INTRODUCTION

Despite progress in understanding the immunoinflammatory response of the bowel and in therapeutic options in inflammatory bowel disease (IBD), there is still much to learn about disease etiology. Epidemiological studies examining differences in occurrence in different places and among different age groups, as well as at different times, can provide clues as to factors that influence the origin of these diseases. Also, new hypotheses regarding etiology can be generated. Defining disease epidemiology also leads to an appreciation of the magnitude of public health concern a disease poses. Epidemiological data about IBD have highlighted important public health concerns. For instance, the highest incidence of disease is seen in young adults. Thus, morbidity relating to disease and its therapy (i.e., surgery) will affect school and work productivity and possibly socialization and personal and family development. Furthermore, ulcerative colitis and Crohn’s colitis are associated
with an increased risk for intestinal cancer and the associated increased mortality risk. Finally, the morbidity of these conditions is associated with considerable expenditure of health care resources and large indirect costs.

METHODOLOGICAL ISSUES
The validity of early epidemiological studies (of periods prior to the early 1970s) is problematic as diagnostic techniques (in particular, colonoscopy) have improved substantially over the past three decades and categorization of different forms of IBD continues to evolve. This particularly applies to distinguishing Crohn’s colitis from ulcerative colitis (1,2). Modern era studies are required, particularly because it has been suggested that the incidence of Crohn’s disease of the colon (as opposed to small bowel disease) was increasing in the 1970s (3–6) and in some areas markedly increasing in the 1980s (7).

Regarding specific epidemiological approaches to studying IBD, a main problem has been the lack of population-based approaches. Often, hospital-based data have been used to represent the population as a whole. For a number of these studies, the investigators supplemented their hospital-based data with surveys of community physicians and with perusal of community radiology, pathology, and chart records. In the era of the 1950s through the early 1970s, hospital-based data likely gave much more reasonable estimates of true disease incidence than they would for the past 15 yr. The advent of corticosteroids and other effective therapies between 1950 and the ensuing two decades might have precipitated increased referral by general practitioners to more specialized centers and therefore, inclusion in their hospital-based studies. With the proliferation of high-quality endoscopic technology, IBD has become easier to diagnose and treatment options have also become more varied. Furthermore, community clinicians have become more educated regarding diagnosis and therapy, as the understanding of these diseases and their differences has expanded and as the medical community has become bombarded by marketing of various new therapies. These changes have all led to IBD becoming more of an outpatient problem and fewer new diagnoses require hospitalization. Therefore, modern epidemiological studies have not relied solely on hospital-based data and have had broad access to population-based data.

INCIDENCE AND PREVALENCE RATES
Owing to the early average age of onset and chronicity of IBD, the prevalence generally ranges from 10 to 20 times higher than the incidence. In areas of high incidence such as the United Kingdom and
northern Europe, it has been estimated that as many as 1 in 100 people will develop IBD in their lifetime (8). Epidemiological data in IBD generally reflect only detected cases. One interesting study from the United Kingdom using mass screening for fecal occult blood suggested that as many as 33% of IBD cases may be undetected at one time in the community (9).

**Ulcerative Colitis**

Much of the available epidemiological information about IBD is from northern Europe. The incidence in that area of the world of ulcerative colitis ranges from approx 1.8/100,000 person-years in Finland (1956–1961) (10) to 15.1/100,000 person-years in North Tees, England (1971–1977) (4). Generally, the incidence varies from 6.3 to 15.1/100,000 person-years (4,11–19). The estimated prevalence rates in Northern Europe ranges from 38/100,000 person-years in Leiden, Holland (1983) (16) to 157/100,000 person-years in the Faroe Islands (1983) (17). The most recent Scandinavian data are from Norway which reveal an incidence rate of 13.6/100,000 for the years 1990–1993 (20). This was a study of four Norwegian counties and the incidence varied from 11.7/100,000 to 18.6/100,000. These more recent data reflect a higher incidence rate than that which had previously been reported from northern Europe. This is particularly noteworthy because it had been considered that the incidence of ulcerative colitis had somewhat plateaued through the 1970s and the 1980s. Incidence rates in more southern areas have been much lower, closer to 1.5–5.8/100,000 person-years (21–26).

In North America there is a paucity of population-based data. In the United States incidence rates are less homogeneous, although few data are available. In 1973, the incidence of first hospitalizations in 15 different geographic centers was 0–14.3/100,000 person-years, with a mean incidence of 3.5/100,000 person-years (27). This type of study is skewed to reporting only severe or complicated cases, since they represent the cases likely to have been hospitalized. In Olmsted County, MN (Mayo Clinic catchment area), the incidence reported for the years 1960–1979 was 15/100,000 person-years, with a prevalence of 225/100,000 person-years (28). The incidence rates remained stable throughout the 1980s up until 1993. The reported prevalence rate in 1993 was 229/100,000 (29). This contrasts to a lower incidence of 2.8/100,000 person-years reported from urban Baltimore in the early 1960s (30). Recent studies based on hospitalization data from United States Medicare discharge data and from a group of United States Veterans’ hospitals (31,32) have both suggested an increased prevalence of ulcerative colitis in the northern United States compared with the southern United States.
Just north of the United States border, two Canadian studies have yielded very disparate prevalence rates in ulcerative colitis. In the northern areas of the province of Alberta around 1980, the prevalence rate was 37.5/100,000 (33). In southern Alberta prevalence rates were less than 25/100,000 (34). Patients were identified for these studies through hospital discharge records and through private gastroenterologists’ charts, and may have underestimated the true prevalence. Data from the early 1990s in the province of Manitoba, whose population ethnicity is similar to that of Alberta’s reveals a prevalence rate in 1994 of 167/100,000 (35). This study was population-based and may more accurately reflect the modern epidemiology of this disease. This study found that 20% of patients were being regularly followed by a family physician and nearly 20% (particularly in rural areas) were being followed by general surgeons. This points out the potential flaw in assessing disease burden by solely pursuing gastroenterologists’ practices. The incidence of ulcerative colitis in 1990–1994 was 14.5/100,000 in Manitoba.

Crohn’s Disease

The incidence of Crohn’s disease in northern Europe ranges from 0.8/100,000 person-years in Oxford, England (1951–1960) (11) to 6.1/100,000 person-years in Uppsala, Sweden (1965–1983) (19). Generally, the incidence rates have varied between 1.6–5.4/100,000 person-years with prevalence rates of 27–48/100,000 person-years (12,16,36–45). A recent update of the data from Northern Scotland found an overall mean incidence of 5.4/100,000 person-years in Aberdeen in the years from 1955 through 1987. However, for the years of 1985 through 1987 the mean incidence for this area was 11.6/100,000 person-years (7). There was a trend toward higher rates in the latter years of most studies, but incidence rates in general have remained less than that seen with ulcerative colitis. Incidence rates in Stockholm County between 1955–1989 also appear to have plateaued at a rate of approx 4.6/100,000 through the 1970s and 1980s (45). Incidence rates for southern areas including Spain, Italy, Cuba, and South America are <1.0/100,000 person-years (46) and from central Israel 1.3/100,000 person-years (47). The most recent Scandinavian data are from Norway that reveal an incidence rate of 5.8/100,000 for the years 1990–1993 (48). This was a study of four Norwegian counties and the incidence varied among the counties from 4.7/100,000 to 8.7/100,000.

In the United States, incidence rates for Olmsted County were reported as 4.3/100,000 person-years in 1978–1982 (49). A recent update of these data revealed an incidence rate that was 5.8/100,000 (and essentially unchanged over the 30 yr between 1964–1993) whereas
the prevalence rate in 1993 was 144/100,000 (50,51). First, hospitalizations in the 15 different American geographic areas varied from 0–4.9/100,000 person-years (27). Data from the recent United States Medicare and Veterans’ studies show an increased prevalence in the northern United States compared with southern United States for Crohn’s disease, as well (31,32). Interestingly, the lowest rate among the fifteen states was in Minnesota, which somewhat corroborates the much lower rate in Olmsted County than in Manitoba, a nearby Canadian province (35).

The Alberta studies revealed a slightly higher prevalence of Crohn’s disease than ulcerative colitis, 44.4/100,000 in the north (33) and up to 63.7/100,000 for females in the south (34). The highest incidence and prevalence rates for Crohn’s disease yet to be reported were data from Manitoba (35). The incidence rate was 15/100,000 in 1990–1994 and the prevalence rate of Crohn’s disease in 1994 was 198/100,000 (35). In support of these widely disparate data from Alberta and Manitoba a decade apart are data generated by Statistics Canada from hospital discharge diagnoses across the country. Discharge rates for Crohn’s disease and ulcerative colitis from hospitals across Canada between 1971 and 1989 for Crohn’s disease approx tripled from 9 to 25/100,000 in males and from 12 to 36/100,000 in females (52). Furthermore, a population-based cohort in Britain initiated in 1970 was assessed in 1996 for the prevalence of IBD among the 26 yr olds in the cohort (53). The rate for Crohn’s disease was 214/100,000 and for ulcerative colitis was 122/100,000 for all confirmed cases. These authors attributed these higher rates than that reported previously from the United Kingdom to either enhanced accrual secondary to a population basis of the cohort or to the high likelihood that by examining young persons the prevalence rate was high.

An important and unresolved epidemiological issue, globally, are the trends in incidence of both Crohn’s disease and ulcerative colitis (46,54). For ulcerative colitis in Northern Europe alone, the incidence into the 1970s was thought to be rising in Norway and Scotland, falling in Stockholm and stable in Britain, Denmark, and Finland. In the 1970s, the incidence of Crohn’s disease was thought to be rising in Britain and Denmark and falling or stabilized in Stockholm and Scotland. The incidence rates in Scotland and in Copenhagen County, Denmark, in the 1980s had been rising considerably (7,44). Among other nations, Crohn’s disease is thought to be on the rise in Israel, South Africa, and Japan, and in other countries where traditionally IBD was rarely seen. For instance the hospital prevalence of Crohn’s disease increased by approx eight-fold between 1986 and 1993 in the Singapore Chinese population (35) Overall, the incidence rates of Crohn’s disease in the
1970s were rising greater than the rates for ulcerative colitis. Although these diseases share many common features, the epidemiological data help to define that they are very distinct entities.

POTENTIAL CLUES TO ETIOLOGY BASED ON THE EPIDEMIOLOGY

Geographic Variation

A potentially important issue that might provide clues to IBD etiology is that the highest incidence and prevalence rates are in the northern hemisphere and areas with generally colder climates. Studies from Australia (23), South African whites (56,57), central Israel (22,47), and smaller studies from southern Europe and the South Pacific revealed low incidence and prevalence rates of either ulcerative colitis or Crohn’s disease (25,26,46,54,58). One aspect of the north–south issue is the imbalance in data collection methods (59). Northern countries such as in Scandinavia and in the United Kingdom have well-established population-based registries, whereas these types of data collection are not available in southern Europe or other southern hemisphere countries. An important lesson on the ability to extrapolate epidemiological data in terms of geographic variation comes from Manitoba and Minnesota. The only population-based North American data of IBD epidemiology come from these two neighboring areas separated by the 49th parallel. In the early 1990s, the incidence of Crohn’s disease was 15/100,000 in Manitoba but only 7/100,000 in Olmsted County. How can these rates be reconciled considering a distance of less than 500 miles between the Manitoba border and Olmsted County? The incidence of 15/100,000 is the average incidence in the province. Based on postal forward sortation areas we found a seven-fold variation in age-adjusted incidence for ulcerative colitis (60) and a six-fold variation in Crohn’s disease incidence (60). Although some of these differences likely reflect differences in demographic mix, they also suggest the presence of environmental influences as well. It is also interesting to note that there is a geographic correlation between Crohn’s disease and ulcerative colitis incidence rates (60) in Manitoba that is consistent with the existence of some common environmental risk factors. These data also suggest that the clues to disease etiology might be derived from studying small area variations in incidence.

Age and Gender

Almost uniformly, epidemiological studies reveal a peak incident age in the second through third decades of life. Many studies report a
bimodal incidence, particularly for ulcerative colitis, with a second incident peak in the sixth through seventh decades. The second and third decades are the ages of social expansion, family development and significant economic contribution to society. Thus, chronic debilitating disease in this age range may have broader societal implications. Age differences may reflect specific alterations in the immune systems that evolve with aging. Crohn’s disease is rarely seen under age 5. However, the peak incidence in the second and third decades suggests that exposure to important environmental causes are likely to be experienced in early life (61). Crohn’s disease that presents after age 60 often has a different phenotypic pattern of expression, with a predilection for the left colon as opposed to more typical terminal ileal disease of younger patients. Thus, immunological alterations identified in IBD might best be analyzed in the context of the age of the subjects in whom they are discerned.

Regarding gender, there is an approximate excess of females by 30% in Crohn’s disease, but on average no gender preference in ulcerative colitis. Data from Manitoba similarly revealed a 30% excess of females with Crohn’s disease and no gender predilection in ulcerative colitis (35). However, on analysis of birth cohorts an interesting finding was that of a reversal in the gender predilection for males born between 1968 and 1981 who presented with Crohn’s disease by the age of 20. This led us to consider what environmental factors might have accounted for such a male predominance. One hypothesis is that in Manitoba females were vaccinated against rubella prior to 1981, but males were not. On exploring the incidence rates of Crohn’s disease in comparison to incidence rates of rubella revealed an interesting parallel (Fig. 1). This has led to a pursuit of infection rates of rubella and other paramyxoviruses in the Manitoba IBD population compared to a matched population based control group. Gender differences may point to the potential importance of the sex hormone milieu in either the initiation or perpetuation of the disease.

Elsewhere, recently an emerging male predominance has been shown. A review of Crohn’s disease patients presenting to clinics in Athens found a male:female ratio of 1.58 (62). It is noteworthy that most recent reports of incident pediatric Crohn’s disease reveal a male predominance. The male:female ratio was reported as 4:1 in children in Wales for the years 1995–1997 (63). In a study of all newly diagnosed children presenting to a New York hospital the ratio was 1.51 (64). Perhaps the changing gender pattern from female to male predominance may provide some etiologic clues.

Race and Ethnicity

Although the clinical features do not exhibit significant racial differences (65), populations of European ancestry are thought to be at great-
est risk for developing IBD. This is supported by data showing lower rates among the Maoris in New Zealand (66), the Japanese (67) and possibly in the black and Native American Indian populations of the United States (68,69). The study from urban Baltimore, however, suggested an incidence among urban blacks that approaches (but is still somewhat less than) that for whites (30), however, these data are nearly 40 yr old. A recent study from a large Health Maintenance Organization in California revealed that the hospitalization rate for IBD in the black population was comparable to the rate seen in whites (70). In this study, there was a much lower rate of hospitalization for IBD in the Hispanic and Asian populations. One paper from South Africa, where there is thought to be a low incidence in the black population, reported a rising incidence among black urbanites in Johannesburg (57). Racial differences highlight the potential importance of genetics on disease etiology. The population-based data from Manitoba and Olmsted County mostly reflect populations of mostly northern European origins.

There is an increased incidence of IBD among Jews. This was found to be true in studies from United States Veterans in the 1950s (71), from a United States college in the 1970s (72), and from Baltimore (30), South Africa (56), and Sweden (39,40). Because studies from central Israel suggested a lower incidence among the population there (all Jews) than incidence rates reported for the rest of the Western world, this challenged the notion of a Jewish predilection. However, the rates among Ashkenazie Jews (versus Sephardic or Oriental Jews) and among
those born in the United States and western Europe who immigrated
to Israel approached those of the United States and northern Euro-
pean studies (22,47). Furthermore, a more recent study from south-
ern Israel revealed higher incidence rates approaching those
previously reported from the United States and Europe (24). None-
theless, the early Israeli data raised potential etiologic questions,
including considerations of climate, culture, or diet that may have
accounted for the different rates among Jews in Israel compared with
western and northern European and American Jews. Some authors
have advocated that future epidemiological studies in IBD must address
environmental issues (7,61).

An interesting aspect of studying ethnicity is to examine the epide-
miological trends among ethnic groups of typically low incidence in
their homeland in comparison to the incidence rates for these groups
when they migrate to areas of typically high incidence. In Leicestershire,
the incidence of ulcerative colitis among second-generation South Asian
migrants was significantly higher than that among native Europeans by
a factor of nearly 2.5-fold (73). It had previously been shown that South
Asians immigrants in Leicestershire had a higher prevalence of ulcer-
ative colitis than native Europeans, whereas the prevalence of Crohn’s
disease among the South Asian group was lower (74).

Birth Cohort

Changes in incidence rates based on birth cohort may point to some
environmental factors. The existence of a birth cohort phenomenon
implies an exposure to an environmental risk factor early in life which
plays a crucial role in the development of a disease. Alternatively, it may
relate to an exposure that affects individuals at a specific age and oc-
curred at only specific intervals. For instance, investigators in northern
Europe have assessed eras of measles and mumps epidemics and corre-
lated this with changes in IBD incidence rates (75–77). The birth cohort
of people born in 1945–1954 was thought to be at increased risk in
Uppsala, Sweden (19) and in Stockholm, Sweden (40), but no birth
cohort effect was found in studies from Cardiff, Wales (6) or from
Copenhagen, Denmark (12). An interesting report from six different
western countries revealed a similar peak mortality rate from ulcerative
colitis for the birth cohort born between 1880–1890. These authors
speculated that perhaps enhanced infant hygiene in that period led to
increased rates of ulcerative colitis (and ultimately deaths attributed to
ulcerative colitis). Nonetheless, the long periods of follow up and con-
sistency of the data across countries pointed to the importance of an
environmental factor(s) (78).
Socioeconomic Factors

There is a suggestion of predilection among single versus married people but these data are complicated by a potential effect that the disease may have on a patient’s likelihood of marrying. Urbanites have a greater incidence in Baltimore (30), Olmsted County (29), Uppsala, Sweden (19), Northern Scotland (7), and Manitoba (35). In Alberta studies where the prevalence rates were as low as 44/100,000 the rates were 234.1/100,000 in 30–39-yr-old urban dwelling females (33) and 373/100,000 in urban-dwelling Jewish males (34). Obviously issues regarding gender, ethnicity, and possibly other confounding factors affect these high rates.

There are conflicting data as to whether patients with IBD are more likely to have a higher socioeconomic standard of living and there are data that suggest a greater likelihood of attaining postsecondary education among patients with IBD (79-81). Much of these data have come from tertiary referral centers which undoubtedly see a selected population. Epidemiological data gathering regarding ethnicity, marital status, urban versus rural living, and socioeconomic standard of living may be confounded by the specific health care utilization patterns of the different groups. This is particularly true in the American health care system of the past four decades where access has been unequal, but less of a problem in studies from Scandinavia where health care access is more universal. This would also be less of a problem in Canada. The Manitoba data suggest that in fact there are few socioeconomic differences between patients with IBD and matched controls (82).

SUMMARY

There are a variety of reasons as to why it is essential to pursue population-based epidemiological studies in IBD. First, it is important to quantify the magnitude of the problem. This helps health planners understand the resources that are necessary to manage these patients. Trends in the epidemiology more importantly can lead to disease etiology clues. Currently in Manitoba we are utilizing our population-based database to pursue studies of possible microbial factors. Ultimately, when one is searching for etiological clues whether they are environmental such as microbial, or related to ingestion of toxins such as cigarette smoke or the oral contraceptive (83–87), or whether one is simply pursuing genetic studies it is critical to define the appropriate population of both patients and controls.

Based on data from Manitoba derived from nearly 5000 subjects with IBD in 1995 in a population of 1.1 million, we believe there are over
Chapter 2 / Epidemiology of IBD

120,000 Canadians and well over 1 million Americans with IBD. Furthermore, our data suggest that incidence rates are among the highest in the world in our area (Manitoba), and that prevalence rates are continuing to rise in Crohn’s disease. These diseases will continue to be among the more challenging faced by gastroenterologists and our estimates point to an increasing burden of these challenges in gastroenterology practices over the next several years.

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