Inflammatory Bowel Disease

Translating basic science into clinical practice

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Preface

Inflammatory bowel disease research is changing. Progress in defining and treating these diseases is advancing in lock step with the furious pace of technological advances that continue to refine the tools of discovery. With sequencing of the entire genome completed, genetics research is providing direction for molecular and immunological *in vivo* and *in vitro* investigation, which in turn directs the development of targeted therapeutics. As translational investigation evolves, what is learned in clinical research is combined with what is learned in basic science research and is leading to a "personalized medicine" approach for managing inflammatory bowel diseases and is bringing the potential of prevention into view.

As Editors, our intention is that this book will provide insight along the entire continuum from basic science to clinical practice. The basic science chapters present findings in the context of what has already been established about the clinicopathological nature of the diseases. The clinical chapters describe the most effective applications of all available diagnostic and therapeutic approaches. This book reflects today's trends toward globalism and is a truly international effort. We encouraged our contributors to editorialize and provide thought-provoking, progress-stimulating content in their manuscripts. Now, more than ever, is the combination of all disciplines working in concert with the pharmaceutical industry key to the development of better treatments, with fewer side effects, and for predicting patient responses. As drugs become more specialized, it is vitally important to describe carefully patient populations both for study and for treatment. With ever increasing evidence that the inflammatory bowel diseases are heterogeneous disorders, drugs will likely only be effective in certain subpopulations of patients.

Above all, we hope that this book will stimulate future research to the point that achieving a diagnosis and development of a treatment plan will be directed by genetic, immunological and clinical markers of phenotypic distinctions.

We would like to express our sincere gratitude to each of the authors, our colleagues and partners, for nearly three decades of commitment to inflammatory bowel disease, and for their insightful, field-leading contributions. We would also like to acknowledge the commitment, patience and support of our publishers, Wiley-Blackwell, particularly Alison Brown, Adam Gilbert, Gill Whitley, Elisabeth Dodds and Oliver Walter.

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Chapter 1
Introduction: the Science and the Art of Inflammatory Bowel Disease

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This book is about the science *and* the art and the science *of* the art of gastroenterology as it pertains to inflammatory bowel disease. Once described as disabling and under-researched diseases, the inflammatory bowel diseases now attract intense interest from clinical and basic investigators, but remain an important cause of suffering and a major burden on healthcare resources.

Why another textbook, in this era of rapid information access? The answer is simple – there is a continuing need for informed opinion and perspective on the deluge of data generated in recent years spanning a diversity of aspects of inflammatory bowel disease. Many wish for a single repository of information from authoritative sources. With this in mind, the authors for this textbook were selected because they are expert and currently active contributors to their respective areas of the field. Each was charged with delivering a crisp, timely and opinionated account of their area with a futuristic perspective.

A recurring theme within modern biology in general and inflammatory bowel disease, in particular, is the need to think across traditional boundaries of intellectual pursuit and to be aware of research at the interface of disparate disciplines. The convergence of different research avenues in inflammatory bowel disease is represented by the host–microbe interface; other pertinent examples have been variably expressed as the brain–gut axis, immunoepithelial dialogue and neuroimmunology. Each is embraced in this textbook in various chapters dealing with disease mechanisms.

One of the great lessons of the recent past in gastroenterology was the failure of traditional epidemiologic and biologic approaches to identify a transmissible agent as the cause of peptic ulcer disease. A more important lesson was that the solution to some complex diseases may never be found by research focused exclusively on the host, without due regard for host–environment interactions, particularly host–microbe interactions. In the future, investigators involved in epidemiologic, genetic or other areas of research in inflammatory bowel disease will have to approach their challenge with some form of rapprochement with disease mechanisms. It is noteworthy, for example, that the genetic risk factors for inflammatory bowel disease are responsible for sensing and interpreting the microenvironment (e.g. NOD2/CARD15) or are involved in the regulation of the host immune response to that microenvironment (e.g. autophagy, IL23R). The complexity and clinical implications of these interactions are discussed by several authors in this volume.

Advances in technology have greatly facilitated research in inflammatory bowel disease. These include automated approaches to gene sequencing and genotyping large numbers of study subjects and molecular strategies for studying the intestinal microbiota, most of which is still unculturable and, therefore, neglected or considered until recently to be obscure. The human organism is now viewed as a composite of the human genome and its commensal microbial genome (microbiome), both of which interact with environmental and lifestyle modifying factors. As the human microbiome project and other similar metagenomic collaborations around the world deliver new information on the diversity and individual variations in the intestinal microbiota, it is anticipated that some of the heterogeneity of inflammatory bowel disease may be resolved. Thus, genetic risk factors will have to be reconciled with variations in microbial composition and with patterns of immunologic responsiveness to the microbiota. The challenge for epidemiologists and biologists will be to relate the aspects of a modern lifestyle with changes in the microbiota and thence with immunologic behavior and susceptibility to disease. Thus, the elucidation of the "IBD genome" provides the foundation for micro- and macro-environmental epidemiologic investigation. The contributing authors to this text have provided the background to this futuristic scenario.

Inflammatory Bowel Disease. Edited by S. R. Targan, F. Shanahan and L. C. Karp.

Has the relentless march of the biotech and genotech era of research delivered for the patient? Unquestionably patients are better off today than they were only a generation ago. A more coherent understanding of fundamental disease mechanisms is being translated into improved patient management with a progressive shift toward evidence-based approaches and away from therapeutic empiricism. This is reflected throughout those chapters of this book dedicated to patient care.

Although not quite at the stage of personalized healthcare, the splitters are in the ascendancy over the lumpers in today's approach to the patient with inflammatory bowel disease. Refinement of clinical phenotypes by fusing genetic variation and the functional consequences thereof will lead to the reclassification of standard clinical phenotypes into physiologically determined subgroups and ultimately to individualized therapeutic targeting. These critical steps will continue to inform the interpretation of data on the genotype. This represents just one of many opportunities for clinicians and basic scientists to engage in a mutually beneficial manner in translating bench-to-bedside research to improved management of inflammatory bowel disease.

But some things never change. Clinical care of chronic disease will always require attention to detail, compassion and a commitment to long-term follow-up. In the face of the extraordinary advances in therapeutics, which continue apace, there is substantial patient dissatisfaction with modern medicine, either because of increasing expectations or reduced tolerance of illness. Most patients place greatest emphasis on the doctor–patient relationship. In this relationship, the attitude and level of interest of the former will always be a major determinant of the outcome of the latter.

Textbooks like this cannot confer attitude, energy or enthusiasm on the reader, but they can sensitize and equip the reader with the necessary background information, opinion and perspective. Therein lies the essence of what is intended with this book – to provide stimulus and steerage for the interested clinician, scientist and clinician–scientist in what is already an intriguing and rewarding field of endeavor.

Chapter 2
Heterogeneity of Inflammatory Bowel Diseases

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Summary
- Heterogeneity in the inflammatory bowel diseases exists at the genetic, immunologic, subclinical and clinical levels.
- The mucosal inflammation that characterizes inflammatory bowel diseases is underpinned by multiple combinations of genes and innate and/or adaptive immune responses that determine disease expression and behavior.
- Serum immune responses are markers of underlying disease activity.
- Multiple genetic variants have been associated with inflammatory bowel diseases.
- Combinatorial genomics, studying the genetic variants and associated immune pathways in combination with disease markers, is leading to the development of distinct phenotypic subgroups and is identifying targets for the development of personalized therapeutic approaches.

Introduction

The chapters in this book describe the foundation of our premise about the heterogeneous nature of the inflammatory bowel diseases (IBDs). In the basic science chapters, we learn that mechanisms underlying disease expression vary genetically and immunologically and that potentially, the possibilities are as many as can be made with the known genes and variants, cells and microorganisms. In the translational and clinical chapters, we read evidence that distinct genetic and immunologic underpinnings differentiate groups of patients, setting the stage for a personalized medicine approach to treating these disorders.

Heterogeneity of inflammatory bowel diseases has been documented in the medical literature for more than a century. In 1905, Dr J.E. Summers Jr wrote, "Colitis of its different types is not uncommon; clinically, they are at some stages so much alike that a proper classification has not been made" [1]. In one simple sentence, we learn that early in the 20th century it was acknowledged by the medical field that there are many types of colitis, but defining them is confounded by their similarities and differences. Clinical heterogeneity of Crohn's disease is mentioned in the literature as early as 1932, when Dr Burrill Crohn published the first report of what he called "regional enteritis" in *JAMA* [2]. Dr Crohn described four "various types of clinical course under which most of the cases may be grouped: (1) acute intra-abdominal disease with peritoneal irritation, (2) symptoms of ulcerative enteritis, (3) symptoms of chronic obstruction of the small intestine and (4) persistent and intractable fistulas in the right lower quadrant following previous drainage for ulcer or abdominal abscess." Similarly, in 1953, Dr Bryan Brooke, writing about ulcerative colitis in reference to the likelihood that no single pathogen can be identified as causal, stated, "It is suggested that ulcerative colitis is not a specific disease, but a pathological state . . ." [3]. Dr J.B. Kirsner, in noting that ulcerative colitis has symptoms similar to other diseases, said, "Ulcerative colitis is merely a name for a class of disease which hitherto had been included under the name dysentery" [4]. From this era, when original observation and description were the hallmarks of excellence in medical research, decades of scholarly activity ensued, with an emphasis on trying to categorize the vast variability in clinical expression of inflammatory bowel diseases into descriptive categories for the purpose of diagnosis and treatment.

Attempts by physicians and scientists to harness IBD heterogeneous expression into the foundation of a framework by which to study these disorders has evolved into the modern hypothesis of disease pathogenesis. Early theories were based on the expectation that a single pathogen was to blame, although in the 1970s and 1980s this notion was abandoned by many and the immune response became the focus. By 1989, many of the elements of the contemporary hypothesis were in place. At that time, it was hypothesized that "tissue damage might be due to a

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direct attack by the mucosal immune system on a specific target, such as the surface, or glandular epithelial cell" [5]. The possibility of "a non-specific outcome of disordered mucosal immune regulation" was suggested, "with uncontrolled over-reactivity to environmental antigens based on a defective downregulation of this response" [5]. It was further postulated that "genetic predisposing factors and exogenous triggers might operate at the level of the 'target' cell or at the level of the mucosal immune system" [5]. In 1990, Dr Stephan Targan, leading an effort by a panel of experts to set a scientific agenda for inflammatory bowel disease research, advanced the concept of "reagent grade populations" [5]. Available treatments at the time were not aimed at any particular cause of disease. In the resulting "white paper", he described the need for defined populations of subgroups of patients with varying clinical and subclinical markers should be assembled. He further stated that:

> Such "reagent-grade" populations will be invaluable in reducing the time and improving the accuracy of all studies using tissues or dependent upon clinical signals from patients. These patients would be a source of materials for the tissue banks and would serve as an extant "pure" population for clinical trials of new therapeutic agents.

Over the last 20 years, three working parties have attempted to formalize an inflammatory bowel disease classification system. In 1991, an international working party assembled in Rome devised a classification for Crohn's disease based on anatomical distribution, surgical history and disease behavior. Seven years later, the "Rome Classification" was re-evaluated by a group attending the World Congress of Gastroenterology in Vienna. The resulting "Vienna Classification" of Crohn's disease proposed the parameters of age of onset, disease location and disease behavior. Most recently, a group meeting in Montreal expanded upon the three phenotypic parameters and modified the criteria. The "Montreal Classification" added distinctions made by serum immune markers and genetic markers and also proposed a classification for ulcerative colitis. The changes were "supported by an evolving body of evidence demonstrating that site of disease, behavior and disease progression are all variables that are likely to be identified by genetic and serological markers" [6].

It was not until the study of serological markers and their use for identifying pathophysiologically distinct subgroups that science yielded to the biologic reality that although it may be of clinical benefit and of benefit to researchers to define subgroups, numerous types of disease expression, with unique biologic processes and distinctive genetic, immunologic and clinical manifestation, exist. Nevertheless, to rein in the possibilities, focus investigation and to test treatments, groups of patients must be identified based on common, known variables. In the current hypothesis, that IBD results in a genetically susceptible individual via a dysregulated immune response to commensal flora, it has been established that there are multiple gene variants that are conferring susceptibility and that IBD patients mount immune responses to numerous microbes.

These authors long ago proposed that the classifications of Crohn's disease, ulcerative colitis and indeterminate colitis are somewhat false. This assertion was based on our emerging understanding of the underlying pathogenesis. Somewhat homogeneous groups of patients can be determined by similar genetic and immunologic and clinical data. Already a case is being made for determining whether to start biologic therapy early in the disease course for certain patients whose profiles suggest the likelihood of more severe disease. In the coming year, the first clinical trials of patients selected not by diagnosis of ulcerative colitis and Crohn's disease, but by a range of genetic and immunophenotypic characteristics, will begin.

Classical clinical heterogeneity

Classically, three major entities of IBD have been defined based on symptoms of disease and standard clinical laboratory, radiologic and histologic parameters: Crohn's disease, ulcerative colitis and indeterminate colitis. Abdominal pain, weight loss, diarrhea, urgency bloody stools and fever may be seen in all three. Crohn's disease is characterized by transmural inflammation with the potential to affect the entire gastrointestinal tract from mouth to anus. In ulcerative colitis, inflammation is superficial and localized to the large intestine and rectum. Indeterminate colitis is the term applied to 10–15% of IBD patients for whom the distinction cannot be made.

Disease behavior is also variable across subtypes of patients with Crohn's disease and ulcerative colitis. Although both disorders are considered to be relapsing and remitting diseases, some patients experience one flare and others experience constant symptoms. Some patients will have a mild course of disease, treatable with 5-ASA products, and others will have very severe disease that is refractory to all modalities attempted. Of course, presentations by individual patients will vary, with some at every point along the continuum. A somewhat arbitrary distinction has been made between Crohn's disease that is "inflammatory" or stricturing and penetrating. The presentation of extra-intestinal manifestations of inflammatory bowel diseases can often be heterogeneous. Some patients may develop rheumatologic, hepatic, ophthalmic and dermatologic effects secondary to their intestinal inflammation and others may not. Any potential combination of these is also possible.

Pouchitis, an inflammatory disease of the reservoir surgically constructed in ileal pouch–anal anastomosis, is

generally thought to occur in patients with underlying ulcerative colitis. The pathogenesis of pouchitis is not firmly established; however, consistent with the hypothesis described above, it is likely the result of an immune response to microbes in the pouch. As described in Chapter 30 by Shen, specific genetic variants have been associated with pouchitis, including IL-1 receptor antagonist [7,8] and NOD2/CARD15 [9]. Expression of a serum immune marker profile including perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), anti-*Saccharomyces cerevesiae* antibodies (ASCA), antibodies to *Pseudomonas fluorescens* (anti-I2) and antibodies to the *Escherichia coli* outer membrane porin-C (anti-OmpC) is associated with chronic pouchitis [10–12].

Classical diagnostic aids are used to differentiate from among many disorders with overlapping symptoms. In Chapter 21 by Schlenker, Eng and Surawicz, we learn that infectious colitides can be confused with IBD, as can other colitides, including diverticular disease and ischemia and colitis caused by therapeutics and radiation treatment for cancer. In the chapter on pathology by Royston and Warren (Chapter 17), we likewise learn that there are multiple potential pitfalls to histopathologic differentiation of these disorders.

One diagnostic tool, capsule endoscopy, has been useful in differentiating Crohn's disease in a specific subset of patients. In Chapter 18 by Dai and Lo, we learn that capsule endoscopy may discover Crohn's-like lesions in 16% of symptomatic patients with a prior diagnosis of indeterminate or ulcerative colitis [13].

Laboratory heterogeneity

C-reactive protein (CRP) is an important acute phase protein. In the acute phase of inflammation, CRP production is increased resulting from influence of interleukin (IL)-6, tumor necrosis factor α (TNF-α) and IL-1β. CRP is generally highest at the onset of a flare of inflammation and decreases in association with treatment. Patients with Crohn's disease tend to have elevated CRP responses, whereas patients with ulcerative colitis tend to have low or no CRP response. Ulcerative colitis and Crohn's disease have heterogeneous CRP responses [14]. Whereas Crohn's disease is associated with a strong CRP response, ulcerative colitis has only a modest to absent CRP response. Simple biologic explanations have failed to understand the reason for this difference; however, recently it has been reported that polymorphisms in the CRP gene may explain the differences in CRP production in humans [15–17]. In another study, however, no association was found [18]. A recent study demonstrated that the CRP 717 mutant homozygote and heterozygote status is associated with lower levels of CRP and that CRP levels are influenced by specific genetic polymorphisms [19].

Genetic heterogeneity

The symptomatic and clinical and immunologic heterogeneity of IBD summarized above is underpinned by multiple genetic variations. To date, 33 variants have been defined and many more are expected. These genetic associations can roughly be considered to contribute to either innate or adaptive immune responses. In Chapter 4 by Vermeire, McGovern, Van Assche and Rutgeerts, the genetic underpinnings of IBD heterogeneity are explored. Variants of the CARD15 gene have received by far the most attention and account for only about 20% of susceptibility in Crohn's disease, highlighting the certainty that many variants are at play in producing IBDs. Studies of the functional effects of the relevant genes in unaffected individuals and IBD have demonstrated the importance of immune pathways in the disease pathogenesis. This chapter also introduces the emerging role of autophagy in pathogenesis. The autophagy-related 16-like 1 gene (*ATG16L1*) and the IRGM gene [20,21] are both involved in autophagy, a process involved in the elimination of intracellular bacteria, and suggest that autophagy may play a protective role.

With genetic research ever more rapidly producing data, efforts to associate disease behaviors are making rapid progress. Specific gene variations have been associated with particular disease phenotypes (reviewed in [22]). For example, *NOD2/CARD15* variants are associated with onset at a young age and with complicated ileal disease (reviewed in [22]). Further studies of IBD subgroups with homogeneous clinical phenotypes may increase the likelihood of finding new susceptibility genes that are specific to those phenotypes.

Since the advent of techniques such as genome-wide association studies (GWAS), the rate of discovery has skyrocketed. Using findings from GWAS as a starting point, new pathways associated with disease pathogenesis are being discovered, as has been mentioned above with autophagy. This pathway was discovered only after the two related genes had been found. Also described in Chapter 4 is the developing information regarding *TNFSF15*. TL1A, the product associated with this gene is considered to be a master regulator of mucosal inflammation and among other functions, induces NFkB. In a sub-population of patients with IBD, TL1A levels are elevated in the mucosa. It has been shown recently that that *TNFSF15* haplotypes are associated with TL1A expression that is further delineated when considered with serologic responses and ethnic background [23]. Genetic information has also helped to elaborate understanding of other IBD processes. For example, the innate immune and the IL23/IL17 pathways, both of which contribute to an increased risk of developing IBD.

Multiple combinations of genetic variants and immunologic pathways lead to IBD. Therefore, it is likely that

progress in understanding susceptibility, improving tools for diagnostic accuracy and developing new treatment targets will depend on parallel investigations that pursue both the genetic underpinnings and the resultant pathway abnormalities. Dubinsky and Denson, in Chapter 20, suggest that the future application of candidate genes is that they may ultimately be used as predictors of immune responses to drugs designed to intercede at the relevant immunologic pathway, in keeping with trends toward personalized medicine.

Biomarkers of disease

Much progress has been made in identifying biomarkers, discovering the underlying inflammatory processes and sub-stratifying disease groups based on these markers and certain genetic variants.

Chapter 20 by Dubinsky and Denson delineates the currently known array of serologic markers associated with IBD. ANCA, ASCA, anti-OmpC, anti-I2 and antibodies to the CBir1 flagellin (anti-CBir1) have been associated with IBD. The presence of one or more antibody and the level of expression have been linked to different disease phenotypes. Levels and combinations of antibody expression have been linked to inflammatory bowel disease phenotypes.

pANCA is associated with ulcerative colitis and with an ulcerative colitis-like presentation of Crohn's disease. Some 60–80% of ulcerative colitis patients express pANCA, as do approximately 20% of patients with Crohn's disease. The pANCA associated with ulcerative colitis is distinguished by perinuclear highlighting upon immunofluorescence staining and by DNAse sensitivity. The ulcerative colitis-related pANCA differs from those associated with vasculitides. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is a marker that is present in approximately 60% of Crohn's disease patients and 10% of ulcerative colitis patients. Antibodies to the *E. coli* outermembrane porin C (OmpC), the *Pseudomonas fluorescens* Crohn's disease-related protein (I2) and the CBir1 flagellin have also been associated with IBD, predominantly Crohn's disease. Antibodies to OmpC are found in 30–60% of patients with Crohn's disease, sero-reactivity to I2 has been demonstrated in 55% of Crohn's disease patients and an immune response to CBir is detected in 50% of patients with Crohn's disease.

As mentioned, IBD has a vast spectrum of clinical presentations that range from purely inflammatory disease to that which progresses to severe, as defined by fibrostenotic/obstructive or penetrating features, usually associated with fistulization and/or abscess formation. Much progress has been made in the effort to define the nature of the relationship of immune responses to the different phenotypic expressions.

It has been established that subgroups of patients can be stratified based on antibody expression: (1) patients who respond to only one microbial antigen such as either oligomannan ANCA, ASCA, OmpC, CBir or I2, (2) patients who respond to two or three antigens, (3) patients who respond to all known antigens and, finally, (4) patients with no reactivity to any of the confirmed antigens. Patients with the highest complication rate (stricturing, fibrostenosis, etc.) are those who react to most or all of the microbial antigens and those who had the lowest complication rate or progression were in the group without antibody expression. When factoring in amplitude of antibody response, the patients with the highest level antibody expression had the highest complication rate and those in the low level or no response group were least likely to develop complications. Virtually all patients with the highest level response to all antigens experience at least one of these complications, compared with less than a 5% chance among patients with low level antibody expression.

Associations have been found between variants in NOD2/CARD15 and disease phenotypes [24,25], leading to the supposition that the severe innate immune responses lead to higher adaptive immune responses, and thus a more severe disease phenotype. In this model, more genetic defects in innate immunity (NOD2−/NOD2− vs NOD2+/NOD2+) result in a more aggressive adaptive immune response as expressed by higher serum immune markers, and thus a more severe dusease course [26]. See Figure 20.3 in Chapter 20 by Dubinsky and Denson.

Heterogeneity of treatment responses

Why do some patients respond to some therapies and others do not? Why does the effectiveness of a certain therapy wane over time? These are ongoing questions with better and better answers. For example, in Crohn's disease, lack of anti-TNF effectiveness in some patients could be because the immune process may be TNF-α independent. Decreasing response could be because the global suppression of TNF may result in activation of a different immune pathway (see Chapter 7 by Abreu, Fukata and Breglio, and Chapter 8 by McDonald and Monteleone.

In the chapters on cytokines and chemokines by Maillard and Snapper (Chapter 10) and healing/repair by Playford and Podolsky (Chapter 12), we learn about their multiple effects and the potential presented by many as targets for therapeutic development. Because of the complex interrelationships among growth factors/cytokines/chemokines, targeting one specific cytokine might have considerable effects on a large number of others. There is an ever-growing number of these targets, but even those seeming to be the most central to inflammation do not necessarily render a therapeutic that will work in more than a subset of patients, as demonstrated by the

experience with antibodies to TNF, antibodies to IFN and others.

Evidence of IBD heterogeneity from animal models

Over the last two decades, the technology for development of animal models has become increasingly exact. In Chapter 5 by Elson and Weaver, we learn that many combinations of gene protein insertions and deletions result in colitis. The numerous animal models that emerged over the last two decades show that the final common pathway of many alterations is mucosal inflammation. Animal model investigation has highlighted the roles of both innate and adaptive immunity in IBD. This process is revealing the genes, proteins and pathways that are likely to produce dysregulated inflammation and also the key elements of gut homeostasis. The work is becoming increasingly translational, with findings from animal models quickly tested *in vitro* in humans and findings from human research to be researched in animals. As genetic research identifies the relevant immunologic disease pathways, this information will result in improved animal models, an example of which is described below in the case of TL1A.

Harnessing heterogeneity – the future of IBD research

An excellent example in which utilizing concepts of heterogeneity translates to clinical care is found in a review of the recent work on *TNFSF15* and TL1A. This work has taken a linear path of investigation and demonstrates the foundation of a basic, translational and potentially clinical opportunity. The initial discovery of TL1A has given way to subsequent genetic, human and animal investigation at the bench and will reach the bedside in the form of a clinical trial in 2009–10. Furthermore, *TNFSF15* and TL1A fit superbly into the personalized medicine paradigm, in which the combination of genetic, biologic and microenvironmental information may well combine to inform the design of a therapeutic for the subgroup of CD patients that will be uniquely likely to benefit.

TL1A protein was first cloned in 2002 at Human Genome Sciences [26]. TL1A is a very potent enhancer of IFN-γ production. Microbial activation of TL1A plays an important role in modulating the adaptive immune response. TL1A levels are elevated in the mucosa of patients with Crohn's disease. Work in animal models has shown that neutralizing TL1A antibodies attenuates colitis. In genetic research, GWAS have established that the *TNFSF15* gene is a Crohn's disease susceptibility gene [27]. Variants of the *TNFSF15* gene have been found in all ethnic groups studied. Interestingly, however, the associations vary among the cohorts in terms of diagnosis and conferred risk. A recent GWAS revealed a significant association of genetic variants of the *TNFSF15* gene with Crohn's disease in a large cohort of Japanese patients, in several European cohorts [27,28], in US Jewish patients [29] and combined data from the NIDDK IBD Genetics Consortium, Belgian–French IBD Consortium and the WTCC [30]. Haplotypes A and B are associated with susceptibility in non-Jewish Caucasian Crohn's disease and ulcerative colitis. In addition, *TNFSF15* haplotype B is associated not only with risk, but also with severity in Jewish Crohn's disease [23,29,31]. We recently discovered that in addition to Crohn's disease, variants in the *TNFSF15* gene are also associated with both Jewish and non-Jewish severe ulcerative colitis needing surgery. Moreover, monocytes from Jewish patients carrying the risk haplotype B express higher levels of TL1A in response to FcγR stimulation [23]. These results show that Crohn's disease-associated *TNFSF15* genetic variations contribute to enhanced induction of TL1A that may lead to an exaggerated Th1 and/or Th17 immune response, resulting in severe, chronic mucosal inflammation. TL1A is an ideal molecule to link genetic variation and functional protein expression to *severity* and, ultimately, to targeted therapy in the appropriate subset of CD patients. If the results of animal model, genetic and immunologic investigation are combined to select the population of patients most likely to respond to TL1A blockade, it is expected that increased efficacy will be shown in that population. Such investigations are already producing results consistent with this expectation. Current research efforts are aimed at defining mechanisms of TL1A expression and function in inducing a more severe Crohn's disease mucosal inflammation and at defining the population of patients who will respond best to therapeutic blockade of TL1A function.

Conclusion

With more complete understanding of the "IBD genome", genomic-based epidemiology can guide our efforts to determine the process by which disease is initiated and perpetuated in groups of patients with specific profiles. As technology improves, further definition of the microbiome may prove that in different populations, different types of bacteria may be most relevant. These micro-epidemiologic findings can be linked with macro-epidemiologic information to reveal these precise relationships.

As biomedical progress moves more closely to the personal medicine paradigm, the understanding of the heterogeneous nature of IBDs will highlight potential targets for therapeutic development at the genetic and immunologic levels. The most productive avenues of investigation will select populations of patients for study, based on specific phenotypic criteria. The ultimate goal of harnessing

heterogeneity of IBD is an integration of scientific discovery that impacts on patient care. In this scenario, a patient presenting with symptoms would receive a panel of laboratory tests to establish their serotype, genotype and phenotype. The specific IBD phenotype will indicate the likely prognosis of the patient's disease and will further indicate a patient-specific treatment plan using newly discovered, integrated, target-specific therapeutics.

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Chapter 3
Epidemiology of Inflammatory Bowel Disease: the Shifting Landscape

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Summary

- One theory proposed to explain the emergence of IBD as a disease of western or developed nations through the middle of the 20th century has been the "hygiene hypothesis". This hypothesis posits that IBD (and other chronic immune diseases) emerged in the developed world, concurrent with a marked enhancement of personal and societal hygiene and decrement in infant mortality. This meant that there emerged a loss of tolerance to organisms that might otherwise be encountered in childhood, in a dirtier environment, which leads to aberrant immune responses when those organisms or mimicking antigens are presented at an older age.
- The hygiene hypothesis can apply to the emergence of late of IBD in the developing world where the developing world is now encountering more and more IBD, as it becomes "cleaner". Other environmental and societal factors in the developed world include westernization of diets and the broader introduction of western medicines including antibiotics and vaccines.
- Data from the past decade from developed countries have revealed that the incidence rate of Crohn's disease has overtaken that of ulcerative colitis. In areas where the incidence rate of ulcerative colitis is still higher, the trends are suggesting increasing rates of Crohn's disease. In developing countries ulcerative colitis is the predominant form of IBD.
- There seems to be a rising incidence of isolated colonic disease among Crohn's disease phenotypes, begging the question as to whether the emergence of a greater incidence of Crohn's disease over ulcerative colitis was real or whether much of the former high rates of ulcerative colitis encompassed misdiagnosed colonic Crohn's disease.
- Clues to disease etiology are more likely to arise from studies in pediatric and developing world populations where dietary and environmental impact may be more evident than in studies from developed nations with longstanding burdens of IBD.

Introduction

The epidemiology of inflammatory bowel disease (IBD) has been described for over 50 years with early population-based data being available from the Olmsted County, MN, USA and Northern Europe. In the past decade, there has been an onslaught of data from a variety of countries, including developing and Asian countries where IBD had rarely been seen. For the casual reader of the IBD epidemiology literature, it is easy to gloss over the study details and simply focus on the reported incidence and prevalence rates. However, epidemiology studies are conducted very differently in different jurisdictions. The study process is often dictated by what type of data collection or access is available. For example, in Scandinavia, the UK and Canada, administrative health data are collected comprehensively, inclusively and are accessible to researchers. In developing nations and countries of Eastern Europe, there are not only poor administrative data collection resources, but also variable access to care and in some instances various standards of care. This clouds the interpretation of clinic-based or single hospital-based studies and lessens the applicability of their findings to the broader population of the area under study. Some studies are presented as being population based where they are derived from a compilation of practices and not administrative data. Although the comprehensiveness of data collection from any one center is believable, the percentage of non-participation or a comparison between participating practices and those not participating are often missing from the methodology description. In the USA, arguably the country with access to the most advanced health technology for some sectors of its population, population-based studies are nearly impossible, because of the varied health insurance programs that exist. Multi-clinic and/or hospital studies in the USA are always subject to criticisms of bias.

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It is clear in western Europe, Canada and the USA that IBD has emerged as predominately an outpatient disease at diagnosis and for chronic management. Most diagnoses are made on outpatients and 50% of patients avoid hospitalization in the first 15 years from diagnosis [1]. However, it is possible that in eastern Europe and the developing world and in developed nations where IBD is uncommon (such as Japan and Korea), a sizeable number of IBD patients will be diagnosed in a hospital setting. Hence hospital-based or centralized specialty clinic-based studies may be more representative of the whole population than if such a study was conducted in the USA.

Pediatric studies, like adult studies, are more robust and representative when population based. However, pediatric studies conducted from hospital practices or centralized specialty clinics are more likely to be representative and less subject to bias than adult studies since it is more typical for children to be referred to centralized specialist care than adults. Pediatric gastroenterologists are fewer in number and more likely to congregate in group practices, particularly in pediatric hospitals. When assessing pediatric IBD studies, it is important to note the ages included. For many it is 15 years or younger. However, for some it is less than 18 years and those extra 2–3 years can markedly affect the final incidence data. On the one hand, children ages 16 and 17 years may be evaluated by adult gastroenterologists and not captured in pure pediatric settings. On the other hand, the incidence rates typically rise through later teenage years into the third decade and the inclusion of older children will increase incidence rates.

Why do we care so much about IBD epidemiology data and why does this topic still warrant a chapter in a state-of-the-art textbook on IBD where new gene discoveries and biological therapies are reviewed? First, it is important to appreciate the burden of disease with regard to sheer numbers. It is important to consider in the allocation of research resources as to whether the disease is rare, common or increasingly emerging. Second, patterns of disease can give clues to disease etiology. Just because researchers have yet to assemble conclusively the epidemiological clues into a defining etiologic paradigm in IBD does not mean that the clues are not emerging accurately. The failure to have clinched an etiologic cause(s) does not negate the potential that epidemiologic observations provide. The hygiene hypothesis [2] is one hypothesis to emerge from epidemiologic studies. In brief, with the epidemiology showing an emergence of IBD in the developed world, concurrent with a marked enhancement of personal and societal hygiene and decrement in infant mortality, this hypothesis suggests that it is in fact the loss of tolerance to organisms that might otherwise be encountered in childhood, in a dirtier environment, that leads to aberrant immune responses when those organisms or mimicking antigens are presented at an older age. This hypothesis can be applied to the evolving epidemiology where the developing world is now encountering more and more IBD, as the developing world becomes "cleaner". The emergence of IBD in the developing world in the past decade may also be a side effect of globalization. People in Asia, Africa and the former Soviet Union are now doing what people in the developed world have been doing for decades, including diets higher in fat and refined sugars, fast foods, reduced in fiber and reduced physical activity and increased refrigeration of foods. There is also increasing ingestion of pharmaceuticals even in the developing world, including therapeutics, additives and vaccines. Hence the clearer the picture of IBD presentation can be made based on a global view, the more clues will emerge as to what may be causing it. In parallel with genetics research, it is fascinating to observe the increasing incidence rates in various countries that are far outpacing what genetic evolution could instigate.

In this chapter, the recent epidemiology of IBD will be reviewed. The chapter is focused on reports published since 2000 and, where possible, on data from the mid-1990s into the 2000s.

The emergence of Crohn's disease as the most common form of IBD

Almost uniformly, the data from the past decade from developed countries have revealed that the incidence rate of Crohn's disease has overtaken that of ulcerative colitis. In areas where the incidence rate of ulcerative colitis is still higher, the trends are suggesting increasing rates of Crohn's disease. Not unexpectedly, where available, prevalence data have lagged behind and in many jurisdictions the prevalence of ulcerative colitis remains higher than that of Crohn's disease. The incidence data for Crohn's disease have been remarkably consistent in Northern Denmark (9.3/100,000) [3], Copenhagen County, Denmark (8.6/100,000) [4], Northern France (8.2/100,000) [5] and Olmsted County, MN, USA (8.8/100,000) [6]. The incidence rates of ulcerative colitis are more varied, including Northern Denmark (17/100,000), Copenhagen County, Denmark (13.4/100,000), Northern France (7.2/100,000) and Olmsted County, MN, USA (7.9/100,000) [3–6]. A very interesting contrast is posed by data from Canada and New Zealand [7,8].

Using the administrative definition of IBD validated in Manitoba in 1995 [9], investigators applied the definition to similar administrative health databases in British Columbia, Alberta, Saskatchewan, Manitoba and Nova Scotia for the years 1998–2000 [7]. The mean incidence rate for Crohn's disease was 13.4/100,000. An interesting finding was that the incidence rate in British Columbia was 8.8/100,000, which was significantly lower than that in the other provinces. It is interesting to speculate whether

Table 3.1 A summary of European IBD epidemiology data from 1991 to 1993.

	Males	Females
Crohn's disease		
North	6.2/100,000	7.9/100,000
South	3.8/100,000	4.0/100,000
Ulcerative colitis		
North	12.5/100,000	11.1/100,000
South	10.3/100,000	6.9/100,000

Based on data from Shivananda S, Lennard-Jones J, Logan R *et al.* Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996; **39**:690–7.

the lower rates in British Columbia relate to its environment (i.e. Pacific coast, Rocky Mountain range) or to the fact that nearly one-quarter of its population are visible minorities, many of whom were recent immigrants within the past two decades. Nonetheless, the incidence rates for Crohn's disease in Canada are among the highest in the world. Considering its northern location, it reminds us of the original hypothesis proposed from Europe in the 1980s that the high rates in the UK and Scandinavia versus the low rates in Mediterranean countries reflected a north–south gradient. Might this gradient be explained by sunlight exposure or climate differences? Incidence data from 2004–05 from New Zealand were 16.3/100,000, comparable to Canadian data [8], diminishing the likelihood that lack of sunlight or temperate versus tropical climate is an important disease trigger.

A re-evaluation of European data in 1996 suggested that perhaps the earlier proposed north–south gradient was overstated based on primitive southern European data, since the updated data revealed a lessening of the gap between northern and southern European data [10]. Table 3.1 reveals rates reported from Europe up to the 1990s adapted from the European Collaborative Study on IBD [10]. These data show not only differences between northern and southern European rates of Crohn's disease and ulcerative colitis but also summarize an era when ulcerative colitis was more common than Crohn's disease. A recent study from northern Spain suggested incidence rates of 9.5/100,000 for Crohn's disease and 7.5/100,000 for ulcerative colitis (ever closer to rates from northern Europe) [11], while a study from northwest Greece reported low rates for both diseases (rates could not be calculated) [12]. In Greece, like other emerging countries, however, the incidence of ulcerative colitis far exceeded that of Crohn's disease [12].

There have been population-based data from France and Scotland that suggested within each country that the northern areas have higher rates than southern areas [13,14]. However, the fact that the northern areas may have higher rates than southern areas may be more coincidental and less informative than more global north versus south patterns. Within each country there may be ecological, topographical, socioeconomic or genetic factors that drive higher rates in some areas versus others. Perhaps etiological clues can emerge from these differences within any one country, and these differences should be sought. However, the likelihood that these differences reflect something specific about a northern location within any one country is low. In Manitoba there is wide variation between areas in terms of incidences of ulcerative colitis and Crohn's disease, but these did not follow a north–south pattern [15]. In fact Canada's north has very low rates of IBD compared with Canada's south, owing in part to the genetic makeup of the majority of northern dwellers in Canada (mostly Aboriginals). However, the sparseness of the population, the topography or the different dietary and childhood patterns of disease and infection may in fact provide important clues. However, this pattern of higher disease density in the south of Canada does not refute an overall north–south gradient of disease, much as the higher density of IBD in France's north does not prove that on a global basis northern countries have higher incidence.

It is unknown whether the high Canadian rates reflect a north–south gradient within North America. The only population-based data from the USA are from Olmsted County, MN [6], which is only 400 miles south of the Canadian border, and rates there have been reported to be just over half the rates reported from Manitoba. However, an unpublished update of the Olmsted County data to 2004 suggest rates much closer to those of Manitoba (Crohn's disease 12.9/100,000 and ulcerative colitis 12.5/100,000) [16]. Unfortunately, data from the southern USA where there is greater ethnic diversity are unavailable. Previously, using Veterans Administration data and also Medicare data, a north–south gradient within the USA was reported [17,18]. Hence it may be premature to dispense with the possibility that a north–south gradient exists. Even if the gap narrows in incidence rates between north and south (such as the high rates reported in New Zealand), it does not negate the potential clues to etiology that might exist by having seen high rates in northern countries initially and the recent emergence of the disease in the south. If the incidence rates in southern Europe are rising, then what is driving this progression?

It was recently suggested that much can be learned by studying the western Europe–eastern Europe dichotomy in IBD incidence [19]. Recently, the incidence rates of Crohn's disease and ulcerative colitis, respectively, in Hungary were 2.2/100,000 and 5.9/100,000 [20], in the Czech Republic were 3.1/100,000 for ulcerative colitis (rates for Crohn's disease in the non-pediatric population are lacking) [21], in Romania were 0.5/100,000

Table 3.2 Studies of adults with IBD.

Jurisdiction	Years	Study design*	Incidence rate per 100,000	
			Crohn's disease	Ulcerative colitis
North Denmark [3]	1998–2002	Population based	9.3	17
Copenhagen County, Denmark [4]	2003–2005	Population based	8.6	13.4
North France [5]	2000–2002	Population based	8.2	7.2
Olmsted County, MN, USA [6]	1990–2000	Population based	8.8	7.9
Canada [7]	1998–2000	Population based	13.4	11.8
New Zealand [8]	2004–2005	Population based	16.3	7.5
Northern Spain [11]	2000–2002	Clinic based	7.5	9.1
Hungary [20]	1997–2001	Clinic based	2.2	5.9
Czech Republic [21]	1999	Clinic based	1.5	1.5
Romania [22]	2002–2003	Clinic based	0.5	0.97
Croatia [23]	2000–2004	Clinic based	7	4.3
French West Indies [33]	1997–1999	Clinic based	1.9	2.4

*Clinic based refers to hospital- and/or outpatient clinic-derived data. In some instances these sources may facilitate a population-based study, but where there was any uncertainty the references were identified as being clinic based.

and 0.9/100,000 [22], in Croatia were 7/100,000 and 4.3/100,000 [23] and in Poland ulcerative colitis was considerably more common than Crohn's disease (rates were not calculated) [24]. These studies are mostly specialty clinic or hospital derived, although in Hungary an extensive effort has been made to recruit gastroenterologists across the country. What can be learned from these data is that in general the rates of Crohn's disease and ulcerative colitis were lower than elsewhere in Europe and that mostly ulcerative colitis is more common than Crohn's disease. This is typical of the emergence of IBD in developed nations and hence we can expect to see rates of Crohn's disease overtaking those of ulcerative colitis over the next decade.

Data from emerging nations such as South Korea [25], China [26,27], India [28,29], Iran [30], Lebanon [31], Thailand [32] and the French West Indies [33] reveal a clear pattern of greater rates of ulcerative colitis over Crohn's disease. Although these rates are lower than in the developed world, there are indications that they are greater than what might have been seen two decades ago. Of course, in many of these countries there remain issues of the comprehensiveness of data collection, and also access to care of the populations. It is noteworthy that amidst Manitoba's high rates of IBD exists the First Nations Aboriginal community (comprising 10% of the entire population). Much of the First Nations communities are located in the more sparse north of Manitoba and have living conditions that in some communities are more akin to the developing world, without flush toileting and in crowded conditions. Another sizeable First Nations community exists in the core of the city of Winnipeg. All of these communities, both rural and urban, have been shown to have significantly lower rates of Crohn's disease and ulcerative colitis than the non-First Nations Manitoba population [15]. However, the rate of ulcerative colitis is approximately four times that of Crohn's disease. This mirrors the rates of IBD from the mid-20th century in developed countries and from the developing world at present. Table 3.2 lists recent era studies of incidence data among adults with IBD.

Pediatric IBD

With peak incidence rates typically in the third decade of life, it is possible, if not probable, that events in childhood are shaping the ultimate development of IBD. The other aspect of assessing pediatric data is that children's lives are sufficiently short that clues to etiology might be more easily discerned. Dietary intake, living conditions and demographics can be more easily and accurately recorded in children than for adults. Almost uniformly, the modern pediatric data are from northern Europe and much of it is population based. Nearly all of the data show higher incidence rates for Crohn's disease than ulcerative colitis. These rates for Crohn's disease ranged from 2.3/100,000 to 4.9/100,000 and for ulcerative colitis from 0.8/100,000 to 2.4/100,000 (Table 3.3) [4,33–39]. Data from Finland in 2003 were contrary to this trend, with incidence rates in Crohn's disease of 2.6/100,000 and in ulcerative colitis of 3.2/100,000 [40]. In Copenhagen County, Denmark, the incidence rates in 2003–05 for Crohn's disease were 2.7/100,000 for those aged 15 years and under and 4.4/100,000 including all those younger than 18 years [4]. In fact, for ulcerative colitis the incidence rate for those younger than 18 years was 5.0/100,000, greater than the rate for Crohn's disease. Even in southern and eastern European countries such as Northern Spain [11] and the Czech Republic [41,42], Crohn's disease is outpacing ulcerative colitis among the pediatric population. In Saudi Arabia, in a single hospital in Riyadh, the rates of

Table 3.3 Studies of children with IBD.

Jurisdiction	Years	Age (years)	Study design*	Incidence rate per 100,000	
				Crohn's disease	Ulcerative colitis
Copenhagen County, Denmark [4]	2003–2005	<15	Population based	2.7	2.4
Copenhagen County, Denmark [4]	2003–2005	<18	Population based	4.4	5.0
Scotland [14]	1981–1995	<16	Population based	2.3	1.2
France [34]	1988–1999	<17	Population based	2.3	0.8
Sweden [35]	1990–2001	<16	Population based	4.9	2.2
Norway [36]	1999–2004	<16	Clinic based	3.6	2.1
The Netherlands [37]	1999–2001	<18	Population based	2.1	1.6
South Wales [38]	1996–2003	<16	Population based	3.6	1.5
Wisconsin, USA [39]	2000–2001	<18	Population based	4.6	2.1
Canada [7]	1998–2000	<20	Population based	8.4	3.9
Finland [40]	2003	<18	Clinic based	2.6	3.2
Northern Spain [11]	2000–2002	<15	Clinic based	5.7	1.4
Eastern Czech Republic [41]	1998–2001	<16	Clinic based	2.7	1.8
Czech Republic [42]	1998–2001	<16	Clinic based	1.3	Not stated

*Clinic based refers to hospital- and/or outpatient clinic-derived data. In some instances these sources may facilitate a population-based study, but where there was any uncertainty the references were identified as being clinic based.

ulcerative colitis were similar to those of Crohn's disease [43]. For those studies reporting trends, all reported an increase of Crohn's disease with either stagnation or a decrease in rates of ulcerative colitis (Copenhagen, France, Sweden, Norway, Czech Republic) [4,34–36,41,42]. Hence it is clear that Crohn's disease is emerging as the predominant form of IBD. In adults, rates of ulcerative colitis are not diminishing but in some areas they are in children. Hence the environmental factors contributing to Crohn's disease persist and may even be more easily identified. Children have led shorter lives than adults with likely more routine eating and lifestyle habits and with little movement between jurisdictions. Their habits are also often carefully tracked by parents and caregivers, making survey data potentially more reliable than in adults, who present at various ages and are asked retrospectively to consider events of the distant past.

The demographics of IBD

While Crohn's disease has emerged as the more predominant form of IBD, there has also been a swing towards more males with disease than females. In the past, the sex ratio has been mostly equal for ulcerative colitis, with a 30% predominance of females in Crohn's disease. While a female predominance of Crohn's disease has remained in northern Denmark, France, Canada, New Zealand, Northern Spain and French West Indies [3,5,7,8,11,33], rates are similar between males and females in Copenhagen County, Denmark, Olmsted County, MN, USA and Hungary [4,6,20]. Further, there was a male predominance in emerging IBD areas such as Greece, China, Lebanon, Romania and Croatia [12,22,23,26,27,31]. In the pediatric literature, a male predominance was evident in all studies in which it was reported (Scotland, Sweden, The Netherlands, Wisconsin, Czech Republic [14,35,37,39,42]), except for France and Finland, where the sex distribution was equal [34,40]. Hence for Crohn's disease the trends amongst children and emerging nations and in many of the adult studies are of an increase in males presenting with Crohn's disease. In ulcerative colitis, the equality of the incidence by sex was evident in studies from northern Denmark and Copenhagen County, Denmark, Canada, Northern Spain, Hungary and Croatia [3,4,7,11,20,23], with a male predominance in studies from France, Olmsted County, MN, USA, Romania, China and Lebanon [5,6,22,26,27,31]. In ulcerative colitis, the equality of the incidence by sex was evident in pediatric studies from Scotland, Sweden, Finland and the Czech Republic [14,35,40,42], with a male predominance in studies from The Netherlands and Wisconsin [37,39]. Only in the French West Indies was there a female predominance [33]. So what is it about males that has led to their emergence as the increasingly more affected sex by IBD, all over the world?

Another uniform finding in areas where IBD has long been established, such as northern Europe and North America, and also in emerging areas such as southern Europe, eastern Europe and Asia, is that the peak age of onset for Crohn's disease is typically in the third decade (northern Denmark, Copenhagen County, Denmark, France, Canada, Olmsted County, MN, USA, New Zealand, Hungary, Croatia, Korea, China, Lebanon) [3–8,20,23,25–27,31]. For ulcerative colitis, the peak age is typically in either the third (northern Denmark, Copenhagen County, Denmark, Olmsted County, MN, USA,

Korea, Lebanon) [3,4,6,25,31] or the fourth decade (France, Hungary, Croatia, China) [5,20,23,26,27]. Furthermore, recent large population-based studies show no second peak of either Crohn's disease (France, Olmsted County, MN, USA, Canada) [5–7], although this is not uniform (Copenhagen County, Denmark, New Zealand) [4,8].

As the incidence of Crohn's disease has overtaken the incidence of ulcerative colitis, it is of interest to consider whether the pattern of presentation has changed over time. Isolated colonic disease has been estimated formerly to be primary locus of disease in approximately 20%. Recent data show isolated colonic disease in approximately 30% in such disparate jurisdictions as Olmsted County, MN, USA, Croatia and China [6,23,26,27] and 50% of cases in northern Denmark [3]. In pediatric studies, the prevalence of isolated colonic disease ranges from 10% in France [34], to 17% in Copenhagen County, Denmark [4], to 25% in Norway [36], to 32% in Wisconsin [39], to 50% in Finland [40] and to 55% in Sweden [35]. In a study from six major pediatric referral centers in the USA, not only was Crohn's disease more commonly seen than ulcerative colitis, but of all cases of Crohn's disease 30% were isolated colonic disease [44]. Is it real that an emergence of colonic Crohn's disease, particularly in adults, but also in some pediatric studies, contributed to more Crohn's disease overall than ulcerative colitis, or was much of the former high rates of ulcerative colitis encompassing misdiagnosed colonic Crohn's disease?

Conclusion

The recent trends in the epidemiology of IBD show that there are higher incidence rates of Crohn's disease than ulcerative colitis in northern European and North American studies. While incidence rates of Crohn's disease in Manitoba have been high for several years, they appear to be rising in most other countries. This trend has emerged both in hospital- and clinic-based studies and in population-based studies. There remain higher rates of ulcerative colitis in the developing nations of eastern Europe and Asia, mimicking what was originally evident in the developed western world decades ago. The peak age of onset has been constant for years, with most cases of Crohn's disease presenting in the 20s and of ulcerative colitis presenting in the 20s to 30s. However, there has been an emergence of Crohn's disease among males and more IBD cases overall are males than females. What clues can we draw from this in terms of seeking etiologies? Pediatric environmental studies should be pursued. Dietary changes can likely be more easily tracked in children and over shorter lifetimes. It is important to explore differences between males and females, for instance vaccine patterns or hormones. In particular, environmental studies in the developing world are critical. Changes in dietary and lifestyle patterns of communities may be more evident over the past decade in Asia or eastern Europe, where an introduction to western lifestyles has been very recent. The introduction of cleaner water sources, diets higher in fats and refined sugars, electronic technology, novel food additives, broader access to antibiotics and other medications, lower infant mortality rates secondary to lesser critical pediatric infections and vaccine programs may all in some way contribute to the emergence of IBD in the developing world. The etiologic clues may be hidden amongst these observations.

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