Review

Helicobacter pylori and Peptic Ulcer Disease: Evolution to Revolution to Resolution

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Radiology of the upper gastrointestinal tract has largely been supplanted by fiberoptic endoscopy as the diagnostic procedure of choice for dyspeptic patients. However, as managed care directs a growing share of health care resources, and market forces increasingly require clear cost-effectiveness for diagnostic procedures, a renewed interest in diagnostic radiology for evaluation of dyspepsia is emerging [1, 2].

The bacterium *Helicobacter pylori* is now recognized as the most important cause of chronic gastritis, gastric and duodenal ulcer, and distal gastric adenocarcinoma. Because of the pivotal role of *H. pylori* in management of a number of upper gastrointestinal diseases, clinical decisions will depend not only on findings of radiologic or endoscopic examinations but also on results of testing for *H. pylori*. This review will attempt to summarize for the radiologist important features of *H. pylori* and its related diseases.

Historical Perspectives of *H. pylori*

Before 1983, the stomach was regarded as a sterile environment because gastric acid was presumed to serve as a barrier to colonization by bacteria and other microorganisms [3]. Dietary indiscretions, stress, smoking, alcohol, and hyperacidity were felt to play important causal roles in the development of peptic ulcer. Highly effective acid suppression therapy became available in the mid 1970s with the introduction of the first H_2 receptor antagonist. However, although dramatic symptom control and ulcer healing were possible with H_2 receptor antagonists, cessation of therapy was all too often associated with ulcer recurrence, leading to the need for long-term H_2 receptor antagonist therapy to control symptoms and reduce complications. The clinical adages "once an ulcer, always an ulcer," and "no acid, no ulcer" became even more firmly entrenched.

In the early 1980s, Marshall and Warren [4] isolated *H. pylori* (originally called *Campylobacter pyloridis*) from gastric biopsies obtained from patients with chronic gastritis and peptic ulceration, after which interest in a bacterial cause for ulcer disease exploded. Because of the lack of a suitable animal model, two human volunteers, Marshall in Australia [5] and later Morris in New Zealand [6], ingested pure cultures of the bacteria and developed endoscopic and histologic gastritis, confirming that *H. pylori* did indeed cause significant inflammatory changes in gastric mucosa. Subsequent to multiple studies showing that eradication of *H. pylori* in patients with duodenal ulcer drastically reduced ulcer recurrences [7–11], the 1994 National Institutes of Health Consensus Conference on *H. pylori* in peptic ulcer disease concluded that ulcer patients with *H. pylori* require treatment with antimicrobial agents in addition to antisecretory drugs [12], thus firmly establishing an infectious cause for peptic ulcer disease.

Since 1991, several reports have linked *H. pylori* and gastric cancer [13–15], leading the International Agency for Research on Cancer of the World Health Organization to declare this bacterium a class I (the most dangerous rank) carcinogen [16]. *H. pylori* has also been associated with a unique form of gastric lymphoma derived from mucosa-associated lymphoid tissue [17]. When these low-grade B-cell lymphomas are confined to the stomach, they are usually associated with *H. pylori* gastritis and can be cured in more than half the cases by eradicating *H. pylori* infection [18, 19]. Thus, for the first time, a clear causal association has been shown between an infectious disease and a neoplastic process, and, most exciting, such early malignant change can be reversed by cure of the infection.

H. pylori Microbiology and Pathophysiology

H. pylori is a gram-negative, curved or spiral, flagellated organism (Fig. 1) that colonizes only gastric-type epithelium. It may be cultured on sheep blood or chocolate agar

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in a microaerophilic environment (5–10% O_2); it will not grow under standard aerobic or anaerobic conditions [20].

The bacterium survives in gastric acid by means of its potent urease enzyme activity, which breaks down urea to ammonia and bicarbonate, generating an alkaline microenvironment for itself within the mucous layer [21]. From this location, *H. pylori* produces an acute inflammatory reaction in the mucosa that leads to neutrophil-mediated tissue injury, followed in a few weeks by a more chronic (lymphocyte, macrophage, plasma cell) reaction. Acute *H. pylori* infection causes gastric inflammation associated with parietal cell failure and achlorhydria [6]. In most cases, a mild vomiting illness occurs, followed by a return to an asymptomatic state. Acid secretion may remain low or absent for months until the infected individual is able to clear most of the organisms from the body of the stomach. The mature state of infection occurs when *H. pylori* causes chronic inflammation localized to the distal part of the stomach (antral gastritis) and duodenal bulb (duodenitis). Because parietal cell function in the proximal stomach is restored, acid secretion returns to normal or even to high levels. This is the stage at which the individual is susceptible to peptic ulceration, which occurs in about 1% of infected adults each year [22].

Why infection with *H. pylori* leads to peptic ulcer is not entirely known. Virtually all infected persons have histologic evidence of chronic gastritis reversible by eradication of *H. pylori* infection, whether or not peptic ulcers develop. Factors that, in the presence of *H. pylori* gastritis, may predispose a patient to ulceration include extrinsic factors, such as smoking [23], and physiologic factors indirectly induced by the infection, such as increased acid secretion, both basal and stimulated [24, 25], and reduced bicarbonate secretion in the duodenal mucosa [26]. The most important factor dictating the development of peptic ulcers appears to be whether *H. pylori* organisms produce certain cytotoxins that lead to a more pronounced inflammatory reaction [3, 27].

In some persons *H. pylori* chronic gastritis extends proximally from the antrum to involve the gastric body. Pangastritis, gastric mucosal atrophy, and intestinal metaplasia with resultant acid hyposecretion can occur. In this setting duodenal ulcer is uncommon because of low acid levels, but the risk for development of gastric carcinoma is increased [28, 29].

Epidemiology of *H. pylori*

H. pylori has a worldwide distribution but is much more prevalent in developing countries, where more than half the population is infected by age 10 years and the prevalence of infection is more than 80% in young adults. In the United States, about 20% of persons less than 40 years old and 50% more than 60 years old are infected with *H. pylori*. This increasing prevalence by age in the United States is accounted for by two factors: the natural history of infection—once established, infection doesn't resolve spontaneously; and the cohort effect—acquisition of infection was more common in the past than it is today, probably because of improved economic conditions and sanitation [30]. Contrasting *H. pylori* acquisition curves between developing and developed countries are shown in Figure 2.

H. pylori infection is more common in United States ethnic and racial minorities, lower socioeconomic groups, and immigrants from areas of high *H. pylori* prevalence [31]. Additionally, clustering of *H. pylori* infection within families and within institutions for the mentally handicapped has been shown [32, 33].

The precise mechanism of transmission for *H. pylori* is unknown. Because *H. pylori* has occasionally been found in saliva, dental plaque, and the stool of infected individuals [34–36], oral–oral or fecal–oral transmission (or both) may occur. Gastric–oral transmission has been documented by several reports of nosocomial infection in patients undergoing endoscopy or acid secretion studies [37, 38], and a recent hypothesis implicated epidemic vomiting of childhood as the most likely mode of transmission [39]. Contaminated water supplies may play a role in the transmission of *H. pylori* in some developing countries [40].

Disease Associations of *H. pylori*

Chronic Gastritis

The characteristic pathologic lesion caused by *H. pylori* is chronic superficial gastritis (also called chronic active gastritis). Superficial gas-

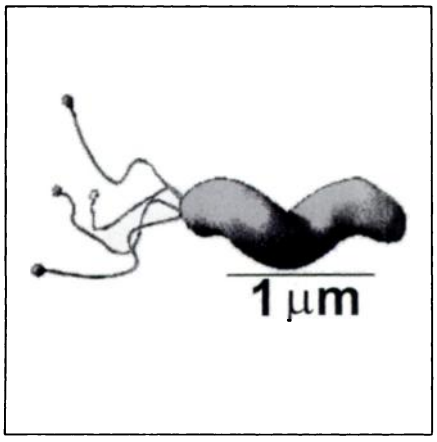

Fig. 1.—Drawing of *Helicobacter pylori* shows typical spiral, flagellated morphology.

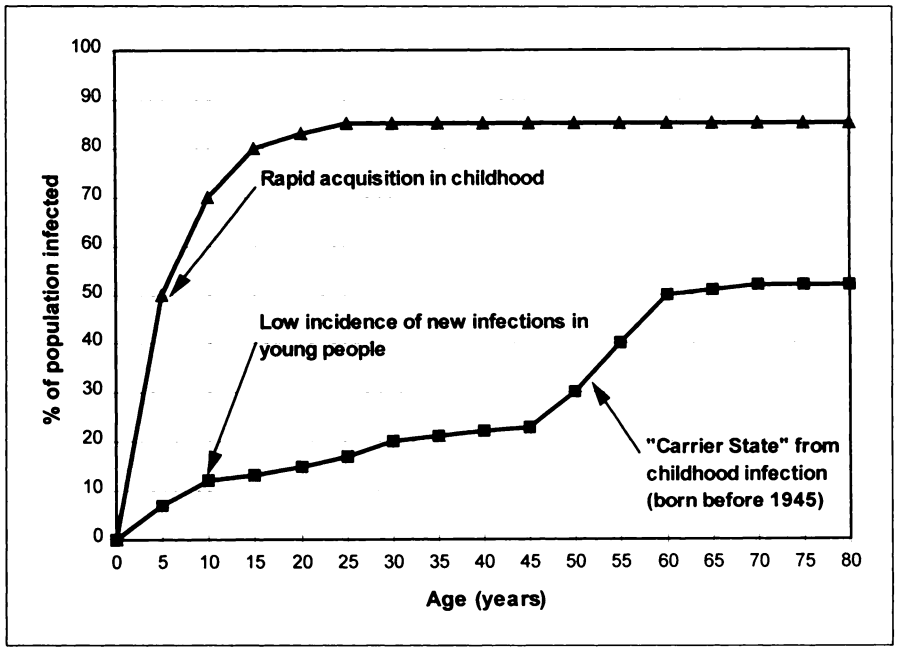

Fig. 2.—Graph shows age-specific prevalence of *Helicobacter pylori* in developing (▲) and developed (■) countries. In developing countries, *H. pylori* infection is acquired earlier in life and more frequently than in developed countries.

tritis is rarely found in the absence of *H. pylori* [41] but is nearly always noted in the presence of *H. pylori*. Inflammation may be predominantly antral or predominantly corporic or may affect the entire stomach (pangastritis). The correlation between the presence or severity of *H. pylori* gastritis and endoscopic appearance is generally poor, with the exception of antral nodularity, which is specific [42]. Other diseases associated with *H. pylori* are shown in Table 1.

Duodenal and Gastric Ulcer

The most clinically apparent disease associated with *H. pylori* is peptic ulceration; 95% of duodenal ulcers are caused by this bacterium, with the remainder a result of acid hypersecretory states (e.g., Zollinger-Ellison syndrome, duodenal Crohn's disease, viral infections, penetrating pancreatic cancer, or surreptitious or unknowing nonsteroidal antiinflammatory drug [NSAID] use) [43].

In gastric ulcers two causes prevail, and many patients will have both. Most gastric ulcers are associated with *H. pylori*, but the stomach is also directly exposed to ingested agents such as NSAIDs and is more likely than the duodenum to ulcerate in response to these agents. Thus, in the United States, about 30% of gastric ulcers are not associated with histologic chronic gastritis or *H. pylori* but are caused by NSAIDs [30].

Gastrointestinal Malignancy

Two histologic types of gastric cancer exist: diffuse (signet-ring or anaplastic) and intestinal (well-differentiated) adenocarcinoma. The latter type is found most frequently in the gastric body, antrum, or both (distal cancers) and is common in areas where the prevalence of *H. pylori* is high. The incidence of gastric cancer (currently six per 100,000 per annum) has declined in the United States since 1930, when it was the most common cancer. This reduction in gastric cancer may be partially explained by the decreasing incidence of *H. pylori* infection. Worldwide, gastric cancer is the second most common cancer, with high-incidence areas being Brazil, Korea, China, and Japan; *H. pylori* infects more than half the population in these countries [30]. The presence of *H. pylori* increases by sixfold the risk for gastric cancer and accounts for about half of all such cancer [44]. Studies suggest that acquisition of *H. pylori* at an early age favors development of gastric cancer, whereas infection in adulthood is more likely to result in duodenal ulcer [45].

Retrospective biopsy studies reveal that 90% of mucosa-associated lymphoid tissue lymphomas are associated with *H. pylori*, and these tumors are sometimes driven by continuing *H. pylori* antigenic stimulus. Treatment of the infection has been shown to result in complete regression of the neoplastic process in 74% of patients, with an additional 10% showing partial regression [46].

Nonulcer Dyspepsia

This condition may be defined as persistent or recurrent pain or discomfort localized to the upper abdomen (which may or may not be related to meals), a sense of fullness, nausea, and belching in the absence of peptic ulceration or other lesions of the upper gastrointestinal tract. Although *H. pylori* is present in about 50% of such patients [47], conflicting data [48] about the efficacy of *H. pylori* eradication led the National Institutes of Health Consensus Conference on *H. pylori* in peptic ulcer disease to advise against antimicrobial treatment of *H. pylori* in this subset of patients [12].

Putative Disease Associations

H. pylori gastritis as a chronic inflammatory condition may have other effects on health. Studies have shown a possible association between *H. pylori* and such diverse diseases as coronary artery disease, colonic adenomas, childhood growth retardation, diabetes mellitus, and rosacea [49–53]. Further data will be required to clearly establish a causal relationship of *H. pylori* with these conditions.

Diagnosis of *H. pylori*

Diagnostic tests for *H. pylori* can essentially be divided into those that require endoscopy (invasive) and those that do not require endoscopy (noninvasive). The accuracy and relative cost of the diagnostic tests are listed in Table 2. With the exception of serology, all the tests for diagnosis of *H. pylori* infection may be falsely negative in patients who have recently taken omeprazole or lansoprazole, antibiotics, or bismuth compounds.

Endoscopic Tests

Endoscopic biopsy for histologic examination constitutes the current gold standard for *H. pylori* diagnosis if read by an expert pathologist using special stains (Fig. 3). Even within these parameters, accuracy is not 100% and interobserver differences may occur [54]. Rapid urease tests contain urea and a pH indicator and rely on the potent urease activity of *H. pylori*: if the bacteria (and therefore urease) are present in a gastric biopsy specimen, urea is metabolized to ammonia and bicarbonate, with the ammonia producing an elevation in pH and a resultant color change in the pH indicator [55].

Culture of biopsy samples is 100% specific but only 80–90% sensitive, is expensive, and requires special expertise to achieve acceptably high sensitivity [56]. Thus, culture is not widely used currently, although the need to determine antibiotic sensitivities may render culture increasingly useful in the future because of the emerging antibiotic resistance of *H. pylori*.

TABLE 1 Prevalence of *Helicobacter pylori* Infection with Upper Gastrointestinal Disease

Disease	Prevalence (%)
None (asymptomatic populations[a])	20–55
Active chronic gastritis	100
Duodenal ulcer	95
Gastric ulcer	60–80
Nonulcer dyspepsia[a]	35–60
Gastric cancer of body or antrum	80–95
Mucosa-associated lymphoid tissue lymphoma	90

[a] Dependent on age and ethnic background.

TABLE 2 Accuracy and Relative Cost of Diagnostic Tests for *Helicobacter pylori*

Test	Sensitivity (%)	Specificity (%)	Relative Cost
Noninvasive			
Serology[a]			
In-office serology	93	90	$
In-office whole blood	90	87	$
Enzyme-linked immunosorbent assay	95	95	$$
Urea breath test	95	98	$$
Invasive (includes cost of endoscopy)			
Rapid urease test	90	98	$$$$$
Histology	95	95	$$$$$$
Culture	90	100	$$$$$$

[a] Does not define active disease.

Nonendoscopic Tests

Serologic tests.—Commercially available tests include rapid, in-office, qualitative tests (serum or whole blood) that are inexpensive and relatively accurate. A more expensive but generally more accurate semiquantitative enzyme-linked immunosorbent assay test must be sent to a reference laboratory for analysis. Serology may lead to inaccurate results in elderly patients, patients who take NSAIDs, and patients who have taken antibiotics that led to unknowing eradication of *H. pylori* [57]. Excluding this group of patients, it can be assumed that a positive serologic test indicates current infection because spontaneous clearance of infection is rare [56].

Urea breath tests (UBTs).—These tests also rely on the urease activity of *H. pylori*. After a patient ingests radiolabeled urea (^{13}C or ^{14}C), the presence of *H. pylori* urease will break down the labeled urea into ammonia and bicarbonate (expired as CO_2, which is labeled with ^{13}C or ^{14}C [Fig. 4]). Ten to 30 min later, the patient breathes into a collection device. The breath is then analyzed by either mass spectrometry (^{13}C) or scintillation counter (^{14}C) to determine the presence or absence of *H. pylori*. The ^{13}C UBT uses a stable isotope but currently takes longer to perform (30 min), uses a test meal, and requires more specialized analysis equipment than does the ^{14}C UBT, which uses a trivial 1-μCi (37-kBq) dose of radioactive isotope, is performed fasting, uses a sample at only 10 min, and may be analyzed by the more widely available scintillation counter [58, 59]. The UBT will be the preferred diagnostic test to document eradication of *H. pylori* after therapy and, depending on cost–benefit analyses, may also be considered for primary screening for patients with dyspepsia or as a means to document active infection in those patients screened for *H. pylori* by serology.

Other Noninvasive Tests

Saliva and urinary tests for *H. pylori* antibodies have been investigated but have, as yet, unacceptably low sensitivity for practical clinical use [60, 61].

Barium studies have also been evaluated as a noninvasive approach for the diagnosis of *H. pylori*. A recent study found thickened gastric folds, predominantly in the antrum, as the best radiographic criterion for *H. pylori* (Fig. 5). However, this finding was noted in only 44% of infected patients; 62% of these patients had thick polypoid folds [62]. Masslike changes caused by *H. pylori* may be difficult to differentiate from malignant gastric tumors. CT scanning may be the most sensitive technique for detection of infiltrating carcinomas with relatively normal mucosa [63]. A recent review [2] has advocated serology or UBT screening for *H. pylori* combined with a double-contrast upper gastrointestinal examination as a cost-efficient, rational diagnostic approach for patients with dyspepsia if the appropriate skill level with double-contrast studies is present.

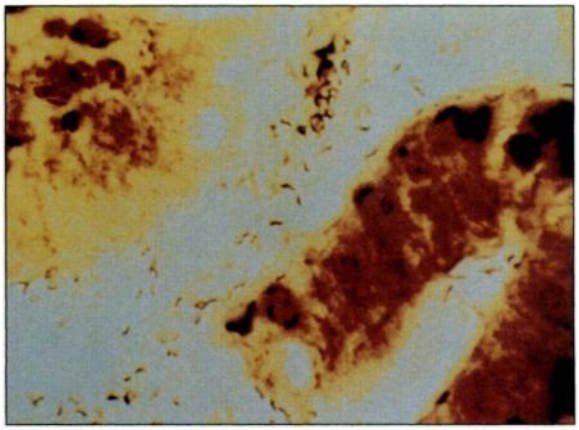

Fig. 3.—Photomicrograph of gastric biopsy shows *Helicobacter pylori* with Warthin-Starry stain. Most of organisms are in mucus adjacent to surface cells of gastric mucosa. (Courtesy of Marshall BJ, Charlottesville, VA)

Treatment Indications for *H. pylori*

As noted, the National Institutes of Health Consensus Conference on *H. pylori* in peptic ulcer disease has recommended that all patients with gastric or duodenal ulcer and *H. pylori* should be treated for the infection with antimicrobials as well as receive antisecretory therapy. Overall, permanent duodenal ulcer cure rates approaching 90% are seen with this approach. Only about 10% of patients with ulcers so treated will have relapses, presumably because of persistent basal acid hypersecretion or some other undetermined permanent mucosal defect [7].

If a gastric ulcer is associated with both NSAID therapy and *H. pylori*, the drug should be stopped and the infection treated. A preliminary study has shown that eradicating *H. pylori* before NSAID use markedly reduces the subsequent risk of ulceration from the NSAID [64].

Successful eradication of *H. pylori* has been shown to decrease the risk of ulcer rebleeding [65, 66]. Also, in the presence of *H. pylori* gastritis, suppression of acid production involves an immediate increase in gastric corpus inflammation and significantly increases the risk for atrophic gastritis involving the corpus mucosa. This fact por-

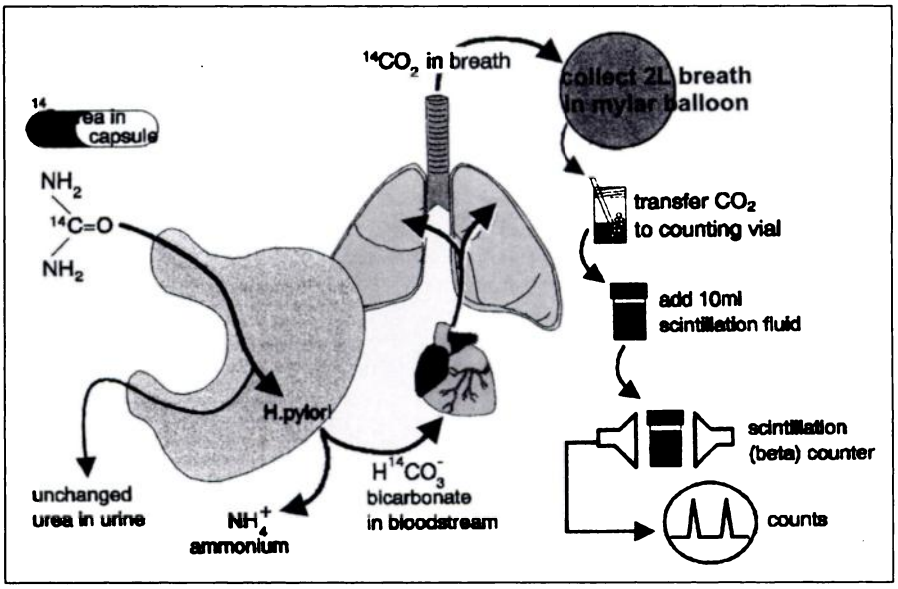

Fig. 4.—Diagram shows principle of ^{14}C urea breath test. Ingested ^{14}C urea, in presence of *Helicobacter pylori* urease, is metabolized to ^{14}C-labeled bicarbonate and collected in breath sample as ^{14}C-labeled carbon dioxide. Level of ^{14}C is then measured using scintillation counter.

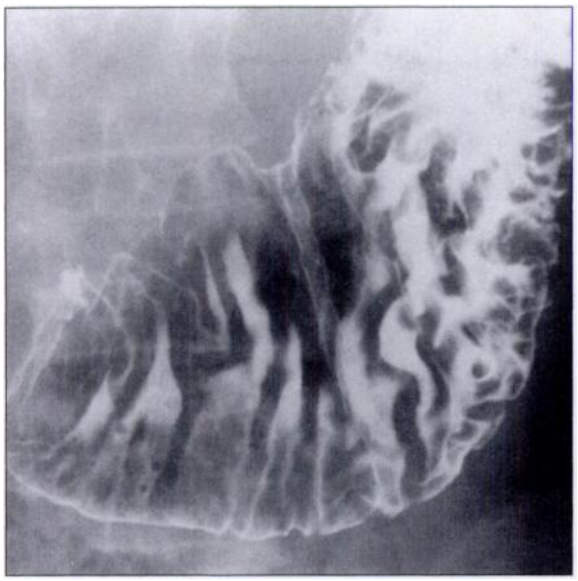

Fig. 5.—Radiograph obtained in patient with *Helicobacter pylori* gastritis showing thickened folds in gastric antrum and body. (Courtesy of Levine MS, Philadelphia, PA)

tends clinical concern for those patients on long-term proton pump inhibitor therapy, and eradication of *H. pylori* has been advocated in this patient population [67].

Because the lifetime risk of gastric cancer in asymptomatic persons infected with *H. pylori* in the United States is only 0.5%, screening and therapy of asymptomatic gastritis in this country are not currently recommended. However, in certain subgroups, such as persons with a family history of gastric cancer, *H. pylori* eradication is appropriate [68].

Lastly, a percentage of patients with nonulcer dyspepsia and *H. pylori* will likely respond to eradication therapy, and a therapeutic trial may be of benefit in patients with refractory symptoms. Moreover, many patients in this category may prefer to have eradication of *H. pylori* on the basis of the organism's class I carcinogen status.

H. pylori Infection Control

With an ultimate goal of worldwide eradication of *H. pylori* and its associated diseases, definition of a precise transmission mode or modes will be important so as to modify factors that facilitate spread of the disease. In addition, identification of specific strains of *H. pylori*, bacterial virulence factors, or host or environmental characteristics predisposing to peptic ulcer or gastric cancer would allow for more precise screening of high-risk populations.

Improved therapies (tolerance, cost, and effectiveness) are also needed. Hundreds of treatment regimens have been tested for *H. pylori* eradication; these are usually a combination of two to four drugs. Successful regimens have usually involved a drug to decrease acid secretion (omeprazole, lansoprazole, or ranitidine), one or more antimicrobials (amoxicillin, tetracycline, metronidazole, or clarithromycin), and sometimes a bismuth-containing compound. Regimens have now been identified that can reliably cure infection in up to 90% of patients after the first treatment course. However, the two clarithromycin-based dual therapies recently approved by the Food and Drug Administration for *H. pylori* eradication have not reached this level of efficacy, indicating a continued need for simpler and more effective therapies.

In developed countries, antibiotic therapy for *H. pylori* might eliminate the disease because the reinfection rate is low (about 0.5% per annum), even in children. However, in developing countries, vaccination may have a role because water supplies may be contaminated, overcrowding and poor hygiene are constant problems, and reinfection will soon occur in treated patients. Moreover, the occurrence of resistance to antibiotics will make this therapeutic approach less effective over the long term. For these reasons, vaccination may play an important role in *H. pylori* disease control in these countries [30].

In animal studies using a variety of *Helicobacter* species, *H. pylori* antigens (usually urease) given orally with an adjuvant have been shown to protect against challenge with viable *Helicobacter*, and therapeutic vaccination has also been successful in animal models [69, 70]. These results now provide the rationale to move into clinical trials.

The next decade should offer more dramatic developments that we hope will allow eradication of *H. pylori* from humanity and virtually relegate peptic ulcer from a disease with major morbidity, mortality, and enormous medical costs to one of only historical interest.

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The reader's attention is directed to the commentary on this article, which appears on the following pages.