Protective Role of *Helicobacter pylori* Against Inflammatory Bowel Disease: A Hypothesis

INTRODUCTION

During the past century, gastroenterologists have experienced major shifts in the occurrence of several common diseases affecting the digestive tract. The historic fall in the occurrence of gastric cancer and peptic ulcer disease during the twentieth century was accompanied by a simultaneous rise in the occurrence of inflammatory bowel disease and gastroesophageal reflux disease during the same time period (1,2). The fall of gastric cancer and peptic ulcer, as well as the rise of gastroesophageal reflux disease, are now mostly ascribed to the decline of *H. pylori* infection in the general population (3,4). Have the concomitant changes affecting inflammatory bowel disease been just a coincidence, or does yet another hidden association with *H. pylori* underlie these opposing times trends? The present article pursues the hypothesis that *H. pylori* infection may have protected its carriers against developing inflammatory bowel disease and that the increase of inflammatory bowel disease was in part caused by the loss of this protective influence.

TIME TRENDS OF ULCERATIVE COLITIS

Mortality from ulcerative colitis during the past century has been shaped by an underlying birth-cohort pattern with rising trends among subjects born before the turn of the twentieth century and falling trends among all subsequent generations (Figure 1). The risk of developing and dying from ulcerative colitis has been highest among subjects born shortly before the...
Protective Role of *Helicobacter pylori* Against IBD

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #55

(continued from page 23)

Figure 1. Standardized cohort mortality ratio of ulcerative colitis. Data from England and Wales between 1931 and 2005.

Figure 2. The superimposition of falling infection (solid line) and rising susceptibility (broken line) could have resulted in the birth-cohort pattern of ulcerative colitis as the product of these two opposing trends.
easier to accept than the concept of one single rising and falling factor, which immediately begs the question of what made the single factor rise and fall in the first place. As suggested by graph of Figure 2, the superimposition of simultaneously falling infection and rising susceptibility trends could have resulted in the birth-cohort pattern of ulcerative colitis with its initial rise and subsequent fall. Although the model in Figure 2 assumes that ulcerative colitis is caused by some type of enteric infection, whose incidence has declined in the general population over the past 150 years, the exposure to any other environmental influence besides infection could serve as an explanation as well. Many epidemiologic and clinical features of ulcerative colitis, however, strongly suggest that exposure to some yet unidentified enteric pathogen may play a crucial role in the development of the disease. If the falling component can be associated with falling infection rates, what could possibly explain the rising susceptibility to develop ulcerative colitis?

TIME TRENDS OF H. PYLORI INFECTION

Because of increasing standards of hygiene in western countries, the incidence of infection with H. pylori started to decline in the general population at the beginning of the nineteenth century. Although few studies have measured the changing incidence and prevalence rate of H. pylori infection over prolonged time periods, there are some rather convincing data to suggest a logistic decline in the incidence rate among consecutive birth-cohorts throughout the twentieth century (9,10). The higher sero-prevalence of H. pylori antibodies in the elderly reflect on the remnants of previously higher exposure rates, when the infection was still much more common than today (11–13). The decline of H. pylori infection is also evidenced by the dramatic decline in the occurrence of its associated diagnoses, such as gastric cancer, gastric and duodenal ulcer. Figure 3 depicts the declining trends of H. pylori infection, as well as those of another potential enteric infection resulting in ulcerative colitis. Rather than causing inflammatory bowel disease, as suspected by the initial investigators, infection with H. pylori may actually protect against the primary infection associated with inflammatory bowel disease. Patients with inflammatory bowel disease are found to have a lower prevalence of H. pylori than the rest of the population (14–16). Both types of inflammatory bowel disease tend to cluster among the well educated and more affluent social classes of the population, who are also less likely to harbor H. pylori. Two potential mechanisms are conceivable. First, infection of the upper gastrointestinal tract with H. pylori may directly interfere with the acquisition of another infection responsible for the subsequent development of inflammatory bowel disease. Second, it could also be that H. pylori-induced reduction in acid secretion indirectly affects a different type of infection that ultimately results in inflammatory bowel disease. Thus, the inverse of the time-dependent H. pylori incidence, that is, \( \text{UC susceptibility} = 1 - \text{H. pylori incidence} \), could represent the increasing susceptibility factor for ulcerative colitis shown in Figure 2.

HOW DOES CROHN’S DISEASE FIT INTO THE PICTURE?

Mortality from ulcerative colitis alone or analyzed jointly with Crohn’s disease is shaped by an underlying birth-cohort pattern, but mortality from Crohn’s disease alone does not behave in a birth-cohort fashion (17). When the age-specific mortality trends of
Crohn’s disease are superimposed on those of ulcerative colitis, however, it appears as if the level of ulcerative colitis mortality presents a limit for a continued rise in mortality from Crohn’s disease (Figure 4). In each age group alike, the trends of Crohn’s disease start to decline upon approaching the level of mortality from ulcerative colitis. After leveling off, the death rates of Crohn’s disease start to run a similar downward course as those of ulcerative colitis (18). This phenomenon is obvious in mortality data from many different countries (Figure 5). Again, mortality statistics only serve as an easy means to accumulate large and representative groups of patients with inflammatory bowel disease, but the underlying time pattern itself is independent of death as morbidity parameter. The interaction between ulcerative colitis and Crohn’s disease is not restricted to mortality data but can be observed similarly in other types of health statistics, such as incidence, hospitalization, or physician visits (6,7,19). The phenomenon is remarkable, because the time trends of different age groups or countries exhibit a different course, yet always the same type of relationship between ulcerative colitis and Crohn’s disease. The general emergence of such pattern suggests that the time trends of Crohn’s disease are influenced by those of ulcerative colitis. It seems as if one primary environmental risk factor has been responsible for the long-term birth-cohort pattern of ulcerative colitis, as well as inflammatory bowel disease in general. The decrease in exposure to this unknown primary risk factor caused the recent decline in ulcerative colitis and must have prevented a further rise in the occurrence of Crohn’s disease. The exposure to this primary factor has fallen among the populations of developed countries. Although the nature of this risk factor is unknown, its epidemiologic patterns make one suspect that it relates to some type of intestinal infection. The nature of the second environmental influence causing the initial rise in the occurrence of Crohn’s disease remains presently unknown.

(continued on page 32)
CAVEATS TO THE MODEL

Obviously there are patients infected by *H. pylori* who also harbor inflammatory bowel disease. Does such comorbidity invalidate the hypothesis underlying the present article? The protection provided by *H. pylori* against inflammatory bowel disease is most likely far from being absolute or perfect. Because not everyone with *H. pylori* develops chronic gastritis or low acid output, different levels of infection could be associated with various levels of protection. The hypothetical infection causing inflammatory bowel disease may occasionally precede a subsequent infection with *H. pylori*. Lastly, any type of protection that exerts its influence on a general population level may not necessarily materialize in the individual patient.

The inverse relationship between *H. pylori* infection and reflux disease helps to clarify the latter issue. Within historical times and on a population level, the decline of *H. pylori* infection resulted in increased levels of acid secretion and a marked rise of reflux disease and its various complications in the general population. Such inverse relationship between *H. pylori* infection and acid secretion and acid reflux does not necessarily become effective in every patient. Presence of *H. pylori* does not rule out the comorbid existence of reflux disease, and in the individual patient eradication of *H. pylori* will not predictably cause reflux disease.

---

Figure 5. Time trends of death from ulcerative colitis (full line) and Crohn’s disease (dashed lines) in six countries. Each point represents the average death rate of 5 consecutive years.
CONCLUSION

It is hypothesized that infection with *H. pylori* protects against inflammatory bowel disease. The sudden decline in the prevalence of *H. pylori* infection could have precipitated an epidemic of inflammatory bowel disease during the twentieth century. This hypothesis rests on the peculiar time trends of inflammatory bowel disease and *H. pylori* during the past century. The time trends of ulcerative colitis and their interaction with those of Crohn’s disease, as depicted in Figures 1, 4, and 5, are based on large national databases. Their ubiquitous and similar occurrence in different countries and various health statistics are difficult to ignore. However, the interactions drawn schematically in Figures 2 and 3 are at the present time mostly speculative. It is possible that parts of the hypothesis or all of it are wrong. First and foremost, the decline in the prevalence of *H. pylori* infection and the rise in the occurrence of inflammatory bowel disease could have been just coincidental. Not a single infection, but the interaction the immune system with multiple enteric organisms may initiate the development of ulcerative colitis. The relationship between the time trends of ulcerative colitis and Crohn’s disease may have other reasons than a rate-limiting infection common to both diseases. Moreover, many other environmental factors besides an infection could have shaped the peculiar time trends of inflammatory bowel disease. The science of epidemiology studies disease variation in human populations and then correlates such variation with the variation in exposure to potential risk factors. The ultimate goal of such scientific endeavor is to find patterns of disease associations and behavior, which can lead to novel hypotheses about disease etiology. It has been proposed that it is more important for a good hypothesis to be interesting and to lead to new avenues for research than to be correct.

References