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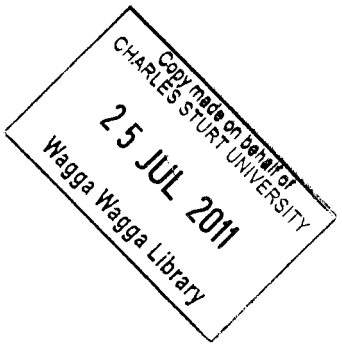

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Campylobacter pylori and Peptic Disease

Therapeutic Implications

Stephen H. Caldwell, MD, and Barry J. Marshall, MD

Since Campylobacter pylori *was isolated in 1982, the organism has been at the center of a growing controversy regarding its possible role in peptic disease.* C pylori *is isolated in virtually 100% of patients with histologic gastritis, and the presence of the organism significantly increases the tendency of duodenal ulcers to relapse when H_2-blocking drugs are discontinued. Infection with* C pylori *also occurs in 70% of gastric ulcer patients, 50% of patients with nonulcer dyspepsia, and 20% of asymptomatic adults. The pathogen can be diagnosed by endoscopic pinch biopsy or noninvasive breath tests. While* C pylori *is very sensitive to bismuth compounds, the most effective therapy appears to be a combination of a bismuth compound and an antibiotic.*

Drugs Discussed in This Article

Amoxicillin
Antibiotics
Antiulcer drugs
Bismuth subsalicylate (Pepto-Bismol)
Bismuth subcitrate (investigational)
Cimetidine (Tagamet)
Erythromycin
Metronidazole
Tetracycline
Tinidazole (investigational)

First isolated in 1982, *Campylobacter pylori* is a unique, spiral, gram-negative organism that we now know is associated with gastritis and peptic ulcer disease.[1] Spiral organisms have been observed on the gastric mucosa since the turn of the century when they were described in association with gastric ulceration.[2] Nevertheless, these bacteria were ignored until recently, because the acidic stomach was thought of as only a temporary home to a few organisms destined either to be destroyed by acid or, rarely, to pass into the lower gastrointestinal tract.

That such a hostile environment could host a chronic bacterial infection was a remarkable finding. In fact, *C pylori* infection has been documented to last as long as four years if not treated, and probably persists for much longer.

C pylori is virtually always associated with histologic gastritis, and the presence of the organism significantly increases the tendency for duodenal ulcers to relapse when H_2-blocking drugs are discontinued. Although much remains to be learned about *C pylori* infection, the controversy regarding its possible role in peptic ulcers has been far-reaching and has caused a broad reevaluation of the classic tenets of peptic diseases.

C pylori is found in the gastric tissue of 85% to 95% of patients with histologic gastritis.

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COLONIZATION SITES

C pylori has been encountered only from gastric epithelium (Figs 1 and 2). It can, however, infect gastric tissue in locations other than the stomach, such as the epithelium of Barrett's esophagus[3] and, perhaps more importantly, the metaplastic gastric epithelium that commonly surrounds duodenal ulcers.[4,5]

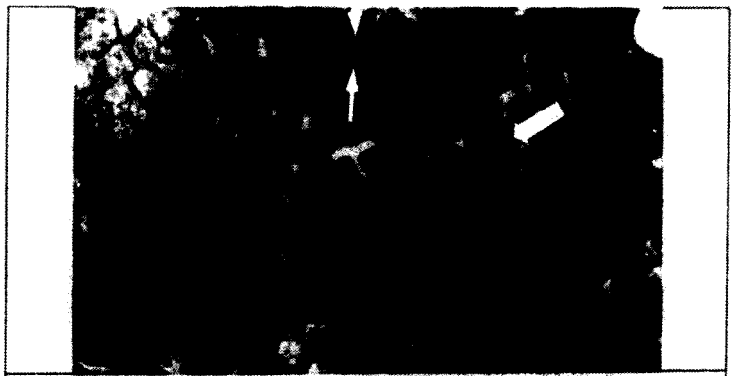
Moreover, *C pylori* can colonize heterotopic gastric epithelium anywhere along the intestinal tract, and has been observed in Meckel's diverticula and in heterotopic gastric epithelium of the rectum.[6] Although the finding of *C pylori* in these areas suggests that the organism can exist in the stool and that fecal-oral spread is possible, the organism has not been cultured from feces.

ADAPTIVE MECHANISMS

Natural infection with *C pylori* has been observed only in primates. A related spiral organism, however, is known to colonize the stomachs of cats, monkeys, dogs, and rats. This bacterium, *Spirillum rappini* (Fig 3), is morphologically distinct but shares many adaptive mechanisms with *C pylori* that allow survival in the stomach.

Figure 1

...ained antral biopsy showing chronic active antral gastritis in a patient with *Campylobacter pylori* infection



Note polymorphonuclear leukocytes infiltrating the gland (thin arrow) and plasma cells (thick arrow) (400 ×).

The spiral shape of these organisms facilitates penetration of gastric mucus. In addition, both *C pylori* and *S rappini* produce urease, which splits urea into ammonia and carbon dioxide. The ammonia may protect the bacteria from gastric acid.

Human infection with an organism similar to *S rappini* has also been documented.[7] On Giemsa-stained gastric specimens, this organism can be easily distinguished from *C pylori* by its plump, tightly coiled appearance and propensity to colonize gastric parietal cells.

Figure 2

Giemsa stained antral biopsy showing numerous *Campylobacter pylori*

The organisms appear in small clumps and as scattered isolated organisms (arrows) (1,000 ×).

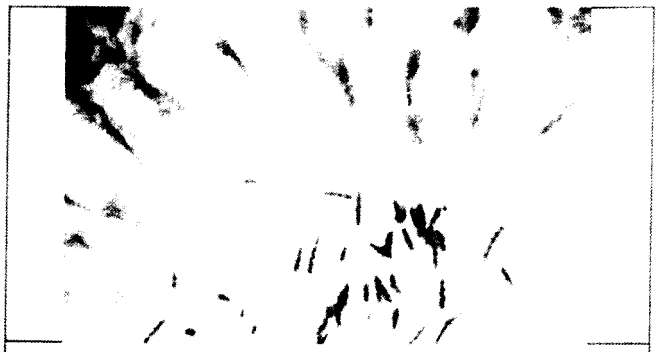
GASTRITIS

Numerous studies have confirmed the close association be-

Hypochlorhydria appears to be the initial manifestation of infection with *C pylori*.

Figure 3

Spirillum rappini on human gastric tissue



Human infection, although rare, is sometimes seen as shown here. Note the plump, tightly coiled appearance (Giemsa-stained, 1,000 ×).

tween *C pylori* and histologic gastritis. The organism is found in from 85% to 95% of patients with this condition.

Type A

It is important to distinguish the types of gastritis observed on gastric biopsies (Table). Type A gastritis, the lesion thought to cause pernicious anemia, is an autoimmune disease that predominantly involves the acid-producing portion of the stomach (body and fundus). The illness is characterized by a chronic inflammatory infiltrate (most frequently a mononuclear cell), atrophy of the gastric glands, and the presence of autoantibodies directed at the parietal cells and intrinsic factor. *C pylori* is not associated with type A gastritis.

Type B

Type B gastritis affects predominantly the gastric antrum and, to a lesser extent, the gastric body. The most common form of chronic gastritis, type B is strongly associated with *C pylori* infection.

The histologic changes seen in type B gastritis can be further divided into two categories: active (indicating the presence of polymorphonuclear cells) and chronic (characterized by a mononuclear cell infiltrate).

Does *C pylori* cause type B gastritis? Even the most ardent critics now generally concede that the evidence strongly supports this link. *C pylori* is almost never observed in histologically normal gastric tissue, and the prevalence of the organism is not increased in patients with gastritis or gastropathy due to other causes, such as Crohn's disease, eosinophilic gastritis, alcohol ingestion, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs).[8,9]

These associations alone would be inadequate to prove a causal relationship. However, Koch's postulates have been fulfilled in two studies in which healthy male volunteers ingested the organism.[10,11] In both trials, within days of ingestion, histologically normal gastric mucosa was converted to a diffuse and symptomatic gastritis with abundant *C pylori*. One subject spontaneously cleared the organism, while the other developed chronic antral gastritis and transient hypochlorhydria.

This syndrome—acute hypochlorhydric gastritis or epidemic hypochlorhydria — appears to be the initial manifestation of *C pylori* infection. Because its symptoms of nausea, vomiting, and abdominal pain are nonspecific and common, the initial event is seldom diagnosed.

Nevertheless, the syndrome has been observed in epidemic form in two groups of volunteers who underwent multiple gastric analyses in research laboratories; the organism may have been spread by the contamination of a wet pH probe. Both epidemics have been retrospectively associated with acute *C pylori* infection.[10,12,13]

The reason that only some patients are able to clear the acute infection is unknown but may involve differences in both the strain of *C pylori* and, perhaps more importantly, the immune status and genetic constitution of infected individuals. *C pylori* infection has been described worldwide in persons

Table

Types of Gastritis and Their Characteristics

Type A	
Autoimmune disease	
Chronic inflammation in the body and fundus of the stomach	
Atrophy of the gastric glands	
Production of antibodies against parietal cells and intrinsic factor	
Associated with pernicious anemia	
Type B	
Predominantly affects the antrum	
Associated with *Campylobacter pylori* infection, which causes both active forms (characterized by polymorphonuclear cell infiltration) and chronic forms (characterized by mononuclear cell infiltration)	
Almost always present in patients with duodenal or gastric ulcers	

C pylori may be the link between the hydrogen ion, pepsin, and increased mucosal susceptibility to ulceration.

gastric analyses in research laboratories; the organism may have been spread by the contamination of a wet pH probe. Both epidemics have been retrospectively associated with acute *C pylori* infection.[10,12,13]

The reason that only some patients are able to clear the acute infection is unknown but may involve differences in both the strain of *C pylori* and, perhaps more importantly, the immune status and genetic constitution of infected individuals. *C pylori* infection has been described worldwide in persons with acid peptic disease, but the organism is also present in some individuals with asymptomatic gastritis.

Among volunteers studied endoscopically, about 20% of young, otherwise healthy adults harbor *C pylori*.[14] Serologic studies have shown that prevalence is age-related; *C pylori* is found in fewer than 5% of children up to 9 years old, 5% to 10% of people 20 to 40 years old, and up to 50% of those over age 50.[14] A history of frequent antacid use is also associated with an increased prevalence of seropositivity for *C pylori*.

Furthermore, although the mechanism of spread is unknown, a recent study has shown a markedly increased prevalence of *C pylori* seropositivity at all age levels among the residents of an institution for mentally retarded patients. This finding, again, suggests the possibility of fecal-oral transmission.[15]

Table

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DUODENAL ULCER

Ten percent of adults develop duodenal ulcer disease sometime in their life, and 60% to 80% of healed duodenal ulcers recur within one year. Current therapy is aimed at suppressing acid production by the stomach or protecting the mucosa from acid and pepsin. Although duodenal ulcer patients often produce increased amounts of acid, there is so much overlap in this measurement with nonulcer patients that no clear distinction can be drawn between those individuals who develop ulcers and those who do not.

Impaired defensive mechanisms, such as mucosal bicarbonate production or prostaglandin synthesis, have been extensively studied in duodenal ulcer patients. Still, no adequate explanation for these impairments has been documented. *C pylori* may be the link between the hydrogen ion, pepsin, and increased mucosal susceptibility to ulceration.

Antral gastritis due to *C pylori* is found in 95% to 100% of duodenal ulcer patients,[16] and gastric metaplasia of the duodenum commonly occurs among patients with *C pylori* infection. A recent controlled trial demonstrated the continued susceptibility of patients to reulceration when *C pylori* infection persists after initial ulcer healing.[17]

At one year after ulcer healing, 79% of patients in whom the initial therapy failed to eradicate the organism had an endoscopically documented relapse. This compared with a relapse rate of 27% ($P < 0.1$) among those in whom initial

Prior to testing for *C pylori*, patients should discontinue antiulcer drugs for at least 12 hours and antibiotics or bismuth-containing drugs for four weeks.

therapy cleared the infection. Moreover, the majority of patients who initially cleared the infection but suffered ulcer relapses also had a recrudescence of *C pylori* infection.

In a larger trial from Western Australia, investigators have made similar observations.[18] Emerging from these and other studies is the fact that classic acid suppressing therapy rarely affects *C pylori* infection and does not heal the underlying gastritis. Likewise, ulcer surgery that spares the antrum (eg, vagotomy and pyloroplasty or highly selective vagotomy) does not appear to affect the prevalence of *C pylori* infection.[19]

Thus, the pathogenesis of the common duodenal ulcer appears to involve the effect of the hydrogen ion on infected and susceptible mucosa. The prospect of more curative therapy aimed at *C pylori* and the avoidance of endless cycles of acid-suppressing drugs appears promising.

GASTRIC ULCER

The prevalence of *C pylori* among gastric ulcer patients is 70%. Gastric ulcers not associated with *C pylori* are related to NSAID use and, less frequently, to malignancy. Nonetheless, among patients with gastric cancer, *C pylori* is also very common.

As with duodenal ulcer, *C pylori*–associated gastric ulcer occurs in the setting of histologic gastritis, although the inflammation more often involves the whole stomach. (In duodenal ulcer, the inflammation is usually localized to the antrum.)

Healing of gastric ulcers with bismuth compounds and antibiotics has been documented, and relapse rates may be lower after such therapy. Still, these data have not been correlated with *C pylori* status.

NONULCER DYSPEPSIA

About 50% of patients with nonulcer dyspepsia are infected with *C pylori*, and the association is being actively investigated. While theories of a causative role for *C pylori* in this syndrome are particularly controversial, uncontrolled clinical trials have supported the possibility of a causal relationship.[20] Indeed, the lack of other proven therapeutic measures makes antibacterial therapy an attractive alternative.

DIAGNOSIS

C pylori infection can be documented by several means. Prior to testing, patients should discontinue all antiulcer medications for at least 12 hours and should not have taken antibiotics or bismuth-containing substances for four weeks.

Biopsy

The most widely available means of diagnosis is simple endoscopic pinch biopsy of the greater curvature aspect of the antrum within several centimeters of the pylorus. Visual inspection of the stomach at endoscopy is inadequate, because marked histologic gastritis and *C pylori* infection may be present in grossly normal mucosa.

Visualization of the organism is best achieved by the relatively simple Giemsa stain. This method has a sensitivity of 93% and a specificity of 100%.

CLOtest

Placing an antral pinch biopsy into the urea-impregnated agar of the CLOtest (manufactured, in Australia, by Delta West and distributed in the United States by Tri Med) provides the most rapid means of diagnosis; results are often available within 20 minutes (Fig 4). This test takes advantage of the abundant production by *C pylori* of urease, which splits urea into ammonia and carbon dioxide.

The conversion of ammonia into ammonium ion causes a

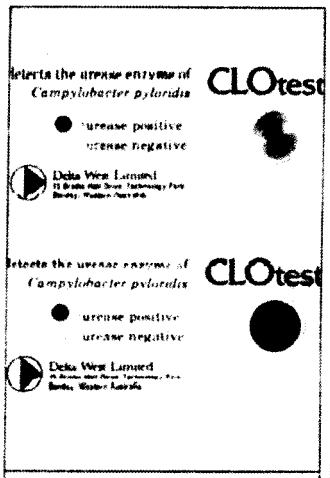
continued on p 103

C *pylori* appears to be one of the organisms that are most sensitive to bismuth compounds.

continued from p 96

Figure 4

CLOtest with antral biopsy in patient without infection (top) and positive CLOtest after inoculation with antral biopsy (bottom)



The magenta color in the positive test results from the activity of preformed bacterial urease on urea impregnated into the agar.

rapid rise in pH. As a result, the CLOtest's pH-dependent color indicator (phenol) turns magenta. Test kits should be refrigerated prior to use, because heat exposure will cause an orange discoloration that complicates interpretation.

The CLOtest has a sensitivity of 90% to 95% and a specificity of 95%. Warming the test to body temperature prior to use increases the speed of the reaction.

Breath Tests

There are also two types of noninvasive breath tests, both of which involve the ingestion of radioactively labeled urea and the subsequent detection of the radiolabeled substance in exhaled carbon dioxide.

The simpler of the two tests utilizes carbon-14, which is collected when the patient blows bubbles through a straw at five- to ten-minute intervals for a half hour. The samples can then be counted on a scintillation camera available in many hospital nuclear laboratories.

The radiation exposure is less than that of the average chest x-ray and, with a sensitivity of over 90%, the test is highly accurate.

TREATMENT

C pylori appears to be among the organisms that are most sensitive to bismuth compounds.[21] Ultrastructural changes in *C pylori*, including loss of adherence to epithelial cells, vacuolation, and lysis, have been documented shortly after ingestion, by infected individuals, of bismuth subcitrate, which is not yet available in the United States, and bismuth subsalicylate (Pepto-Bismol).

Bismuth seems to alter enzymes in susceptible bacteria. Suppression of *C pylori* with either bismuth subcitrate or bismuth subsalicylate is, however, only temporary, and relapse of the infection is common after therapy with bismuth alone. Neither preparation has significant acid-neutralizing capacity.

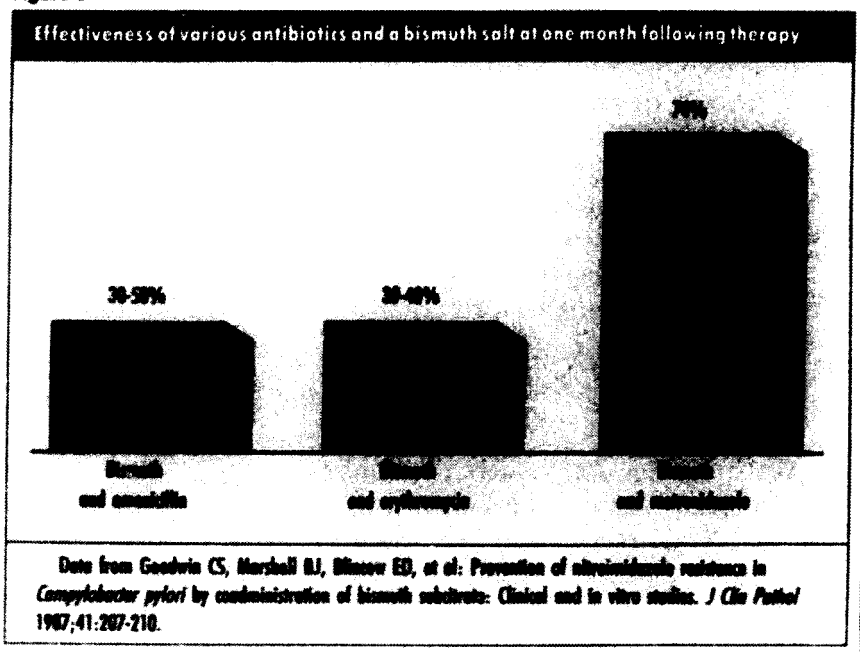
The most effective therapy appears to be a combination of bismuth and antibiotic. Borody and his group[22] reported 94% initial clearance of *C pylori* and 94% sustained clearance at 18 months using a triple regimen of bismuth, tetracycline, and metronidazole. The most common side effect was temporary nausea, which occurred in 32% of patients. Diarrhea was reported in 7% of patients and *Clostridium difficile*–associated diarrhea in 1%.

We have achieved a 74% cure rate with the combination of metronidazole, 1 to 1.5 g/d, and bismuth subsalicylate, 520 mg (or two tablets) chewed four times daily, given for 14 to 28 days. When the initial isolate is sensitive to metronidazole (as judged by disk inhibition of more than 20 mm), the success rate increases to 86%. In other trials, amoxicillin/bismuth and erythromycin/bismuth combinations have proven substantially less effective (Fig 5).

In this series of dose to 100 patients, *Clostridium difficile*–associated diarrhea was not

We begin therapy with several days of bismuth alone, followed by a variable period of combination therapy with bismuth and an antibiotic.

Figure 5



Data from Goodwin CS, Marshall BJ, Blincow ED, et al: Prevention of nitroimidazole resistance in *Campylobacter pylori* by coadministration of bismuth salts: Clinical and in vitro studies. *J Clin Pathol* 1987;41:207-210.

encountered. Only 4% of patients experienced diarrhea, but none had to discontinue therapy.

In a recently published Australian study of duodenal ulcer relapse and *C pylori*,[18] the investigators were able to eradicate the infection in 70% of patients treated with bismuth subcitrate and tinidazole (an antibiotic similar to metronidazole but not available in the United States). None of the patients treated with cimetidine (Tagamet) alone were cured of the infection. In those patients who were not cured, 84% suffered a relapse of the ulcer within one year (on no maintenance therapy). This compared to a one-year relapse rate of only 21% among those initially cleared of the infection.

Treatment Guidelines

Because *C pylori* is often difficult to eradicate, follow-up studies are needed one month after the completion of therapy. The carbon-14 breath test may prove to be a particularly useful follow-up test since it is noninvasive.

Side effects of bismuth compounds are infrequent and generally well tolerated. Patients should be warned that they may notice darkening of the stool (which is negative on guaiac testing) or temporary darkening of the tongue. Both of these side effects are due to the bacterial formation of bismuth sulfide rather than true changes in pigmentation.

Small amounts of bismuth normally can be detected in the serum during therapy. Excreted in the urine, the drug has a half-life of 14 to 21 days. Because of this long half-life, bismuth is relatively contraindicated in renal failure patients, although there are no strict guidelines.

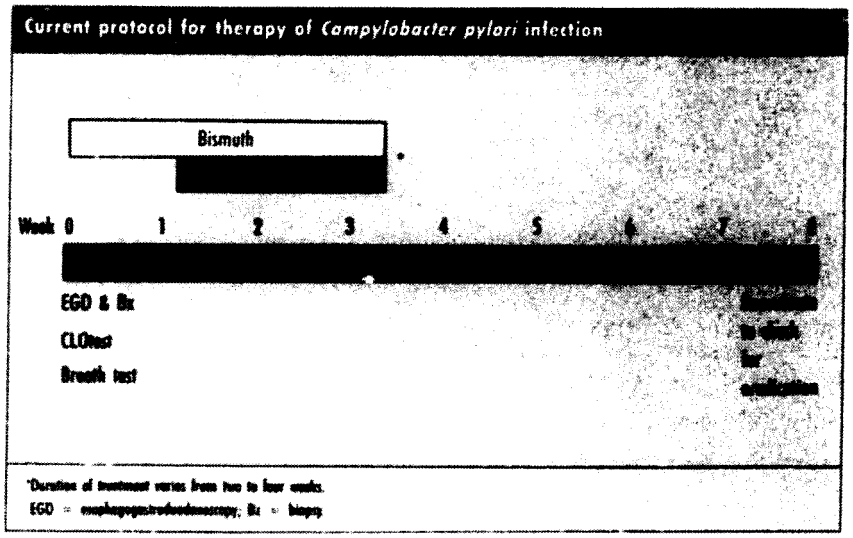
Bismuth toxicity is manifested by encephalopathy, which only occurs at serum levels of over 100 μg/L. In patients with normal renal function, serum bismuth levels seldom exceed 15 μg/L at the usual dosage (520 mg four times daily), even when the drug is administered continuously over several weeks.

Antibiotic therapy generally follows traditional guidelines. We usually discontinue other antiulcer medications during the 14- to 28-day treatment period and begin therapy with several days of bismuth alone, followed by a variable (one- to three-week) period of combination therapy (Fig 6).

Many patients are on other essential medications, and care regarding drug interactions should be exercised. In particular, blood clotting parameters should be monitored in patients receiving simultaneous metro-

Recent studies that have shown decreased ulcer relapse rates following eradication of *C pylori* are exciting.

Figure 6



nidazole or tetracycline and coumarin preparations.

IN CONCLUSION

Many studies of C pylori *are in progress and new information about the pathogen is being published each month.* C pylori *gastritis has been observed on all continents and in people of all ages, from very young infants to very old adults.*

It seems clear that C pylori *causes acute and chronic gastritis and that its presence increases the risk of ulcer relapse. The organism's marked production of urease potentiates its survival in an acid environment to which it would otherwise be susceptible.*

Urease has also been shown to have cytopathic effects on cell cultures, which are independent of pH and may relate to cellular ammonia toxicity.[27] *Ammonia production may also have significant systemic effects, especially among cirrhotic patients who may not be able to tolerate the excess nitrogen load.*

It is possible that whatever causes local tissue damage in C pylori *infection in some way blunts the immune response and allows the organism to thrive for years in the setting of an intense inflammatory reaction. This inflammatory reaction includes the production of specific antibodies and the accumulation of both mononuclear cells and neutrophils. Further studies are required to elucidate these processes.*

Recent studies that have shown a decreased rate of ulcer relapse following eradication of the organisms are very exciting. They offer the hope of a one-time cure for what previously has been a chronic, relapsing disease associated with numerous potentially devastating complications. Certainly, in the next decade we will see a large number of changes in the way we diagnose and treat peptic diseases. Many of these changes will hinge on current studies of the role of C pylori.

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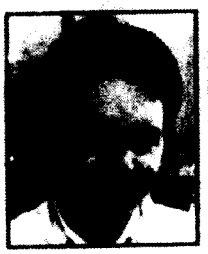

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A native of Australia, Dr Marshall received MB and BS degrees in 1974 from the University of Western Australia. This was followed by postgraduate training at Queen Elizabeth II Medical Center, Royal Perth Hospital, and Port Hedland Regional Hospital. Before coming to the University of Virginia in 1986, Dr Marshall was on the staffs of Fremantle Hospital and Royal Perth Hospital.

Keeping up with...

Cancer drugs

Predicting breast cancer recurrence

In a Texas study utilizing DNA flow cytometry, one group of women with node-negative breast cancer were shown to have a particularly good prognosis. The investigators examined 345 frozen node-negative tumor samples for ploidy (DNA content) and proliferative capacity as estimated by S-phase fraction (the percentage of cells in the synthesis phase of the cell cycle).

The women with diploid (normal DNA content) tumors and low S-phase fraction had a five-year disease-free survival rate of 90%, compared with 70% for the women with diploid tumors and high S-phase fraction and 74% for those with aneuploid (abnormal amount of DNA) tumors regardless of S-phase fraction (*N Engl J Med* 1989;320:627-633).

The authors speculate that for the low-risk group (women with diploid, low S-phase tumors), who represented 28% of the study population, the risks and expense of adjuvant systemic therapy may not be justified.