial \(^{33}\) and which in turn has a strong association with HLA-B27 histocompatibility antigen in over 90% of cases \(^{34,35}\). Ankylosing spondylitis is of unexpectedly high frequency in both ulcerative colitis and Crohn’s disease \(^{36,37,38,39,40}\). The magnitude of the association varies with the diagnostic criteria and epidemiological techniques used \(^{41}\). This was well shown when 47 patients with ankylosing spondylitis were subjected to sigmoidoscopy, rectal biopsy, and barium enema examinations. Eight had evidence of IBD of whom three had no gastrointestinal symptoms \(^{42}\).

Among those IBD patients who also have spondylitis it appears that about 80% of ulcerative colitics have the HLA-B27 antigen and a smaller proportion of those with Crohn’s disease have the antigen; however, the numbers in the published series are relatively small \(^{43,44,45}\). In our Liverpool series (Table 3) four of the five men with HLA-B27 already had ankylosing spondylitis, an incidence of 80%, whereas in the general population only 7% of the HLA-B27 positive men have ankylosing spondylitis \(^{46}\). These and comparable findings in seemingly disparate diseases such as psoriasis \(^{47}\) and Still’s disease \(^{48}\), also associated with ankylosing spondylitis, indicate that IBD greatly increases the risk of HLA-B27 positive subjects also having spondylitis. The reason for the remarkable sex difference is obscure. Approximately 10% of patients with typical uncomplicated ankylosing spondylitis do not have the HLA-B27 antigen, although some of these patients have relatives with ankylosing spondylitis, HLA-B27, or both \(^{47}\). This may suggest that genes for ankylosing spondylitis are separate from but closely linked to the second HLA locus. These genes may be the common denominator between ankylosing spondylitis and IBD but if so their gene product has yet to be identified.

Some histocompatibility determinants are detectable by mixed lymphocyte culture techniques and these lymphocyte or ‘LD’ determinants are sometimes associated with the better known serologically defined HLA antigens. One of these determinants ‘LD8a’ has been shown to be a common denominator in the clinically and family grouped conditions, Addison’s disease, Graves’ disease, and juvenile diabetes mellitus \(^{48}\). There might be a comparable mechanism underlying the association of ankylosing spondylitis, ulcerative colitis, and Crohn’s disease but it must be tenuous because the association of ankylosing spondylitis and HLA-B27 is not restricted to ‘LD27a’ positive subjects \(^{49}\).

There is an association of IBD with an increased frequency of eczema, allergic rhinitis \(^{50}\), hay fever, and asthma, both in patients and their families \(^{51}\). The mode of inheritance of these atopic illnesses is uncertain but in the present context it is of great interest that a specific allergy to ragweed pollen has been shown in one family study to segregate with a particular HLA haplotype \(^{52}\).

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>HLA-B27 present with:</th>
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<tbody>
<tr>
<td></td>
<td>Ankylosing spondylitis</td>
<td>Normal sacroiliac joints on x-ray</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>37</td>
<td>2 (both male)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>33</td>
<td>2 (both male)</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>4 (all male)</td>
</tr>
</tbody>
</table>

Table 3  Ankylosing spondylitis and HLA-B27 in seventy Liverpool patients with IBD

The frequency of HLA-B27 in this series, 9/70 is spuriously increased because of some selection bias for spondylitis.
Many genetic polymorphisms remain to be investigated in patients with ulcerative colitis and Crohn’s disease. Some may have greater relevance to individual susceptibility than others. One worthy of attention is the recently described polymorphism of antigenic specificities in the colonic mucosa.

Environmental and infective agents

The search for environmental causes of IBD has been disappointing. Infective agents have received the most sustained attention because of the resemblances to dysentery and intestinal tuberculosis. Perhaps the nearest approach to the fulfilment of Koch’s postulates is the induction of granulomata in some mice and rabbits after injection with Crohn’s tissue homogenates. Comparisons have been drawn suggesting that the relationship of ulcerative colitis to Crohn’s disease might be similar to that of the lepromatous and tuberculoid forms of leprosy or the relationship of tuberculosis and sarcoidosis. The same or similar causative agents might thus produce variability in disease patterns determined by genetic or non-genetic host factors. Like Crohn’s disease, sarcoidosis is sometimes familial but there is little evidence of a common genetic background to the two conditions except for a report of both conditions in a sibship.

During the last half century many bacterial and viral pathogens have been suggested as possible causes of IBD but none has been consistently present. Only in recent years has the hypothesis been explored that IBD could be the result, in some genetically predisposed individuals, of abnormal responses to infective agents which are non-pathogenic or are of low pathogenicity in the majority of the population. The evidence concerning E. coli is of particular interest. The organism E. coli 014 contains an abundance of the Kunin antigen common to many of the Enterobacteriaceae, including the commensal flora of the bowel, and it cross reacts with antigens present in normal colon. High antibody titres to E. coli 014 have been found in both ulcerative colitis and Crohn’s disease. This could reflect excessive absorption of coli through the mucosa damaged by disease, or represent an atypical response to the normal flora and be a basis of disease. The idea of a heritable predisposition is supported by a report of increased titres of E. coli 014 antibodies in asymptomatic relatives of patients with ulcerative colitis, although the increase was confined to female relatives. This report is reminiscent of the increased incidence of rheumatoid factor in the healthy relatives but not spouses, of patients with rheumatoid arthritis.

The molecular mimicry of the streptococcus in its cross-reactivity with heart antigens is well known in the pathogenesis of rheumatic fever, and E. coli may have a comparable role in IBD. It is of interest that cross-reactivities have been demonstrated between certain HLA antigens and both Streptococcal M protein and some E. coli antigens.

The HLA polymorphism assumes more than conjectural importance in the host response to infection with Yersinia enterocolitica, which may produce an acute terminal ileitis. There has been speculation concerning the relationship of this infection to Crohn’s disease. After infection, some subjects develop a reactive arthritis and sacroiliitis or ankylosing spondylitis and most of those who react in this manner have the HLA-B27 antigen. Although it is relevant only by analogy, this observation of a HLA associated, and hence genetically determined pattern of responsiveness, may be one of the most significant findings in recent years relating to the genetics of IBD.
Heredity or environment?

Familial aggregations of cases of a particular variety of disease may be due to: (1) random chance; (2) the effects of shared environment; (3) the effects of shared genes; (4) the effects of shared genes controlling the responses to shared environmental influences.

In the case of IBD, the first two explanations are improbable because of the epidemiological evidence. Familial cases are far more frequent than would be randomly expected from the available overall incidence figures. Reports of affected spouses would be expected if the cause of IBD were simply an infective or dietary factor or other environmental agent. External factors must, however, be invoked to account for the apparent increase in the incidence of IBD in the last few decades: the genes in a population would not change to any appreciable extent during such a short time.

The inheritance of IBD does not follow Mendelian principles and cannot therefore be a matter of one or two genes unless the penetrance is very low. The epidemiological data in familial IBD follows the pattern expected in polygenic inheritance. Variable individual "liability" is characteristic of this form of inheritance. Here "liability" encompasses genetically determined innate tendencies and the whole combination of external circumstances that makes an individual more or less likely to develop a particular disease. Assuming polygenic inheritance, the affected patient's liability has exceeded the threshold for disease, although between individuals the balance of heredity and environment may vary considerably.

The familial associations of Crohn's disease and ulcerative colitis may be explained by two genetic mechanisms:

1. Crohn's disease and ulcerative colitis may be the same disease with similar causes and with a quantitatively related genetic basis. Crohn's disease would be the result in people with a large concentration of genes, while fewer of the relevant genes would result in ulcerative colitis. In support of this explanation is the finding (Table 1) that 39 patients with Crohn's disease had 12 affected relatives, while 103 patients with ulcerative colitis had only nine affected relatives. Other workers have similarly reported a greater familial tendency in Crohn's disease. In addition, ulcerative colitis is almost as common as Crohn's disease in the relatives of patients with Crohn's disease. This suggests that, if there is summation of genes in a quantitative manner, then Crohn's disease represents a more complete or coherent genotype. A similar conclusion may be drawn from reports of IBD in monozygous twins which show (Table 2) a higher concordance rate (and by inference a greater genetic component) for Crohn's disease than for ulcerative colitis. This quantitative relationship would also account for patients who have an intermediate picture with features of both conditions.

2. The two diseases may be due to different environmental factors which result in different pathology, but the genotypes which determine liability may have a number of genes in common. This could result in the relatives of patients with one disease being more likely to develop the other than people in the general population. In favour of the explanation of overlapping genotypes is the association which both diseases have with ankylosing spondylitis.

Conclusion

There are clear clinical and pathological distinctions between most cases of
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References


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