ANNALS OF GASTROENTEROLOGY 2009, 22(3):158-167

Review

Incidence and prevalence of Crohn's disease and its etiological influences

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SUMMARY

Epidemiologic studies are of paramount importance in investigating disease etiology. Medical literature for individual countries on the incidence of CD, were retrieved from published medical literature and reports from relevant international congresses. Increasing trends have been observed almost worldwide, with a broad north–south gradient still prevailing in Europe. Distinct regions of New Zealand, Canada, Scotland, France, the Netherlands, and Scandinavia represent the highest incidence areas. Industrialized status and affluence are the common denominators between endemic areas, but are too broad terms to strongly indicate any particular etiological role. The increasing trends observed in Asia still account for a low prevalence of the disease and may represent increased detection and diagnostic ability of local health systems.

Keywords: Crohn's disease, epidemiology, incidence, etiology

INTRODUCTION

Crohn's disease (CD) was first recognized as a distinct entity 75 years ago, and although significant progress has been achieved in demystifying aspects of its molecular pathogenesis, diagnosis and treatment, its etiological origins remain unknown. At present, CD is considered a result of multifactorial interplay between genetic, immune-related, environmental, and infectious triggers that coalesce into evolution of clinical disease.[1] The correlation of CD with the genetic background of the disease, has been variably reproduced, indicating that genetic alterations may be pre-requisites but not independently adequate to induce CD development. The continuing study of, both local and systematic, an immune response alteration in CD patients has greatly augmented new therapeutic options; yet, this immune dysregulation may actually be an epiphenomenon and not an actual trigger. Attempts at incriminating certain infectious agents in the etiology of CD have been resurfacing, implicating among others alterations of the normal enteric flora, but also de novo potential pathogens as *Mycobacterium avium paratuberculosis* (MAP);[2] once more, observations of a possible etiological significance have been counter-challenged by other studies.

The most intriguing, yet vague in concept, suggestion of recent years has been the implication of environmental, particularly dietary, factors in CD evolution, a model of successive disease development triggering, the critical part of which is the local and systematic effect of non-pathogenic microbial species that may be ingested or acquired otherwise in endemic situations. This concept encompasses genetic susceptibility and environmental influence, possibly of infectious origin, and cumulates in a malfunctioning local immune equilibrium.

Epidemiologic studies are of paramount importance in investigating disease etiology: A burst of scientific literature on CD incidence observed during the last decade has mostly supported the idea of a disease of the developed world, with a typical North to South gradient observed in Europe.[3] The reasoning behind this incidence has been inconsistent; most studies have been localized, often retrospective and thus subject to inadequate data collection, and usually covering limited time periods. Yet, the major existing cohort studies indicate a significant CD incidence rise in the second half of the 20th century. The rationale behind this increase remains speculative though.

We reviewed all clinical studies on the evolution of CD incidence in the last 25 years, and search for poten-

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tial implications of this evolving epidemiology for disease etiology.

MATERIALS AND METHODS

Data on the incidence and prevalence for each country from 1980 onwards were sought from relevant medical literature, abstracts presented at international congresses (including Digestive Disease Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization- ECCO meetings). Medical literature was searched through Medline using "Crohn's disease"/ "Inflammatory bowel disease", "incidence"/ "prevalence" and individual country names as keywords.

Serial data on incidence were evaluated for the presence of epidemiological trends during the period of the last 25 years. Annual incidence, when not directly provided by the sources, was calculated using individual national population.

RESULTS

The current global status of Crohn's disease incidence is depicted in Table 1.

North America: Estimates on the burden and distribution of CD in the US vary: prevalence ranges between 26 and 198 cases per 100,000 population, depending on the source. It is estimated that 400-600,000 patients with CD reside in the US, but national incidence rates have not been reliably reported.[53]

The most notable example of long-term surveillance for CD incidence evolution is the Olmsted County, Minnesota database, encompassing registries from the 1930s onwards[52]. A gradual increase has been continuously observed, with the median annual incidence for the 1990-2001 period reaching 7 cases per 100,000 population, compared to $6.6.10^5$ for the 1965-1975 period. An inversion of the usual female predominance has been observed in recent years, with more male than female patients diagnosed. The typical patients are young and of urban origin, while ulcerative colitis (UC) incidence is estimated as slightly higher.

Other US studies offer less information: The incidence in Rochester, New York reportedly peaked at the early 1980s at about $6/10^5$/ year, while an older study from Spokane, Washington, showed a significant incidence increase through the 1970s, culminating in an annual incidence of $8.8/10^5$ for 1981.

Studies on pediatric CD in the US have been scarce: In Wisconsin, the annual incidence of $4.5/10^5$ is double that of pediatric UC, while the incidence in children of Afro-American origin in Georgia was much higher ($7.1/10^5$/ year).[55]

In Canada, the district of Mannitoba consistently reports one of the highest incidences of CD worldwide,

Table 1. Incidence Rates and Trends for Crohn's disease Worldwide

Country [reference]	Incidence (Cases/10^5)	Trend
Belgium [4,5]	4.1-4.5	Minimally rising
Brazil (Janeiro)[6]	14.6	Rising
Canada [7,8]		
-Alberta	16.5	Rising
-Manitoba	15.4	Steady
Chile [9]	Low	Rising
China [10]	0.3	
Croatia (Rijeka) [11]	6.5	Rising
Denmark [12, 13]	8.6	Rising
France [15, 16,17,18]	6.4-9	Fluctuating
Germany [19,20]	5.2	Moderately Rising
Greece		
-NW Greece [21,22]	0.9	Rising
-Crete [23]	3	
Hungary [24]	4.68	Rising
Iceland[25]	5.5	Rising
Ireland [26]	6	Rising
Israel [27]	4.2-5	
Italy [28]	2.3	
Japan[29]	0.5-1.2	Rising
Lebanon [30]	1.4	
Netherlands[31]	6.9	
New Zealand [32]	16.5	
Norway [33]	5.8	Fluctuating
Poland [34]	Low	
Portugal 16	4.2	
Puerto Rico [35]		Rising
Saudi Arabia [36]	1.66	Rising
Slovakia [37]	Low	
Spain [38- 44]		
-Aragon	3.9	Rising
-Huelva	6.6	Steady
-Vigo	5	
Sweden [45]	8.9	Fluctuating
United –Kingdom		
-England and Wales [46-51]	5.9-11.1	Fluctuating
-Scotland	11.7	
US (Minnesota) [52-56]	7	Steady

reaching 14.6/10^5 for the 1987-1994 period: the incidence is slightly higher than the one of UC, the disease predominates in young females, exhibits a significant variability between smaller geographical regions, and the incidence is characteristically lower in Indian aboriginals; the latter discrepancy raises questions about its background, i.e. is it related to a different genetic profile or to the lower hygiene standards of this population (although in the latter case one would expect the opposite effect on CD incidence)? Nevertheless, even in this population, a recent increase has been noted, especially in the 30-40 age group.

Older studies from Canada, from the region of Alberta, indicated that a steady increase in CD incidence (also higher than UC here) was noted in the 1960s, reaching a plateau in the late 1970s, with disease predominance in urban females, the incidence in females in South Alberta reaching 6.5/10^5, more than double that of males. On the other hand, reports from the 1980s from Quebec and Ontario exhibited significantly low rates: incidence of 0.7/10^5, and prevalence of 33/10^5 (reflecting a low incidence), respectively [56,57].

Central and South America: The incidence of the disease in Puerto Rico was recently investigated for the 1996-2000 period, and an increase from 0.49 to 1.96/10^5 was observed, with a similar increase, but double incidence for UC, and a CD predominance in young males (of interest, the age group with peak incidence was significantly higher in females). The authors, in attempting to explain the low, but still increasing incidence of the disease in a Hispanic population, raise among others the possibility of a relation with low breastfeeding rates.[35]

The disease seems to be scarce in Latin America: A study from a region of Panama and a region of Argentina showed a practically non-existent disease in the 1987-1993 period [58], while the cumulative cases reported from Chile in the 1990-2002 period account to a very low incidence also [9]. A Brazilian study from the region of Janeiro also showed low incidence in the 1980-1999 period, although the total new CD cases reported in the 1995-1999 timeframe exhibited an increase of 166 percent compared to the 1980-1984 cases.[6]

Europe: The development and continuing evolution of the European Crohn's and Colitis Organization- ECCO and the European Collaborative study of IBD (EC-IBD) has significantly augmented our understanding of the epidemiologic dynamics of CD and IBD in general. The landmark report on the North- South Europe gradient of CD incidence (7 versus 3.9/10^5), Alps being the North-South border, has allowed for a better understanding of the potential genetic and environmental factors involved in the evolution of CD.[16]

The original studies showed that Iceland had a high annual incidence (8/10^5), although isolated reports from Iceland show lower incidence rates: a 1980-1989 study showed a continuous increase compared to the median annual incidence of 1/10^5 for the 1970-1979 period, with a median annual incidence of 3.1/10^5 and a predilection for older patients, while UC was almost four times more common; a 1990-1994 study showed a continuing incidence increase, culminating in a median annual incidence of 5.5/10^5 (with UC being three times more common) with a predilection for younger ages.[16,24]

The EC-IBD study showed a similar incidence for Norway: few isolated national studies exist. In a prospective study for the 1990-1993 period from Southeast Norway the incidence was 5.8/10^5/year. Two studies focusing on paediatric IBD in Norway have shown annual incidence rates of 2.5/10^5 and 2/10^5 (western Norway, 1984-1985, and Southwest Norway, 1990-1003 respectively).[33]

A review of CD epidemiologic trends in the capital area of Sweden for the years 1990-2001 showed that the median annual incidence increased from 7.7/10^5 in the first period half to 8.9/10^5 in the second half, although the increase was not continuous and the peak was reached mid-period. The overall increase compared to 1985-1989 was 70 percent. The 1955-1989 period had shown a gradual increase (from 1.1 to 4.8/10^5 for 1955-1959 to 1970-1974 respectively), which was deemed to have reached a plateau in the years 1975-1989. The most important observations arising from Sweden though relate to a birth cohort phenomenon which is localised in the 1946-1950 or 1945-1954 period, according to different studies. Reports on the incidence of paediatric CD are contradicting: Stockholm data for 1990-2001 show a huge increase in CD in children (1.7 to 8.4/10^5 from 1990 to 2001) and a double incidence compared to UC, while data from Orebro, a city of the same latitude, show a low stable incidence of paediatric CD during 1984-1995, a period during which UC rates more than doubled, being far higher than CD rates.[59-62]

Recent reports from Denmark indicate annual incidence rates of 8.6/10^5 for the 2003-2005 period, while UC rates are higher. These rates represent a significant increase compared to the median rates for 1981-1992 (4.6/10^5, higher in females), although the phenomenon is more pronounced for UC. Very high rates, similar to present day's were also reported in 1977 though [12]. Older studies in isolated regions as the Faroe Islands had shown low steady rates for CD but a massive increase for UC.

Of interest are the limited studies from the Baltic former Soviet republics, which one would expect to follow the latitude rule and have a high CD incidence. There is only one study from this area, focusing on Esthonia in the years 1993-1998, showing a low incidence ($1.4/10^5$), which is increased compared to the annual median $0.27/10^5$ of the 1973-1992 period, but is still low compared to Scandinavia [61]. The acknowledged different infant microflora between Sweden and Estonia may offer general etiological hypotheses for the disease.

United Kingdom may serve as a more localised typical model of North-South gradient, with a potentially higher incidence in Scotland compared to England and Wales. The city of Aberdeen, located in Northern Scotland, demonstrated one of the highest incidences worldwide ($11.7/10^5$/year) in 1985-1987, with a young urban female predominance, while the incidence was also relatively high in isolated regions, such as the Orkney and Shetland islands for the better part of the second half of the 20th century. Increasing trends have also been observed in numerous reports on paediatric CD, with the incidence doubling in the 1990s, reaching a median annual rate of $4.4/10^5$ in the region of Aberdeen, a trend that overall Scotland is more prominent in males though. One would expect that rates would be lower going south to England and Wales. Data on hospitalised patients from 1979-1998 showed an overall stable incidence of $5.9/10^5$/year, with a female predominance, a rate which was similar to the one elicited for the 1971-1985 period. A 1995 study from Newcastle (which practically neighbours Scotland) yielded a higher incidence of $8.3/10^5$, consistent with a North-South gradient. A study from the 1991-1992 period estimated though that the incidence may be higher, reaching $10.1\text{-}11.1/10^5$/ year, with no environmental associations. Other English studies have focused on the racial trends of CD incidence, showing lower prevalence in Southeast Asian residents compared to Europeans, or West Indians compared to Caucasians [62]. The Wales data are of interest mainly in a potential etiologic context: Studies have shown that the increase of CD incidence in the Cardiff region was mainly located to districts bordering with Taff river, where MAP was repeatedly isolated, and thus theoretically implicated through aerosol-mediated infection in CD pathogenesis [63]. The incidence is not rising in the Cardiff region overall though, since the peak was reached in the 1980s. Overall, incidence rates average $5.6/10^5$/year, with a young male predominance in 1991-1995, while data on paediatric disease are contradicting, showing incidence rates ranging from stable around 1.3 to increasing up to $3.1/10^5$/year during the 1990s. Comparing the regional UK data, a North-South gradient seems to exist, although typical study limitations (to be discussed subsequently) exist. The incidence rates for Ireland reported in the EC-IBD study are roughly similar to the British ones ($6/10^5$/year). Amiens, located in Northeast France was one of the regions with the highest incidence in the original EC-IBD study ($9/10^5$/year) [16]. A gradual increase was observed during the 1990s in North France, with the median annual incidence rising from 5.2 to 6.4 from 1988-1990 to 1997-1999, with a female predominance. Meanwhile, the increase in paediatric CD rates during the same period was non-significant. A study from the, also Northern, Bretagne form the mid-1990s, showed much lower rates, although adequacy of patient recruitment in this study is questionable [15,16,17]. A study from the mid-southern French area of Puy-de-Dome on the other hand, again from mid-1990s, showed rates comparable to those of Northern France [18].

Amiens was accompanied by Maastricht, Netherlands, in exhibiting the highest incidence in the original EC-IBD study. Other than that report, limited data exist: A prospective 1991-1995 study from Maastricht had shown annual incidence rates of $6.9/10^5$ (lower than the UC ones), still much higher than the ones reported from Leiden in the early 1980s.[31]

In Belgium, a minimal but stable increase is observed through time in Lieges, with annual rates of 4.5 new cases per 10^5, while similar trends were observed in a 1992-1993 Brussels study, where, interestingly, the incidence was much higher in the population of Moroccan origin than natives.

In Germany, a study from Essen showed a moderate increase in 1991-1995 compared to 1980-1984 (5.2 versus $4.9/10^5$/ year), although the median age of the patients increased by almost a decade. A similar incidence was observed in the region of Cologne during the 1985-1996 period.[4,5] The overall German rates reported in the EC-IBD study were slightly lower though.[16]

Incidence trends during the last 15 years are of interest in countries previously under Communist regimes, due to the dramatic alteration in lifestyle that has occurred and its potential etiologic implications. A recent report from the Czech Republic on paediatric CD for the years 1990-2001 showed an increase in the annual incidence from 0.25 to $1.26/10^5$, the increasing rate reaching a plateau in 1997-1998 and remaining stable onwards. Prevalence rates reported from Slovakia for 1994 indicate a low incidence. On the other hand, a significant sustained increase is observed through the 1977-2001 period in Western Hungary, incidence reaching $4.68/10^5$ in 2001 (a more than 600 percent increase compared to 1977). A similar study from Bi-

alystok, Poland, showed that CD remains extremely rare, irrespective of the political alterations.[64]

The incidence rates in Southern Europe were invariably low in the EC-IBD study: A North-South gradient was observed in Portugal, where previous studies from Oporto in the north confirmed a steady incidence rise during the 1975-1990 period [16]. Numerous studies from Spain have failed to reproduce this gradient though: A prospective 1991-1993 study from four regions showed an overall annual incidence of 5.5/10^5, which was actually higher in the southern region of Motril (6.5/10^5/year) and the island of Mallorca compared to the northern participating regions.[38-40] Other reports show inconsistent rates: a 1979-1988 study from Granada in the south showed extremely low rates,[41] while a significant increase observed in CD incidence in Central Spain still cumulated in an overall low annual rate of 1.61/10^5 in the 1981-1988 period,[42]. The median annual incidence in Huelva, in southwest Spain, for 1980-2003 was 6.6/10^5, but the increasing trend seems to have reached a plateau in the early 1980s.[43] A non-significant increase and a low overall incidence (2.5/10^5/year) was observed during 1983-1993 in Pamplona in the north, and a similar increase in the province of Asturias, in the northwest, during 1994-1997 might actually be attributed to the increased rates of diagnostic procedures. Nevertheless, in the latter region the median annual incidence for this period reached 6.10^5. A steady increase has been observed in the northeast region of Aragon, incidence reaching 3.9/10^5/year in 1992-1995.[38,39]

Italy exhibits a typical southern European profile in having low CD rates, but, like Spain, there exists no North-South gradient in the country as such, with a study for eight cities from 1989-1992 showing homogenous incidence rates. Another indicator of the various pitfalls of CD epidemiological studies though is that this study reported for Florence an annual incidence below 2/10^5, while another Florence study, focusing on roughly the same period, reported a rate of 3.4/10^5.[27]

The lowest European incidence reported initially from Northwest (NW) Greece,[21] although an increasing trend observed recently [22] and a significantly higher incidence reported from the southern island of Crete [23] (data for both areas until mid-1990s, rates 0.1 and 3/10^5 respectively).

Of the rest of the Balkan countries, Croatia exhibits a unique profile: Reports from Rijeka show a rapid incidence increase reaching its peak in 2000 (7.2/10^5), followed by a short decline, stabilizing in a median annual 21st century incidence of 6.5/10^5. Past data have shown incidence rates to grow slowly (1973:0.34/10^5; 1994: 3.4/10^5). The disease is more prevalent than UC, and urban males predominate. Of interest though is that Rijeka is an industrial region; data from a prospective study in Zagreb had shown a much lower incidence during the 1980s.

Asia: Numerous voices have raised concern about the increasing appearance of CD in Asia, where the disease was considered an all too rare entity in the recent past. The disease's affinity for patients of Jewish origin is acknowledged, especially for Askhenazi versus Shephardic Jews. However, a 2003 study showed similar prevalence rates for both origins, although disease natural history may differ. An Israeli study covering the 1968-1992 period showed that the incidence was higher in non-European, non-American born Jewish (on average, for 1987-1992, 4.2/10^5).[25] The disease was typically rare in Arab populations. A report from the 1987-1997 period yielded similar results (median incidence 5/10^5/year, rare in Arabs).[26] The latter fact was further confirmed in a localized study from Kinneret. Reports from Lebanon suggest that the disease is rare, more so than UC. A report from Saudi Arabia from 1983-2002 showed an increasing incidence: the median annual incidence for 1993-2002 was 1.66/10^5, more than 500 percent above the 1983-1992 median incidence. Young females predominate. A study on pediatric IBD for 1993-2002 showed an increasing incidence for both CD and UC, but they still remain rare. Isolated, non-epidemiologic reports exist from Qatar[66] and Kuwait.[67] A report from Iran[68] shows that UC vastly predominates at a rate of 9:1. In India, CD was considered as non-existent until 1986, and is still frequently misdiagnosed as enteric tuberculosis, or even amebic colitis [69]. Although concern about its incidence in India is obvious in the literature, epidemiologic data are inadequate. Patients from Bangladesh have been studied as UK immigrants, showing a rapid increase in disease incidence in 1997-2001 compared to 1981-1989 (7.3/10^5/year versus 2.3/10^5/year), a trend also observed for UC and paediatric CD [70]. Reports on CD in Thailand indicate a random existence[71]. In Malaysia, a 2001-2003 study including only 34 patients showed an increased prevalence in Indians, compared to Chinese and particularly Malays populations [72]. Reports from Singapore show a majority of Chinese patients, and a trend towards increased prevalence, although the number of patients reported indicates an extremely low incidence.[73]

A recent retrospective study on the Chinese medical literature on CD retrieved only 1526 patients from 1950 onwards. The estimated median annual incidence of 0.3/10^5 precludes comments on incidence evolution. A study focusing on Wuhan city for 1990-2003 showed that CD was much less common than UC, predominant in patients with

higher education, and tending to increase through the study period (although this increase was more obvious for UC).[74] The acknowledged increasing trends in CD incidence in Japan have often been attributed to the westernization of the Japanese society, although still remains low: the incidence doubled, reaching $1.2/10^5$/year from 1986 to 1998 according to a study, while a nationwide 1995 report yielded an incidence of $0.5/10^5$, less common than UC, with a male predominance.

Oceania: Early Australian reports indicated an incidence similar to that of Northern Europe and US. A 1971-2001 study on pediatric disease showed an increase in annual rates from 0.13 to $2/10^5$, and a typical urban patient profile.[75]

The Canterbury district in New Zealand is currently the region with the highest worldwide incidence, estimated at $16.5/10^5$ for 2004. This recent study may have escaped many of the pitfalls of other epidemiological reports: twenty five percent of the included patients self-referred, minimizing underestimation of prevalence. The increasing CD trends are not accompanied by similar UC rates in this area. The disease was extremely rare in Maoris, at least partly attributed to the low percentage of CARD mutations in this population.[76].

Africa: In a continent where infectious threats impose a huge burden on mortality and life expectancy is often below the expected age peaks of CD, little may be discussed for CD, at least at present. An old report on Africans in South Africa showed that IBD was very rare; a study from Sudan showed 12 patients in a period of 12 years; significantly more patients were recently reported from the city of Algiers for the 1993-2003 period.[77-80]

DISCUSSION

What is the common denominator between Canterbury in New Zealand, Manitoba in Canada, Aberdeen in Scotland, Amiens in France, Maastricht in Netherlands, and Minnesota in US (apart from the existence of scientists alert enough to reveal the evolving epidemiologic trends)? Unlocking this strange relationship would subsequently unlock the mystery of Crohn's etiology, still speculated upon 75 years after its baptism.

Differences in the genetic profile may play a difference indeed: the Maori example in New Zealand is typical; furthermore, CARD mutations are not universally reproduced as implicated in CD development.[81] Furthermore, the evolution of CD incidence is a matter of decades, and genetic factors, alterations of which might take centuries to cause a phenotypic difference, cannot account for these changes.[82]

Environmental factors should obviously then take their toll: but environment is a broad and vague concept. Researchers have long speculated that CD may be an infectious disease, and the most prominent candidate was MAP. Admittedly there is a striking resemblance between enteric tuberculosis and CD; MAP has been persuasively epidemiologically correlated with CD in Wales and Sicily among other areas, while isolated clusters of cases may imply a similar infectious origin.[83-85] MAP however, endemic in the developing world is in an inverse distribution compared to CD. The concept that CD as a disease of wealth tells us a few things about etiology. The popular model of immune-mediated disease development is intriguing but vague: It has been suggested that higher incidence rates among those of higher socioeconomic status may be due to a delayed and/or low level of exposure to common infectious agents during childhood because of improved domestic hygiene, resulting in persistent infection or altered immune responses in genetically susceptible hosts. This has been termed the *hygiene hypothesis*. Recently Hugot's intriguing "cold chain" hypothesis also provided a link with hygiene by incriminating psychrotrophic bacteria, the presence of which is maintained in refrigerated foodstuff [86]. The westernization of Japanese life and the increased incidence in certain former Communist countries may be compatible models. Yet, whatever the actual effect imposed by environmental triggers in the CD incidence, this effect would require a latent period for disease pathogenesis to evolve and clinical presentation and diagnosis to be made. Even if bacteria or diet were implicated, their pathogenetic effect would require protracted exposure over time, and thus the changes in socioeconomic status should actually precede the changes in CD incidence by a period of 5-10 years at least. Although the hygiene hypothesis is based on a similar concept, it would actually require a far longer latent period (otherwise the majority of new patients contributing to an increased in CD incidence would belong to the paediatric population).

Birth cohorts may offer interesting information in this context, yet they have not been adequately utilized. What makes the Swedish population born after World War II more susceptible to Crohn's? One could argue that World War II is not necessarily the important event that characterizes this cohort: Yet a more obvious disruption of "environment" as a global war cannot be imagined. What changed so significantly then post WWII? Whatever it was, affluence can serve as an indirect marker of CD in-

cidence. Acknowledged as a disease of the developed world, a disease of the industrialised North, or an urban disease, the environmental factor seems to be crucial in its development. But again, what is the main component of "environment"? What makes educated or rich people more susceptible? The immune tolerance hypothesis satisfies most of these scenario needs, and the gradual rise in incidence in Southeast Asian immigrants to the Western world further agrees. Once more, existing studies fail to provide answers. Designing a proper epidemiologic study for CD is difficult: Many studies have focused on hospital registries. Another pitfall is that one cannot be certain that the increased incidence observed is not in fact attributed to increased detection due to the increasing availability of sophisticated endoscopic techniques worldwide. Long-term studies, such as the ones from UK, Canada, Sweden, or Minnesota can overrule this objection, but that may just be the case for reports from the developing world or former communist countries. Furthermore, there is a striking absence of information on population characteristics: affluence in a selected region can be indirectly estimated by gross domestic product for example, or the percentage of rural/urban population. Selecting such personal data may be a violation of privacy though. Evaluating educational status tells us few things about the environmental influences of childhood (the age per se may act as a trigger for disease). Estimating the prevalence of various potential pathogens is a broad task, and body would know where to start; furthermore, both a pathogen's prevalence and disease incidence may serve as epiphenomena to hygiene status.

Summarizing the lessons learned from these studies, Crohn's disease is definitely emerging worldwide as a major public health threat. The increasing reports of paediatric disease further underline this. Changes in lifestyle, in regional, national, or international level seem to play an etiologic role in the increasing incidence of the disease: whether these factors are pure exogenous triggers or part of an exogenous-endogenous immune chain we still do not know. Seventy-five years after Crohn's characterization as a unique entity we are still in the dark.

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