

Clinical Epidemiology and Natural History of Gastroesophageal Reflux Disease

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*In the MUSE classification of gastroesophageal reflux disease (GERD), esophagitis is assessed by the presence of metaplasia, ulcer, stricture, or erosion, each being graded as absent, mild or severe. Daily reflux symptoms affect about 4 to 7 percent of the population; erosive esophagitis occurs in about 2 percent; the prevalence rate of Barrett's metaplasia is 0.4 percent; and esophageal adenocarcinoma leads to two deaths per million living population. In persons with GERD symptoms, about 20 percent are found to have erosive esophagitis, while ulcers or strictures are found in less than 5 percent of all patients with erosive esophagitis. No clear-cut temporal progression exists between successive grades of disease severity, as the most severe grade of GERD is reached at the onset of the disease. Mild forms of GERD tend to be more common in women than men, while severe GERD characterized by erosive esophagitis, esophageal ulcer, stricture or Barrett's metaplasia are far more common in men than women. All forms of GERD affect Caucasians more often than African Americans or Native Americans. The prevalence of GERD is high among developed countries in North America and Europe and relatively low in developing countries in Africa and Asia. During the past three decades, hospital discharges and mortality rates of gastric cancer, gastric ulcer and duodenal ulcer have declined, while those of esophageal adenocarcinoma and GERD have markedly risen. These opposing time trends suggest that corpus gastritis secondary to *Helicobacter pylori* infection protects against GERD. This hypothesis is consistent with the geographic and ethnic distributions of GERD. Case-control studies also indicate that cases with erosive esophagitis are less likely to harbor active or chronic corpus gastritis than controls without esophagitis.*

INTRODUCTION

The general epidemiology of gastroesophageal reflux disease (GERD)^b was presented in several previous articles [1-3]. Rather than provide another comprehensive review of GERD epidemiology, in the present article we will discuss primarily its clinical epidemiology and natural

history and focus attention on recent developments in these two areas. New data are emerging to suggest that, besides peptic ulcer and gastric cancer, gastrointestinal infection with *Helicobacter pylori* may also explain several characteristic features of GERD epidemiology. We conclude by listing the many remaining open questions of GERD.

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^b Abbreviations: GERD, gastroesophageal reflux disease; NSAIDs, non-steroidal anti-inflammatory drugs.

CLINICAL EPIDEMIOLOGY

Clinical presentation

The term gastroesophageal reflux disease (GERD) is used to describe the symptoms and changes of the esophageal mucosa that result from reflux of stomach contents into the esophagus. GERD patients present with symptoms of epigastric pain, heartburn, pharyngeal burning, regurgitation of gastric contents, acidic taste and dysphagia. Such symptoms may be experienced daily, weekly or only few times per month. With respect to GERD, individual symptoms carry a sensitivity or specificity that, in general, do not exceed 65 percent or 80 percent, respectively [4]. The frequency and severity of symptoms from gastroesophageal reflux do not correlate with the amount of morphologic changes of the mucosa seen on endoscopic examination of the esophagus.

Most commonly used grading systems of GERD are based on the Savary-Miller classification [5]. Subjects with reflux symptoms but no macroscopically visible lesions are said to have reflux disease without esophagitis, sometimes referred to as "grade 0." Peptic esophagitis is graded according to the extent and severity of macroscopically visible erosions: single patchy, large confluent or circumferential erosions representing grade I, II, or III, respectively. The terms "complicated esophagitis" or "grade IV" relate to esophagitis accompanied by Barrett's mucosa, ulcers or strictures. The synonyms "Barrett's esophagus," "epithelium" or "metaplasia" refer to the replacement of esophageal squamous epithelium by a gastric type of columnar epithelium with (or without) intestinal metaplasia that reaches 2 to 3 cm above the lower esophageal sphincter. Barrett's epithelium is more susceptible than the regular squamous epithelium of the esophagus to the development of deep ulcers that reach into

the submucosa. In a minority of patients, healing of erosions or ulcers results in scarring and formation of a peptic stricture.

The Savary-Miller classification of GERD puts much emphasis on various types of erosions, but lumps esophageal metaplasia, ulcers and strictures into one grade. Moreover, it does not account for the frequent concurrence of Barrett's epithelium with stricture or stricture with erosions. The newer, more refined, MUSE classification grades esophagitis according to presence of metaplasia, ulcer, stricture or erosion, each being assigned a value ranging from 0 to 2, that is, absent, mild or severe, respectively [5].

Barrett's epithelium is considered a premalignant lesion, as the incidence rate of esophageal adenocarcinoma developing from Barrett's mucosa is 1 percent per year [6]. In the International Classification of Diseases, esophageal adenocarcinoma is listed as "cardiac cancer." The demographic characteristics and time trends of esophageal adenocarcinoma (or cancer of the gastric cardia) are very similar to those of GERD. They are strikingly different from those of adenocarcinoma in the gastric body and antrum or squamous carcinoma of the esophagus. Despite these obvious similarities and its origin from Barrett's metaplasia, however, esophageal adenocarcinoma is not included in the classification of esophagitis.

Prevalence rates

Daily reflux symptoms affect about 4 to 7 percent of the population, while esophageal adenocarcinoma leads to 2.5 deaths per million living population [2-3]. The prevalence rates of the other presentations of reflux disease in the middle range between these two extremes are far less well characterized. A recent study from China estimated a 5 percent prevalence rate of erosive esophagitis [7]. Of those

presenting with symptoms suggestive of GERD, 18.5 percent were found to have erosive esophagitis. A Swedish study reported an incidence rate of 120 new cases of erosive esophagitis per 100,000 per year [8]. Assuming a case history of 20 years yields a crude estimate 2.4 percent for the prevalence rate. Ulcers or strictures were found in less than 5 percent of all patients with erosive esophagitis. Lastly, a post-mortem study from Olmsted County in Minnesota found a prevalence rate of 0.4 percent for Barrett's esophagus [9].

Since symptoms are a poor indicators for disease severity, a study trying to assess the true prevalence of erosive esophagitis and its complications would need to subject a large group of persons to upper gastrointestinal endoscopy. For obvious reasons, such a study is difficult and expensive to conduct. Because symptomatic patients are more likely to undergo endoscopy, incidence and prevalence rates based largely on routine endoscopy reports may overestimate the prevalence rate of erosive esophagitis in the general population. The prevalence of GERD varies markedly between different populations [1, 10]. During the past three decades the prevalence of GERD has increased more than two-fold, and previously reported data may no longer apply to present day populations [3]. With all these caveats in mind, one should consider the data cited above as crude estimates only.

Diseases associated with GERD

Esophageal clearance is markedly impaired in CRST syndrome and systemic sclerosis because muscle atrophy results in dysfunction of the lower sphincter and aperistalsis of the tubular esophagus [11-15]. Among the population of U.S. military veterans, we found systemic sclerosis to be associated with a six-fold increased risk for erosive esophagitis [16]. In Sjögren's syndrome, reduced or absent

salivary secretion interferes with normal esophageal clearance and also results in an increased risk for erosive esophagitis [15].

Presently, there are no risk factors known to disrupt tissue resistance, except for non-steroidal anti-inflammatory drugs (NSAIDs). Several authors have suggested that more severe forms of peptic esophagitis, associated with large confluent erosions, strictures and Barrett's esophagus, are more common in patients on chronic consumption of NSAIDs [16-18]. In the population of veterans, many of the diseases commonly treated with NSAIDs, such as osteoarthritis, back pain or tension headache, were associated with a small but nevertheless significant odds ratio of about 1.4 for reflux esophagitis [16].

Frequent occurrence of nighttime reflux can irritate the pharyngeal and laryngeal structures and result in laryngitis or even hoarseness and aphonia. Aspiration of gastric contents has been associated with asthma, pneumonia, and bronchiectasies [19-21]. In our epidemiological study of GERD among U.S. military veterans, we found both erosive esophagitis and esophageal stricture to be significantly associated with sinusitis, aphonia, pharyngitis, laryngeal stenosis, laryngitis, chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, pulmonary collapse and pneumonia [21]. While the odds ratios for sinus, laryngeal and pharyngeal diseases ranged between 1.5 and 2.0, the odds ratios for the association between GERD and pulmonary disease did not exceed 1.5. This may reflect, in part, the a high overall prevalence of respiratory disease in the population of veterans.

Except for the striking example of Zollinger-Ellison syndrome, the association between the amount of acid output and the occurrence or severity of reflux disease has remained elusive [22-24]. There appears to exist a weak correlation

between the amount of acid reflux and the occurrence of Barrett's esophagus, as well as, with its length above the lower esophageal sphincter [25-26]. Several authors have also reported a coincidence of duodenal ulcers and erosive esophagitis in patients without Zollinger-Ellison syndrome [27]. Both endoscopy and, to a lesser extent, barium swallow are primary modalities to diagnose reflux esophagitis, as well as peptic ulcer. This makes it difficult to discern a true association from an association brought forth by a detection bias.

NATURAL HISTORY

Initially, it was thought that in the natural history of the disease, mild forms of GERD progressed to more severe forms. This concept led to the original Savary and Miller classification of GERD by grades of severity [1]. Physicians were advised to prevent the more severe grades of GERD involving Barrett's mucosa or strictures by early and vigorous treatment of mild forms, such as single erosions or even reflux symptoms only.

On one hand, epidemiologic studies show that hiatus hernia is frequently found in patients with GERD and that all forms of GERD tend to cluster in the same patient population [1-3]. In our study of the population of veterans, on average, any

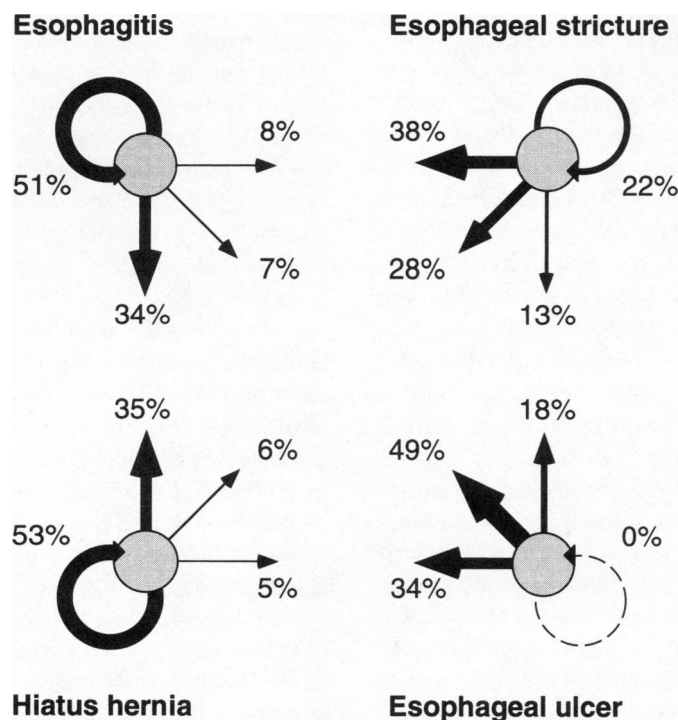


Figure 1. Co-morbid associations between four forms of GERD, each arrow representing one association. The percentage describes the fraction of patients with one form of GERD (where the arrow starts) who also suffer from a second form (to which the arrow points). The circular arrows represent patients who have one form of GERD as their sole presentation. Figure taken from [28].

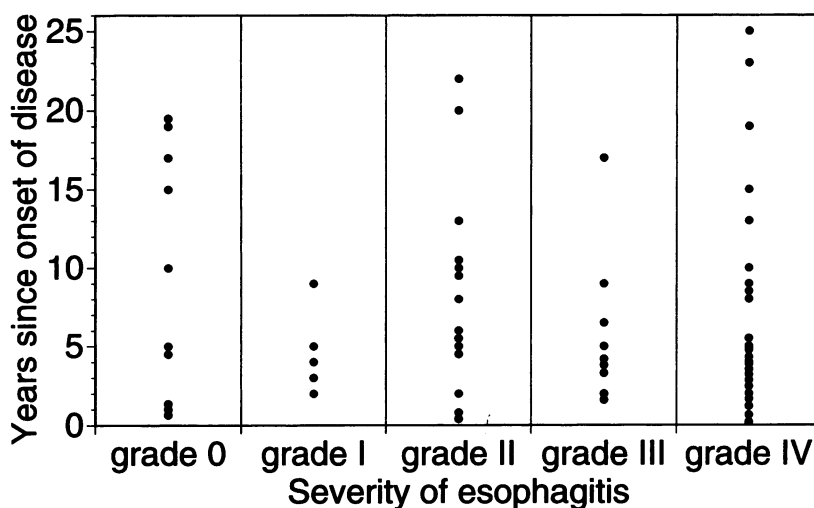


Figure 2. Relationship between disease severity and length of GERD history. Figure adapted from [1].

form of GERD was 10-times more likely to occur in a patient with another form of GERD than without, the highest ratio ($R = 22$) found among esophageal ulcers and stricture [28]. About one-third of all patients with esophageal erosions, ulcers or strictures also had hiatus hernia, and 46 percent of patients a hiatus hernia were diagnosed to have other forms of GERD. While hiatus hernia or erosive esophagitis represented the only diagnosis related to GERD in half of the patients, strictures rarely and esophageal ulcers never occurred alone. This pattern leads one to believe that in a fraction of GERD patients' esophageal erosions may result in scarring or progress to deeper ulcerations (Figure 1). The clustering of different forms of damage to the esophageal mucosa in identical patients clearly points at a close patho-physiologic relationship among them. The more frequent occurrence of mild forms and the less frequent occurrence of severe forms of GERD also suggests that the present grading system truly reflects consecutive stages of increasing pathophysiological derangement.

On the other hand, the same study failed to show a clear-cut temporal relationship between various forms of GERD [28]. In few relationships, it appeared as if less severe forms preceded the more severe ones. For example, hiatus hernia tended to precede esophageal erosions or ulcers. Similarly, esophagitis was diagnosed slightly more often before esophageal strictures. However, appreciable numbers of severe and mild forms of GERD presented simultaneously or with the severe form before the mild one. For example, in the comorbid occurrence of esophagitis, esophageal ulcer represented the initial diagnosis in 39 percent, whereas esophagitis represented the initial diagnosis in only 22 percent. Overall, no consistent progression from mild to severe forms of GERD could be appreciated. One possibility to reconcile the seeming contradiction between the lack of progression and the patterns of clustering (described in the previous paragraph) is to assume that most progression between different grades of severity occurs quite rapidly. Thus, it would appear that the most severe grade of GERD is reached at the very onset of the disease. After this initial

rapid progression, little, if any, further development is noticed subsequently. In the individual patient, the presentation of GERD and its severity of mucosal damage seem to remain stationary or fluctuate only between close grades of severity. This contention is corroborated by other studies that failed to establish a relationship between the length of case history and disease severity (Figure 2) [1].

In a subsequent study, we selected 29,500 patients with erosive esophagitis, but without ulcers or strictures from the population of veterans and followed them over a four-year time period (range 1 to 12 years). Amazingly, not one of these patients was subsequently diagnosed to have developed such complications [29].

This was in striking contrast with a comparison group of 5,100 esophagitis patients who presented initially with esophageal ulcers or strictures. During follow-up, about 80 percent of these patients were diagnosed repeatedly with the same types of esophageal complication.

DEMOGRAPHIC, TEMPORAL AND GEOGRAPHIC VARIATIONS OF GERD

Mild forms of GERD tend to be slightly more common in women than men, while severe GERD characterized by erosive esophagitis, esophageal ulcer or stricture are far more common in men than

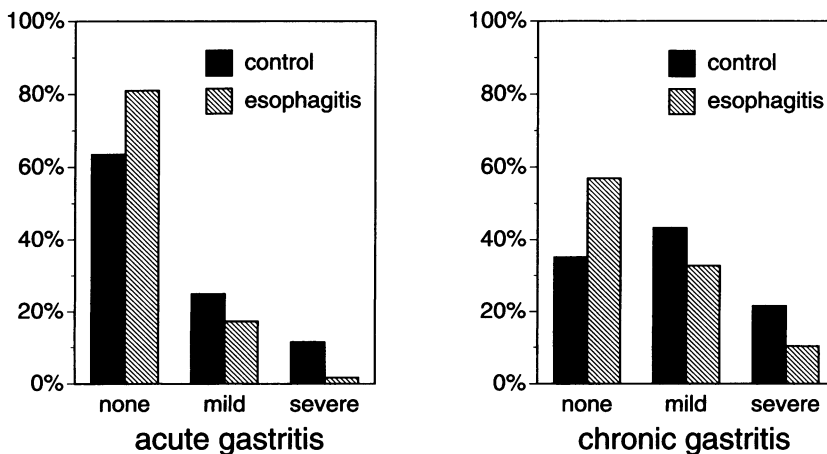


Figure 3. Prevalence rates of various grades of acute (left panel) or chronic gastritis (right panel) of the gastric body in 116 case subjects with and in 148 control subjects without erosive esophagitis. The differences in the prevalence rates of acute and chronic gastritis among case and control subjects were both statistically significant ($df = 2$, $c2 = 6.52$, $p = 0.0013$ and $df = 2$, $c2 = 8.92$, $p = 0.0011$ for the left and right panel, respectively).

women [2]. All forms of GERD affect Caucasians more often than African Americans or Native Americans. Similar patterns characterize the epidemiology of GERD and esophageal adenocarcinoma [30]. In the United States, such variations by gender and ethnicity are revealed similarly by different types of epidemiologic parameters, that is, prevalence data, physician visits, hospitalizations and death rates. The prevalence of GERD is high among residents of developed countries in North America and Europe, but relatively low among those of developing countries in Africa and Asia [1, 10].

Between 1970 and 1987, the rates of hospitalizations in the National Hospital Discharge Survey, secondary to erosive esophagitis, rose two-fold in men and women alike [2]. A less striking increase also occurred with respect to esophageal stricture. The rise in hospitalization for esophagitis was not matched by an equal rise in surgical procedures, as the rate of surgical repair of hiatal hernia declined during the identical time period. The time trends from the National Hospital Discharge Survey are corroborated by similar trends of hospitalizations among U.S. military veterans and U.S. mortality rates taken from the Vital Statistics of the United States [31].

In the population of veterans, as in many other populations, gastric and duodenal ulcer showed a significant decline of their hospitalization rates between 1970 and 1995, the decline being more pronounced in duodenal than gastric ulcer. The hospitalization rates for gastric and duodenal ulcer were similar among whites and nonwhites. In striking contrast with the behavior of peptic ulcer, the hospital discharges involving GERD rose four- and seven-fold among nonwhites and whites, respectively, during the same time period. While hospitalization resulting from cancer of the gastric corpus and antrum declined between 1968 and 1992, hospital-

ization from esophageal adenocarcinoma increased during the same time period. The time trends of mortality from gastric ulcer, duodenal ulcer, gastric cancer and esophageal adenocarcinoma provide an almost exact replica of the corresponding patterns in the hospitalization data.

ROLE OF *H. PYLORI* IN GERD

Because *H. pylori* plays an essential role in the pathogenesis of gastric ulcer, duodenal ulcer and gastric cancer, the general decline of its infection rate in Western societies provides the most likely explanation for the time trends of these three diseases. The acquisition of *H. pylori* results in the development of acute gastritis that, if left untreated, gives way to chronic gastroduodenitis [32]. Both types of peptic ulcer and gastric cancer are strongly correlated with a gastroduodenal infection by *H. pylori* [33-34]. Antral gastritis found mostly in patients with duodenal ulcer, leaves the ability to secrete acid unaffected or even increases gastric acid output by compromising somatostatin secretion of the D-cells and its inhibitory effect on gastrin output. In contradistinction with antral gastritis, gastritis that involves large areas of the gastric body (corpus) results in partial atrophy of the acid secreting mucosa and hypochlorhydria [35-36]. In general, patients with an endoscopically diagnosed reflux esophagitis are less likely to harbor active or chronic corpus gastritis than patients without esophagitis [37-39]. Figure 3 shows data from our own series of consecutive patients undergoing esophagogastroduodenoscopy for various upper gastrointestinal symptoms [39]. The patient population comprised of 116 case subjects with and 148 control subjects without erosive esophagitis. The severity of acute or chronic gastritis in the gastric body, characterized by polymorphonuclear cells and lymphocytes, respectively, were

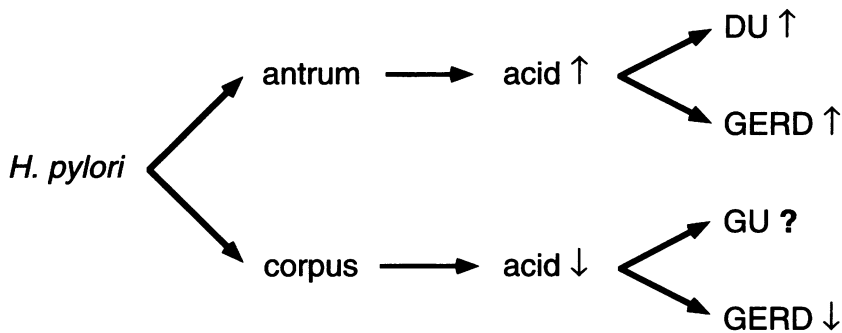


Figure 4. Scheme of the interaction between *H. pylori* infection, acid secretion and disease outcome.

both inversely related to the prevalence rate of erosive esophagitis. Overall, patients with erosive esophagitis showed a significantly lower prevalence rate of gastritis in the body of their stomach. In some patients, the hypochlorhydria secondary to corpus gastritis becomes reversible once the infection with *H. pylori* has been treated with antibiotics [35-36]. Labenz et al. followed patients with duodenal ulcer after antibiotic cure of *H. pylori* infection for three years [40]. The incidence of reflux esophagitis was 25.8 percent after eradication of *H. pylori* compared to 12.9 percent in patients with persistent infection. Besides being responsible for the decline of peptic ulcer and gastric cancer, therefore, the time trends *H. pylori* infection also offer a possible explanation for the rise of GERD and esophageal adenocarcinoma. The opposing time trends of peptic ulcer and gastric cancer on one side versus GERD and esophageal adenocarcinoma on the other side suggest that *H. pylori* infection may protect against GERD.

An additional piece of evidence to support the role of *H. pylori* in GERD is provided by the remarkable differences among ethnic groups. While U.S. nonwhites incurred substantially reduced hospitalizations and mortality related to GERD or esophageal adenocarcinoma, they suffered more from gastric cancer

than whites [31]. In general, nonwhites in the United States tend to harbor higher rates of infection with *H. pylori* acquired at a younger age than whites [41]. Again, this pattern translates into prolonged time periods of chronic gastritis and a greater chance of developing mucosal atrophy of the gastric body associated with reduced acid output. Gastric atrophy and reduced acid output mean a greater risk for gastric cancer and a smaller risk for GERD and esophageal adenocarcinoma, respectively. The geographic distribution of GERD could also relate to the geographic distribution of *H. pylori*. In developed countries the decline in *H. pylori* infection is likely to have resulted in an increases susceptibility to develop GERD.

OPEN QUESTIONS

Figure 4 illustrates a working model for the relationship between the infection with *H. pylori*, its influence on acid secretion and the occurrence of various diseases of the upper gastrointestinal tract. Despite the strong and multifaceted evidence in favor of *H. pylori* playing an important role in the epidemiology of GERD, many issues still remain unresolved. It is presently unclear why some types of infection are confined predominantly to the antrum

while others involve the whole stomach. It was hypothesized that childhood infection versus infection during adolescence or adulthood may, in part, determine the outcome of gastritis [42]. As indicated by this scheme, *H. pylori* infection may exert two diametrically opposite influences on the upper gastrointestinal tract, one associated with an increased and the other with a decreased risk for GERD. Simple case-control studies trying to associate *H. pylori* infection with GERD will not be able to resolve this mystery. Vicari et al., for instance, found that the occurrence of *H. pylori* infection was lower in 153 GERD patients than in 57 controls, that is 34 percent versus 46 percent, but this difference failed to reach statistical significance [43]. The severity, spread and type of gastritis, the immune response by the host and the genetic make-up of the organism may ultimately determine amount of acid output and its influence on reflux disease [43-44].

The second open question concerns the role of gastric acid secretion in GERD. On one hand, vigorous inhibition of gastric acid secretion constitutes the most efficacious means to treat GERD. Moreover, the exposure time of the esophageal mucosa to pH-values less than 4 correlates with the severity of GERD [26]. The extreme in the relationship between acid output and GERD is exemplified by patients with Zollinger-Ellison syndrome who tend to suffer from erosive esophagitis [22]. Lastly, the protective influence of corpus gastritis against GERD also points at the essential role of acid in GERD. On the other hand, Hirschowitz has shown in multiple, well-designed studies that the amount of gastric acid output does not correlate with the severity of GERD [23-24]. How can one reconcile the seemingly contradictory findings? One possible explanation is that gastric acidity

represents a necessary, but taken alone, not sufficient, prerequisite for the development of GERD. Other mechanisms would determine how much of the available acid is capable to exert its corrosive action on the squamous epithelium of the esophagus. The factors that influence the severity of reflux disease have remained mysterious. What determines whether GERD in an individual patient will be characterized by erosions or symptoms only? Why do some patients develop esophageal ulcers, strictures and Barrett's mucosa, while others with similar amounts of gastroesophageal reflux do not develop even the slightest break of their esophageal mucosa?

The normal-appearing gastroesophageal junction can harbor intestinal metaplasia in 18 percent to 36 percent of patients with symptoms of gastroesophageal reflux [45-46]. It appears that both reflux of gastric contents and *H. pylori* infection of the cardia can result in intestinal metaplasia at the gastroesophageal junction. Only intestinal metaplasia associated with reflux, however, seems capable of promoting cardiac cancer, as evidenced by the opposing time trends of cardiac versus body or antral cancer of the stomach. What are characteristics that render one type of intestinal metaplasia particularly prone to malignant transformation?

It seems that the discovery of *H. pylori* has not only furthered our concepts regarding peptic ulcer and gastric cancer, but also that in the near future it will also help resolve some of the enigmas surrounding GERD. The potential role of *H. pylori* infection in the pathogenesis GERD gives the opportunity to develop interesting hypotheses and design new epidemiologic studies. These studies will deepen our understanding of GERD.

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