Inflammatory Bowel Disease: From Bench to Bedside

2nd Edition

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Preface

Why A Second Edition?

The pace of research in inflammatory bowel diseases has accelerated over the last decade, with a particularly rapid sprint occurring as we approached the new millennium. Advances in basic and technologic research have enabled scientists to examine the inflammatory process at the cellular and molecular levels. The powerful research tools of the current biotech and genotech era are now being applied successfully to inflammatory bowel disease research. Although there are many unanswered questions, today as before, the pathogenesis of inflammatory bowel disease can now be discussed at an increasingly fundamental level. Today, new therapeutic strategies are based on understanding of pathophysiology and are no longer introduced merely on an empiric basis. Many hitherto unexplained features of inflammatory bowel diseases can be accounted for because of improvements in understanding of the immune and inflammatory responses in the gut.

Like the first edition of *Inflammatory Bowel Diseases: From Bench to Bedside*, this book is intended to be more than a comprehensive compilation of reviews by individual authors on different aspects of these disorders. It is intended that the individual chapters be components of a coherent, albeit detailed, story of the local and systemic pathophysiology of intestinal inflammation, with a well-reasoned series of management strategies. Our goal was not only to produce a standard reference text, but also to present research advances and current concepts of etiopathogenesis in the context of what is already known of the clinicopathologic features of these disorders. Our vision was to have a book that would blend recent advances in the basic and clinical sciences as they relate to inflammatory bowel disease. It is our hope that that the book will illustrate the effectiveness of a team approach of basic scientists and clinician investigators in the field of inflammatory bowel disease. The book will give the reader a glimpse of where the field is moving and an idea of likely research directions in the future. Of course, it is our personal wish that this book will stimulate ideas for future research.

In early 1994, when the first edition of *Inflammatory Bowel Diseases: From Bench to Bedside*, was released, our introductory pages included predictions and considerations for the future of management of these disorders, as follows: (1) heterogeneity and the 'reagent grade' patient; (2) combination drug therapy rather than a stepwise progression; (3) emphasis on intestinal immunophysiology; (4) mucosa-specific rather than systemic immunomodulation; and (5) focus on factors promoting healing and remission rather than relapse. Each of these concepts has been validated and extended in the ensuing years, and are now the very foundation of current laboratory and clinical research on the inflammatory bowel diseases.

In addition, we posed three questions related to the predictions that we felt fundamental to research both at the bench and at the bedside. Perhaps the single most important technological advance toward answering these questions has been the application of molecular technology to the creation of a new society of colitic animal models, from which to learn about human disease. With the use of such models much progress has been made on first question, "Are Crohn's disease and ulcerative colitis different expressions of the same disease or are they discrete entities?" Based on numerous factors, including genetic associations, marker antibodies, and environmental agents, it has become increasingly clear that the varying clinical manifestations of inflammatory bowel disease reflect unique pathogenic processes in the mucosa. Indeed, there are numerous discrete entities that can be stratified by a variety of subclinical and clinical markers that may well identify which patients are likely to respond to any particular therapeutic intervention.

The second question, "Do infectious agents have a role in the etiology or pathogenesis of inflammatory

Stephan R. Targan, Fergus Shanahan and Loren C. Karp (eds.), Inflammatory Bowel Disease: From Bench to Bedside, 2nd Edition, v–vi.

bowel disease?" is a major focus for researchers at the present time. Mounting evidence, including the identification of specific bacterial products, implicate such agents in the pathogenic process. A key objective for investigators is to understand the interplay between bacteria and the altered immune response leading to mucosal inflammation. Evidence suggests that these immune responses are to normal commensal bacteria rather than any specific pathogen. In 2001, a Crohn's disease associated gene mutation was discovered in NOD2, a protein that is responsible for regulating appropriate responses between bacteria and host. This finding corroborates that an abnormality in this interaction is fundamental to the disease process in at least some forms of Crohn's disease, and further confirms that is unlikely that infectious agents will be directly correlated with the disease responses that are characteristic of the inflammatory bowel diseases. More likely, the process is indirect, requiring any number of combinations of genetics, immune responses, and environmental triggers, to manifest as disease. Specific manipulation of bacterial expression and the corresponding immune response may be the basis of very effective therapies in the near future.

Finally, we posed the questions, "Where is research taking us? How will it change the management of inflammatory bowel disease?" The effect of the research has already become apparent in the example of therapeutic anti-tumor necrosis factor-α monoclonal antibodies (anti-TNF-α). This treatment is targeted at a very specific point in the immune response, over-production of TNF-α, commonly found in patients with Crohn's disease. That this treatment is only effective in a portion of patients with Crohn's disease points to the fact that there are unique immune mechanisms that underly the intestinal inflammation in different subpopulations of patients. An even more recently developed therapeutic approach for those not responding to anti-TNF-α – or even those that do – involves using an antibody to α4 to prevent the recirculation of cells into the mucosa, a method which has been shown to decrease inflammation.

In the second edition, chapters across the spectrum of *Inflammatory Bowel Disease: From Bench to Bedside* will reflect the advances delineated above and lay the groundwork for ongoing research and treatment of these disorders. In the near future, the molecular basis of the interaction between host genetics and the environment will become more clear, and the linkage with the immune system will reveal not only more effective therapy but the ability to predict responders and non-responders to individual therapies.

We would like to express our gratitude to each of the authors for their carefully conceived contributions. In encouraging the authors to include their individual perspective and philosophical approaches, we likely made their job more difficult.

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Table of Contents

Section I

THE LABORATORY BENCH

1 Introduction: Inflammatory bowel disease: from bench to bedside

FERGUS SHANAHAN, LOREN C. KARP AND STEPHAN R. TARGAN

The adventurous physician goes on, and substitutes presumption for knowledge. From the scanty field of what is known, he launches into the boundless region of what is unknown (Thomas Jefferson)

The introductory section of the first edition of this book closed with the following upbeat comments: 'inflammatory bowel disease is now an exciting field for the basic researcher, the clinician–investigator, and the clinical practitioner. Much work remains to be done ... Onward!'. In the same year the late Professor Anne Ferguson challenged the medical, political and research communities with a provocative editorial in which Crohn's disease and ulcerative colitis were referred to as 'important and disabling diseases, still under-researched.' Since then there have been remarkable improvements in our understanding of the pathophysiology of these disorders. The molecular mediators and major pathways of tissue injury have been identified. Improvements in molecular genetic technology have ensured that fundamental questions regarding mucosal inflammation can now be asked and answered. The new information promises to be translated into improvements in patient management. This is reflected in a progressive shift from therapeutic empiricism to evidence-based management.

Changes in research strategy have perhaps been even more important than technological progress in providing an integrated and coherent overview of disease mechanisms. Complex disorders require research input from a diversity of perspectives, including traditional disciplines, such as biochemistry, microbiology and immunology. It is at the interface of these seemingly disparate disciplines where incisive advances have been made; hence the emergence of hybrid disciplines such as microbial pathophysiology, immunophysiology and psychoneuroimmunology. This is a recurring theme throughout this text with emphasis on transdisciplinary topics such as intercellular crosstalk within the mucosa, lymphoepithelial dialog, neuroimmune interactions, and epithelial–microbe signalling (Chapters 3–11). This approach is also reflected in chapters explaining the fundamental basis of systemic symptoms and signs and extra-intestinal manifestations experienced by patients with Crohn's disease and ulcerative colitis (Chapters 11–13 and 16).

Understanding the role of endogenous outcome modifiers such as psychological stress, the brain–gut axis, and even the placebo response of the individual, requires the same transdisciplinary perspective. Perhaps the most intriguing convergence of research avenues is the interaction among the three major ingredients of the pathophysiology of inflammatory bowel disease (genetic predisposition, environmental bacteria and immune dysregulation). Indeed, the interface at the center of this triad appears to have become the basis of a unifying concept for the development of most autoimmune disorders. It is perhaps not surprising that one of the genes associated with increased susceptibility to Crohn's disease (*NOD2*) is linked to the mechanism of immune perception of the bacterial microenvironment (Chapter 2). One might predict that additional genes will be identified which regulate how the host immune system handles the microbial flora within the gut.

Unraveling the pathogenesis of inflammatory bowel disease is of more than passing interest to the clinician and has several immediate implications for patient management. Genetic studies have already come to the patient bedside with increasing emphasis on phamacogenomic prediction of drug efficacy and toxicity (Chapters 25 and 26). Immune mechanisms of tissue damage in inflammatory bowel disease have been successfully exploited for diagnostic and therapeutic purposes. Thus, immunologic alterations in patients with Crohn's disease and ulcerative colitis have utility as noninvasive diagnostic tools (Chapter

Stephan R. Targan, Fergus Shanahan and Loren C. Karp (eds.), Inflammatory Bowel Disease: From Bench to Bedside, 2nd Edition, 3–4.

20), and blockade of specific immune mediators has been one of the most elegant examples of bench to bedside medicine in recent years (Chapter 27). The challenge for clinicians now will be to establish the hierarchy of importance of site-specific therapeutics versus more traditional nonspecific modalities (Chapter 26) for different patients and the place of combination therapy.

What of the remaining contributors to the pathogenesis – the enteric bacteria? Here again there is already evidence for translation of research data to the clinical setting. Clinicians have been using the bacterial flora for decades to metabolize the prodrugs sulfasalazine or olsalazine to the active aminosalicylate moiety. The impact of enteral feeding in Crohn's disease is now thought to be mediated in part though effects on the flora and epithelial barrier function. Today, manipulation of the enteric flora with probiotics, prebiotics and synbiotics is an emerging therapeutic strategy as a safe adjunct to immunomodulation (Chapter 28). Tomorrow, perhaps one can predict that molecular fingerprinting of the enteric flora will help explain the timing of disease onset, the subset of bacteria driving the inflammatory response and the influence of the host on the composition of the indigenous flora. Because of the lesson of *Helicobacter pylori* and peptic disease, basic investigators and clinicians will be reluctant to dismiss the possibility of a specific infectious etiology in some or all patients with inflammatory bowel disease. Although this could account for the changing nature and prevalence of Crohn's disease and ulcerative colitis (Chapter 2), the information from animal models of disease suggests that more than one pathogenic pathway may be involved in leading to the same phenotypic outcome (Chapter 4). The animal models also indicate that a genetically determined defect in immune regulation can indeed lead to chronic inflammation in the presence of the normal bacterial flora, and this does not require a specific pathogenic infection in the traditional sense of a transmissible agent. Thus, these diseases are unlikely to represent a simple cause and effect relationship with a simple struggle between microbe and humans (Chapter 6).

Extrapolation of the diversity of animal models to the human condition has the obvious implication that clinicians need to contend with an extraordinary degree of patient heterogeneity. While this has not been particularly evident from conventional clinical criteria, improvements in genetic, immunologic and microbial molecular diagnostics are poised to facilitate categorization of patient subsets to improve the design and interpretation of clinical trials in the future (Chapter 23). Today the splitters appear to have the advantage over the lumpers. But the learning curve may have reached the point of inflexion, and with more research data the apparent complexity is likely to give way to commonalities and patterns of disease and therapeutic responsiveness.

Of course, the management of inflammatory bowel disease today must not only be evidence-based (Chapter 30), but must also be accountable in the context of modern concepts of disease management (Chapter 22) and outcome assessments (Chapter 23). In the midst of relentless scientific progress, clinicians will do well to uphold the traditional principles of caring for patients with chronic disease. Despite all the advances at the research bench, patients seem to have increasing expectations of health care and lower tolerance of illness. Dissatisfaction with modern medicine is reflected in greater litigation and expenditure on alternative medicine. Patient surveys consistently reflect the importance of the doctor–patient relationship. Compassion, time, and a commitment to long-term management are unlikely to become obsolete or superseded by any novel drug therapy.

In summary, inflammatory bowel disease is more exciting than ever; it remains a rewarding field for basic researchers and clinicians. Notwithstanding the extraordinary advances brought about by the genotech–biotech era, clinical clues at the bedside continue to pose the correct questions to be tackled in the research laboratory. Likewise, observations at the laboratory bench will continue to be translated into enhanced diagnostic and therapeutic strategies in the clinic. This bench-bedside interface shared by the clinician and the basic investigator needs to be nurtured, as it can pay handsome dividends for patient welfare. Therein lies the essence of what is intended with this book.

2 The changing faces of Crohn's disease and ulcerative colitis

ANDERS EKBOM

Introduction

There are few diseases which have changed faces to such an extent as the inflammatory bowel diseases, i.e. ulcerative colitis (UC) and Crohn's disease (CD). At the beginning of the 20th century inflammatory bowel disease (IBD) was a rarity, and at the end of the same century these disease entities were something gastroenterologists in the Westernized world encounter not once, but repeatedly, on a daily basis. Fifty years ago high socioeconomic status and Jewish ethnicity were two commonly accepted risk factors, associations that today are either questioned or have been refuted in observational studies. Pancolitis, in the case of UC and CD confined to terminal ileum, were the most common clinical features during the first part of the 20th century as opposed to today. Nowadays ulcerative proctitis is the most common clinical presentation among UC patients and CD confined to the terminal ileum constitutes a minority of CD patients. Geographically there was a north–south gradient; a finding reproduced in different settings and continents that does not seem to exist today. Instead, we can see the emergence of an east–west gradient. A hypothesis of the origin of the diseases included *Mycobacterium paratuberculosis* as a potential agent, a hypothesis that was refuted early on, then reintroduced, and later refuted again.

These different faces of the two diseases are probably in part due to bad methodology or science, but this also illustrates that the two diseases have changed faces over time. It is a rather straightforward endeavor to describe the different faces over time, as we are fortunate to have clinicians and epidemiologists who, during the past 100 years, have taken a great interest in IBD. The difficult part is to interpret these findings and to make sense of them. The goal is to provide benchmarks for other scientists, which can be used to test the different hypotheses, which will emerge. This way we will eventually understand the etiology of IBD and primary prevention will become a possibility.

Occurrence

Temporal trends

Although historic figures such as Alfred the Great [1] and Bonnie Prince Charles [2] have been proposed to have suffered from CD and UC, respectively by clinicians turned historian, it is obvious that the two disease entities were rare until the 20th century. However, at the end of the 19th century there were quite a few case reports of patients with UC in Great Britain, and a symposium was held at the Royal Society of Medicine, London, as early as 1909, at which 317 patients from different hospitals in London were presented [3]. Similarly, in 1913 Kenneth Dalziel, a Scottish surgeon, reported nine patients with a new entity described as 'chronic intestinal enteritis and not tuberculosis' [4]. There is a consensus that those nine cases constitute the first case series of what later was called CD. Moreover, a retrospective study from Ireland has described 29 cases of CD treated during the latter half of the 19th century [5]. There are also reports outside the Anglo-Saxon world of early cases. For instance, the earliest bona-fide case of CD in Sweden is a 13-year-old boy operated on in 1918 due to suspected appendicitis. A bypass procedure was performed because of stenosis of the terminal ileum and, interestingly, the surgeon dismissed the diagnosis of tuberculosis as highly improbable. Nothing was heard from the patient until 1969 when he was admitted for perianal fistulas. As a subsequent barium enema was difficult to interpret, a laparotomy was performed and a resection including the bypassed segment of the ileum was done. The subsequent histopathologic examination revealed changes typical for CD of the terminal ileum. However, it was not until Dr Burrill B. Crohn,

Stephan R. Targan, Fergus Shanahan and Loren C. Karp (eds.), Inflammatory Bowel Disease: From Bench to Bedside, 2nd Edition, 5–20.

in 1932, introduced the term 'regional ileitis' for the disease that was later named after him, when CD became a distinct clinical entity [6].

There are no incidence figures available for either UC or CD until the 1930s. During this decade there are incidence rates from two retrospective studies in two defined populations. The first was done retrospectively in Rochester, Minnesota, where the authors were able to demonstrate an annual incidence of UC of 6.0 per 100 000 for the period 1934–1944 [7] and an annual incidence of CD of 1.9 per 100 000 for the period 1935–1954 [8]. In Europe there is only one estimate during the 1930s for CD, from Cardiff, United Kingdom, of 0.2 per 100 000 for the period 1935–1945 [9].

Thereafter, there have been an increasing number of incidence studies published either for both UC and CD, or for one of these conditions for different populations and different time periods. Besides cancer and cardiovascular diseases there are probably no other disease entities where so many incidence studies have been undertaken in so many different populations during the later part of the 20th century. However, most of these studies have generally dealt with small populations and/or short time periods; in most instances less than 10 years. Moreover, different case-finding methods have been used, and in many instances no age standardization has been done, making comparisons between different populations and time periods impossible to perform. In spite of these shortcomings there are remarkable similarities in the temporal trends for UC and CD in different populations in the Westernized world. There is a consistent finding from both western Europe and northern America of a substantial increase in incidence of both CD and UC since the Second World War.

There is also a strong correlation in the occurrence of the two diseases. Areas or populations with a high incidence or mortality attributed to UC also have a high incidence or mortality due to CD, and vice-versa [10]. Although misclassification of either disease could lead to a false correlation, the consistency of these findings in different settings argues convincingly against such a bias. Moreover, although this chapter will not deal with genetics, relatives of patients with UC are at higher risk for UC and also, to a lesser extent, for CD. Relatives of patients with CD are at higher risk for CD and, to a lesser extent, UC [11]. The temporal trends for both diseases and genetics consequently leave us with two different hypotheses: (1) UC and CD represent the opposite ends of a continuous spectrum of IBD, but with different clinical characteristics; or (2) there are some shared genetic and/or environmental risk factors for UC and CD.

Another common feature, with regard to the temporal trends for UC and CD, is that, in those instances where there are incidence figures for the shift from a low-incidence area to a high-incidence area, an increasing incidence of UC precedes an increase in CD with a time lag of around 15–20 years. The time lag is apparent in studies from Sweden [12–15], Iceland [16–18], Copenhagen [19–21], the Faroe Islands [22, 23], and the US [7, 8, 24–27]. In Fig. 1 the incidence figures for UC and CD are given for Uppsala County, Sweden, from 1945 to 1983. These figures are the result of four different studies performed in this population [12–15]. These studies are of additional interest as the different researchers have failed to identify more than a handful of prevalent cases, i.e. patients with symptoms or a diagnosis before 1945 for either disease. Different case-finding methods have been utilized in the different studies, but yielding the same results. These findings, like those from Cardiff [9, 28] and Minnesota [7, 8, 24–27], where a constant monitoring has been present, strongly suggest that the low incidence figures in the 1930s and 1940s are not due to flawed case-finding methods, but that this increase in incidence for both UC and CD is real.

Since the 1960s and 1970s the excess mortality compared to the background population is only marginal in patients with UC and CD. Thus, the presence of a shift, i.e. transition between low and high incidence of either UC or CD, makes prevalence figures less suitable to compare the occurrence of those diseases in different populations. The prevalence will then be a measure not only of the incidence but also of the duration since this change in incidence. Incidence figures should therefore be used in comparing populations and over time.

Another consistent finding in the descriptive epidemiology of IBD up to recently is that the incidence of UC is higher than for CD. In the case of CD there seems to be a leveling-off in most populations with an incidence of up to 6.0 per 100 000 and for UC an incidence between 15 and 20 per 100 000 although higher incidence figures have been reported for both diseases [9, 29]. This corresponds to a lifetime risk for either one of the two diseases in high-incidence areas between 0.5 and 1.0% which is close to the risk for a disease such as rheumatoid arthritis, which no one disputes constitutes a public health problem. How-

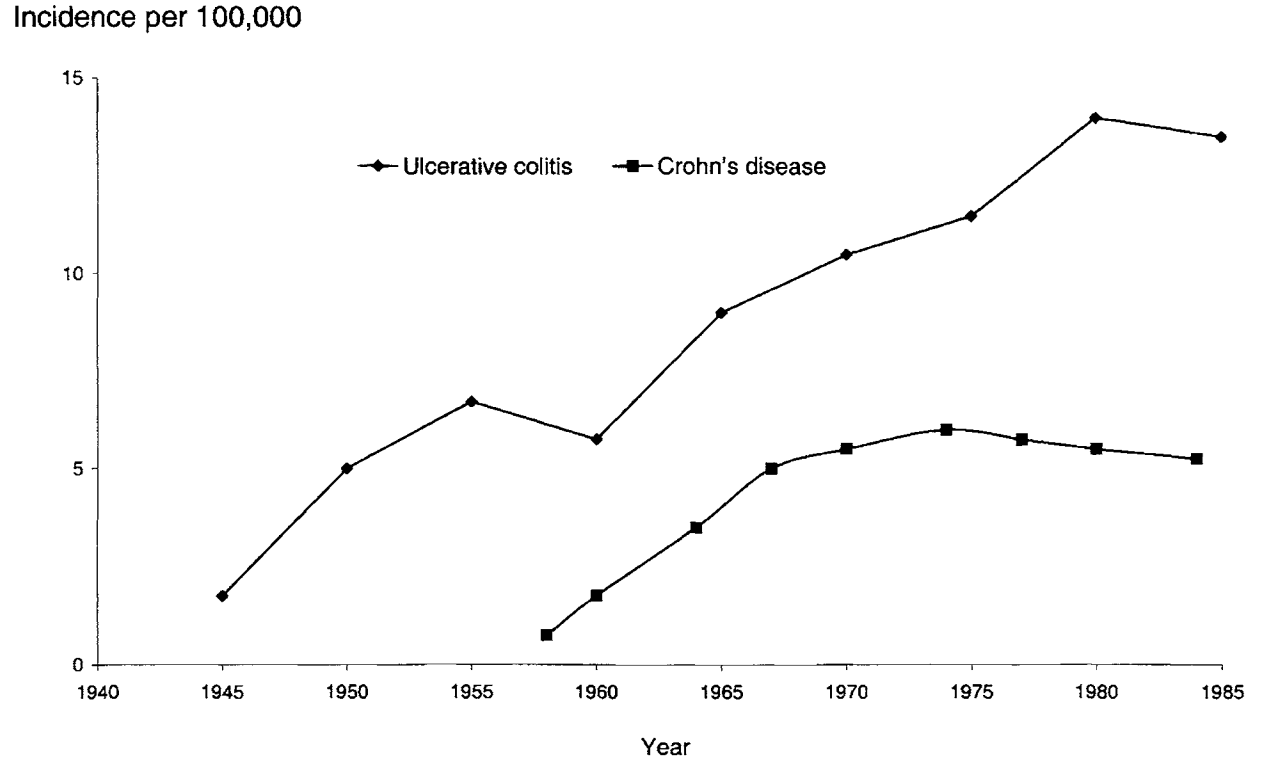

Figure 1. Annual incidence of ulcerative colitis and Crohn's disease in Uppsala County, Sweden, 1945–1983.

ever, as usual with IBD, there are different faces. Recent reports from both Belgium and France [30, 31] play havoc with the notion that UC is more common than CD as the opposite seems to be true in those two adjacent areas.

Age-specific incidence

The age-specific incidence rates for UC and CD vary substantially in different populations and over time. Populations with low annual incidence have an almost flat age-specific curve, and during periods of a rising annual incidence this increase will be most pronounced in the age group 20–40 years for both UC [27, 32] and CD [13, 26]. In Fig. 2 this is demonstrated by comparing the number of CD patients during the transient period in Uppsala County, Sweden, 1956–1961 versus 1962–1967.

To what extent there is a second peak in high incidence areas in the older age groups (60+) remains controversial. It has been argued that this peak represents a delayed diagnosis made when the disease relapses, as demonstrated in the first bona-fide case of CD in Sweden and in the case of President Eisenhower [33]. However, in a study from the United Kingdom the authors demonstrated one of the highest incidence figures for CD ever reported, which was mainly due to a second peak [9]. The authors expressed concern that this would be the start of a new trend, but further data from the same population have to some extent challenged this [28].

Another area of recent interest is pediatric IBD. The incidence rates among juveniles have been stable for both diseases in different populations since the Second World War. However, during the 1980s there were reports of a substantial increase in juvenile onset of CD in Scotland [34]. An incidence of 1 per 100 000 inhabitants per year in 1968–1976 has changed to 3 per 100 000 in 1990–1992, with the largest increase in the age group 12–16 years. A similar finding was reported from Stockholm, Sweden, where an annual incidence of 1.1 per 100 000 during late 1980s has changed to an incidence of 5.4 during the late 1990s [35]. No such changes in the incidence of UC could be demonstrated. There was also a change in the pattern of the disease appearance, with a higher frequency of fistulating disease than could

Figure 2. The number of patients with Crohn's disease in different age groups for the years 1956–1961 and 1962–1967 respectively according to the year of first diagnosis. (From Norlen BJ, Krause U, Bergman L. An epidemiological study of Crohn's disease. Scand J Gastroenterol 1970; 5: 385–90; permission to publish given by author BJ Norlen).

previously be demonstrated, as well as the presence of children with CD at very young age (below 5 years). This increase in incidence in juvenile CD seems to be confined to Stockholm, as other areas in Sweden have not been able to demonstrate any changes [36].

Gender

The sex distribution of UC and CD has also changed faces over time. In the case of UC there is a male predominance in high-incidence areas, most pronounced in patients with ulcerative proctitis or distal colitis [15]. Fig. 3 illustrates the change in sex distribution documented by 59 different descriptive studies over time [37]. In the case of CD there is an opposite trend compared to UC. Mortality from CD is higher among males in low-incidence areas but higher among females in high-incidence areas [10]. Temporal trends in incidence also show a similar trend, from an even sex distribution to a female predominance in high-incidence areas [15].

Extent of disease

Extent of disease is probably the best example of the changing faces of IBD. In the case of UC, pancolitis constituted the majority of cases in some early epidemiologic studies [38] but not all [27]. In the 1960s and 1970s ulcerative proctitis or distal colitis started to emerge to an extent of disease as common as pancolitis. Patients with ulcerative proctitis have a more pronounced male predominance than patients with more extensive disease and also seem to have an older age at onset. It has therefore been discussed to what extent ulcerative proctitis should be a disease entity of its own [39], but it is quite common that patients with ulcerative proctitis will eventually experience a more extensive disease [40, 41], but very little is known about the long-term prognosis with regard to extent of disease in patients diagnosed with

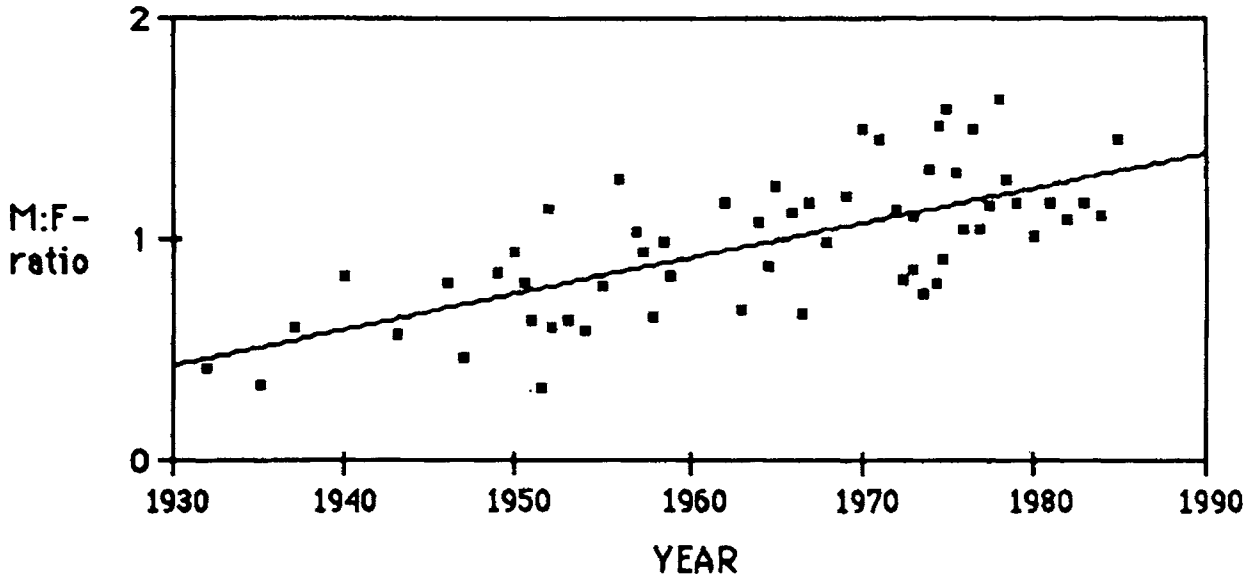

Figure 3. Male:female (M:F) ratio versus time period in 59 reported studies of uclerative colitis from 1930 to 1990. (From Tysk C, Jarnerot G. Has smoking changed the epidemiology of ulcerative colitis? Scand J Gastroenterol 1992; 27: 508–12; permission to publish given by author C Tysk).

ulcerative proctitis the past 20 years. This is a concern as patients with ulcerative proctitis or distal colitis presently constitute 50% of all patients with UC diagnosed in a defined catchment area [42].

Is this shift toward a less extensive disease only a sign of better ascertainment of cases? This might be, at least partly, the explanation in some studies, but it is not the underlying reason for the results in studies from Belgium and France. The proportions of ulcerative proctitis or distal colitis do not differ from those of other centers, arguing against the theory that the 'differences francaise and/or belgique' should be due to underascertainment.

In the case of CD, terminal ileitis was the original disease [6]. It is therefore of great interest to follow the patient's clinical characteristics at the original center over time even if a denominator is lacking [43]. Terminal ileitis was followed by ileocolitis and finally, during the 1960s, a new disease entity emerged – Crohn colitis. This shift can partly be explained by the understanding of Crohn colitis as an entity in the 1960s [44], but even thereafter there has been a decreased proportion of patients with terminal ileitis and an increased proportion of CD with colonic involvement at Mount Sinai as well as in most population-based studies.

Lately, a new entity has been introduced: indeterminate colitis [45]. Is this a new clinical entity or not? It has been argued that this is not the case. Classical CD of the colon is not always clear-cut in a clinical setting. The introduction of this entity could also be due to methodological problems. Most incidence studies published since the Second World War have been retrospective, i.e. data on cases have been assembled years or even decades after diagnosis. One major advantage of such a study design is that the evaluation process will include a long duration of follow-up of the clinical course. This additional information, compared with what is available at the time of diagnosis, will give an additional edge to retrospective studies compared to prospective ones. It has been shown repeatedly that in any cohort of patients with IBD there will be a continuous change in the diagnoses over time, and up to 10% will have a different final diagnosis to that originally assigned [15]. This is also shown by the frequent reports of patients with a definite UC being operated on with a pouch, who later will have a recurrence typical of that for CD [46]. Thus, the pressure to assign a definite diagnosis when a patient presents with a disease, which unequivocally can be classified as IBD, is probably one major reason for this disease entity.

In a prospective study from 20 European centers [47], 5% of all patients with IBD were classified as having indeterminate colitis, and there was a wide variation of that percentage in different populations. In Norway, for instance, there were 93 cases of indeterminate colitis compared to 525 cases of UC [29]. In a reevaluation of the Norwegian material 1 year after diagnosis [48], which included endoscopy and new histopathologic examination, 33% of the patients with indeterminate colitis were reclassified with UC and 17% with CD. There were also patients originally classified with UC or CD who were reclassified as indeterminate colitis. There are very few studies which have tried to assess the specific characteristics in patients with indeterminate colitis, but patients with indeterminate colitis seem to have a younger age at onset, a more extensive disease and a more severe clinical course than patients with UC [48, 49]. However, so far there are no compelling reasons to introduce a third clinical entity – indeterminate colitis.

Geographic differences

Observational studies during the 1960s and 1970s, both in Europe [50] and northern America [51], suggested a north–south gradient in IBD. As the existence of such a gradient could give new clues to the etiology of both diseases, a major study was undertaken in Europe to test this hypothesis [47]. Twenty European centers identified patients with either UC or CD prospectively during a 2-year period. There was a uniform diagnostic approach in all centers and close collaboration during the study period. Although there was a wide variation of the annual incidence in the different populations, there was no consistent pattern which would substantiate the presence of a north–south gradient. Even after adjusting for tobacco consumption as well as education no substantial gradient emerged.

Another interesting feature of IBD is the uniformity in incidence figures in different countries, and these features seem to follow not natural boundaries, but national borders. For instance, until 1 July 2000, there was 10 miles of water easily accessible by ferry between Copenhagen, Denmark, and Malmö, Sweden. In Fig. 4 the temporal trends for CD in these two adjacent cities are shown [20, 52], and it is obvious that the increase in incidence in CD occurred later in Copenhagen than in Malmö, and a similar time difference is present for UC [21, 49].

In contrast, the incidence of IBD in the northern part of Sweden [53] and the middle part of Sweden [14, 15, 32, 54–56] are similar to the one in Malmö, and likewise the temporal trends. A uniform incidence of IBD also seems to be present in Italy [57, 58]. Comparisons of the incidence of IBD made in Greece during the 1990s, on the other hand, revealed substantial differences, especially for CD which seems to be almost nonexistent in the northern part of Greece [59] as compared to Crete where the incidence does not differ from that of the rest of Europe [60, 61]. However, there are now strong indications of an east–west gradient evident from case reports [62, 63] and incidence figures [64] from Eastern Europe and the former Soviet Union.

Cohort effects

It is obvious from descriptive epidemiology that the increasing incidence in IBD occurred after the Second World War. However, this does not seem to be due exclusively to a period effect, but there are reports of a birth cohort phenomenon. This was first reported as early as the 1970s in a major incidence study of CD in Stockholm County, Sweden [54]. This finding was confirmed in an adjacent population in the Uppsala Health Care Region where a birth cohort phenomenon could be demonstrated both for UC and CD [15]. In the case of UC the birth a cohort phenomenon was more pronounced for extensive colitis than ulcerative proctitis. The existence of such a birth cohort phenomenon has, however, been questioned, and two studies [20, 55], one from Sweden and one from Denmark, failed to show any such effect. Both these studies, however, had problems with statistical power, and that could be the underlying reason for the inconsistent results.

In a slightly different approach, mortality data from England and Switzerland were used in order to analyze temporal trends in both UC and peptic ulcer disease [65]. The authors were able to demonstrate similar patterns for both diseases and the results were consistent with a birth cohort phenomenon. The major shortcoming with this study is that the authors have utilized mortality figures instead of incidence figures, and their finding of a peak in the incidence of UC among those born in the latter half of the 19th century is probably a result of this. However, the similarity in the temporal trends between duodenal ulcer disease and UC implicates early exposures, possibly of infectious origin. Moreover, a birth cohort phenomenon argues against genetic determi-

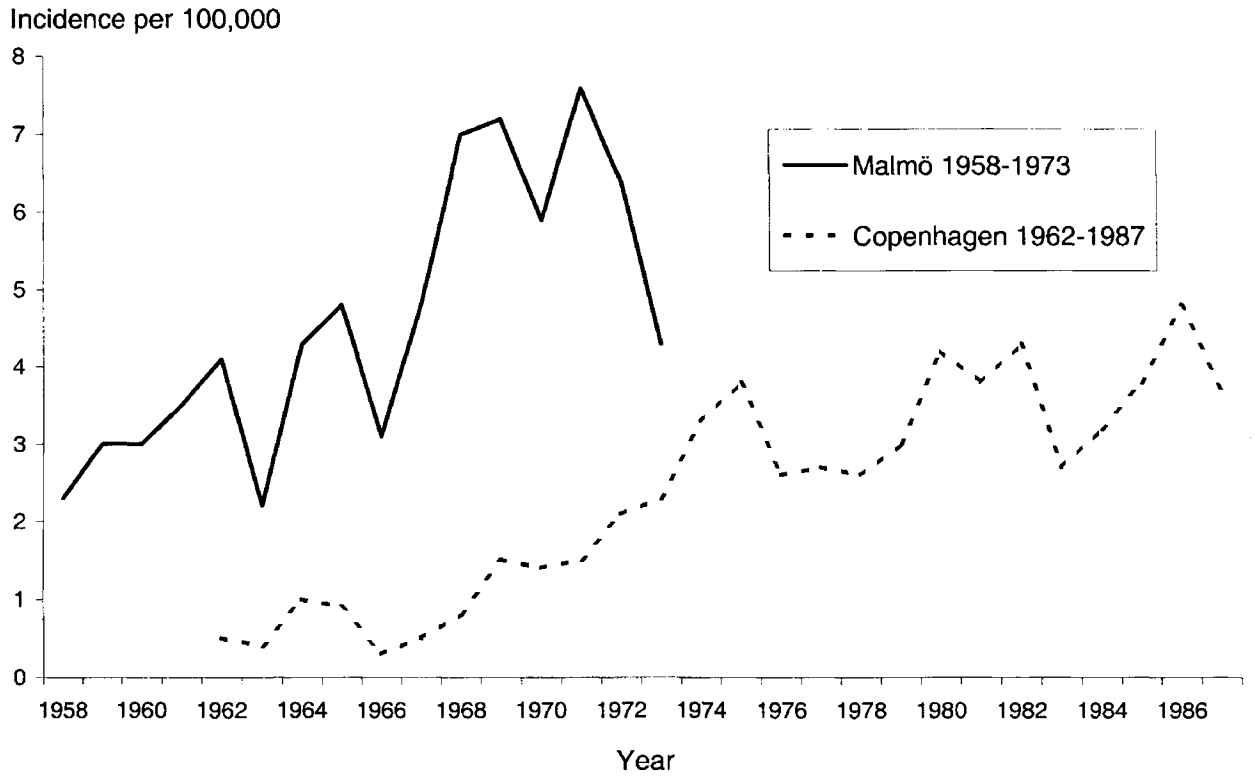

Figure 4. Annual incidences of Crohn's disease in Copenhagen County during the period 1962–1987 and Malmö during the period 1958–1973.

nants as the major cause, but strongly indicates environmental factors interacting with genetic susceptibility for the diseases.

Risk factors

There is no good hypothesis to explain and identify what sort of exposures are of importance for the emerging epidemic of IBD during the 20th century. This is probably the underlying reason for the abundance of different risk factors which have been proposed. With the exception of smoking, they all have in common that the results from different observational studies are not consistent, and quite often lack any biologic rationale. There has been an uniform pattern during the past 50 years: a hypothesis is proposed, followed by enthusiastic early reports of an association, and then a nullifying of the initial results in better-conducted epidemiologic studies. This includes different dietary habits, food items such as margarine and cornflakes, toothpaste, chewing gum, etc. There are, however, some exposures which are worth discussing more in detail.

Ethnicity

In Crohn's original description all 14 patients were Jewish [6]. Ever since that time there has been a perceived association between Jewish ethnicity and an increased risk of IBD. This has been further substantiated by data from the US Army, where the risk of UC in 1944 was higher among those with a Jewish ethnicity compared to other groups [66]. Analytical studies from Sweden [52, 54], South Africa [67], the United Kingdom [68] and the US [69] have given further credence to such an association. However, there are reasons to question the methodology in most of these studies. In the two Swedish studies [52, 54] the nominator – that is the number of subjects with Jewish ethnicity – was assessed through the family name, but the denominator was assessed in a different manner, an

approach that would yield an incidence rate which is bound to be inflated. The study from South Africa [67] has similar drawbacks as the denominator was unknown and therefore ascertained from old census data, probably too low, thus generating inflated incidence rates. It is also of interest that descriptive epidemiologic studies from Israel do not find any incidence or prevalence rates, which differs from other high-incidence areas such as the United Kingdom and Scandinavia [47]. The country of origin seems to be a strong predictor for the risk of IBD, and in subgroup analyses of data from Israel, Jews born either in North America or western Europe seemed to be at highest risk [70]. Similar findings have been reported from Los Angeles, US, where the authors could demonstrate that the Jews originating from Central Europe had a higher risk for CD compared to those originating for Poland or Russia [71]. The authors' conclusion that there is a subset of individuals of Jewish origin with an especially high predisposition for CD might be valid, but the suggestion that all individuals with a Jewish background show an increased risk of either UC or CD still remains to be proven.

In areas with high incidence of IBD, certain ethnic minorities, especially those with lower socioeconomic status, often have a lower annual incidence. Such associations have been seen among blacks in Baltimore [69], Indian migrants in the United Kingdom [72], blacks in South Africa [67] and Bedouin Arabs in Israel [73]. However, these observations are not constant over time – changing faces – and there are examples of these differences being diminished over time [72, 74, 75]. In some instances, as in Great Britain, even opposite associations have been reported. In a study using data from the National Representative British Birth Cohort utilizing everyone born in Britain during one week in 1970, the authors could demonstrate a more than 6-fold increased risk for IBD among those with a parent from India, Pakistan or Bangladesh compared to the indigenous British population [76]. Similar results were found in a study from Leicester in the United Kingdom, where the mean incidence in the south Asian community was more than double that of those of European descent [77]. Thus, although ethnicity previously was a good predictor for the risk of IBD, this does not seem to be the case today.

Socioeconomic status

Another consistent finding in early observational studies of both UC and CD was the association between high socioeconomic status and an increased risk [78, 79]. This finding has been used by some authors to explain the lower incidence of IBD in minority groups. However, this accepted truth is another example of the changing faces of IBD, as recent studies in different populations have failed to find such an association [80, 81].

Socioeconomic status as such is of course not a biologically relevant marker. It stands for differences in diet, crowding, and hygiene, exposures that change over time in various ways in different populations. Thus, it is not surprising that the faces have changed, but the question which remains to be answered is: 'What is the underlying mechanism?'

Diet

Because both UC and CD mainly affect the gastrointestinal tract, it is natural that different dietary exposures have been proposed as the main etiologic factor for the increase in incidence. As early as 1925 it was proposed that UC was due to food allergy [82]. Further credence to this has been lent by the fact that an elimination diet has a beneficial effect on quite a substantial number of patients with UC, where avoidance to cow milk was recognized early to have an effect [2, 83].

Exposure to dairy products therefore seems to be of importance for a clinical course of the disease, and it has been shown that patients with more severe UC have decreased levels of lactase compared to other patients with UC [84]. It is, however, highly unlikely that milk or milk products are of any etiologic relevance for either UC or CD, as there is no consistent finding of such an association in different etiologic studies [85].

Besides milk and milk products, an abundance of other dietary compounds have been implicated in different studies. However, in a review of all such studies conducted up to the mid-1980s for both UC and CD [86], the authors were highly critical of those studies and concluded that both the study design and data analysis made it impossible to infer anything from the results presented that far. Studies since then have not improved our understanding, as they face substantial methodologic problems as in most instances they rely on retrospective assembled data. Any researcher dealing with diet and IBD has to face

one major issue: the insidious onset of the disease, i.e. symptoms might have changed the dietary habits, and this is probably one of the reasons why exposure to refined sugar, as well as an inverse association with diet rich in fiber, have been implicated repeatedly, especially for CD [86]. One should also refrain from infering a causal association through ecologic data such as the rise in incidence in IBD and the introduction of margarine in the Westernized world [87], a hypothesis which could be refuted by a well-conducted correlation study [88]. Cornflakes [89], fast food [85], and cola drinks [90] are examples of other food items which have been proposed to be casually linked with IBD, but here also the underlying biologic mechanisms remain elusive [85]. In conclusion, although some interactions with diet cannot be ruled out, it is at present highly unlikely that the increase in incidence of IBD is due to any of those dietary compounds mentioned above.

Smoking

During the 1950s an Austrian physician made the observation that smoking was less prevalent among patients with UC than among other patient groups [91]. Unfortunately, he used as a comparison group patients with duodenal ulcer disease, where smoking is an accepted risk factor. A report from Sweden during the 1970s, published only in Swedish, reported the same association [92]. It was not until the 1980s that this observation spread to the Anglo-Saxon medical literature [93]. Since then there has been an abundance of studies which have shown that smoking is protective against UC, and non-smoking or former smoking is associated with an increased risk [94]. This finding is present in both sexes, all age groups and all extents of disease. It has, however, been argued to what extent smoking cessation is an even stronger risk factor than lifelong non-smoking status [56]. The consistency of these results has even led to the initiation of pharmacologic therapy by nicotine, mostly as patches, which in most instances have shown beneficial effects [95].

In contrast to UC, smoking is a risk factor for CD in almost all analytical studies with a more than doubled risk [74], but even higher risk estimates have been reported [96]. There are clear signs of a dose–response gradient, which further strengthens the hypothesis of a causal association. However, the risk of former smoking does not differ from the risk of never smoking [97], indicating that smoking is perhaps not an initiator but rather a promoting factor. Further credence to this theory comes from the fact that the clinical course in CD seems to differ among smokers compared to non-smokers where smokers seem to have a more severe clinical course [98].

The contradictory findings in UC and CD have led to speculations that smoking may determine the type of IBD that develops in a predisposed individual. This speculation, as mentioned previously, assumes an otherwise common etiology for the two diseases, which is at least partly contradicted both by the genetics and the temporal trends.

In the case of CD there is a reasonable biologic model for such an association if one assumes that part of the disease process is a multifocal gastrointestinal infarction which would be potentiated by cigarette smoke [99], similar to what has been proposed in the process of arteriosclerosis. This is also in line with smoking as a promoting factor more than initiating. In the case of UC, so far no biologic model exists, but there are quite a few speculations [100].

To what extent can smoking and changes in smoking habits explain the time trends in IBD? In the case of UC we should keep in mind that the majority of patients are never smokers, thus the introduction of cigarette smoking as a common feature in a population during the 20th century could not explain the emergence of this disease. It has been proposed that the change in sex ratios over time in UC can be explained by a higher frequency of former smokers in the male section of the population compared to the female population over time [37]. The authors speculate that this male predominance will eventually disappear when the same frequency of ex-smokers is present among females. So far, however, there are no signs of such a trend.

There are exceptions to the reported associations between IBD and smoking in studies from Israel [101, 102]. It has been proposed that this could be due to a genetic interaction, i.e. higher genetic predisposition to IBD, especially CD, among Jews. The incidence figures for Israel, as mentioned previously, do not substantiate such a predisposition, and even if that were the case, it is rare that a known risk factor will not show up among the genetically predisposed. It is, however, not unlikely that the results from these two studies illustrate the problem with a reported control group in case–control studies.

Oral contraceptives

The introduction of oral contraceptives in the 1960s among women in the Westernized world and the emerging epidemics of IBD have led some authors to infer a casual association, especially for CD [103]. It was therefore not surprising that in the early 1980s there were quite a few case reports describing an association between the use of oral contraceptives and the occurrence of CD [104]. Since then there have been many analytic studies dealing with the subject but, in contrast to smoking, the results have not been consistent [105]. The underlying biologic mechanism which has been proposed is similar to that for smoking, i.e. multifocal gastrointestinal infarction mediated by chronic mesenteric vasculitis which is aggravated by oral contraceptives [99]. Oral contraceptives would then, similar to smoking, be a promoter and not an initiator. However, in contrast to smoking, the use of oral contraceptives does not seem to affect the recurrence rate or severity of the disease [106].

There is also an absence of a consistent interaction between smoking and oral contraceptive use, and opposite findings showing the presence of such an interaction [107] and the non-presence [108] have been reported. However, oral contraceptives are still the focus of interest, and in a study from the US [109], the relative risk of 5.5 was presented following oral contraceptive use for more than 6 years. The authors also calculated the attributable fraction and concluded that almost 16% of all CD patients in the American population was due to oral contraceptives. There are, however, reasons to be very skeptic of such numbers, especially as the incidence of CD in some populations such as Sweden [15] and Great Britain [28] have not increased since the introduction of oral contraceptives.

Clusters

There have been reports of clusters both in time and space for CD [110–112]. This includes CD occurring in spouses [113–115] and affected families in France [116]. These findings have been interpreted as an indication for a transmittable agent. However, in the case of spouses it has so far not been shown that the number of affected pairs differs from that expected. There are always inherent problems in the analyses of clusters. Any researcher has to be aware of the potential presence of a Texan sharpshooter, i.e. the target is decided after the use of the gun. Some of the clusters that have been described can possibly be explained by such a bias, but especially from France the report indicates that some transmittable agent is operating. However, so far the search for this agent has failed [116], but it would be premature to rule out an infectious cause, keeping in mind the history of duodenal ulcer disease. There are also quite a few reports of seasonality of both onset and exacerbation in IBD, especially UC, indicating the existence of an infectious agent triggering the disease [117–121]. To what extent this is of etiologic importance remains unanswered, and the less frequent reports of seasonality for CD could be due to this disease having a more insidious onset, which makes it difficult to establish the start of the symptoms.

Transmittable agents

Chronic mycobacterial infection was proposed by Dalziel as early as 1913 [4] to be the cause for what would later be CD. The similarities between Johne's disease in cattle, sheep, and goats [122] and CD have been used as one of the major arguments. Johne's disease is due to an early infection by *Mycobacterium paratuberculosis* and clusters of patients in England [110] and Wales [123] have been attributed to exposure to this agent [124]. It has been proposed that *M. paratuberculosis* is spread by clinically or subclinically infected animals around the implicated areas, and this could be the underlying explanation for the higher incidence described in urban compared to rural areas.

However, it was pointed out in a recent review [125] that morphologic similarities between Johne's disease and CD are superficial and more suggestive of differing etiopathogenesis. Bacteriologic cultures for *M. paratuberculosis*, immunocytochemistry, use of polymerase chain reaction and trials to transmit CD to animals have all been negative or inconclusive [125]. Moreover, trials with antibiotics directed against *M. paratuberculosis* has also been inconclusive or negative [126, 127]. One should also be aware that in areas such as Iceland, where *M. paratuberculosis* is a problem, especially in sheep, is not characterized by any remarkably high incidence of CD. On the contrary, the increase in incidence of CD emerged later in Iceland compared with other Scandinavian countries [16–18]. Thus, it presently seems very unlikely that *M. paratuberculosis* is an etiologic factor for CD, although one cannot rule out that its presence in patients with IBD can have a

clinical impact. Other transmittable agents which could lead to a persistent infection, such as *Listeria* [128], *Mycoplasma* [129] and viruses, especially measles [130], have also been suggested. There are, however, no consistent results so far, and the search for a transmittable agent will continue. As the story of *H. pylori* demonstrates, one should be cautious before ruling out a persistent infection as a cause.

Psychological factors

An association between stressful events and both UC and CD has been proposed repeatedly. It is, however, highly unlikely that psychological stress should be the underlying reason for the emerging epidemic of IBD. An extensive review published 1990 of 138 studies of psychiatric factors and their relation to UC, and to some extent to CD also, seemingly refutes such an association [131]. The authors were able to demonstrate that those studies where a positive association was found were particularly likely to be flawed, and those reporting solely systematic investigations failed to find any association. However, stressful events as an aggravating or even initiating factor cannot be ruled out, especially with the emerging understanding of a brain–gut interaction [132].

Appendectomy

As early as the 1980s the first report was published which showed that patients with UC were less likely to have been subjected to appendectomy compared to controls [80]. Further research in this area has shown that this protective effect seems to be most pronounced if the appendectomy was done before the age of 20 [133, 134]. There are two mutually exclusive interpretations of these findings. One is that the removal of the appendix is causally linked to a decreased risk of UC, and animal models have given some credence to this [135]. There have even been trials to utilize appendectomy in a clinical setting as an alternative therapy. The other is that there is an association between appendicitis and UC, i.e. patients who will get appendicitis are less likely to succumb to UC [136]. Data from a Swedish study seem to support this latter alternative, as the authors could find no protective effect against UC following the removal of a non-diseased appendix [137].

In Sweden there has been a dramatic decline in appendectomies. For instance, during the past 10 years the decrease was close to 20%, from 13 000 to 10 000, and this decline has been most pronounced in the younger age groups [138]. There are reasons to believe that this decline is not due to better diagnostic procedures, but actually reflects a decrease in the incidence of appendicitis. Appendicitis is another disease where the underlying etiology remains an enigma. There was a rise in appendicitis in the late 19th century, which seemed to peak in the 1950s followed by a decline in the Westernized world. It has been hypothesized that the rise in appendicitis could be due to improvements in sewage disposal and water supplies, leading to an enteric infection in childhood at an older age [139]. It is therefore not unlikely that appendicitis, UC and CD are part of the same disease spectrum, perhaps similar to other disease where hygiene in childhood is of importance for the future risk for disorders such as allergy and asthma [140].

Early exposures

The hypothesis of early exposures as of major importance for the risk of IBD was introduced in the 1970s by Whorwell *et al.* [141]. In two subsequent studies from Canada [142, 143] the authors were able to demonstrate that both early gastroenteritis and bottle feeding was associated with an increased risk for both UC and CD. Early weaning has also been reported as a risk factor [144], but the results have not been consistent [80]. Hygiene in early childhood with access to hot tap water has been implicated as a risk factor for CD [133, 134], as has being a single child or a first-born [146], which indicates later exposure to infectious events. As mentioned previously, similar associations have been proposed for the increasing incidence of appendicitis during the early 20th century.

There has also been a dramatic decrease in perinatal mortality during this century, and this has been proposed to be the underlying reason for the emergence of IBD [147]. Ecologic data (Fig. 5), where perinatal mortality 20–30 years before and incidence figures for CD are compared, are seductive. The underlying hypothesis is that children who previously should have been most vulnerable due to infectious events or an impaired immunologic defense are those who will succumb in a population with high perinatal mortality, and those survivors will be individuals who today will cause the rising incidence. The reasons for the decrease in perinatal

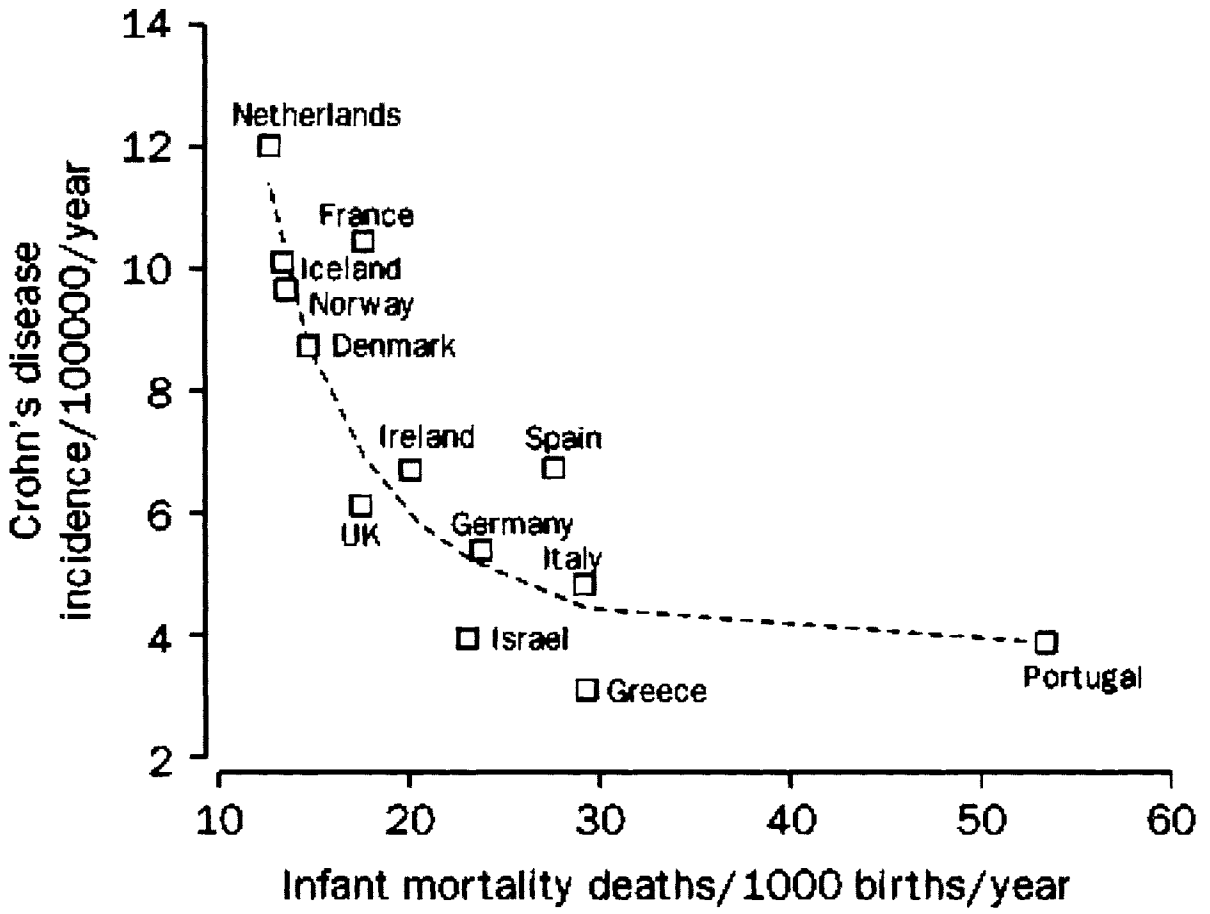

Figure 5. Incidence of Crohn's disease for ages 15–44 in 1991–1993 by infant mortality rate for 1960–1980, when the majority of patients with Crohn's disease were infants. (From Montgomery SM, Pounder RE, Wakefield AJ. Infant mortality and the incidence of inflammatory bowel disease. Lancet 1997; 349: 472–3; permission to publish given by author SM Montgomery).

mortality are better hygiene, better nutrition, and improved maternal and pediatric care, and this could therefore explain the changing faces of IBD from that of a disease much more common in higher socioeconomic classes than lower, during the emerging epidemic until now, when no such difference exists.

Clustering at time and place of birth has been reported for IBD [148], also indicating the importance of early exposures to infectious events. Besides gastroenteritis, different viral infections have been implicated, such as measles, varicella, herpes zoster, influenza and mumps [81]. Although a persistent viral infection has been proposed to be an underlying cause [149] this hypothesis remains unproven. Another hypothesis is that early viral infectious events would affect the immune response, especially if there is a history of repeated infections early in life [150].

The disappearance of a north–south gradient in Europe might be an illustration of what will happen when a society gains affluence. It will therefore be of extreme interest to follow the temporal trends for IBD in Eastern Europe and the former Soviet Union. They have already encountered a substantial increase in childhood disorders such as allergies and asthma since 1989 [140]. One of the more promising hypotheses to explain this phenomenon is that this is due to an altered microflora of the gastrointestinal tract. There have been substantial changes in the diet which will affect the bacterial flora in the intestines. There are strong indications that colonization in

early life will determine the subsequent microflora. Early infectious events can therefore be of importance by interaction with this colonization. If this hypothesis is true, we will see the emergence of an epidemic of IBD during the next decade affecting the younger age groups in countries such as the Baltic States, Poland, Hungary, etc. Japan [151] and Korea [152] are other countries with a low incidence of IBD, which have had substantial changes in their dietary habits during the past decade. We should therefore, in my opinion, focus our interest on these populations in order to learn more about the changes in the microflora of the gastrointestinal tract and the subsequent risk for IBD.

Conclusion

During the past 50 years IBD has become one of the major gastroenterologic problems in the Westernized world. It is disheartening that we have so far been unsuccessful in identifying the underlying reason for this. What we presently know for certain is that there is a genetic component, that smoking is protective against UC, but seemingly a risk factor for CD, and that a history of appendicitis under the age of 20 is protective against UC. All other faces of these two diseases have not been consistent over time. We are not even sure that there is a common factor for the two disease entities, although the uniformity in temporal trends over time in different populations indicates that this is the case. There are also strong reasons to believe that exposures early in life are of major determinance for the risk. However, what exposures, and the underlying mechanisms for them, still remain elusive.

On the other hand, it is very likely that for the next 10 years we will have a unique opportunity to learn more of the underlying mechanisms for IBD by conducting good epidemiologic studies in those populations where we might expect a change in incidence. We should also broaden our understanding of the underlying mechanism for appendicitis in younger age groups as that would probably give us some insights on what factors are operating early in life, determining the two different outcomes, appendicitis or UC. We should therefore not be too pessimistic; we have gained some insights during the past 50 years, but in order to proceed we must accept that both UC and CD change faces at different places and times, and adapt ourselves to this paradigm in both our clinical work and our research.

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