HELICOBACTER PYLORI

Medical Grand Rounds

U.T. Southwestern Medical Center

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A gram-negative, microaerophilic curved bacillus found in gastric biopsies of patients with histologic gastritis was successfully cultured in Perth, Australia during the Easter holidays of 1982 and was soon named *Campylobacter pylori* (1-4). Little attention had been paid to previous descriptions of spiral organisms in biopsies of human gastric mucosa (5-7), but it now appears that the organism is at least responsible for most cases of gastritis not associated with another known primary cause (eg., autoimmune gastritis, eosinophilic gastritis) and may also be a major factor in the pathogenesis of peptic ulcer disease.

The Organism

The successful culture of *C. pylori* was followed by intense scrutiny of its taxonomic features, especially in comparison to other campylobacters. Results of these studies delineated major differences from true campylobacters in ultrastructure (Figures 1 and 2), cellular fatty acid composition, respiratory quinones, growth characteristics,

Figure 1. *Campylobacter pylori*. Note smooth coat, lack of polar pits, monopolar flagella with terminal bulb.

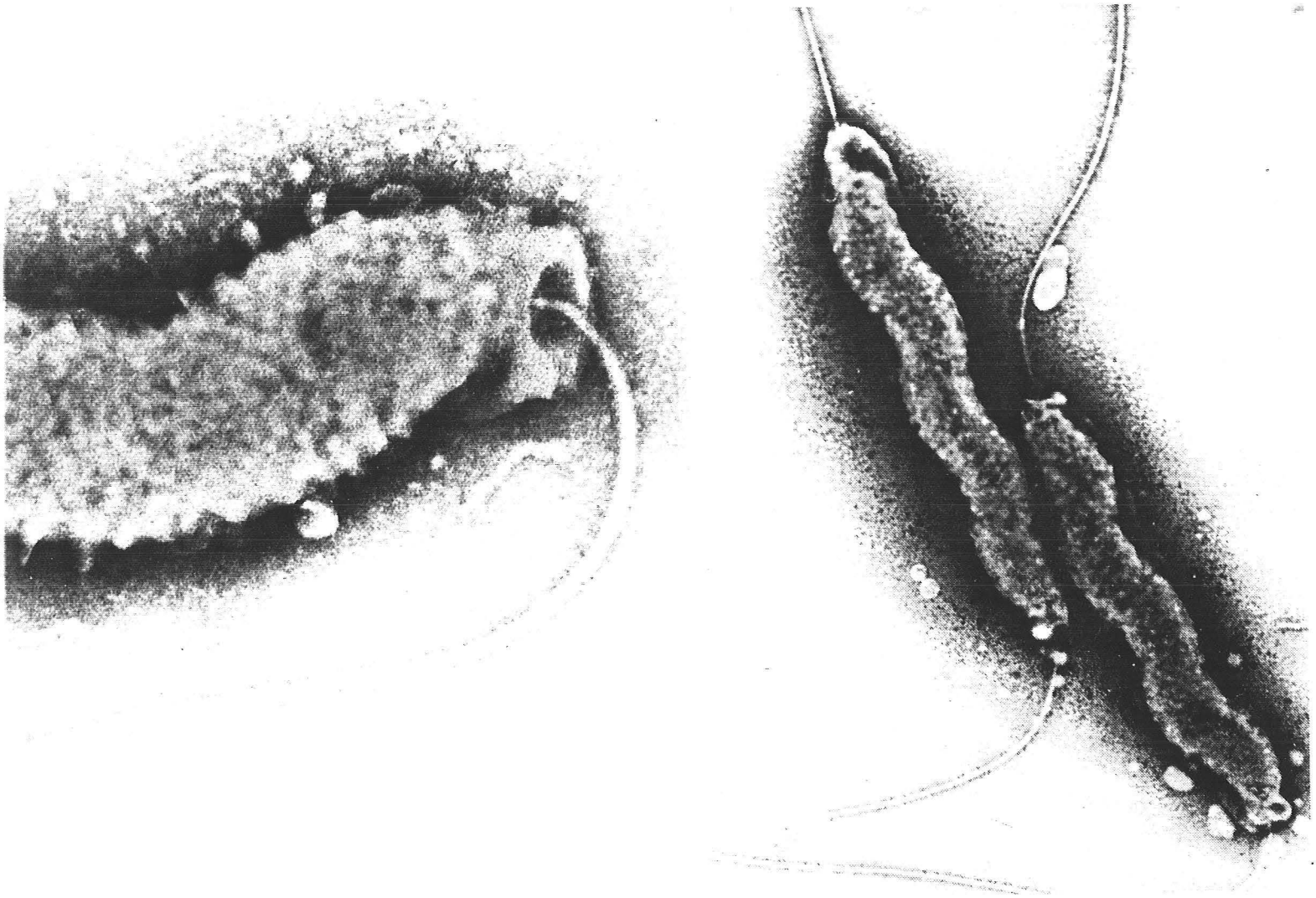

Figure 2. *Campylobacter jejuni*. Note rough coat, polar pits, single bipolar flagella without terminal bulbs (From Pead, J. Med. Micro. 1979;12:383).

RNA sequencing, and enzymes (8) (Table 1). For example, *C. pylori,* unlike true campylobacters, possesses potent urease activity, a property which may have important pathogenetic implications. This cell-surface enzyme is composed of two subunits of approximately 30 and 60 kDa, the genes for which have now been sequenced (9-12). Because of its unique characteristics, *C. pylori* was assigned a new name, *Helicobacter pylori* (13).

Table 1. Enzymes of *Campylobacter pylori* and *Campylobacter jejuni*.

	C. pylori	C. jejuni
Oxidase	+	+
Nitrate	-	+
Hippurate	-	+
Urease	+	-

Organisms very closely related to *H. pylori* have been isolated from the stomachs of primates (14,15) and a different species of Helicobacter (*H. mustelae*) has been cultured from the stomachs of ferrets (16). A few human subjects with gastritis have been found to harbor an organism which is much more tightly-coiled than *H. pylori (17,18) (Figure 3).* Tentatively called *Gastrospirillum hominis*, it may be transmitted from

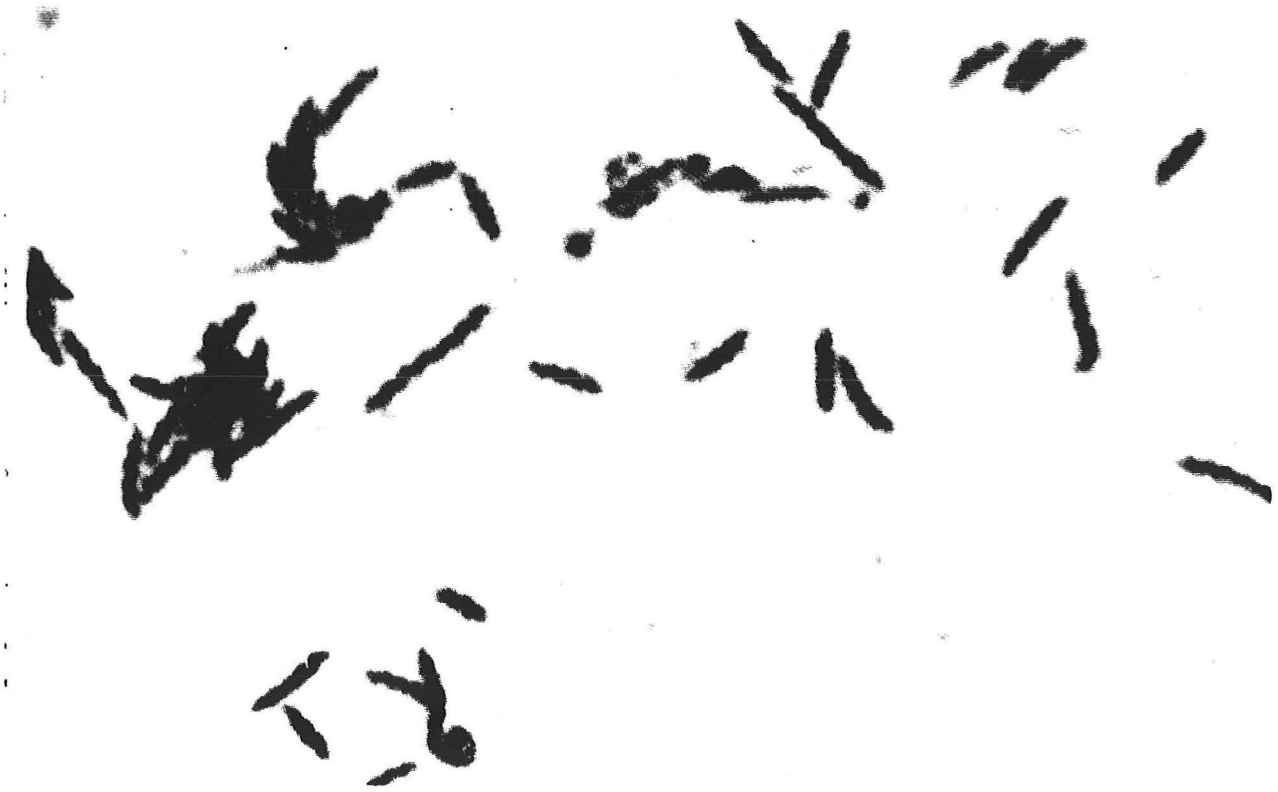

Figure 3. *Gastrospirillum hominis* (From Morris).

animals such as cats and dogs, in whom similar organisms have been seen. Yet another tightly-spiralled organism has been cultured from the cat and tentatively named *H. felis (Figure 4)* (19).

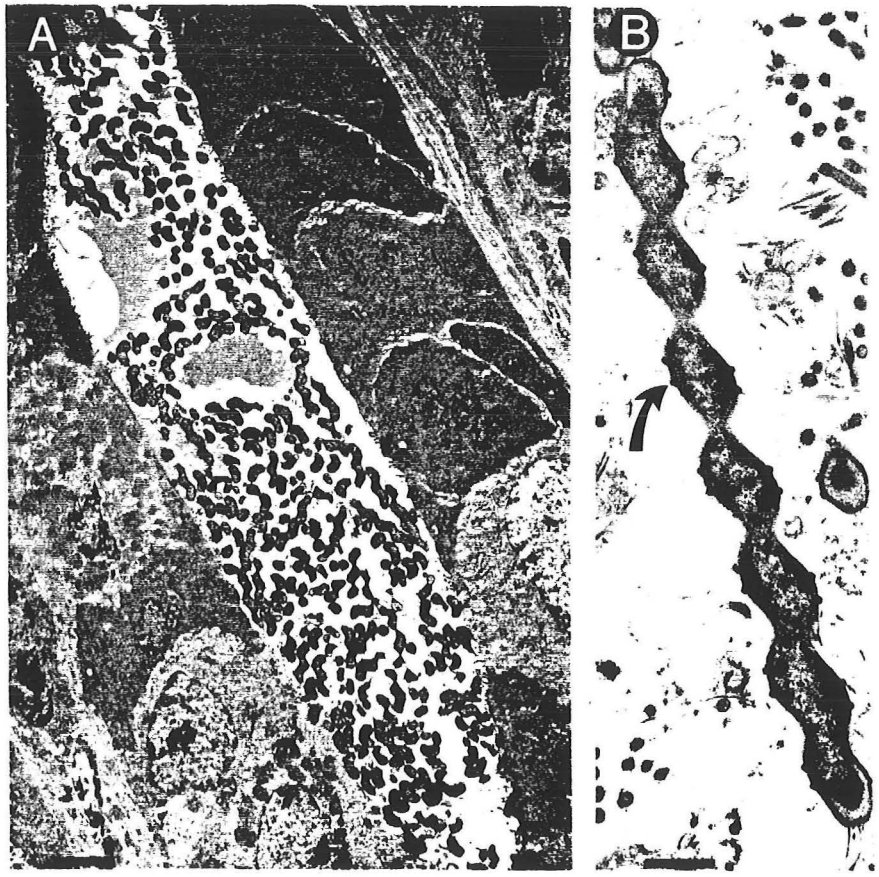

Figure 4. *Helicobacter felis* (From Lee)

H. pylori is found only on gastric epithelium, where the organisms tend to cluster around the junctions between cells (Figure 5) and virtually never penetrate the cells themselves. Individuals with *H. pylori* in the stomach may also harbor organisms in metaplastic gastric epithelium of the esophagus (Barrett's esophagus) or duodenum (20-22). H. pylori is not found in the blood and, with rare exception (23-25), has not been found in other parts of the body.

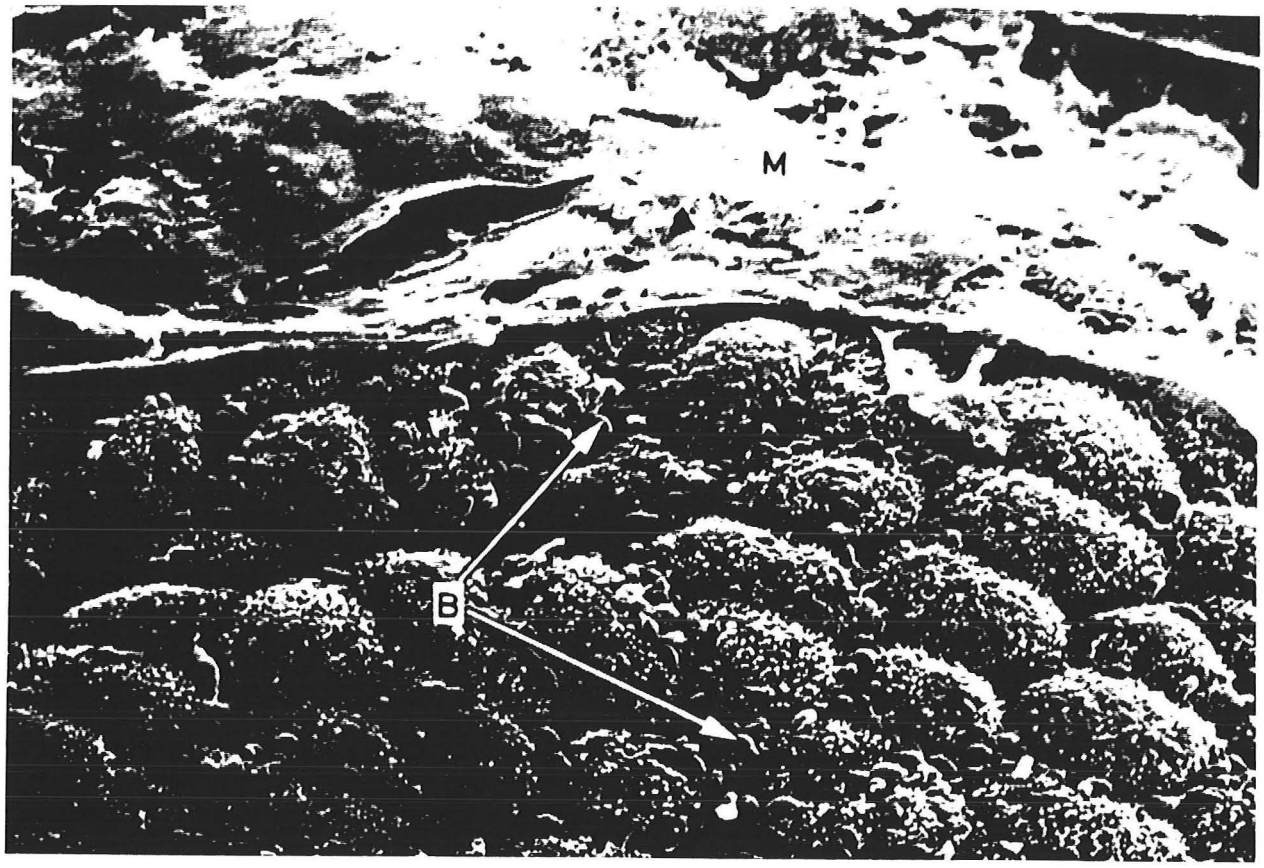

Figure 5. Electron photomicrograph of *H. pylori* (B) in the gutters of gastric epithelium from which mucus has been stripped away (From Steer).

Detection of *H. pylori*

The "gold standard" for detection of *H. pylori* in tissue is a combination of culture (26) and histologic staining (27) of endoscopic mucosal biopsies. A more rapid, but slightly less sensitive, endoscopic technique is the biopsy urease test in which a urea-containing medium with pH sensitive dye is inoculated with the mucosal biopsy (28). If urease is present in the biopsy, urea is split to produce carbon dioxide and ammonia, the latter causing a rise in pH and concomitant color change. This test may be falsely negative when small numbers of organisms are present or if sampling error provides a piece of tissue without the organism. It is also possible that some subjects may have bacterial overgrowth with non-*H. pylori* urease-producing organisms leading to false positive results. A non-invasive test to assess for the presence of urease in the stomach, and one which avoids biopsy sampling error, is the breath urea test (29-32).

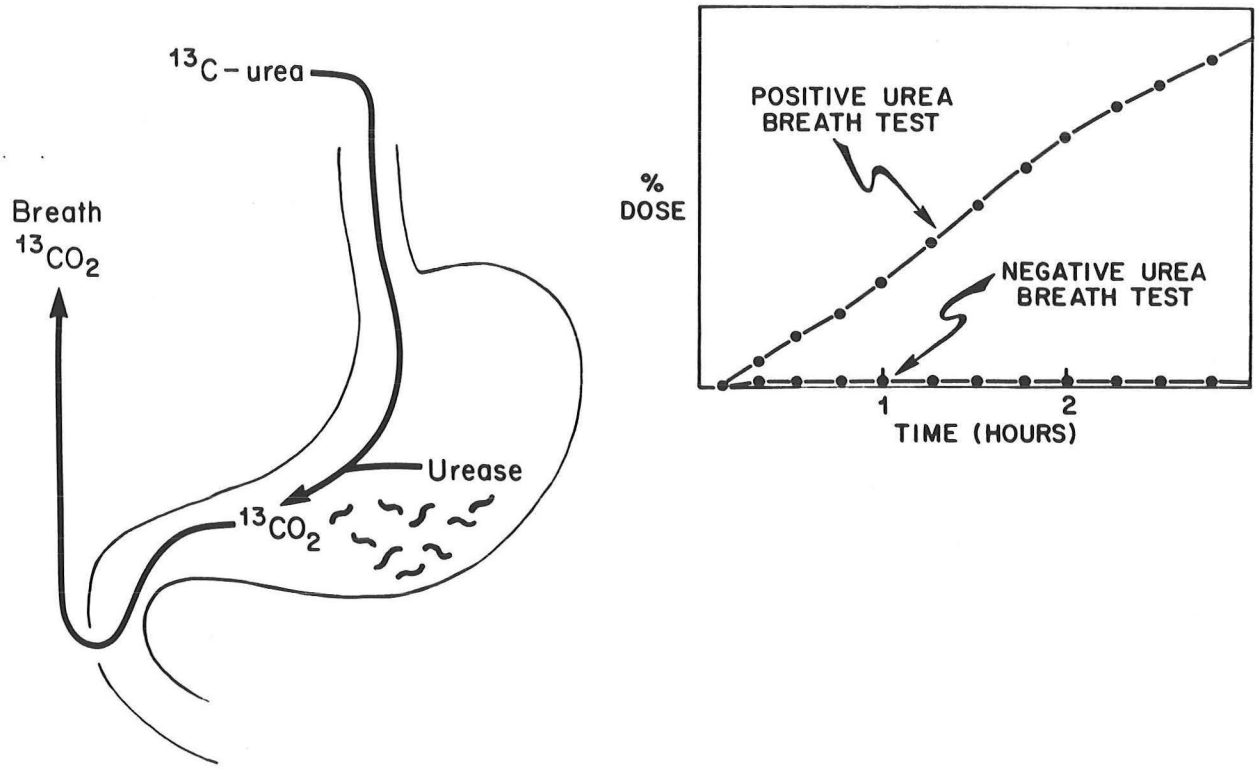

Figure 6. Breath Urea Test (From Graham, et al)

This test (Figure 6) employs ^{13}C or ^{14}C-labeled urea ingested with a liquid meal. If enough urease is present in the stomach, labeled carbon dioxide is split off, absorbed, and expired in the breath. There is a small radiation exposure with ^{14}C, while a mass spectrometer is required for determination of ^{13}C. Tests for detection of urease have sensitivity and specificity ranging between 90-95%. Another non-invasive test is determination of serum antibodies to *H. pylori*. However, because the time course of the decline of antibody levels after eradication of *H. pylori* is not well-described, it remains possible that antibody levels will persist even if the organism itself has been eradicated (33). New techniques using immunocytochemistry (34), monoclonal antibodies (35), and oligonucleotide probes (36,37) are being developed.

Prevalence of *H. pylori*

There is a substantial, age-related prevalence of *H. pylori* in healthy, asymptomatic subjects (38-41) (Figure 7). Healthy individuals less than 30 years of age have

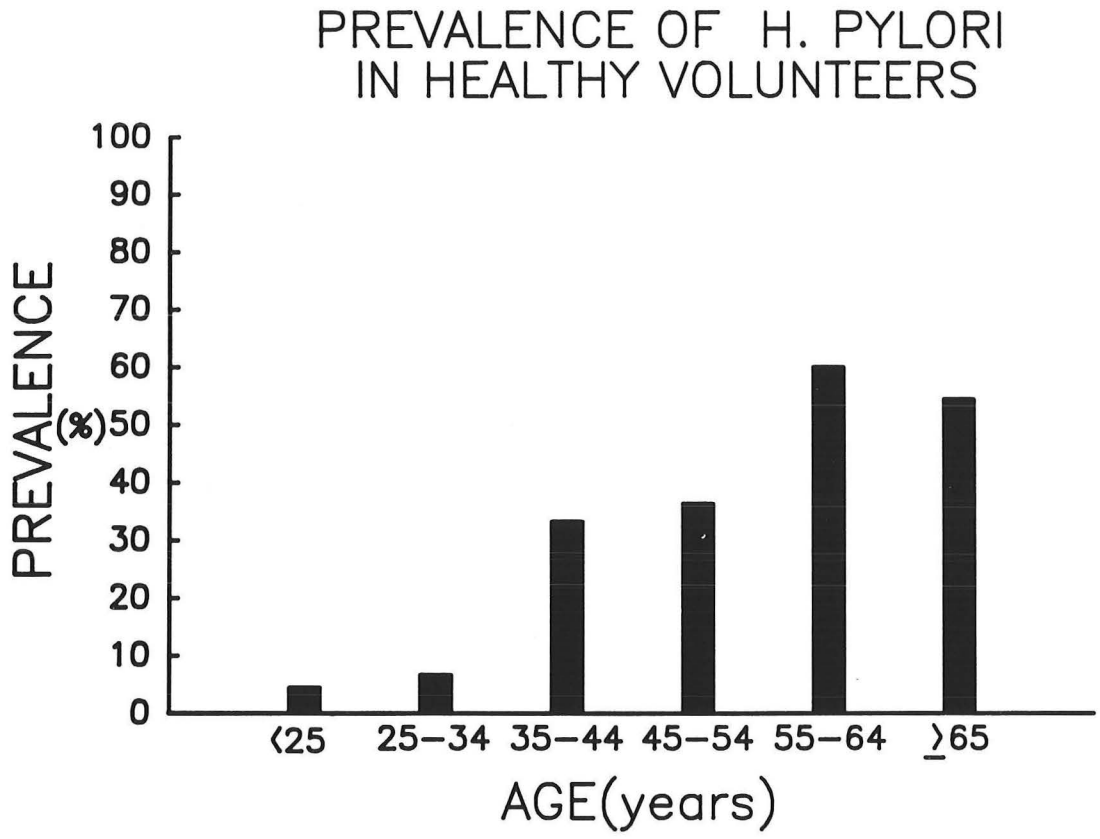

Figure 7. Prevalence (by culture or tissue stain) of *H. pylori* in healthy volunteers studied prospectively at the Dallas VAMC (W.L. Peterson, et al, unpublished observations - See Table 2 for collaborators).

prevalence rates of about 10% while those over 60 have prevalence rates approaching 60%. Factors which are associated with earlier and more frequent acquisition of *H. pylori* infection in healthy subjects include ethnic origin (eg., Afro-Americans and Hispanic Americans) (42,43), socioeconomic deprivation (44-47), and residence in custodial institutions (48,49).

Patients with duodenal or gastric ulcer also have a substantially higher prevalence of *H. pylori* when compared to age-matched controls (38,50). Virtually 100% of patients with duodenal ulcer have evidence of *H. pylori* infection, while about 80% of patients with gastric ulcer will harbor the organism (Table 2). Approximately 50% of patients with

Table 2. Proportion (%) of subjects with *H. pylori* infection (W.L. Peterson, Markus Goldschmiedt, Thomas Faust, Israel Podolsky, Edward Lee, Richard Cohen, and Mark Feldman, unpublished observations).

	<35 y/o	35-54	>55
Normal Subjects	2/37 (5%)	6/17 (35%)	12/21 (57%)
DU	5/5* (100%)	15/17* (88%)	18/20* (90%)
GU	-	10/14 (71%)	23/27 (85%)
NUD	-	-	9/16 (56%)

* $p<0.05$ compared to normal

non-ulcer dyspepsia will be infected with *H. pylori*, but whether this is higher than age and race-matched controls is unresolved (51). Patients with AIDS have lower than expected rates of infection (52-54), possibly because of frequent therapy with antimicrobial agents.

Transmission of H. pylori

H. pylori is most likely transmitted from person to person, although infection from a common exogenous source cannot be completely ruled out (55,56) (Table 3).

Table 3. Prevalence of *H. pylori* infection (by breath test) in Peruvian children under 10.

Family Income	Community Water System	Private Water System
High	33%	5%
Low	63%	14%

From Klein, et al, *Gastro 1990;98:A69*

However, *H. pylori* has yet to be isolated from food, water or animals with whom humans typically come in contact. There is intra-familial clustering of *H. pylori* (57,58) (Table 4), and in one report all 8 family members with *H. pylori* had identical organisms

Table 4. Prevalence of *H. pylori* (by serum antibody test) in family members of children with and without *H. pylori* infection.

	H. pylori Positive Children	*H. pylori* Negative Children
Sibs	18/22 (82%)	5/37 (14%)
Mothers	15/18 (83%)	2/17 (12%)
Fathers	10/16 (62%)	6/16 (38%)

From Drumm, et al, *New Engl J Med 1987;316:1557*

by restriction endonuclease analysis of bacterial DNA (59), a highly unusual phenomenon (60,61). Person-to-person transmission is further supported by the high prevalence of *H. pylori* in residents of chronic care facilities (48,49). In one study, there was a significant correlation between length of stay in the facility and prevalence of *H. pylori* which was not accounted for by difference in ages (62). Of note, 2 residents harbored organisms which were identical by restriction endonuclease analysis.

The means by which person-to-person transmission of *H. pylori* might occur is unknown. The organism has not been isolated from stool and there is only one case in which *H. pylori* was cultured from the oral cavity (63,64). Person-to-person transmission of infection via endoscopy and biopsy has been proven (65) and gastroenterologists have been reported to have more than twice the expected prevalence of infection (66). Perhaps DNA probes will detect the presence of *H. pylori* in locations where culture does not.

Host Response to *H. pylori*

Antral biopsies from adults who harbor *H. pylori* virtually always show focal epithelial cell damage (eg., edema, vacuolation, lysosome accumulation) as well as an inflammatory response in the lamina propria consisting of mononuclear cells and granulocytes (38,67-70) (Table 5). Biopsies from the body of the stomach also demonstrate gastritis in most instances, but may be normal in up to 10% of cases in which *H. pylori* are present (38,68,71). Biopsies in such patients from other areas of the gastric body will frequently show active gastritis as will virtually all biopsies from the antrum (68).

Table 5. Mucosal histology in subjects infected with *H. pylori* (W.L. Peterson, et al, unpublished observations).

	H. pylori Infected Subjects	
Mucosal Histology	Antrum (N=93)	Body (N=101)
Normal	0 (0%)	10 (10%)
Active Gastritis	87 (94%)	87 (86%)
Inactive Gastritis	2 (2%)	1 (1%)
Atrophic Gastritis	4 (4%)	3 (3%)

There is dispute among investigators as to the frequency with which "non-granulocytic" chronic inflammation is seen in adults with *H. pylori* infection (38,39). This may reflect differences in the definitions of gastritis, a problem which may be resolved by quantitative morphometric analysis of mucosal biopsies.

H. pylori associated gastritis could simply reflect colonization of tissue inflamed by another cause, or could represent a primary bacterial infection. There is modest direct evidence to support the latter. Inoculation of *H. pylori* into experimental animals has led to colonization in neonatal gnotobiotic piglets and beagles and 2 month old barrier-born pigs (72-75), although the histologic response is less granulocytic than in the human infection. Germ-free mice inoculated with *H. felis* develop a more pronounced polymorphonuclear response and may prove to be a more convenient animal model (76). Two human subjects who intentionally ingested *H. pylori* reportedly developed an intense inflammatory response with abundant neutrophils, first in the antrum and then the body (77,78). There was spontaneous resolution of infection and inflammation in one. In the second subject, infection was associated with hypochlorhydria, and while acid secretion ultimately returned, he was left with chronic gastritis (78). This pattern is similar to that observed in patients with "epidemic gastritis with hypochlorhydria" (79) and it may well be that *H. pylori* either caused or was associated with these occurrences (80,81). Recent work suggests that *H. pylori* may possess a protein capable of inhibiting parietal cell function (82).

Most of the evidence that *H. pylori* is a primary pathogen is indirect, albeit persuasive. *H. pylori* is not simply a commensal organism with a predilection for inflamed gastric mucosa, since its prevalence is very low in patients with pernicious anemia (83,84), eosinophilic gastritis (85,86), Crohn's gastritis (85,86), Menetrier's disease (86), or lymphocytic ("varioliform") gastritis (87,88). Neither does gastroduodenal injury unassociated with an inflammatory response (ie., postgastrectomy reflux "gastritis", NSAID-"gastritis", or alcoholic "gastritis") predispose to the presence of *H. pylori* (89-93). The stongest indirect evidence that the organism causes gastritis comes from studies in which antimicrobial agents are admininstered to subjects with *H. pylori* gastritis. There is a clear relationship between suppression or eradication of the organism and resolution of gastritis (94-97) (Table 6). Finally, accompanying the robust

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Table 6. Antibiotic therapy of *H. pylori* gastritis.

	Clearance of H. pylori After 2 Weeks	Resolution of Gastritis
Placebo (N=31)	13%	3%
Nitrofurantoin (N=24)	79%	54%
Furazolidone (N=14)	93%	64%

From Morgan, et al, *Gastro 1988;95:1178*

inflammatory reaction to *H. pylori* infection, including T lymphocytes and plasma cells, is a substantial systemic IgG and IgA antibody response (40,98) (Table 7).

Table 7. Serum antibodies to *H. pylori* (ELISA).

	Mean ± SE O.D.	
Antral Culture	IgA	IgG
Positive (N=29)	1.26 ± 0.08	1.71 ± 0.07
Negative (N=30)	0.37 ± 0.07	0.34 ± 0.10
	($p<0.00001$)	

From Perez-Perez, et al, *Ann Int Med 1988;109:11*

Intense interest has developed in potential virulence factors possessed by *H. pylori* which permit it to escape the bactericidal properties of gastric acid, colonize gastric epithelium, damage epithelial cells, and induce an inflammatory reaction. Such factors include motility (99), adhesins (100-102), proteases (103), phospholipases (104), cytokines (105-107), cytotoxins (108-111), and urease (112-115). For example, it was recently reported that a mutant strain of *H. pylori* without urease was unable to colonize any of 10 gnotobiotic piglets challenged with the strain compared to colonization of all 7 animals challenged with the wild-type strain (112). Reasons why urease may be necessary for colonization include protection of *H. pylori* from the bactericidal effect of acid (113) or enhancement of bacterial adherence (116). It has also been suggested that ammonia generated through breakdown of urea by urease may be cytotoxic (114,115) but most workers find this barely plausible. Work is now underway into the role played by plasmids in the pathogenicity of *H. pylori* (61,117-120). In our own series, 12 of 15 isolates of *H. pylori* contained plasmids ranging in size from 3.8 to 16.2 kilobases (Figure 8) (119). Isolates from different anatomical areas of the same subject were identical by restriction endonuclease analysis (Figure 9). Preliminary experiments suggested that 4 strains with plasmids produced a cytotoxin whereas 2 strains without plasmid did not.

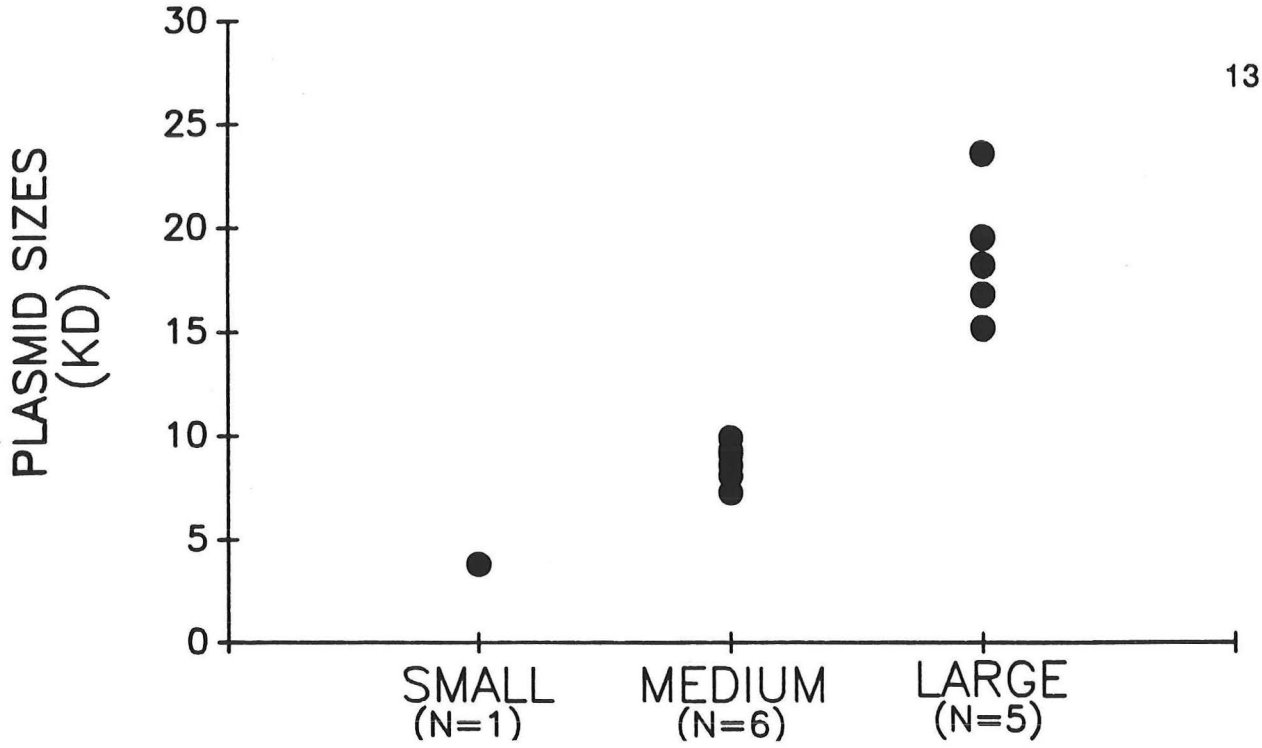

Figure 8. Plasmids detected from 15 isolates of *H. pylori* (McIntire, Cohen and Peterson, unpublished observations).

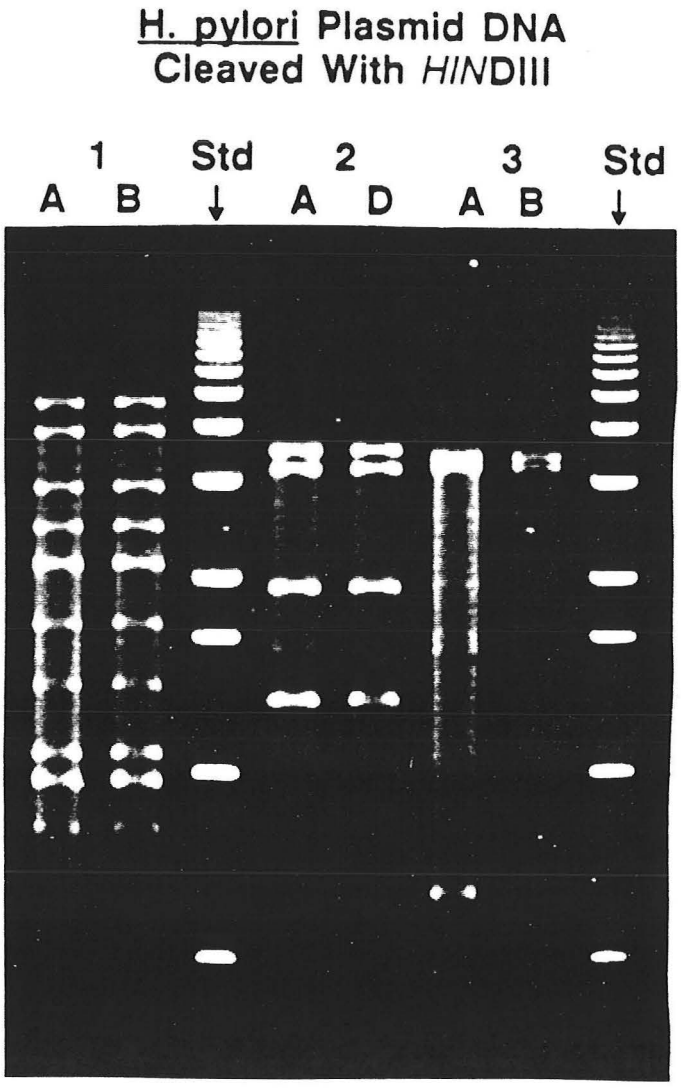

Figure 9. Plasmid profiles (HIN DIII) of *H. pylori* from antrum (A), body (B) or duodenum (D) of 3 subjects (McIntire, Cohen, and Peterson, unpublished observations).

Consequences of *H. pylori* Infection

Gastroduodenal Function

Levi reported that active duodenal ulcer patients infected with *H. pylori* had higher acid output and gastrin response to a meal when compared to such patients without *H. pylori* infection (121). Others have now confirmed that subjects with *H. pylori* infection (either in duodenal ulcer patients or healthy volunteers) exhibit an exaggerated gastrin response to meals (122,123) which is reversed after eradication of the organism (124). The relationship between *H. pylori* infection, gastrin release, and acid secretion remains controversial (122-126), but our data (Table 8) suggest that basal acid secretion is lower in *H. pylori* infected normal subjects and higher in *H. pylori* infected patients with duodenal ulcer.

Table 8. Basal and peak acid outputs, fasting gastrin levels, meal-stimulated acid output, and meal-stimulated integrated gastrin response (IgR) in healthy, normal volunteers who (by serum antibody) are (Hp+) or are not (Hp-) infected with *H. pylori* and in Hp+ duodenal ulcer (DU) patients (W.L. Peterson, C. Barnett, D. Evans, M. Feldman, C.T. Richardson, J. Walsh and D.Y. Graham, unpublished data).

	Hp- Nl (N=73)	Hp+ Nl (N=63)	Hp + DU (N=51)
BAO (mmol/h)	4.4 ± 0.5	2.8 ± 0.4*	6.5 ± 0.8**
PAO (mmol/h)	35.8 ± 1.4	33.1 ± 1.5	51.5 ± 2.2**
Fasting Gastrin (pg/ml)	31 ± 2	42 ± 4*	55 ± 4**
Meal-Stimulated Acid Output (mmol/2h)	40.3 ± 1.8	39.8 ± 2.6	46.5 ± 2.4*
Meal-Stimulated IgR (ng.min/ml)	4.4 ± 0.4	8.0 ± 1.0*	6.0 ± 0.6*

* $p<0.05$ compared to Hp- Nl
** $p<0.05$ compared to both Nl groups

Serum pepsinogen levels have long been recognized as being higher in patients with superficial gastritis, so it is no surprise that such levels are high in subjects with *H. pylori* infection (127). The high levels of pepsinogen found in patients with duodenal ulcer disease, previously believed merely to be concordant with higher levels of gastric

acid secretion, may well be related instead to gastritis. The influence of *H. pylori* gastritis on gastric emptying has not been well-studied, but early reports note no effect (128-130).

Mucosal Histology

Long term follow-up of *H. pylori* infection per se is not available, but from sequential study of subjects with "idiopathic" chronic active superficial gastritis, it appears that varying degrees of antral and body atrophic gastritis may develop over time (131). The role of *H. pylori* in this progression, as well as other factors which certainly play roles, has not been elucidated. Recent reports note that as gastric mucosa becomes more atrophic, especially in the body, *H. pylori* are found by tissue stain with decreasing frequency (33,132,133). Serum antibody levels to *H. pylori* however, remain high suggesting prior infection with the organism (33).

Varying patterns of superficial or atrophic gastritis in antrum and body are found associated with various gastroduodenal diseases. Perhaps 10% of individuals with gastritis in the antrum accompanied by normal mucosa or gastritis in the body will develop duodenal ulcer or distal gastric ulcer (131,134,135). Gastritis in these patients appears not to progress to stages of atrophy as often or as rapidly as in other groups (131). If antral mucosa becomes atrophic, gastric ulcer will predominate over duodenal ulcer (135,136) and as the body becomes atrophic, duodenal ulcers will be seen only rarely, gastric ulcers will occur less often and then high in the body (136), and gastric cancer may develop in some patients. Whether such changes would occur in the absence of *H. pylori* is not known nor is it known why some subjects progress through stages of atrophy and others do not.

Gastrointestinal Symptoms

It is now generally accepted that *H. pylori* gastritis represents a true "infection". It remains controversial whether *H. pylori* gastritis is a "disease" leading to symptoms. It has been suggested that *H. pylori* gastritis is responsible for the symptoms experienced by a subset of patients with non-ulcer dyspepsia. Others have suggested that, because of its almost universal prevalence in patients with duodenal ulcer, *H. pylori* gastritis is a predisposing factor for ulceration, theoretically through infection of areas of gastric metaplasia (6,50). Of course, other factors must also be present, since only a minority of individuals with *H. pylori* gastritis develop duodenal ulcers. *H. pylori* gastritis may be, like acid and pepsin, a permissive factor without which duodenal ulcers seldom occur but with which an ulcer is far from inevitable. The data regarding *H. pylori* and gastric ulcer are, at this time, less compelling.

If *H. pylori* gastritis plays a role in non-ulcer dyspepsia, then patients in whom treatment results in eradication of the organism should experience symptom improvement more often than those in whom a control regimen did not eradicate *H. pylori*. Furthermore, if *H. pylori* gastritis is an important, perhaps essential, factor in patients with duodenal ulcer disease, then eradication of the organism, like suppression of

gastric acidity, should result in markedly lower rates of ulcer recurrence or even, as has been suggested, "cure" of the disease (137).

Antimicrobial Therapy of H. pylori Gastritis

Eradication of *H. pylori*

Eradication of *H. pylori* is no easy matter, nor is interpreting the studies of antimicrobial therapy. Studies are frequently neither randomized nor blinded; dosages of antimicrobial agents and duration of therapy vary widely; and the definition of eradication differs among studies. While some consider absence of *H. pylori* immediately after therapy as evidence of eradication, others insist on waiting a month to exclude those subjects in whom the organism is only temporarily supressed.

None of the standard ulcer therapeutic agents (eg., H_2 receptor antagonists, sucralfate) has any effect on *H. pylori*. Bismuth given alone suppresses the organism, but results in long-term eradication in perhaps as few as 10% of subjects (137). Numerous antibiotics have been tried as monotherapy, including erythromycin, amoxicillin, fluoroquinolones, tinidazole, and metronidazole, but none has proven acceptable. The use of tinidazole or metronidazole alone has resulted in the emergence of resistance to the drug in a substantial number of isolates (97). When one of these nitroimidazoles is combined with either a bismuth compound or with another antibiotic (eg., amoxicillin), the incidence of resistance is decreased (but not abolished) and eradication rates approach 75% (138,139). Some investigators suggest triple therapy with metronidazole, bismuth, and amoxicillin or tetracycline, although it is not clear that such a regimen is more effective than double therapy (137,138).

Eradication of *H. pylori* in Patients with Non-Ulcer Dyspepsia

Seven randomized, "double blind", placebo-controlled trials are available in which eradication of *H. pylori* and symptom response were measured. Five studies employed as the active agent a bismuth compound alone (140-144) and two employed antibiotics alone (nitrofurans or amoxicillin) (94,95). *H. pylori* infection was suppressed immediately after therapy by the active regimen in each study, with accompanying improvement in gastritis, but long term eradication was seldom achieved. Symptoms improved modestly, but significantly, compared to placebo in three of the five bismuth trials (140,141,143) but in neither of the two antibiotic trials. Results from one of these trials are shown in Table 9.

Analysis of these trials discloses more than just conflicting results. First, none of the bismuth studies was truly blind, since bismuth darkens the stools. Patients could

Table 9. Proportion of patients with non-ulcer dyspepsia becoming asymptomatic after treatment with colloidal bismuth subcitrate (CBS) or placebo.

	CBS	Placebo
H. pylori positive	8/11 (73%)*	3/12 (25%)
H. pylori negative	5/17 (29%)	5/11 (45%)

* $p<0.05$ compared to placebo

From Kang et al, Gut 1990;31:476

be influenced by changes in stool color, although in one of the studies patients without *H. pylori* gastritis were also randomized, and the bismuth-treated group did not respond any better than the placebo-treated group (143) (Table 9). Second, antibiotics, especially the nitrofurans (94), are well-known to produce side-effects much like the symptoms of non-ulcer dyspepsia, thereby possibly obscuring any benefit from the eradication of *H. pylori*. Third, symptoms were assessed immediately after conclusion of therapy, so that long-term improvement cannot be assumed. The issue of *H. pylori* gastritis and non-ulcer dyspepsia is, to put it mildly, unresolved.

Eradication of *H. pylori* in Peptic Ulcer Disease

Studies performed in the "pre-*H. pylori*" era had noted that the 12 month incidence of duodenal ulcer recurrence in patients whose ulcer had been healed with bismuth was approximately 55% as compared to a recurence rate of about 85% in patients whose ulcer had been healed with an H_2 receptor antagonist (145) (Figure 10). When bismuth was subsequently observed to suppress *H. pylori*, the hypothesis was put forth that the salutary long-term effects of bismuth were related to eradication of *H. pylori*.

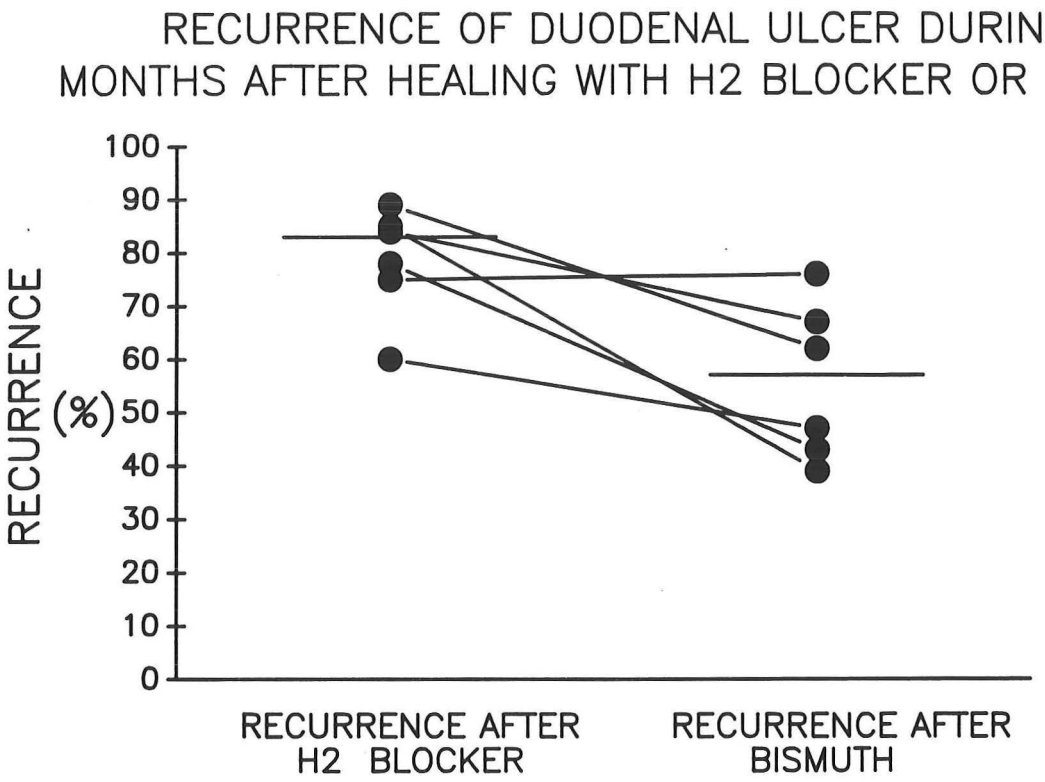

Figure 10. Recurrence during 12 months after healing with H_2 receptor antagonist or bismuth. Horizontal lines represent mean of individual studies (From Dobrilla).

Three randomized studies of bismuth-containing regimens in which ulcer recurrence was correlated with eradication of *H. pylori* have now been published in complete form (137,146,147) (Table 10). Several points from these studies merit comment: 1) Clearance of *H. pylori* was related to the time after completion of therapy that the assessment was made. When performed immediately upon completion of therapy, clearance was reported in 52% of patients (146) but if a four week delay was imposed, clearance was noted in only 10% of patients (137); 2) Overall recurrence in patients whose ulcer had been healed with bismuth was 52-76%, values which are comparable to those observed in previous studies (145); Recurrence in patients treated with bismuth alone, but in whom *H. pylori* were still present was noted in 31/37 (84%); 4) Recurrence in patients in whom *H. pylori* had been eradicated was substantially and significantly lower, especially in those treated with bismuth plus an antibiotic.

Table 10. Recurrence of duodenal ulcer during 12 months after healing with various bismuth-containing regimens or cimetidine.

Ref	Regimens	Time After Completion of Therapy Clearance of H. pylori Assessed	Clearance of H. pylori	Ulcer Recurrence After Healing		
				H. pylori Still Present	H. pylori Eradicated	Total
146	Cim[a]	Immediately	17%	11/14	1/4	12/18 (67%)
	CBS[b]		52%	8/10	3/11	11/21 (52%)
147	Cim[c] ± T[d]		2%	30/34	0/1	30/35 (86%)
	CBS[e]	2 wks	32%	7/8	1/7	8/15 (53%)
	CBS[e] + T[d]		74%	0/2	5/18	5/20 (25%)
137	CBS[f]	4 wks	10%	16/19	0/2	16/21 (76%)
	CBS[f] + A[g] + M[h]		88%	1/2	0/15	1/17 (6%)

[a] Cimetidine 400 mg b.i.d. x 6 wk
[b] Colloidal bismuth subcitrate 120 mg q.i.d. x 6 wk

[c] Cimetidine 400 mg b.i.d. x 8 wk
[d] Tinidazole 500 mg b.i.d. x 10 days
[e] Colloidal bismuth subcitrate 120 mg q.i.d.x 8 wk

[f] Colloidal bismuth subcitrate 120 mg q.i.d. x 4 wk
[g] Amoxicillin 375 mg t.i.d. x 4 wk
[h] Metronidazole 500 mg t.i.d. x 10 days

These results are certainly provocative. However, I believe strongly that it is premature to conclude that eradication of *H. pylori* will result in a reduction in ulcer recurrence, much less a cure of the disease. The sample sizes of the studies so far remain relatively small, the studies were poorly blinded, follow-up was for just one year, and by that time ulcers had recurred in up to 25-30% of patients in whom *H. pylori* had supposedly been eradicated. Even if these results are validated in future well-blinded, long-term studies with larger sample sizes, it may be difficult to prove that it is eradication of *H. pylori* and not some intrinsic effect of therapy on epithelial cell integrity that accounts for the prolonged remission from ulcer. Bismuth itself has many other salutary properties apart from those affecting *H. pylori* (148-150), and the metal may persist in the body for months after ulcer healing (151). Indeed, long term, low-dose maintenance therapy with bismuth, which has no effect on *H. pylori*, significantly reduces the rate of ulcer recurrence (152,153). Against this argument is the observation from the studies listed in Table 10 that bismuth-treated patients in whom *H. pylori* was not eradicated experienced a "normal" rate of ulcer recurrence. One final confounding issue is the suggestion that antibiotics may have "cytoprotective" properties independent of any effect on *H. pylori* (154).

Conclusions

H. pylori may be the most common human gastrointestinal infection and is the most frequent cause of gastritis. Furthermore, a persuasive argument can be made that, while most individuals have no health problems related to *H. pylori* gastritis, a subset develop non-ulcer dyspepsia or peptic ulceration. Why some develop ulcers, but most do not, is likely related to other factors which have been suggested as important in the pathogenesis of peptic ulcer (eg., non-steroidal anti-inflammatory drugs, smoking, acid hypersecretion). On the other hand, it remains possible that *H. pylori* gastritis and peptic ulcer are associated, but not causally. Until more data are available, and because antibiotic therapy may lead to side effects (eg., pseudomembranous colitis) or drug-resistance, attempts at eradicating *H. pylori* as therapy for peptic ulcer or non-ulcer dyspepsia should be limited to randomized, controlled trials.

Having said that, it would be naive to believe that there will not be instances where physicians who cannot enroll their patients with *H. pylori* gastritis in controlled trials will be tempted to go ahead and treat the infection. For example, there may be the patient with non-ulcer dyspepsia and *H. pylori* gastritis who has failed all other forms of therapy but remains debilitatingly symptomatic, or the patient with severe recurrent ulcer disease who is unable or unwilling to undergo surgery or adhere to maintenance therapy. While I would again urge restraint, if a decision is made to attempt eradication of *H. pylori*, the following suggestions are offered:1) Inform the patient of the potential side-effects of antibiotic therapy; 2) Obtain a gastric mucosal biopsy for culture of *H. pylori* to determine antibiotic sensitivities; 3) If the organism is sensitive to metronidazole, treat with metronidazole, 250 mg t.i.d., plus bismuth (Pepto-Bismol, 525 mg q.i.d. or DeNol, 120 mg q.i.d.) for four weeks (138); 4) If the patient's organism is resistant to metronidazole, substitute amoxicillin, 500 mg t.i.d; 5) Check for eradication of *H. pylori* with a biopsy or breath test four to six weeks after cessation of therapy.

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