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Peptic Ulcer: An Infectious Disease?

BARRY J. MARSHALL *University of Virginia*

Campylobacter pylori, isolated in 1982, is likely to change medical thinking about the etiology and treatment of chronic gastritis and peptic ulcer. Up to 90% of patients with duodenal ulcer and 70% with gastric ulcer have *C. pylori* infection. Eradication of the organism can result in resolution of gastritis, with subsequent ulcer healing and a lower incidence of relapse.

Peptic ulcers develop when there is an imbalance between gastric acid–pepsin and mucosal resistance. The balance can be tipped by increased acid-pepsin secretion, decreased mucosal resistance, or a combination of the two. For almost 50 years, the investigation and treatment of peptic ulcer disease has focused on excess acidity. Only recently have investigators begun to examine factors that might weaken the defenses of the gastric epithelium.

One such factor is infection with *Campylobacter pylori*. The bacterium has a unique capacity to modify the environment of the stomach and to interfere with local protection of the mucosa against acid. It attaches to and inflames gastric epithelium and, as its digestion of the protective layer of mucus creates areas of denuded mucosa, the stage is set for ulcerogenesis (Figure 1).

Since its isolation in 1982, *C. pylori* has generated worldwide interest. As more definitive information becomes available, it is likely to change medical thinking about the etiology and treatment of chronic gastritis and peptic ulcer. Up to 90% of patients with duodenal ulcer and 70% of patients with gastric ulcer have *C. pylori* infection and active chronic gastritis of the antrum. Eradication of the organism can result in resolution of gastritis, with subsequent ulcer healing and a lower incidence of relapse. Obviously, *C. pylori* is not the cause of all types of gastritis, nor is it certain that *C. pylori*–induced gastritis alone is responsible for all attendant symptoms in infected patients.

C. pylori is by far the most common gastrointestinal infection in human beings, affecting about 20% of the adult population (Figure 2). Infected persons are 20 times more likely to develop duodenal ulcer than are uninfected persons and at least 10 times more likely to have histologic gastritis. Given the large reservoir of *C. pylori* in the population, it can be assumed that most people are exposed to it at some time in their lives. Moreover, the infected population is in a constant state of flux. Some have a bout of acute gastritis, but their immune system is able to eradicate the organism. Others have an active chronic gastritis of some years' duration and then are cleared of the bacterium with a course of antibiotics for an unrelated illness. But the patient may be left with permanently damaged gastric mucosa that remains susceptible to erosion and ulcer. This subgroup could account for those patients with duodenal or gastric ulcer in whom *C. pylori* cannot be detected.

Gastritis occurs in different forms, and failure to differentiate among them often has led to ambiguity in the literature. *C. pylori* is associated with an active chronic gastritis that has distinctive histologic stigmata; it may or may not coexist with other forms of gastritis.

The term "gastritis" is usually used in the context of dyspepsia or indigestion; however, clinically apparent gastritis may or may not be accompanied by histologic mucosal changes. (And, conversely, histologically documented inflammatory

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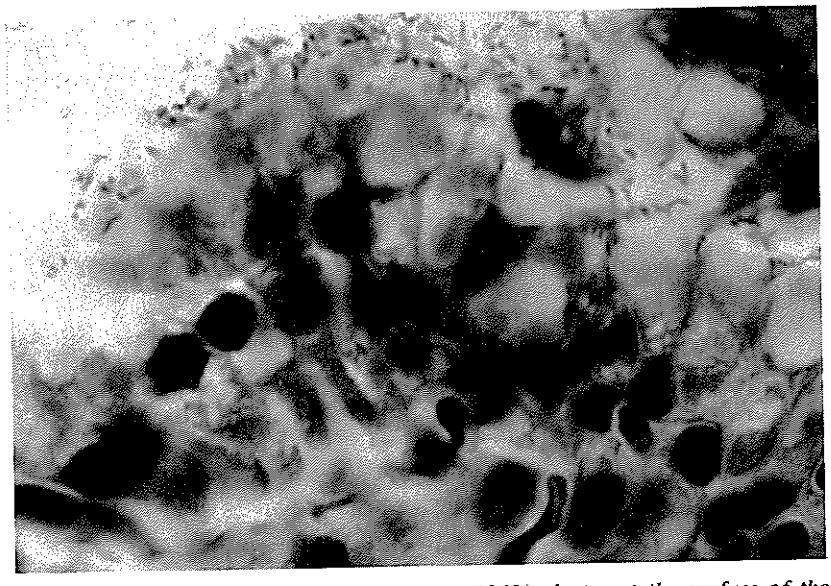
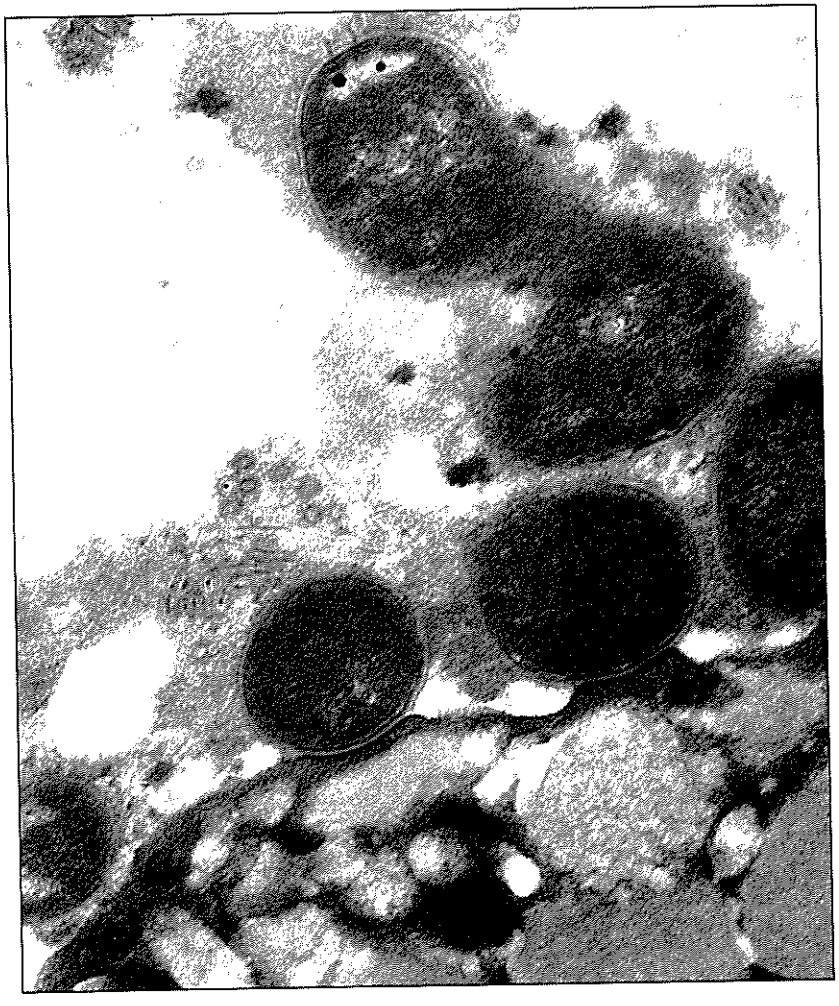


Figure 1. *Curved rods of* C. pylori *(above, ×1250) cluster at the surface of the glandular epithelium and in and under the gastric mucus. It is the only organism capable of colonizing normal human gastric mucosa. In electron micrograph (below), the organisms adhere to a gastric mucous cell, causing inflammation. The surface of the cell typically assumes a pedestal shape at the site of attachment. The next step is destruction of the protective mucus-secreting cell, which leads to ulcer formation. (Courtesy of Henry F. Frierson, Jr.)*



gastritis may be asymptomatic.) Even endoscopically apparent gastritis—as evidenced by erythema, erosions, or bleeding—may be no more than an abrasion of histologically normal gastric epithelium. In the past, gastritis was frequently attributed to gastroduodenal bile reflux or irritants such as alcohol, spicy food, and aspirin-like drugs. Although these agents, particularly aspirin, may cause reddening of stomach mucosa and acute epithelial cell damage, they do not lead to chronic inflammation. Chronic gastritis refers only to the presence of histologically proven inflammation, and it is not necessarily accompanied by dyspeptic symptoms or macroscopic abnormalities of the gastric mucosa.

Chronic gastritis is subdivided into two types. Type A, body mucosa gastritis, is an autoimmune disease that is associated with antibodies to parietal cells and with pernicious anemia. Also known as gastric atrophy and sometimes as atrophic gastritis, it is characterized by chronic inflammation of the acid-secreting mucosa. Since parietal cells are located mainly in the body of the stomach, the inflammation does not affect the antrum. Moreover, because acid secretion is decreased, dyspeptic symptoms and benign peptic ulcers are uncommon. Gastric lesions in this disorder are often the result of malignancy.

Type B, or antral gastritis, affects the mucus-secreting epithelial cells that line the entire stomach. Although inflammation may involve the body of the stomach, it is most severe in the prepyloric region. Acid secretion is usually normal, and there are no antibodies to parietal cells. Antral gastritis is associated with almost all dys-

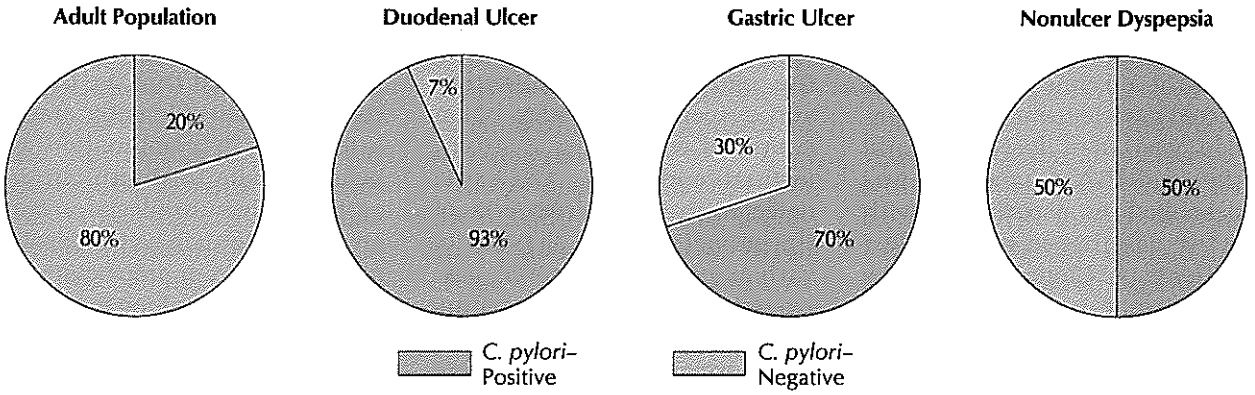


Figure 2. C. pylori *is the most common human GI pathogen, infecting one of five adults. As charts indicate, organism is strongly implicated in duodenal and gastric ulcers as well as dyspepsia not associated with ulcer formation.*

peptic diseases, particularly nonulcer dyspepsia, gastric ulcer, and duodenal ulcer. This type of chronic gastritis is associated with *C. pylori*. Type A gastritis is unrelated to *C. pylori* infection except when antral gastritis coexists.

The histologic appearance of type B gastritis suggests a chronic inflammatory process, which has been described also as superficial gastritis or gastroduodenitis. Such distinctions are both unnecessary and confusing. Instead, it is sufficient to distinguish between chronic and active chronic antral gastritis. If the mucosa is infiltrated with plasma cells and lymphocytes, the gastritis is chronic; if neutrophils are also present in excess, the gastritis is both chronic and active. The epithelial cells are usually abnormal, and mucus-secreting glands may appear to be reduced in number. Other histologic changes, such as intestinal metaplasia, atrophy, edema, and fibrosis, often coexist with chronic gastritis but are not in themselves evidence of gastritis.

C. pylori is a gram-negative, S-shaped bacterium, which colonizes the mucus-secreting epithelial cells of the stomach. In this location, it is protected from gastric acid by the layer of bicarbonate-rich mucus overlying the epithelium. Since the organism will adhere only to the gastric mucus-secreting epithelial cell, it does not usually colonize any other part of the gastrointestinal tract. The role of the bacterium in duodenal ulcer disease may be explained by a tendency for patients to have islands of gastric mucus-secreting epithelium in the duodenal cap—to which the bacterium may adhere.

Initially, *C. pylori* seemed to be very similar to other Campylobacter species. However, *C. pylori* has a number of features that differentiate it from the other Campylobacters (Figure 3), and it will probably be classified as a completely new and different genus. *C. pylori* has four sheathed flagella instead of a single unsheathed flagellum characteristic of Campylobacter species. The cell wall components and DNA also are quite different from those of other species of the genus. Finally, antibodies to *C. pylori* do not cross-react significantly with other pathogenic Campylobacter species, such as *C. jejuni*.

C. pylori is the only organism that has the ability to colonize the normal human gastric mucosa. To survive in the acidic environment of the stomach, the bacteria must sustain a high level of metabolic activity, producing large quantities of urease and catalase. Urease generates ammonium and bicarbonate from urea. Catalase reduces hydrogen peroxide. *C. pylori* is very similar to urease-producing spirilla, which have been found in the stomachs of a number of animal species. In cows and other ruminants, such organisms facilitate the putrefaction of food. Presumably, *C. pylori* was originally transmitted to humans from an animal species. In vitro, it is not a particularly vigorous bacterium; in environments other than the sterile stomach, it is easily overgrown.

Many investigators studied gastric spiral bacteria before those organisms were isolated and associated with gastritis. In 1938, Doenges described spirochete-like organisms that he found in stomach autopsy specimens and, in 1940, Freedberg detected similar organisms in resected stomach tissue of patients undergoing gastrectomy. Two other investigators, Luck in 1926 and Fitzgerald in 1950, who were unaware of the

existence of the bacterium, detected large amounts of its product, the enzyme urease, in resected gastric tissue. The organism was then forgotten until the mid-1970s, when it was described in association with active gastritis in gastric ulcer patients. A Campylobacter-like organism was later noted on inflamed gastric mucosa, an observation that led to its isolation as *C. pylori*.

Our interest in *C. pylori* began in Australia in 1979, when J. R. Warren at the Royal Perth Hospital detected curved bacilli on a silver stain of a gastric biopsy. Warren collected, from patients undergoing stomach biopsy, more than 100 specimens of what was then called a Campylobacter-like organism (CLO).

In 1982, we cultured antral biopsies taken from 100 consecutive patients with indigestion and dyspepsia who were being evaluated with upper gastrointestinal endoscopy. CLO was detected in tissue from 60% of the patients. Almost all patients with histologically proven gastritis harbored the bacterium, whereas those with histologically normal antral mucosa were free of the organism. Furthermore, all 13 patients who had duodenal ulcer and 18 of 22 with gastric ulcer were infected with CLO.

The ability to isolate *C. pylori* and grow it in culture greatly facilitated investigative efforts. Serum antibodies to the organism were identified, and by 1983, various bactericidals were being tested in vitro for their ability to kill the organism. It was determined that the bacterium is most efficiently eradicated with a combination of bismuth salts (bismuth citrate or bismuth subsalicylate) and an antibiotic such as tinidazole, metronidazole, or amoxicillin.

Bismuth salts alone may promote healing of gastritis by protecting inflamed mucosa from gastric juice. However, even though bismuth can clear the organism in some infected patients, its action is better described as bacteriostatic than as bactericidal. Typically, bismuth will produce an eight-log kill (one in 100 million bacteria survives) in a patient with an unimpaired immune system, and after treatment, the bacterium is not detectable in gastric biopsy. But the organism rapidly recolonizes to its original numbers, and within two to three weeks the patient will again manifest symptoms of infection. This bacteriostatic effect may account for bismuth salt's endurance as a remedy for nonulcer dyspepsia for over a century. Antibiotics alone also do not completely eradicate the organism.

In 1984, we administered a combination of bismuth salts and antibiotics to a selected group of 11 patients with gastritis and duodenal ulcer. The drugs were able to eliminate the organism in nine patients and their gastritis healed—circumstantial evidence that *C. pylori* caused the gastritis.

Two healthy volunteers were infected with live *C. pylori* organisms to prove one of Koch's postulates—the ability of the organism to cause disease. The first volunteer developed an acute, biopsy- and culture-proven gastritis, which lasted for two weeks and then cleared

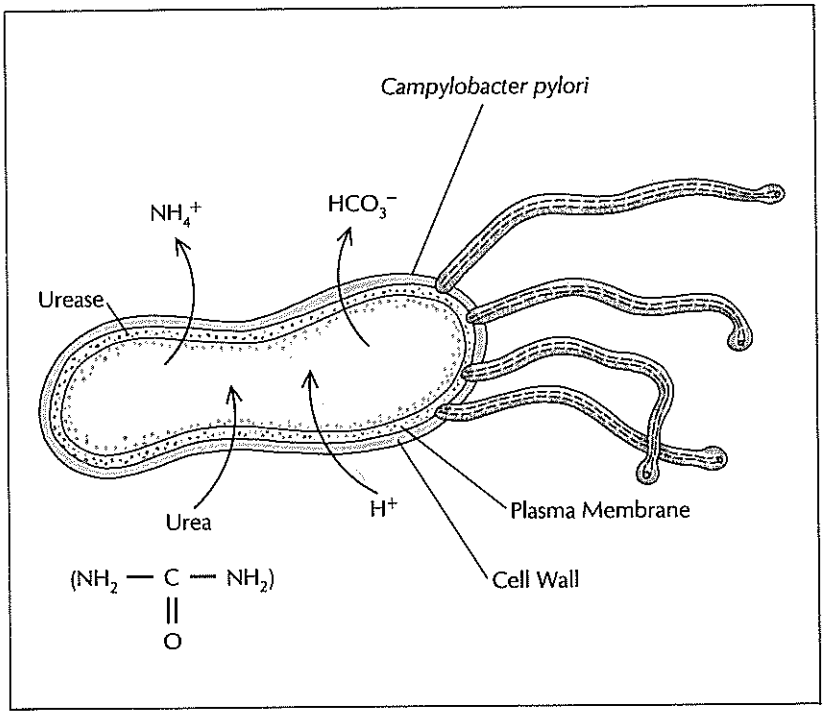


Figure 3. C. pylori, *a microaerophilic gram-negative bacterium, is very different from other Campylobacter species. Main morphologic feature of* C. pylori *is presence of four sheathed flagella rather than the usual single, unsheathed flagellum. Its cell wall and DNA are unlike those of other Campylobacter species, and antibodies to it do not cross-react very much with those of other species. To survive in stomach's acidic environment, organism produces great quantities of urease. Enzyme acts on urea to generate ammonium and bicarbonate ions, which raises the ambient pH. In vitro,* C. pylori *is sensitive to penicillin, erythromycin, tetracycline, and bismuth but resistant to sulfonamides, trimethoprim, and vancomycin.*

spontaneously. The second volunteer also developed acute gastritis. However, his illness did not respond to bismuth salts and antibiotics and evolved into chronic gastritis. Two years later, that volunteer still has asymptomatic chronic gastritis and also has halitosis. Evidently, some patients harbor a resistant organism that cannot be eradicated with current treatment modalities.

Having established a causal relationship between *C. pylori* and gastritis, we undertook to determine what long-term effects eradication of the organism would have on the healing of gastritis and peptic ulcer and on their relapse. In 1985, a prospective double-blind study of 100 consecutive patients with duodenal ulcer and proven *C. pylori* infection was begun at the Royal Perth Hospital. The patients were randomized to eight weeks of therapy with either cimetidine or colloidal bismuth citrate. The two groups of patients were further subdivided by addition of either tinidazole or placebo during the first 10 days of therapy. Endoscopic biopsy for histology and culture was repeated 2, 14, 26, and 52 weeks after completion of therapy. None of the patients received maintenance therapy during the one-year follow-up period.

At the end of eight weeks' treatment, *C. pylori* was eradicated from one of the 51 patients in the cimetidine plus antibiotic and cimetidine plus placebo groups. Seven of the 21 patients in the bismuth plus placebo group and 21 of 28 in the bismuth plus antibiotic group were free of the organism. In the 29 patients cleared of the organism, there was histologic resolution of antral gastritis. These changes were permanent except for two patients in whom *C. pylori* infection reappeared. Gastritis did not heal in the 71 patients in whom the organism was not eradicated.

Ulcers healed in 25 (93%) of the remaining 27 bacteria-negative patients and in 43 (61%) of the 71 infected patients. At the end of one year, ulcers or symptomatic gastritis had recurred in 32 (74%) of these 43 patients, as well as in the two patients who were initially cleared of *C. pylori* but became reinfected. In contrast, relapse occurred in five (19%) of the 27 patients who remained free of *C. pylori* at the end of the one-year follow-up.

Although all patients had severe duodenal ulcer disease at the outset of the study, the definition of relapse included indigestion and dyspepsia; the looseness of the definition is exemplified by the five patients who remained negative for *C. pylori* but were classified as relapsers. Only two had recurrence of erosions in the duodenum; both were asymptomatic.

This study (which has been reported only in an abstract so far) not only supports the hypothesis that *C. pylori* infection is a major factor in the pathogenesis of gastritis and duodenal ulcer disease, it also suggests that a bismuth-antibiotic combination may be the best form of therapy when the conditions coexist with *C. pylori* infection (Figure 4). Cimetidine alone or in combination with tinidazole had little effect on the bacterium and, similarly, had little effect on the progress of the ulcer disease.

C. pylori can be isolated easily by culturing a gastric mucosal biopsy. Since it is the only organism that can survive in the stomach in significant numbers, the culture plate usually will not be contaminated by the growth of other organisms. The biopsy specimen is cultured on blood agar plates for three days at 37 °C in a humid microaerophilic atmosphere, such as room air, with the addition of 10% carbon dioxide. In contrast, other Campylobacter organisms grow best at 42°C, a temperature at which they grow faster than other organisms that might contaminate the culture. Within three days, *C. pylori* forms characteristic transparent colonies 1 mm in diameter. The cultured organisms are gram negative, urease positive, and catalase positive.

Although it is easy to perform, *C. pylori* culture is both time-consuming and expensive. Capitalizing on the organism's ability to produce urease, the rapid urease test can diagnose its presence within 20 minutes of endoscopy. The rapid urease test, which will be marketed as the CLOtest, is already available for research purposes. It has a sensitivity of 95% and an extremely low false-positive rate.

The CLOtest still requires endoscopy and biopsy, which limit its usefulness outside the domain of gastroenterology. The isotopic urea breath test is more widely practical. The fasting patient is given a drink containing urea labeled with carbon-14 (or carbon-13). If the patient is not infected with *C. pylori*, the urea is processed as a waste product. But if the patient is infected, the urea is broken down into ammonia and bicarbonate in the stomach. Within 15 minutes of ingestion, the bicarbonate is absorbed into the blood and exhaled as carbon dioxide. A breath sample read in a scintillation counter measures the amount of $^{14}CO_2$. If carbon-13 is used, a mass spectrometer will detect

this nonradioactive isotope in the breath.

We examined the ability of the breath test to diagnose *C. pylori*-associated gastritis in 32 patients being evaluated for peptic ulcer. On average, patients with documented *C. pylori* infection exhaled 20 times more labeled carbon dioxide than did patients who were not infected.

The carbon-14 urea breath test appears to be comparable to stomach biopsy culture for the diagnosis of *C. pylori* infection. Its sensitivity and specificity are the same as for the CLO-test: close to 95%. The test uses readily available equipment and the radiation dose is less than that of a routine chest x-ray. It can be used both as a screening test and as a post-treatment assessment. However, because of the equipment required, it remains a hospital- or laboratory-based procedure.

Investigators at a number of institutions are developing a serum antibody test (ELISA), which can be used as a large-scale screening measure for detection of *C. pylori*. In addition to being a useful epidemiologic tool, an ELISA would be invaluable for screening family members and close contacts of an infected patient, thus preventing the reinfection that is presumed to occur frequently. But the ELISA for antibody to *C. pylori* is not without its problems.

The organism has at least 10 antigenic proteins of different sizes, and it is estimated that only 80% to 90% of infected patients develop antibodies against the same protein, which gives the test a false-negative rate of 10% to 20%. M. L. Skoglund applied ELISA to 23 patients who were culture positive for *C. pylori* and found that 21 were positive for IgG antibodies to the organism. Of the 14 patients who were culture negative, three were positive for antibody on ELISA. Furthermore, the serum antibody test does not differentiate between patients with active infection and those who have recently eliminated the bacterium, a significant drawback both for screening and for post-treatment evaluation.

Volunteers who ingested live *C. pylori* have served as models of the clinical picture of acute infection and progression to active chronic gastritis. After ingestion, the patient remains asymptomatic for about a week, and then a mild gastroenteritis develops. Epigastric discomfort, bloating, nausea, mucous vomiting, and halitosis occur in the second week, although some patients remain asymptomatic. Acute neutrophil infiltration of both antral and body mucosa is present at this time.

Normally, the stomach is lined with a 0.2-mm layer of mucus, which protects epithelial cells from acid ejected by parietal

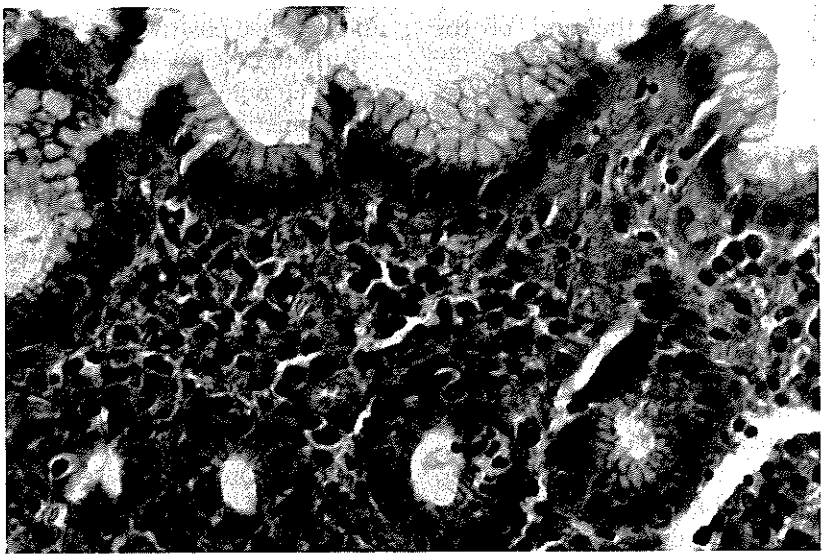
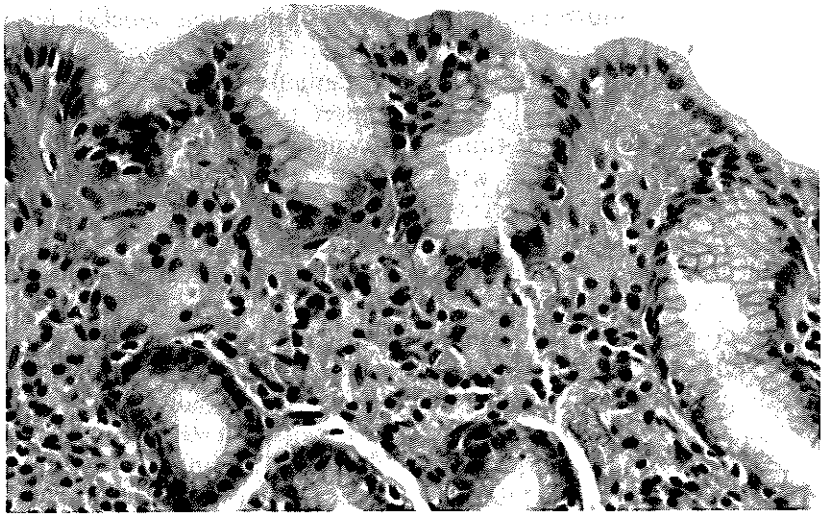


Figure 4. *Gastric mucosa shows acute and chronic inflammation typically present in gastritis associated with* C. pylori *infection (above). After treatment with bismuth subsalicylate and amoxicillin, only a few chronic inflammatory cells remain in the lamina propria (below). (Courtesy of Henry F. Frierson, Jr.)*



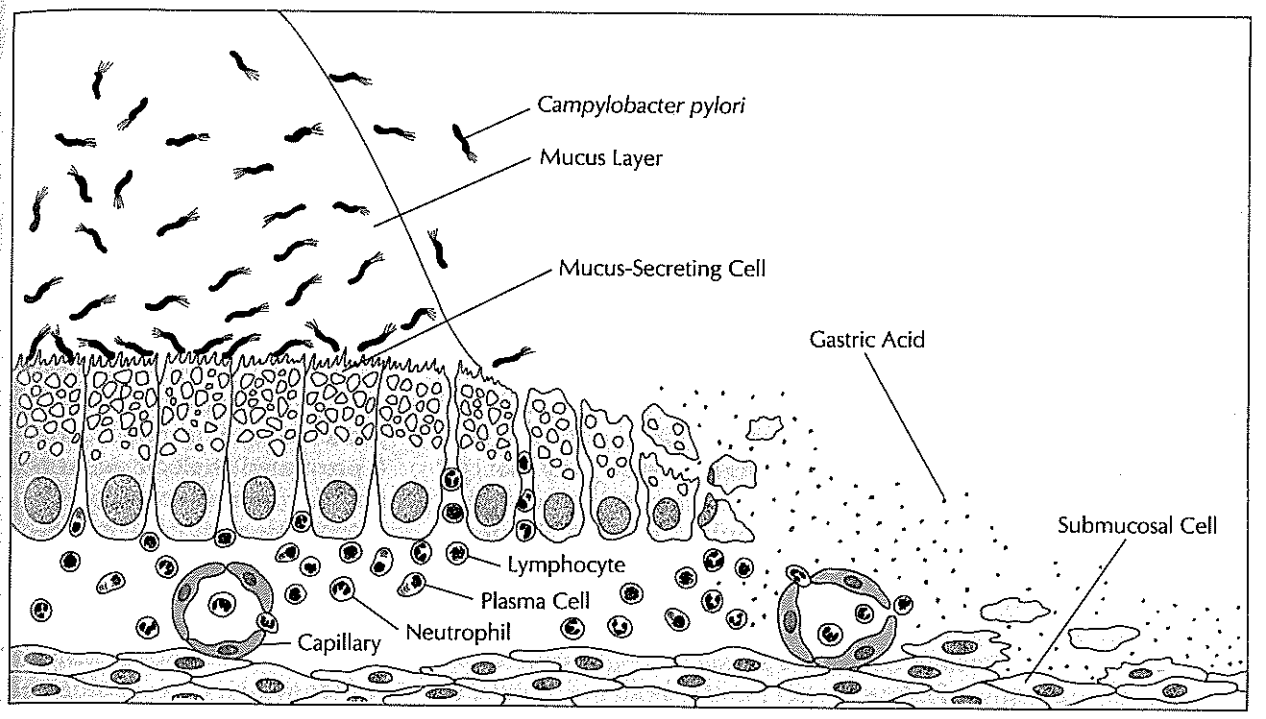


Figure 5. *During acute phase of infection,* C. pylori *burrows through mucus layer and colonizes mucous cells and surface epithelial cells. As mucus layer is digested and mucus secretion is impaired, gastric acid erodes denuded mucosa. Acute neutrophil infiltration is supplemented by lymphocytes and plasma cells as infection enters chronic phase.*

cells into the lumen. During the acute phase of infection, before antibodies against *C. pylori* are formed, it is thought that the organism works its way underneath the mucus layer and colonizes the entire surface of the stomach, including both the body and the antrum. As the bacterium digests mucus, the protective layer becomes thin and runny. In some areas, the mucus layer is eroded completely; acid contact with mucosa produces indigestion or dyspepsia (Figure 5).

Examination of the gastric contents during the second week of infection reveals that acid is absent or greatly reduced. This phenomenon was noted as early as 1890, when W. Osler described a form of gastroenteritis associated with hypochlorhydria, which sometimes progressed to chronic gastritis. The same syndrome was noted in Texas in 1979 among a group of 37 healthy volunteers who were undergoing multiple gastric intubations for an acid secretion study. Half the volunteers suddenly developed gastritis and became achlorhydric. *C. pylori* was subsequently found in gastric biopsies of some of those volunteers, and recent analysis of their serum by Skoglund's ELISA method indicates that seroconversion occurred. In all likelihood, the bacterium was responsible for the outbreak, and the moist pH electrode used in the study may have been the vehicle of transmission.

The hypoacidity during the second week of infection is probably due to ammonia generated by *C. pylori*, which neutralizes gastric acid. It is also possible that organisms burrow into gastric glands of the stomach body and generate enough ammonia to switch off parietal cell acid secretion.

If the bacterium is not eradicated, the illness enters a chronic phase, which may be lifelong. Neutrophil infiltration is supplemented by lymphocytes and plasma cells, which give the appearance of active chronic gastritis. If stomach body mucosa remains inflamed, hypochlorhydria may persist, but in most patients acid secretion returns to normal within four months. As antibodies to *C. pylori* are formed, the stomach body and its gastric glands become relatively free of the organism, and parietal cells can resume secretion of acid. The bacterium localizes in the antrum, near the pyloris, and continues to proliferate there. In this final stage, the patient has a defective, inflamed mucosa, which is susceptible to autodigestion and peptic ulceration. The lesser curve and the duodenal cap are the most susceptible areas.

Several large studies of the

prevalence of type B antral gastritis were performed in Scandinavia in 1968 and 1978. Endoscopic biopsy-proven gastritis was found in 20% of young adults and in 60% of elderly people. Since the histologic evaluation in those reports did not separate active chronic gastritis from gastritis without epithelial cell damage, an exact association with *C. pylori* cannot be made.

However, recent studies indicate that the incidence of *C. pylori* infection correlates with the incidence of chronic antral gastritis. Serologic studies have determined that the organism infects 20% of adults in Western countries, half of whom develop peptic ulcer disease. The remaining 10% can be divided equally into those who are asymptomatic and those who have active chronic gastritis without ulcer. The prevalence of *C. pylori* infection ranges from 10% to 20% in the third decade of life and gradually increases to about 45% in the seventh decade (Figure 6). With time and age, the organism may be either spontaneously cleared or eradicated with antibiotics, and increasing numbers of patients are left with a mild but persistent gastritis.

Even though an etiologic correlation between *C. pylori* and chronic active gastritis and peptic ulcer disease may not yet have been demonstrated beyond all doubt, an antral biopsy should be obtained from all patients undergoing routine endoscopy for the evaluation of dyspepsia. A diagnosis of *C. pylori* infection can be established with the rapid urease test, the urea breath test, culture, or histologic study of the biopsy. For the pathologist, it is no longer sufficient to diagnose "chronic gastritis." The presence or absence of neutrophils, epithelial cell changes, and *C. pylori* organisms must also be carefully described, as it may now affect diagnosis, prognosis, and therapy.

Until now, no effective treatment for gastritis has been available, and treatment of dyspepsia has concentrated on the reduction of, or protection from, gastric acid. That narrow approach is no longer appropriate. A presumed etiologic agent can now be identified in patients with active chronic gastritis.

At this juncture, however, therapeutic efforts should be confined to controlled clinical trials, which are evaluating bactericidal agents as treatments for gastritis and peptic ulcer disease. All study patients must have biopsy-proven *C. pylori* infection. At present, there is no good reason to treat *C. pylori* infection associated with gastritis that is asymptomatic or without complications. But if the patient has severe dyspepsia (with or without ulcer disease) that is recalcitrant to conventional therapy, a course of bactericidal therapy may be justified.

A number of aspects of the treatment regimen remain to be clarified within the protocols and controls of clinical trials. It has not been firmly established that *C. pylori*–associated gastritis causes all of the patients' symptoms, nor is it clear which symptoms will respond to treatment. In addition, the combination therapy currently in use has a one-year cure rate of 75% to 80%; consequently, there would be many treatment failures if the therapy were to be used widely in an uncontrolled fashion. Finally, a two- to three-week course of

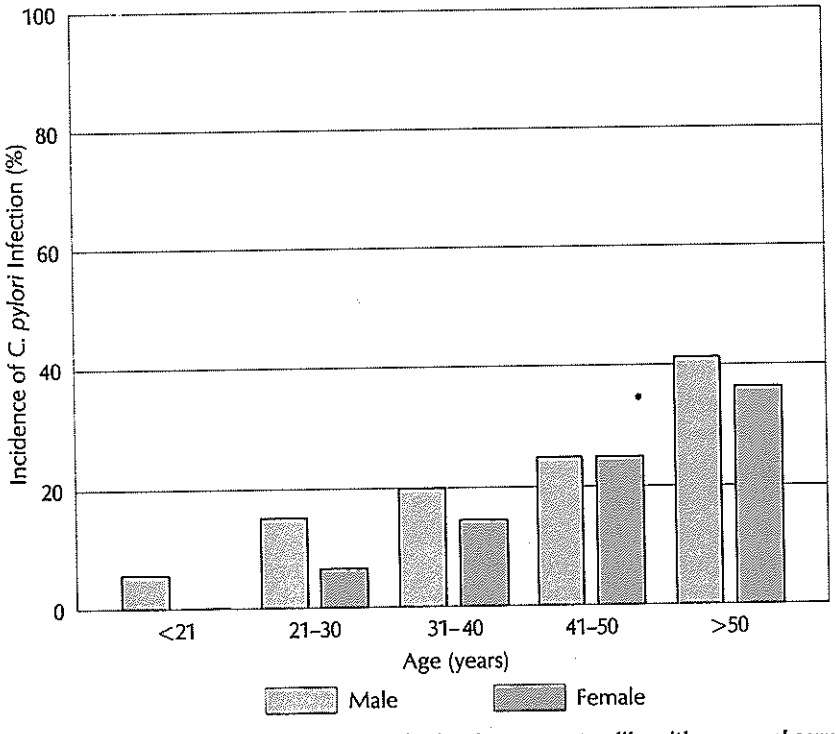


Figure 6. *The prevalence of* C. pylori *infection increases steadily with age, as shown in study results graphed here.* C. pylori *prevalence actually peaks (~45%) after age 60, when peptic ulcer prevalence also is maximal.*

high-dose antibiotics is not without risk to the patient.

In our experience, the best treatment to date consists of a 14- to 21-day course of an antibiotic and a 28-day course of bismuth subsalicylate. It has not yet been determined whether bismuth subsalicylate is more efficacious in liquid or tablet form, so we have opted for the convenience of the tablet. Three weeks after completion of treatment, patients should undergo a follow-up examination: either a gastric biopsy or the urea breath test.

On the basis of culture, histologic, and serologic criteria, investigators have determined that 93% of patients with duodenal ulcer have concomitant active chronic antral gastritis and *C. pylori* infection. In duodenal ulcer disease, the infection extends into the duodenal cap, usually colonizing islands of ectopic gastric mucosa on or near the ulcer border. Gastritis and infection are present in 70% of patients with gastric ulcer. The gastritis extends into the body of the stomach and is more severe than in patients with duodenal ulcer. Many of the 30% of gastric ulcer patients who do not have active chronic gastritis and *C. pylori* infection are taking nonsteroidal anti-inflammatory drugs. Still others have permanent mucosal damage from a previous *C. pylori* infection, and a few have malignant gastric ulcers.

C. pylori infection is also present in 50% of dyspeptic patients whose symptoms are suggestive of peptic ulcer but who do not have an ulcer crater at endoscopy. This population includes patients with hiatus hernia, reflux esophagitis, duodenitis, irritable colon, and gallbladder disease.

We also suspect a link between gastroesophageal reflux disease (GERD) and *C. pylori*. We retrospectively examined antral and esophageal mucosa of 21 consecutive GERD patients and 20 endoscopically normal volunteers obtained at another institution between 1977 and 1982, before the association between *C. pylori* and gastritis was widely known. Since bacterial culture could not be performed, *C. pylori* could not be specifically identified, and only the presence or absence of CLOs could be demonstrated.

Histologic evidence of gastritis was found in 16 (76%) of the GERD patients and in two (10%) of the volunteers. CLOs were identified in 13 (62%) of the GERD patients and in one (5%) of the controls. CLOs and antral gastritis tended to coexist in the same patient. However, CLOs were not found in any of the esophageal biopsies. In patients with GERD, stimulated acid secretion tended to be higher when CLOs were present in the stomach.

The incidence of gastritis in the healthy controls is comparable to the 10% to 20% incidence that has been found in young adults. One of the weaknesses of this study is that the GERD patients were so much older (mean age, 53 years) than the controls (mean age, 30 years). Because of their age, GERD patients could be expected to have a higher incidence of gastritis even without esophageal reflux disease. Nevertheless, the data suggest that both CLOs and gastritis are more often present in patients with GERD than in asymptomatic subjects.

C. pylori infection may also be present in nonulcer dyspepsia patients with vague symptoms, such as burping, halitosis, flatulence, and bloating, in whom no other diagnosis can be made. Burping was the only symptom that correlated well with *C. pylori* infection in one study. Moreover, chronic halitosis may be an early sign of gastritis; intermittent dyspepsia or flatulence and borborygmi eventually develop in 50% of these patients. We have identified *C. pylori* in a number of patients with severe halitosis, and the condition resolved after the organism was eradicated with bismuth subsalicylate and amoxicillin. Patients with low acid secretion and a stomach that is slow to empty appear to be especially prone to chronic halitosis after they are infected with the organism. As the bacterium further reduces stomach acidity, other anaerobic bacteria rapidly putrefy stagnant food. A patient's diet can further contribute to halitosis by affecting the amount of time that the food remains in the stomach and encouraging or inhibiting the proliferation of *C. pylori*.

Investigators are beginning to examine diseases other than gastritis, peptic ulcer, and esophageal reflux for an association with *C. pylori* infection. The organism might, for example, be related to some liver diseases, skin diseases, respiratory diseases, or arthritis. Patients with renal failure often have gastritis and, before the advent of renal dialysis, had a high incidence of ulcer disease. Such patients have three to five times more urea in their gastric juice, which may make them more susceptible to the effects of *C. pylori* infection. The bacterium has also been detected in children with severe abdominal pain and in several infants with the failure-to-thrive syndrome.

Whatever the underlying eti-

ology of peptic ulcer disease, acid erosion of gastric and duodenal mucosa is ultimately responsible for the production of the ulcer crater. However, many patients with ulcers do not have increased secretion of gastric acid and pepsin. That observation suggested that ulcer pathophysiology involves an unexplained decrease in mucosal resistance to acid-pepsin injury or hyperacidity from exogenous factors such as smoking, stress, diet, aspirin, and other drugs.

C. pylori–associated gastritis does much to clarify the pathogenesis of peptic ulcer disease. The unknown factor contributing to decreased mucosal resistance has been identified as a bacterial infection. Gastric acid secretion need no longer be presumed to play a primary etiologic role.

Peptic ulcers can indeed be healed by inhibition of gastric acid secretion with drugs such as the histamine H_2-receptor antagonists. But that approach does not address the underlying etiologic process, and the patient is left with asymptomatic gastritis and areas of denuded, inflamed gastric mucosa—which explains the high rate of ulcer relapse after discontinuance of acid-inhibiting drugs. Similarly, exogenous factors are contributory but not etiologic; they do not produce ulcer in a person with a normal, healthy gastric mucosa. However, in a patient with *C. pylori* infection and active chronic gastritis, any of those factors conceivably could predispose to the development of ulcer. Thus, although acid secretion clearly does play a role in peptic ulcer, decreased mucosal resistance due to *C. pylori* infection will probably prove to be the primary cause in a great many cases. □

Selected Reading

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