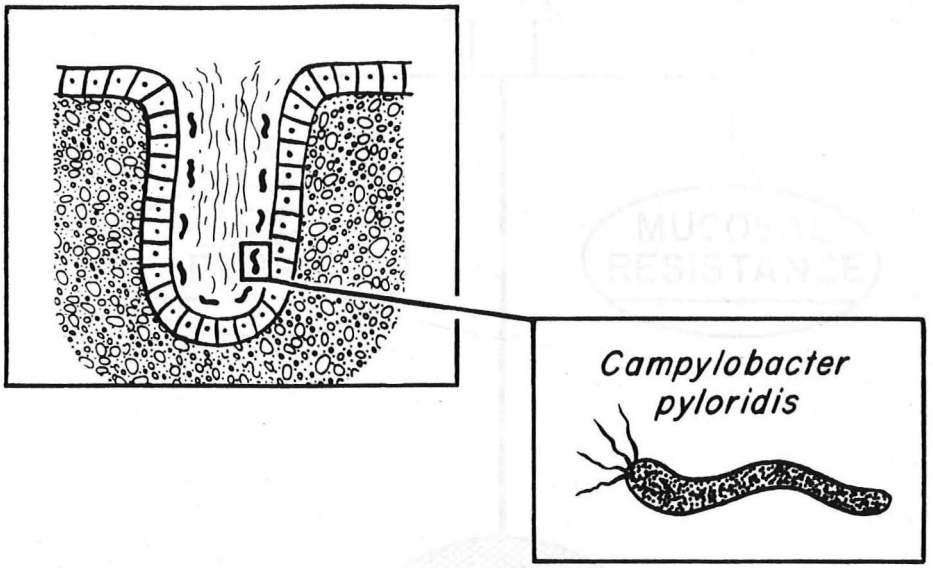
PEPTIC ULCER–
AN INFECTIOUS DISEASE?



MEDICAL GRAND ROUNDS
SOUTHWESTERN MEDICAL SCHOOL

Walter L. Peterson, M.D.

April 2, 1987

Acid and pepsin are present in abundance in the normal human stomach and duodenum. The epithelial cells of the stomach and duodenum are protected from the damaging effects of acid and pepsin by a "balancing" mechanism of mucosal resistance (Figure 1). As long as this balance remains in effect, epithelial integrity remains intact. Whenever this balance shifts, however, a peptic ulcer

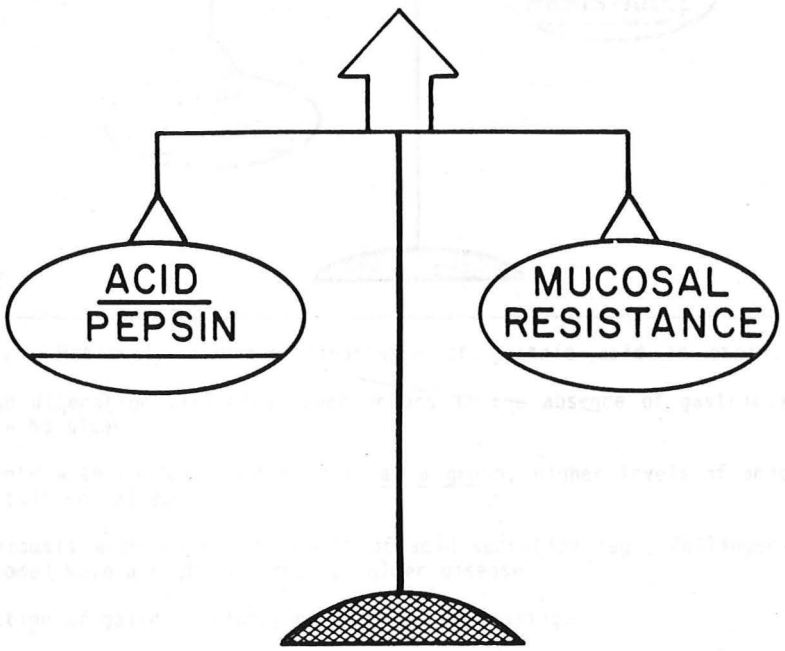


Figure 1. Balance between acid-pepsin and mucosal resistance.

may occur (Figure 2). Stated simply, the normal balance may shift because of excess levels of acid and pepsin, reduced mucosal resistance, or both. Traditional teaching has emphasized the importance of acid (and pepsin) as the cause of this imbalance (Table 1). However, it is clear that acid and pepsin alone are, in most instances, inadequate to produce a peptic ulcer. The evidence against acid and pepsin as the only important factor in peptic ulcer is shown in Table 2. Recently, investigative efforts have been directed toward 1) what constitutes mucosal protection and 2) how it is disrupted to produce ulceration.

PATHOGENESIS OF PEPTIC ULCER

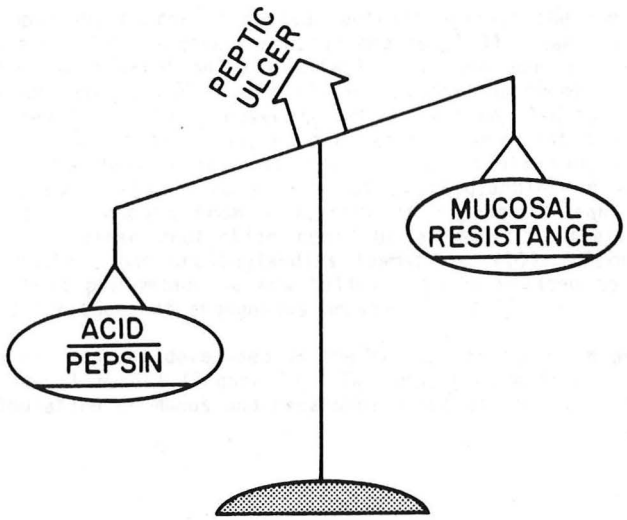


Figure 2.

Table 1. Rationale for the importance of gastric acid in peptic ulcer.

- Benign ulceration virtually never occurs in the absence of gastric acid (No acid - No ulcer)
- Patients with duodenal ulcer have, as a group, higher levels of acid secretion than normal subjects.
- Individuals with very high levels of acid secretion (eg., Zollinger-Ellison Syndrome) have a high incidence of ulcer disease
- Reduction of gastric acidity promotes ulcer healing.

Table 2. Evidence against acid as the only important factor in peptic ulcer.

- Most patients with duodenal ulcer have, as individuals, normal levels of acid secretion.
- Patients with gastric ulcer tend to have levels of acid secretion lower than normal.
- Many individuals with high levels of acid secretion (even Zollinger-Ellison Syndrome) never have peptic ulcer disease.
- Peptic ulcer is an intermittent phenomenon.
- Treatment of ulcers by means other than reducing gastric acidity can promote ulcer healing.

Gastroduodenal Mucosal Protection

The most important factor in mucosal defense against the damaging effects of acid and pepsin may be endogenous prostaglandins (1-3). Early work by Robert showed that prior administration of prostaglandin compounds could prevent the damaging effects on rat gastric mucosa of various noxious agents (4). While it was initially believed that this protective affect was related to the antisecretory affect of prostaglandins (4-6), Robert later showed that the same protective effect could be demonstrated at doses of prostaglandins which did not reduce acid secretion (7-9). The ability of prostaglandins in such doses to prevent damage to rat mucosa from a variety of strong irritants was called "cytoprotection". Similar protection could be accorded by pretreatment with mild irritants, rather than prostaglandins themselves (10). Termed "adaptive cytoprotection", this phenomenon is now believed to be related to the stimulation, by the mild irritant, of endogenous prostaglandins.

Great interest has now developed in the mechanisms by which prostaglandins protect gastroduodenal mucosa (Figure 3). Two important effects of prostaglandins are the stimulation of mucus and bicarbonate secretion (11). As shown in

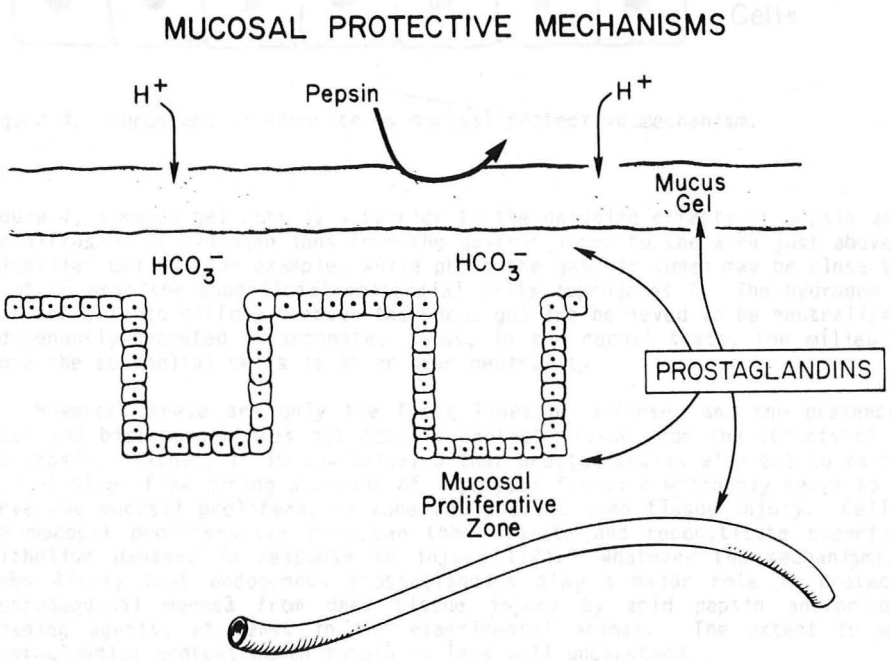


Figure 3. Prostaglandin-mediated mucosal protective mechanisms.

MUCOSAL RESISTANCE TO ACID AND PEPSIN

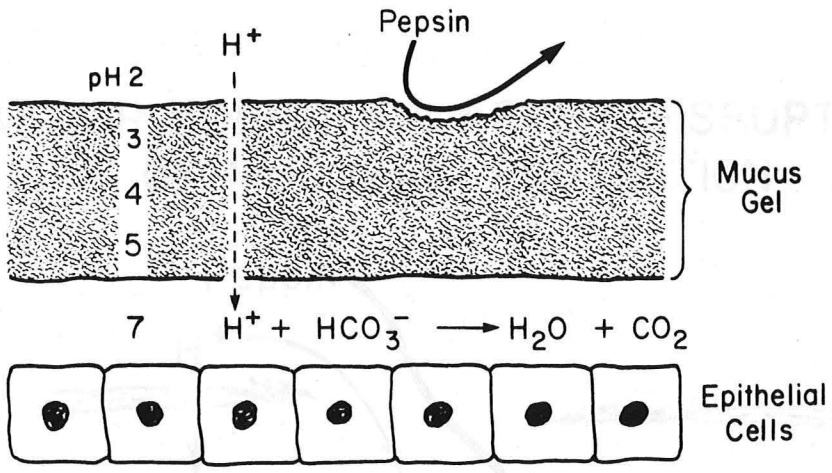


Figure 4. Mucus and bicarbonate as mucosal protective mechanism.

Figure 4, a mucus gel acts as a barrier to the damaging effects of pepsin and to the diffusion of hydrogen ions from the gastric lumen to the area just above the epithelial cells. For example, while pH in the gastric lumen may be close to 2, pH at or near the superficial epithelial cells approaches 7. The hydrogen ions that are able to diffuse through the mucus gel are believed to be neutralized by endogenously-secreted bicarbonate. Thus, in the normal state, the milieu just above the epithelial cells is at or near neutrality.

However, these are only the first lines of defense, and the presence of mucus and bicarbonate does not totally protect tissue from the effects of acid and pepsin. Rather, it is now believed that prostaglandins also act to maintain mucosal blood flow during a period of injury, a function which may serve to preserve the mucosal proliferative zone and prevent deep tissue injury. Cells in the mucosal proliferative zone can then migrate and reconstitute superficial epithelium damaged in response to injury (12). Whatever the mechanisms, it seems likely that endogenous prostaglandins play a major role in protecting gastroduodenal mucosa from deep tissue injury by acid pepsin and/or other damaging agents, at least in the experimental animal. The extent to which prostaglandins protect human mucosa is less well understood.

Disruption of Mucosal Protection

Attention of investigators has now turned to the mechanisms by which mucosal protection is disrupted permitting the formation of a peptic ulcer (Figure 5).

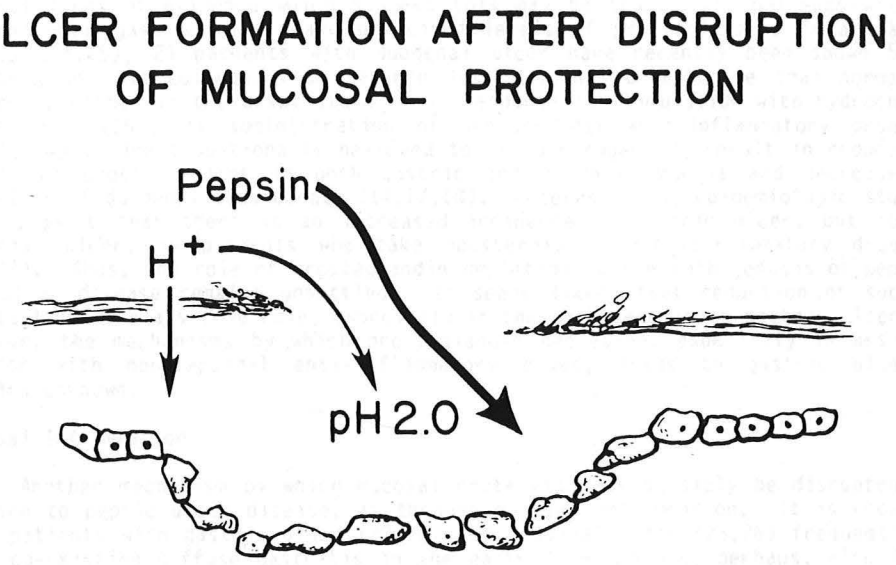


Figure 5.

Reduction of Endogenous Prostaglandins.

In light of the presumed importance of endogenous prostaglandins in protecting gastroduodenal mucosa from damage, it is not surprising that the leading theory for the disruption of mucosal protection involves a depletion of endogenous prostaglandins. Results from experiments conducted by Drs. Redfern and Feldman of our group support this hypothesis. In their experiments, rabbits who were actively immunized with various prostaglandins frequently developed perforating peptic ulcers (13). Such ulceration did not occur in animals who

were immunized with vehicle alone. They have extended their observations by demonstrating that rabbits who are passively immunized with antibodies to prostaglandins will also develop peptic ulceration. A likely hypothesis to explain their results is that these antibodies bind to tissue prostaglandins and functionally deplete the mucosa of endogenous prostaglandins. Such mucosa may then be less able to withstand the damaging influences of acid and pepsin, leading to a peptic ulcer.

In man, evidence that depletion of endogenous prostaglandins is important in disrupting mucosal protection remains inconclusive. There are, however, several lines of evidence which suggest this may be true: 1) patients with duodenal and gastric ulcer have decreased levels of prostaglandins in antral mucosa (14,15); 2) patients with duodenal ulcer have recently been shown by Isenberg and his colleagues to secrete less duodenal bicarbonate than normal controls, either in the basal state or in response to stimulation with hydrochloric acid (16); 3) administration of nonsteroidal anti-inflammatory drugs (NSAID) which are traditionally believed to be "ulcerogenic", result in reduced levels of prostaglandins in both gastric and duodenal mucosa and decreased secretion of duodenal bicarbonate (14,17,18). Interestingly, epidemiologic studies suggest that there is an increased incidence of gastric ulcer, but not duodenal ulcer, in patients who take nonsteroidal anti-inflammatory drugs (19-22). Thus, the role of prostaglandin depletion in the pathogenesis of peptic ulcer disease remains unsettled. It seems likely that reduction of such prostaglandins plays some role, especially in the pathogenesis of gastric ulcer. However, the mechanisms by which prostaglandin depletion, especially in association with nonsteroidal anti-inflammatory drugs, leads to gastric ulcer remains unknown.

Mucosal Inflammation

Another mechanism by which mucosal protection may possibly be disrupted, leading to peptic ulcer disease, is through mucosal inflammation. It is known that patients with gastric ulcer (23-26) and duodenal ulcer (23,26) frequently have co-existing diffuse gastritis in the gastric antrum and, perhaps, also in metaplastic gastric tissue in the duodenum. Several hypotheses are now being proposed to account for such gastritis, which may predispose the patient to the development of a peptic ulcer. The first of these, not surprisingly, involves the reduction of endogenous prostaglandins. This has been studied both in the rabbit model mentioned above (13) and, in a very few papers, in response to nonsteroidal anti-inflammatory drugs. Reduction of endogenous prostaglandins through the antibody model mentioned above, while leading to peptic ulceration, appears not to produce a diffuse mucosal inflammatory process (S. Redfern, personal communication). Thus, reduction of prostaglandins per se, may not lead to antral gastritis. Nonsteroidal anti-inflammatory drugs, on the other hand, have been widely assumed to be a major cause of "gastritis". However, most of these studies have involved endoscopic examination of gastroduodenal mucosa rather than histologic examination. Work by Cohen and MacDonald (27) suggest that nonsteroidal anti-inflammatory drugs, particularly aspirin, produce focally severe histologic mucosal damage but only very mild diffuse damage. In fact, MacDonald reported in 1973 that gastric ulcers which developed in patients taking large quantities of aspirin were much less likely to have diffuse histologic gastritis than gastric ulcers in patients who were not aspirin users (28). Recently, our group has examined the issue of NSAID-induced gastritis in normal subjects (18,29).

Twenty-three healthy volunteers were randomly assigned to receive either a placebo (N=11) or indomethacin 50 mg (N=12) three times a day for three days.

On the fourth day subjects underwent endoscopy at which time pinch biopsies were taken from the gastric fundus and antrum. The severity of acute histologic gastritis was determined blindly with hematoxylin and eosin stain. Acute gastritis, usually mild, was found in the fundus in two subjects taking placebo and three taking indomethacin. In the antrum, three of the eleven (27%) placebo-treated patients had antral gastritis, compared to six of twelve (50%) subjects indocin. While there was a trend toward an increased incidence of antral gastritis in subjects who took indomethacin, the difference did not achieve statistical significance.

In summary, there is an association between the presence of antral gastritis and both gastric and duodenal ulcer, although importance in terms of pathogenesis remains uncertain. Also unclear is the role of nonsteroidal anti-inflammatory drugs in producing either gastritis and/or peptic ulcer disease.

Recently, a new player has entered this arena, with the suggestion that an infectious agent may be responsible not only for the development of antral gastritis, but may play a role in the pathogenesis of gastric and duodenal ulcer.

Gastric Spiral Bacteria

- Historical Perspective -

There has been a long interest in the bacteriology of the stomach in general, and in spiral organisms in particular (30,31). Table 3 lists a number of papers, beginning in 1893, which discuss the issue of spiral organisms in

Table 3

Year	Ref	Investigator	
1893	32	Bizzozero	Spirochetes in dog gastric mucosa
1896	34	Solomon	Spirochetes in ulcerating gastric cancer in man
1905	34	Hoffman	Spirochetes limited to necrotic surface of gastric cancer; do not enter tissue
1919	33	Kasai	Spirochetes in various mammals
1920	32	Lim	Spirochetes in cats
1936	34	Cowdry	Spirochetes in rhesus monkeys
1939	34	Doenges	Spirochetes in gastric pits of 43% of routine autopsies
1940	35	Freedburg	Spirochetes in 37% of fresh stomachs, usually with cancer or ulcer
1954	32	Palmer	Reviewed 1180 biopsy specimens stained with H & E. He found "no structure which could reasonably be considered to be of spirochetal nature
1970	36	Lockard	EM of spirochete from dog gastric mucosa
1975	37,38	Steer	Bacteria in patients with gastric ulcer
1979	39	Fung	Bacteria associated with gastritis
1983	40,41	Warren & Marshall	Curved bacilli in patients with gastritis
1874	44	Steer	Bacteria in patients with duodenal ulcer
1984	45	Rollason	Spiral organisms in human stomach

Figure 6. Spiral bacteria found in a patient with chronic gastritis (ref. 35).

gastric mucosa. Figure 6 shows an example of the spiral organism found by Freedberg in sections of fresh stomach, usually from patients undergoing surgery for cancer or peptic ulcer disease (35). In 1954, Palmer reviewed 1180 biopsy specimens stained with hematoxylin and eosin (32). He found "no structure which could reasonably be considered to be of spirochetal nature." He postulated that all previous reports of spiral organisms represented contaminants of pathologic specimens, and that such organisms did not exist in living tissue. Silver stains were not employed. Biopsy specimens from dog gastric mucosa were examined with electron microscopy by Lockard in 1970. An example of the organisms that he found are shown in Figure 7.

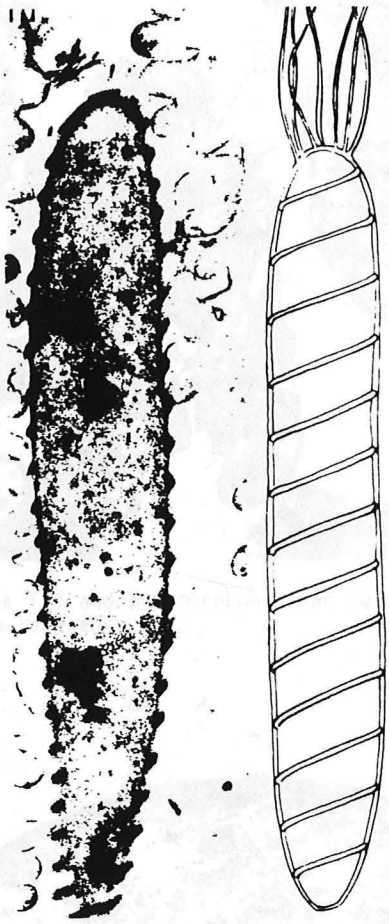


Figure 7. Micrograph and drawing of spiral organism found in gastric mucosa of the dog (From reference 36).

In 1975, Steer described bacteria in close proximity to gastric mucosa in association with gastritis, but not on normal tissue (37,38). Representative illustrations from his two papers are shown in Figures 8-11. Although these organisms were most likely spiral in nature, this was not commented on.

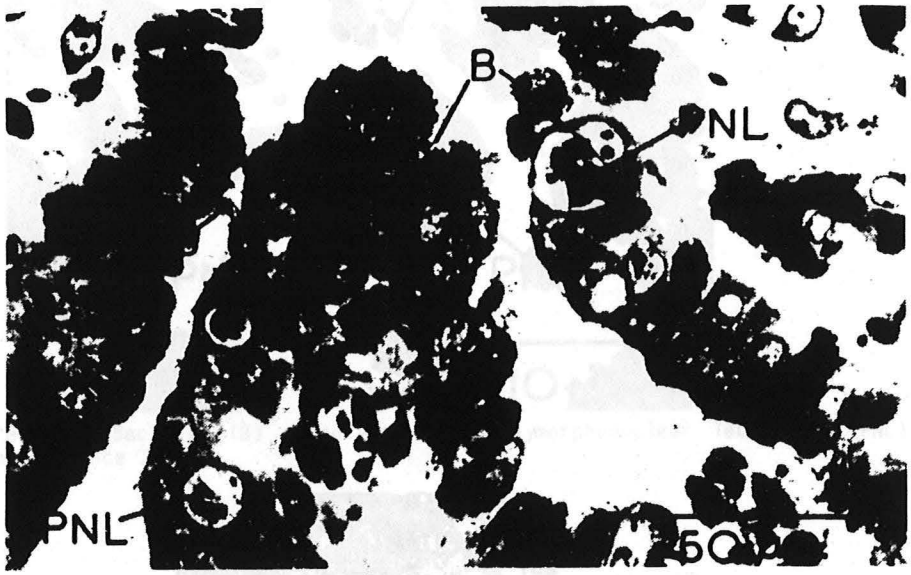


Figure 8. Bacteria (B) and polymorphonuclear leucocytes (PNL) in patient with gastric ulcer (From reference 37).

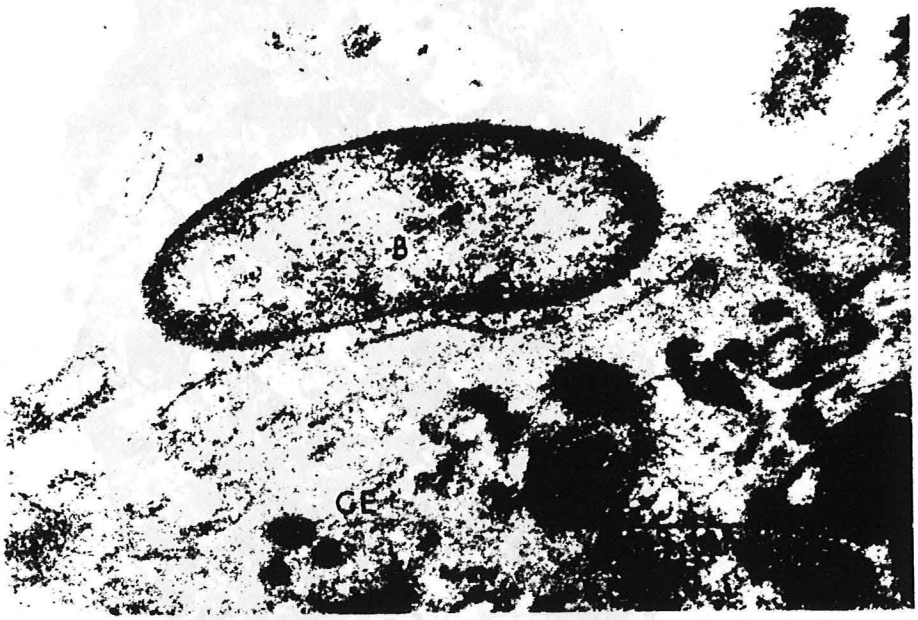


Figure 9. Bacterium (B) apposed to mucus secreting cell of gastric epithelium (GE) (From reference 38).

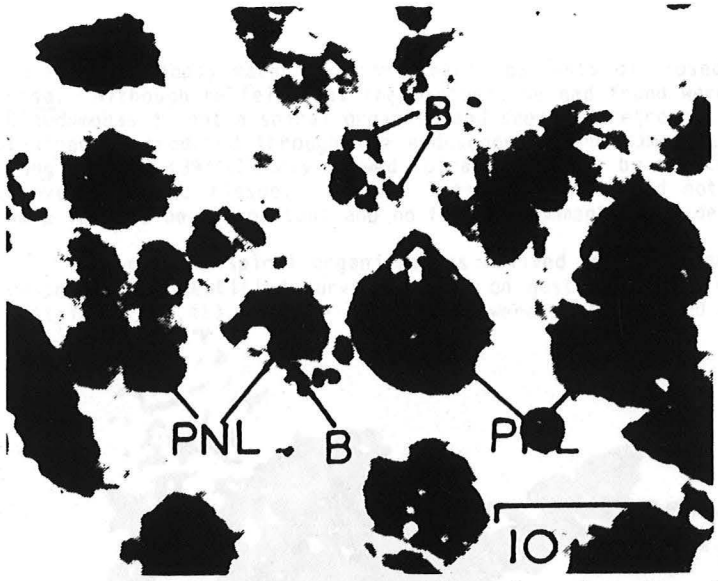


Figure 10. Bacteria (B) phagocytosed by polymorphonuclear leucocytes (PNL) (From reference 37).

Figure 11. PNL lying in gastric lumen with bacterium (B) phagocytosed by cell (From reference 38).

Culture of biopsy material from Steer's patients disclosed Pseudomonas aeruginosa. Although he felt that the bacteria he had found were indeed Pseudomonas, Pseudomonas is not a spiral organism and seems in retrospect to have been a contaminant introduced through the endoscope at the time of biopsy. A paper by Fung in 1979 (39) clearly showed spiral organisms by electron micrography lying above gastritic tissue. Because these organisms did not invade tissue, they were felt to be unimportant and no further comment was made.

Interest in spiral organisms was revived in 1983 when Warren and Marshall described "unidentified curved bacilli on gastric epithelium in active chronic gastritis" (40,41), (Figure 12). These were small, curved and S-shaped bacteria

Figure 12. Curved bacilli on gastric epithelium (From reference 40).

which were difficult to see with H & E stain but stained well with a special silver stain, the Warthin-Starry stain. Culture of involved tissue revealed growth of an organism which had many characteristics of Campylobacter species (41). Because of this, these organisms were named Campylobacter pyloridis (42), a name which has now received official recognition (43). At about this same time, Steer submitted a paper describing electron microscopic findings in gastroduodenal mucosa of patients with duodenal ulcer (44). Several important points were made in his paper: 1) the organisms were clearly kidney or S-shaped; 2) they were located under a mucus layer, in the gutters between cells (Figure 13); and 3) the organisms were associated only with gastric epithelium, either in the stomach or in the duodenum (Figure 14). Bacteria were never seen in association with intestinal type epithelial cells. Finally, at about the same time, Rollason and his colleagues submitted a paper which demonstrated spiral bacteria associated with gastritis in a large number of gastric biopsy specimens (45).

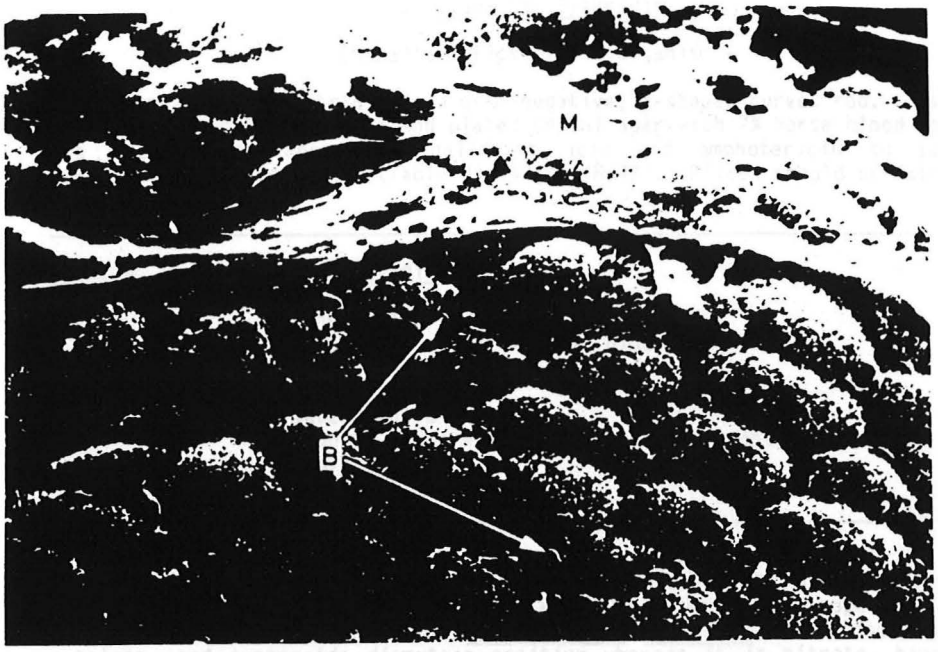


Figure 13. Spiral bacteria (B) under mucus (M) layer in gutters of epithelial cells (From reference 44).

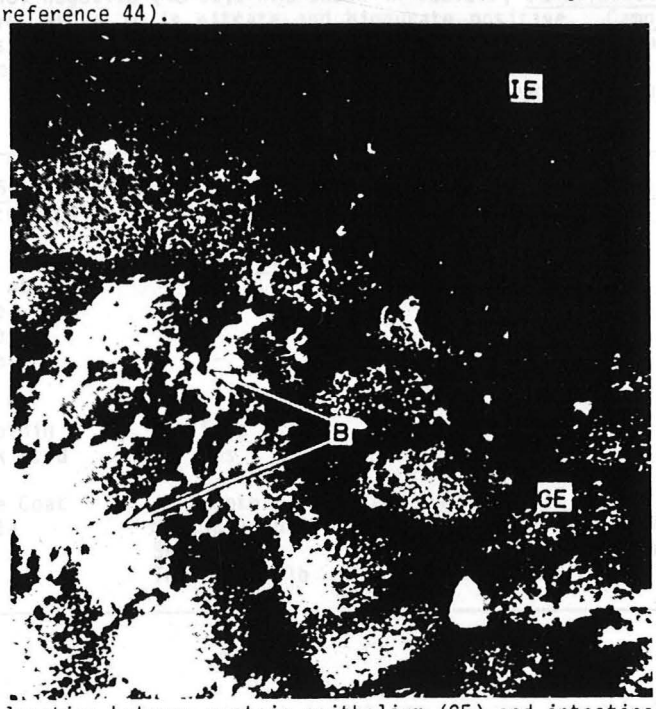


Figure 14. Junction between gastric epithelium (GE) and intestinal-type epithelium (IE). Bacteria (B) are only on GE (From reference 44).

Campylobacter Pyloridis

- Characteristics of the Organism -

Campylobacter pyloridis is a gram-negative, S-shaped curved rod. Tissue to be cultured should be ground and plated on BHI agar with 7% horse blood to which has been added vancomycin, nalidixic acid and amphotericin to suppress overgrowth of contaminants (Table 4) (42,43,46,47). Plates should be moist and

Table 4. Culturing C. pyloridis.

- Grind tissue
- Use BHI agar with 7% horse blood - add vancomycin, nalidixic acid, and amphotericin.
- Plates should be moist
- Incubate under microaerophilic conditions at 37°

should be incubated under microaerophilic conditions at 37°C. (The organism will not grow at 42°). After two to three days, the organism will appear as 1-2 mm translucent, greyish colonies. Campylobacter pyloridis is oxidase, urease, catalase, and superoxide dismutase positive whereas it is nitrate, hippurate, and indol negative (48-51). As shown in Table 5, Campylobacter jejuni is urease negative, while it is nitrate and hippurate positive. Campylobacter pyloridis is sensitive to erythromycin, tetracycline, gentamycin, cephalothin, penicillin, and amoxicillin; it is resistant to nalidixic acid and Bactrim. Campylobacter jejuni on the other hand is resistant to erythromycin, cephalothin, penicillin,

Table 5. Characteristics of Campylobacter pyloridis, Campylobacter jejuni, and Gastric Campylobacter-Like Organism-2 (GCLO-2)

	C. pyloridis	C. jejuni	GCLO-2
Growth at 42°	-	+	-
Oxidase	+	+	+
Nitrate	-	+	-/weak
Hippurate	-	+	+
Urease	+	-	-
Cephalothin	Sens	Res	Sens
Nalidix Acid	Res	Sens	Sens
Surface Coat	Smooth	Rough	-
Flagella	Multiple (unipolar)	Single (bipolar)	Single (unipolar)
	Sheathed	Unsheathed	Unsheathed
	Terminal bulb	No terminal bulb	-

and amoxicillin, while it is sensitive to nalidixic acid and Bactrim (42,43,52-54). Ultrastructurally, Campylobacter pyloridis is 0.5 x 3 um in dimension with 1-2 spirals (42, 43, 55-57). Its surface is smooth and there are 4-6 sheathed, usually unipolar, flagella with terminal bulbs (Figure 15). Campylobacter jejuni, on the other hand, has a rough coat, has pits at the

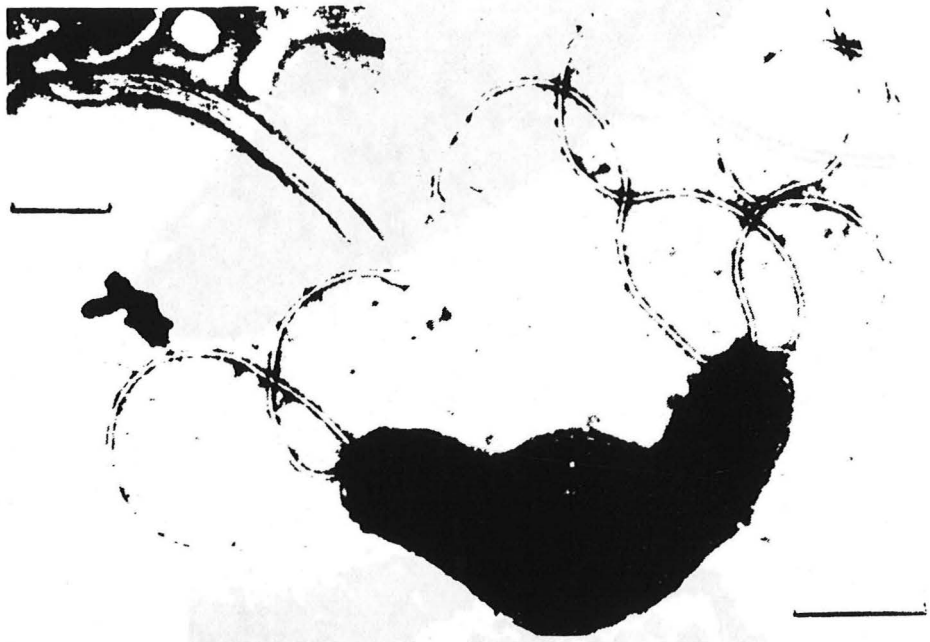


Figure 15. Electron photomicrograph of C. pyloridis (From reference 41).

polar ends, and has single, usually bipolar, flagella without terminal bulbs (Figure 16). Although it became clear early on that C. pyloridis was a true spiral bacteria, rather than a spirochete, it was not certain if the organism was more closely related to campylobacter, spirillum, or vibrio species.

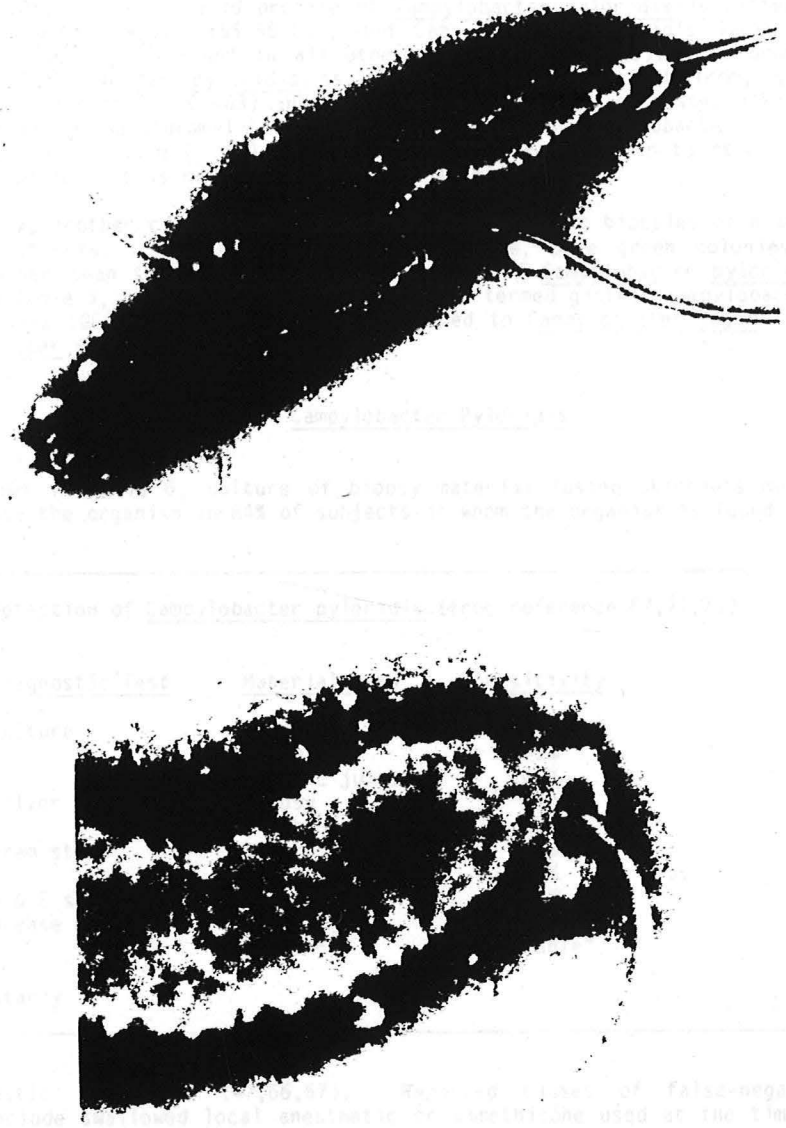


Figure 16. Electron photomicrographs of C. jejuni. Note rough coat, polar pit, and single, bipolar flagella without terminal bulbs (From reference 56).

Thus, other comparisons have been made between Campylobacter pyloridis and other campylobacters. The DNA base composition (guanine plus cytosine) of C. pyloridis is in the campylobacter range, rather the spirillum or vibrio range (43). However, the fatty acid profile of Campylobacter pyloridis is different from Campylobacter jejuni (55,58,59), and Campylobacter pyloridis lacks the methylated menaquinone-6 found in all other Campylobacters (60). The protein profile of Campylobacter pyloridis is similar to, but distinct from, other reference campylobacters (61-63) and Campylobacter pyloridis possesses alkaline phosphatase and gamma-glutamyl transpeptidase while other campylobacters do not (50,60,63). Thus, while C. pyloridis has many features similar to other campylobacter species, it is not a "true" campylobacter.

Recently, another curved rod has been found in gastric biopsies of a small number of patients. This organism produces opaque, pale green colonies on culture, rather than the translucent grey colonies of Campylobacter pyloridis. As shown in Table 5, this organism, which has been termed gastric campylobacter-like organism-2 (GCLO-2), is more closely related to Campylobacter jejuni than to Campylobacter pyloridis.

- Detection of Campylobacter Pyloridis -

As shown in Table 6, culture of biopsy material (using Skirrow's media) will disclose the organism in 84% of subjects in whom the organism is found by

Table 6. Detection of Campylobacter pyloridis (from reference 67,71,73)

Diagnostic Test	Material Used	Sensitivity
Culture	biopsy	84%
	brushings	63%
	gastric juice	40%
Silver Stain*	biopsy	90%
	brushings	86%
Gram stain	biopsy	81%
	brushings	91%
H & E stain	biopsy	77%
Urease	biopsy	91%
	breath ^{13}C	"reliable"

* Warthin-Starry

any diagnostic techniques (47,66,67). Reported causes of false-negative cultures include swallowed local anesthetic or simethicone used at the time of endoscopy, prior administration of antibiotics, use of a histamine H_2-receptor antagonist, contamination of biopsy forceps with glutaraldehyde, biopsies which do not contain gastric mucosa, and biopsies where there are few bacteria present (66). In addition, biopsies which are kept at room temperature for 3 or more hours cannot be reliably cultured for Campylobacter pyloridis. (The tissue can

be kept safely at 4°C for up to 5 hours). Culture plates which are two or more weeks old or are too dry, or incubation at low humidity at a temperature above 37° will result in poor or no growth.

The organism can also be diagnosed microscopically (67-70). As shown in Table 6, use of a silver stain or gram stain of either biopsy or brushing material will detect Campylobacter pyloridis in most instances. Gram stain of a brush specimen is a convenient way of detecting C. pyloridis, especially when the organism is present in abundant numbers (Figure 17). While the hematoxylin

Figure 17. Photomicrograph of gastric brush specimen stained with Gram stain (From reference 67).

and eosin stain is of less sensivity, other investigators have suggested the use of Giemsa or acridrine-orange stains or use of phase contrast microscopy (69,70).

An indirect way of detecting the presence of C. pyloridis is to take advantage of the abundant urease the organism produces (71-73). This can be accomplished either by placing a crush biopsy into a urea medium and noting a color change over time (71,72), or, as shown in Figure 18, utilizing a carbon 13 urea breath test (73).

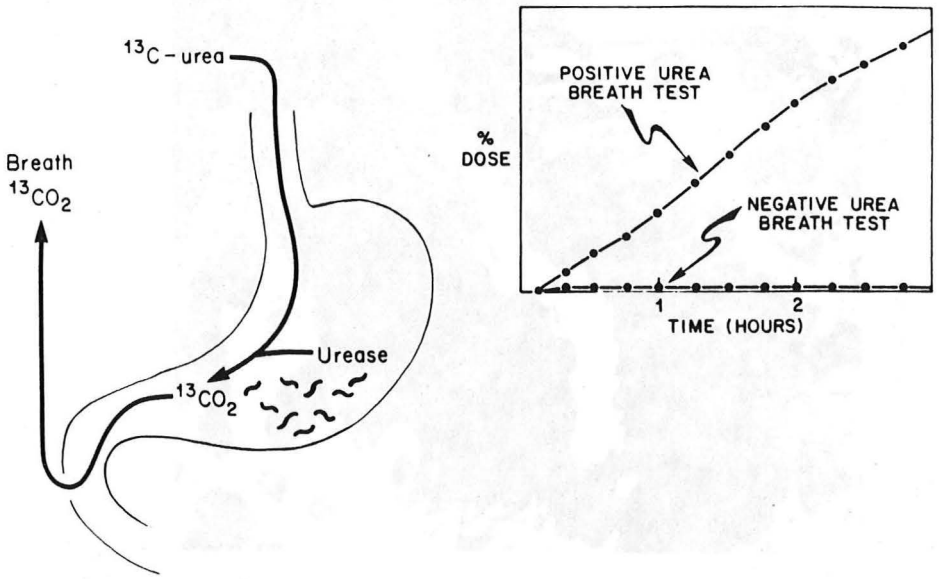


Figure 18. ^{13}C-urea breath test (Inset from reference 73).

- Correlation of Campylobacter Pyloridis with Mucosal Histolgy -

Review of the available literature permits one to make several conclusions regarding the correlation of C. pyloridis with mucosal histology: 1) Campylobacter pyloridis is found only on gastric epithelium and not intestinal epithelium (Figures 19-20) (66,74-79); 2) in the duodenal bulb, Campylobacter pyloridis is found in areas of gastric metaplasia (44,74,76,77); and 3) there is a strong correlation between the presence of Campylobacter pyloridis and inflamed mucosa of the antrum (Figure 21) (45,50,77-90). Utilizing biopsy material from patients who present with symptoms of dyspepsia, Campylobacter pyloridis will be found in an average of 74% of patients whose antra discloses histologic gastritis compared to 7% of those whose antra shows no gastritis. In addition, although not all agree (45,81,83,85), it appears that the organism is more closely associated with active gastritis (defined as gastritis with a predominance of polymorphonuclear leucocytes) as opposed to inactive gastritis (Figure 22). Results from one study which compared the density of C. pyloridis in patients with active gastritis to those with inactive gastritis or normal mucosa is shown in Figure 22 (78).

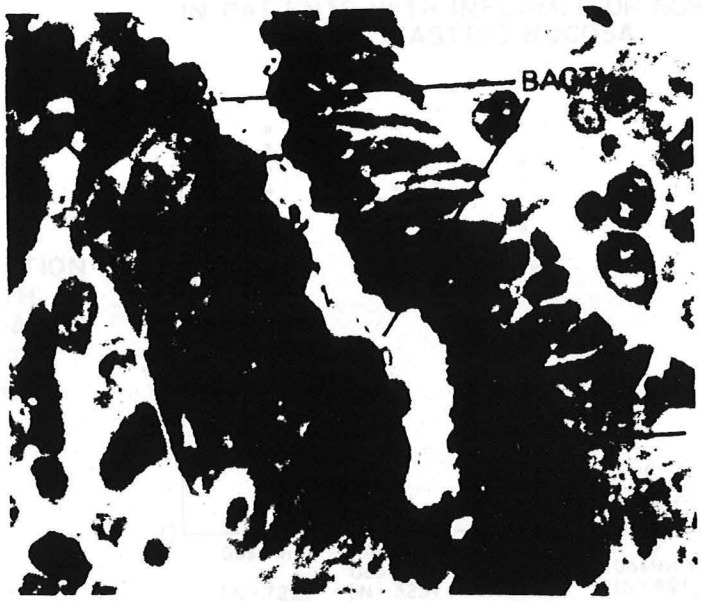


Figure 19. Numerous bacteria (BACT) related to gastric pit epithelium from patient with duodenal ulcer (From reference 76).

Figure 20. Bacteria (BACT) located adjacent to gastric (G), but not intestinal (I)-type epithelial cells (From reference 76).

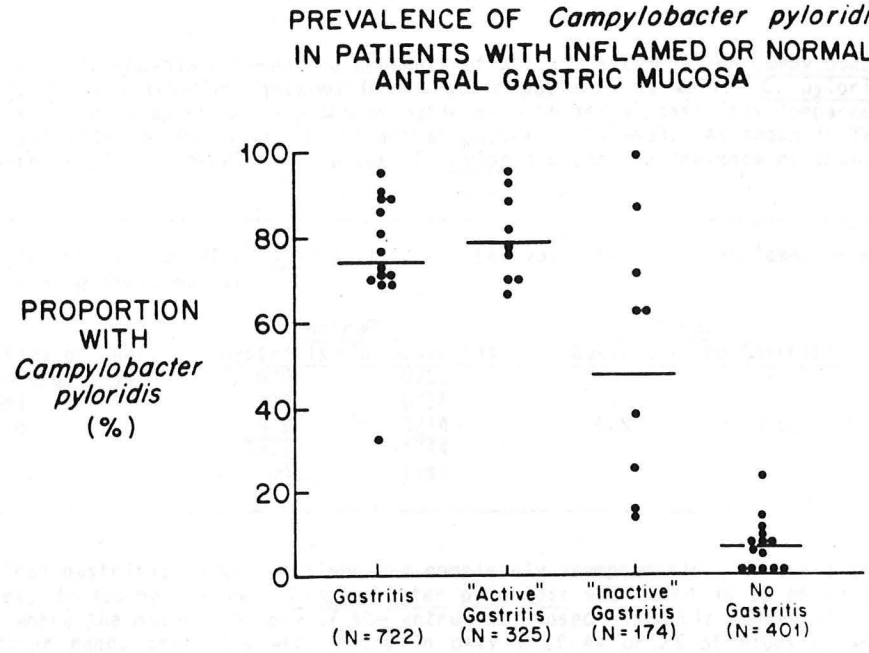


Figure 21.

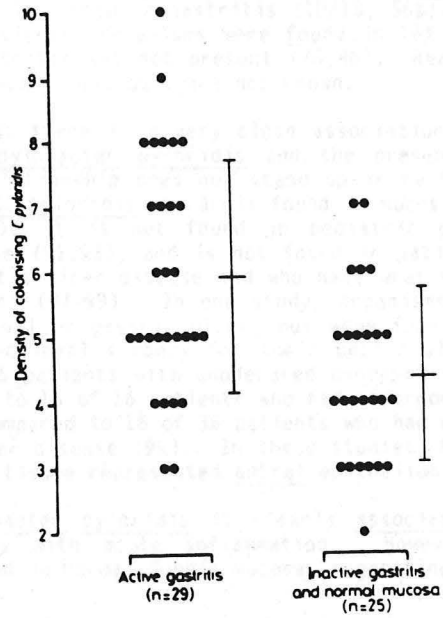


Figure 22. Density of C. pyloridis in biopsy specimens showing active gastritis compared to that of inactive gastritis and normal mucosa (From reference 78).

The relationship between the presence of antral gastritis and Campylobacter pyloridis holds true in symptomatic pediatric patients as well. C. pyloridis will be found in approximately 50% of patients with antral gastritis compared to 3% of patients in whom there is no antral gastritis (91-93). As shown in Table 7, there is also a correlation between C. pyloridis and the presence or absence

Table 7. Prevalence of C. pyloridis in healthy volunteers with inflamed or normal antral gastric mucosa.

		Antrum		Fundus	
Investigator	Ref.	Gastritis	No Gastritis	Gastritis	No Gastritis
Langenberg	50	6/6	0/19	-	-
Barthel	94	3/3	0/11	-	-
Peterson	29	9/9	1/14	5/5	10/18
		18/18	1/44		
		(100%)	(2%)		

of antral gastritis in subjects who are completely asymptomatic. In these three studies, including our own, Campylobacter pyloridis was found in 18 of 18 subjects where the mucosal biopsy of the antrum disclosed gastritis (50,29,94). On the other hand, organisms were found in only 1 of 44 or 2% of biopsies where there was no gastritis seen. We have also examined the relationship between Campylobacter pyloridis and fundic histology in normal subjects. As shown in Table 7, Campylobacter pyloridis was found in all 5 subjects whose fundic biopsy disclosed gastritis. However, the organisms were also frequently found in subjects whose fundic biopsy disclosed no gastritis (10/18, 56%). In two previous studies of symptomatic patients, organisms were found in 16% and 25% of fundic biopsies where active gastritis was not present (78,86). Reasons for the differences between these findings and ours are not known.

While it appears that there is a very close association between the presence or absence of Campylobacter pyloridis and the presence or absence of antral gastritis, this relationship does not stand up in certain patients with gastritis. For example, C. pyloridis is rarely found in mucosa of patients with pernicious anemia (95,96), it is not found in pediatric patients who have gastritis of "known" cause (91,93), and is not found in patients who have had gastric resection for peptic ulcer disease and who have what some investigators consider "reflux gastritis" (97-99). In one study, organisms were found in 46 of 56 patients with duodenal or gastric ulcer, but were found in only 6 of 23 patients who had had resectional surgery for their peptic ulcer disease (98). In another study, 34 of 35 patients with unoperated duodenal ulcer had evidence of C. pyloridis, compared to 15 of 16 patients who had undergone non-resectional parietal cell vagotomy, compared to 16 of 38 patients who had undergone gastrectomy for their peptic ulcer disease (99). In these studies, however, it is not always clear that gastric tissue represented antral epithelium.

In summary, Campylobacter pyloridis is clearly associated with inflamed antral mucosa, especially with acute inflammation. However, Campylobacter pyloridis may also be found in normal fundic mucosa, suggesting that this may be its normal reservoir.

- Relationship of Campylobacter Pyloridis to Gastric Epithelium -

A number of studies have assessed via light and electron microscopy the relationship of Campylobacter pyloridis to epithelial cells. Several points emerge from this literature: 1) bacteria lie singly or in clusters over the luminal surface of gastric epithelium, including the gastric pits (Figures 23

Figure 23. Diagramatic representation of C. pyloridis in gastric pit.

and 24); 2) there is a predilection for mucus-secreting antral epithelium, with organisms lying beneath the mucus layer. Organisms are found in association with intercellular junctions (gutters) (Figures 25-31) of mucus secreting gastric epithelial cells, and can be found wandering deep between cells (44,74-76,85,100-102); 3) abundant phagolysosomes are seen and occasionally organisms can be seen in phagocytic vacuoles or neutrophils (100,103); 4) bacteria are well preserved and do not invade tissue (82,100-102); 5) despite the lack of cellular invasion, there is evidence of cytopathic effects. The surface microvilli are depleted, there is disruption of submucous cytoskeletal supporting microfilaments, intercellular mucin granules are depleted and often confined to apical cytoplasmic protrusions, there is cellular edema, and there is infiltration with polymorphonuclear leucocytes and lymphocytes, with an occasional polymorphonuclear leukocyte crossing the basal lamina to penetrate between epithelial cells (38).

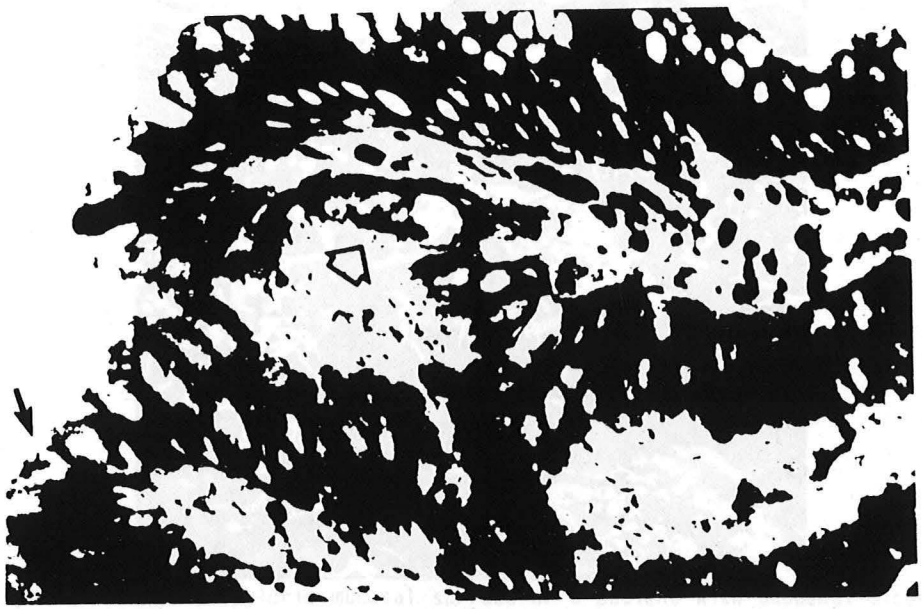


Figure 24. Antral biopsy specimen stained by Warthin-Starry technique, showing colonising C. pyloridis. Organisms are present on surface (arrow) and in upper and deep sections of pits. Both pits contain organisms, although of varying population density. (From reference 78)

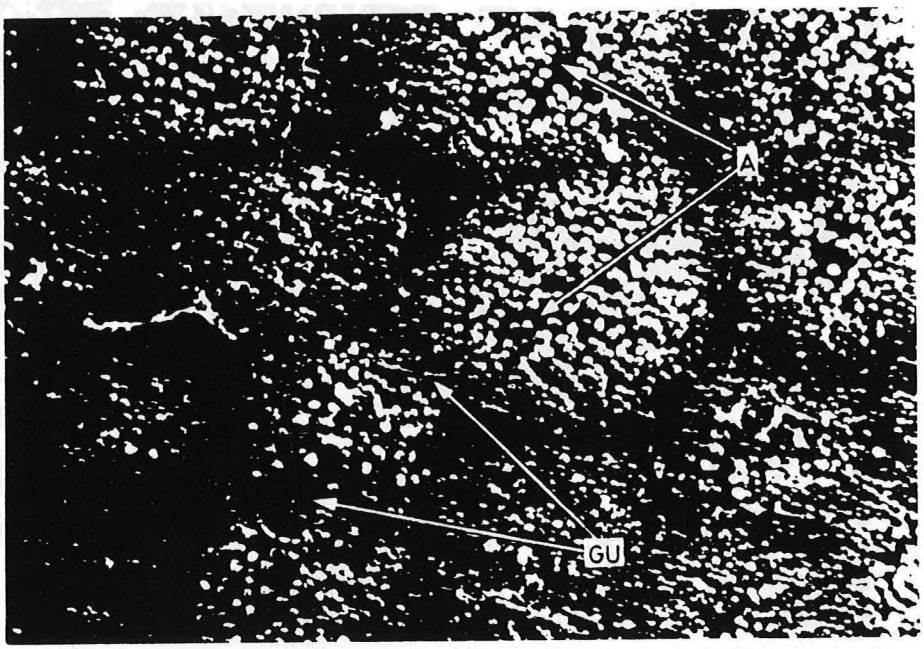


Figure 25. Detailed study of the dome shaped surface of normal gastric epithelial cells showing the densely packed microvilli in the gutters (GU) at the edges of the cells and the less dense microvilli at the apex of the cell surface (A). (From reference 44)

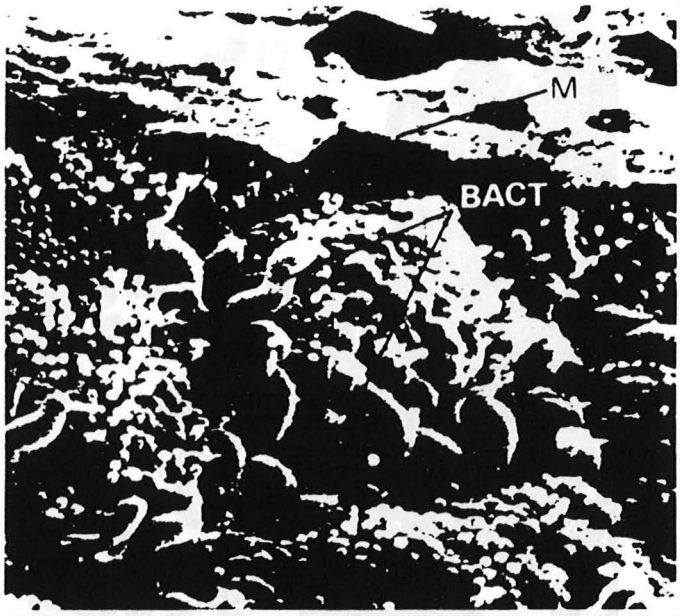


Figure 26. The prepyloric mucosal surface of a patient with duodenal ulceration. The edge of the surface mucus (M) can be seen. Covering the gastric epithelial cells are numerous bacteria (BACT) which are absent from the visible surface of the mucus (From reference 76).

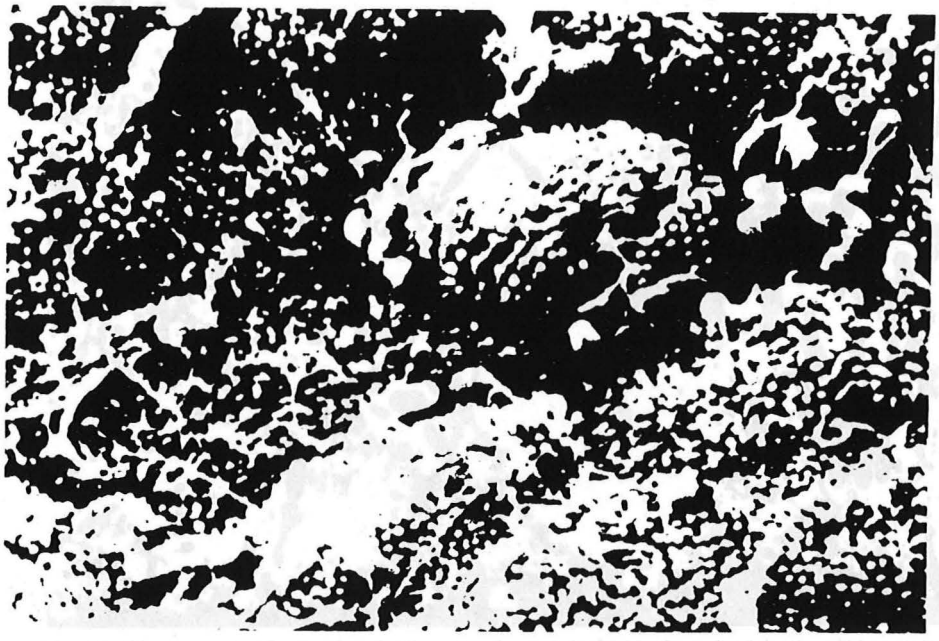


Figure 27. C. pyloridis on the gastric mucosa (From reference 85).

Figure 28. A transmission electron micrograph of numerous bacteria (BACT) apposed to the luminal surface of the gastric-type epithelial cells (From reference 76).

Figure 29. Luminal surface of antral epithelium from patient with gastritis. Clusters of Campylobacter pyloridis lie close to bulging membranes of mucus secretory cells. Note retention of microvilli in isolated bacteria-free pocket (*). M=mucin granules (From reference 102).

Figure 30. Electron micrograph shows the localization of C. pyloridis (P) close to the intercellular junction (arrows) of mucus-secreting gastric epithelial cells. Bacteria can be seen in among the microvilli (MV) (From reference 101).

Figure 31. Transmission electron micrograph showing a curved bacillus with apical flagella (small arrow) deep in the space separating two mucus cells. The junctional complex (TJ) normally seen near the surface (S) is absent. Numerous phagolysomones are seen (large arrow) (From reference 100).

It is not clear exactly how Campylobacter pyloridis maintains its relationship to gastric epithelium. In general, there are three types of mechanisms which permit an organism to "stay put" (104). These include adhesion, surface mucus colonization, and colonization of the deep mucus and crypts. Adhesion has been most carefully studied. For example, E. coli have plasmid-mediated fimbrial antigens (adhesins) which allow the organism to attach to the brush border of the cell by an adherence pedestal from the epithelial cell surface to the outer bacterial wall (105-108). There is no invasion, but as the organism adheres to the epithelial cell, a toxin is released and cell damage ensues. Although some investigators believe that Campylobacter pyloridis adhers to the mucosa by adherence pedestals (Figure 32) (102), others believe that

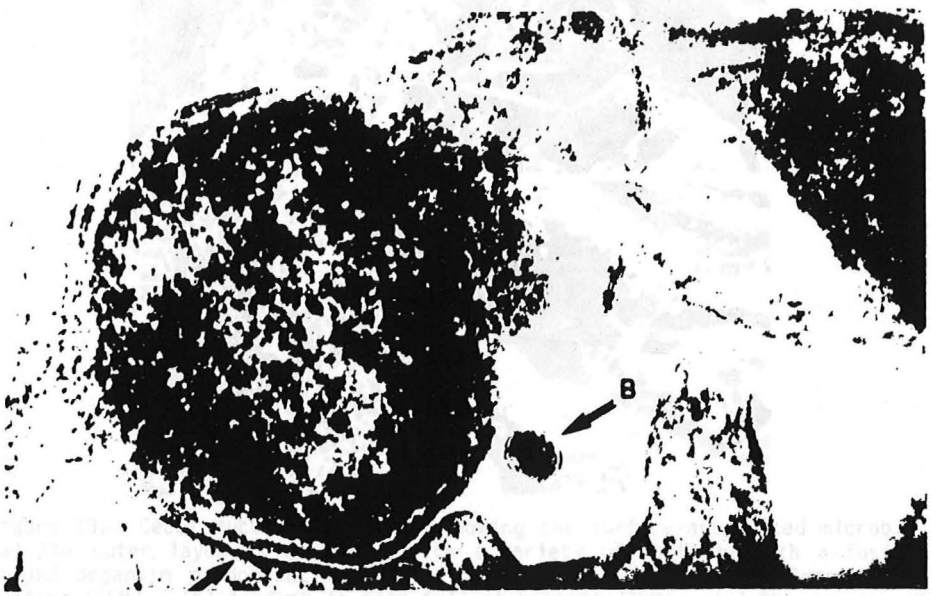


Figure 32. Photomicrograph shows intimate "adherence" between Campylobacter pyloridis and antral cell membrane (arrows). Sectioned terminal bulb (B) is present (From reference 102).

Campylobacter pyloridis is one of the broad group of spiral bacteria that are adapted to the peculiar niche provided by intestinal mucus (101).

Mucus-associated spiral bacteria (borellia, treponema, spirillum) are widespread throughout the animal kingdom and are seen in large numbers in crypts of the small and large intestine of most animal species (Figure 33) (104,109,110). All such organisms are microaerophilic and all possess a spiral

Figure 33. Cecal mucosa of a mouse showing the surface-associated microbiota. (a) The outer layer is colonized with a variety of bacteria with a fusiform-shaped organism predominating; spiral-shaped bacteria are seen closest to the surface (SEM). (b) A crypt is seen full of baceria (TEM). (c) The opening of a crypt shows the closely packed spirals (SEM). (From reference 104).

morphology. If a pathogenic organism possesses these characteristics, it may be able to displace the normal biota and exert its cytotoxic effects. For example, the fact that Clostridium jejuni is microaerophilic and has a spiral morphology may permit it to survive in mucus and exert its pathogenetic capabilities (Figures 34,35) (104).

Figure 34. Cecal mucosa of a mouse treated with antibiotics and magnesium sulfate given C. jejuni (strain Cj. Vic.) by mouth. Inverted back-scatter SEM. Upper. The crypts are seen to be heavily colonized with the spiral-shaped campylobacters. Lower left. Higher-power shot of the left boxed section above. Lower right. Higher-power shot of the right boxed section above (From reference 104).

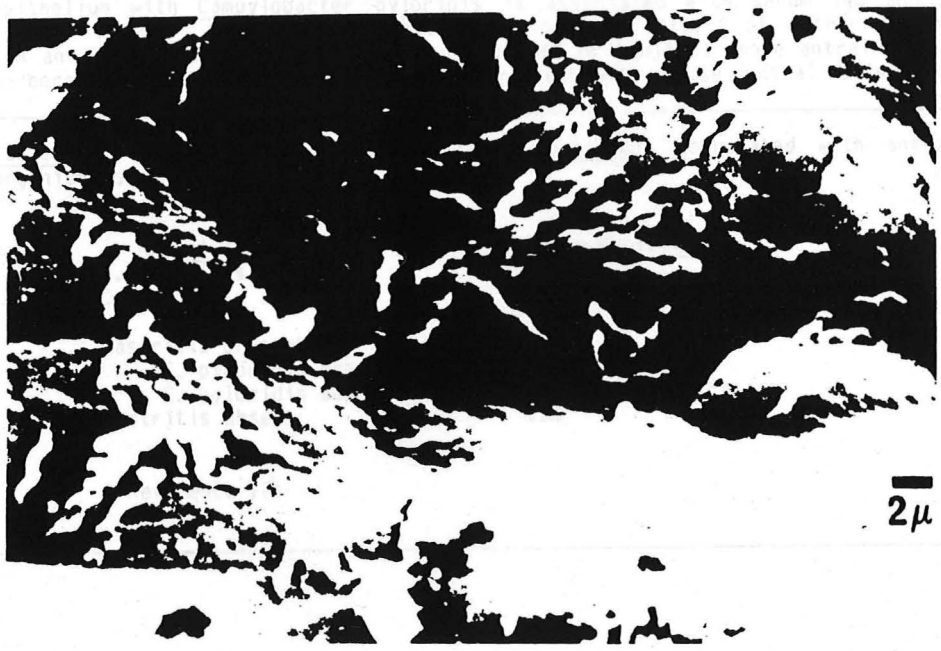


Figure 35. C. jejuni on cecal epithelium of colonized mouse giving the impression of adhesion to tissue (From reference 104).

Hazell and Lee suggest that C. pyloridis acts in a fashion similar to C. jejuni. Support for their hypothesis is that there is no firm evidence of cell invasion or adherence by C. pyloridis, the organism moves very freely in viscus solution, and can be seen to corkscrew rapidly through mucus that impedes conventional rod-shaped organisms. It is interesting to note that Western blot analysis of antigens in spiral-shaped pathogens shows that the only strong cross reaction between Campylobacter pyloridis and other Campylobacter species is with flagellin antigen (111).

Another characteristic of C. pyloridis which may be of importance in its relationship to gastric epithelium involves its high urease activity. (101,112-115) It is postulated that hydrolysis of urea which diffuses across the mucosal wall may raise levels of ammonia and create a more alkaline invironment to protect the organism in the otherwise acidic stomach (101). Analysis of gastric juice from patients who are colonized with C. pyloridis shows increased levels of ammonia and decreased levels of urea compared to subjects who do not harbor Campylobacter pyloridis (114,115). Indeed, urease activity of Campylobacter pyloridis is said to be a thousand times greater than that of Proteus vulgaris, another well known urease-producing organism (116).

Whether or not C. pyloridis adheres to epithelial cells by adherence pedestals or is simply well-adapted to colonize mucus in close proximity to epithelial cells, it is clear that the organisms do not actually invade the epithelial cells. The mechanism by which Campylobacter pyloridis may produce cytopathic effects is not known. It has been speculated that C. pyloridis may produce a toxin.

- Immunologic Response to Campylobacter Pyloridis -

Using complement fixation techniques (83,117) hemagglutination (118) and ELISA techniques (29,87,119-121), it is clear that colonization of antral epithelium with Campylobacter pyloridis is associated with serum IgG and/or IgA antibodies. As shown in Table 8, a "positive titer" of either IgG or IgA antibodies to C. pyloridis is found in 86% of subjects whose antral tissue harbors the organism compared to 20% of subjects whose antral tissue is

Table 8. Serum antibody response to C. pyloridis correlated with antral organisms or antral histology.

Antral Tissue	Serology Positive	
C. pyloridis present	86%	
C. pyloridis absent	20%	
Gastritis present	80%	
C. pyloridis present		89% *
C. pyloridis absent		56%
Gastritis absent	13%	

* Reference 121

negative for C. pyloridis (83,117,118,120,121). This association also holds if one correlates the presence or absence of gastritis with a serologic response to C. pyloridis (29,83,90,117,118,121,122). A positive titer will be found in 80% of subjects with gastritis compared to 13% of subjects without gastritis. It is of interest that in one study a positive serology was found in over 50% of subjects with gastritis even when there was no evidence of C. pyloridis infection (121). In our series (29) we found that serum IgG antibody titers to C. pyloridis were significantly higher in subjects with C. pyloridis-associated antral gastritis than in subjects in whom C. pyloridis was absent.

Serum antibodies to C. pyloridis are primarily related to two antigens (122). Using immunoblot techniques, antigens with a molecular weight of 14-21 X 10^3 and of 33 X 10^3 were most closely related to the antibody response. Serum antibodies were not directed toward flagella.

Studies of gastric juice has shown IgA and IgM, but not IgG, antibodies to Campylobacter pyloridis (87). Immunoperoxidase staining of tissue shows predominantly IgA antibodies, predominantly in surface epithelium (78,123).

- Prevalence of Campylobacter Pyloridis in the Population -

There is increased prevalence of Campylobacter pyloridis in patients with peptic ulcer disease and nonulcer dyspepsia than in normal controls (Figure 36) (29,50,66,79-82,85,86,88,90,96,98,99,124-129). However, as shown in Table 9,

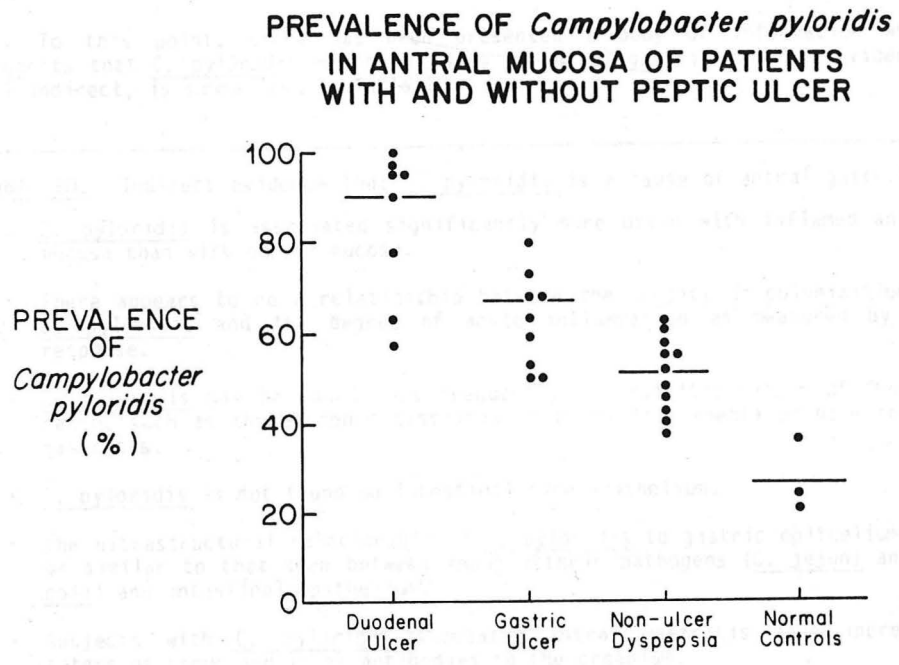


Figure 36.

Table 9. Prevalence of C. pyloridis and antral gastritis in several populations.

	Duodenal Ulcer	Gastric Ulcer	Non-Ulcer Dyspepsia	Normal
C. pyloridis Present	90%	67%	51%	26%
Gastritis Present	94%	81%	58%	23%

this may well be due to the fact that such patients are more likely to have gastritis present in their antrum than are normal controls (29,50,78,82,85,88, 124,130,131). The prevalence of Campylobacter pyloridis may also vary with different ethnic groups (121) and rises with age (78,86,118,121,122,126,132,133). In one study of asymptomatic subjects, the frequency (by breath test) of C. pyloridis infection was <5% in those 25-44 years old, 20% of those age 45-54, 50% of persons 55-64 years, and 75% of those aged 65-84 (133).

Campylobacter pyloridis

- Pathogen or Opportunist -

To this point, there has been presented a body of information which suggests that C. pyloridis may be a cause of antral gastritis. This evidence, all indirect, is summarized in Table 10.

Table 10. Indirect evidence that C. pyloridis is a cause of antral gastritis.

- C. pyloridis is associated significantly more often with inflamed antral mucosa than with normal mucosa.
- There appears to be a relationship between the density of colonization of C. pyloridis and the degree of acute inflammation as measured by PMN response.
- C. pyloridis may be found less frequently in gastritic tissue of "known" cause, such as the atrophic gastritis of pernicious anemia or bile reflux gastritis.
- C. pyloridis is not found on intestinal type epithelium.
- The ultrastructural relationship of C. pyloridis to gastric epithelium may be similar to that seen between known enteric pathogens (C. jejuni and E. coli) and intestinal epithelium.
- Subjects with C. pyloridis-associated antral gastritis have increased titers of serum and local antibodies to the organism.
- The increased frequency of antral gastritis with age (134,135) is paralleled by increased seropositivity to C. pyloridis.

However, these data, while consistent with the hypothesis that C. pyloridis is a cause of antral gastritis, are also consistent with the hypothesis that C. pyloridis may colonize ("graze") on antral tissue made acutely inflamed by another, as yet unknown, cause (Figure 37).

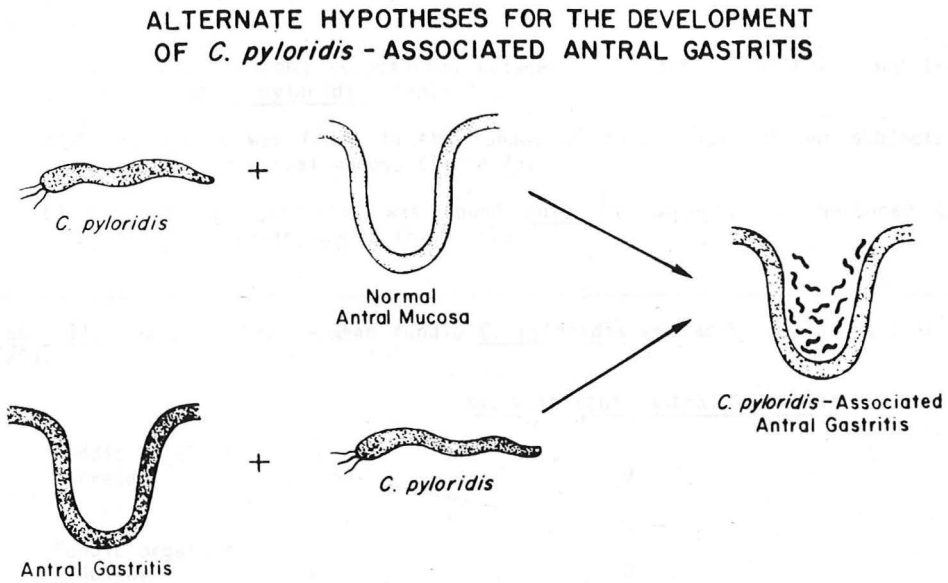


Figure 37.

Experimental Data to Support C. pyloridis as a Pathogen

1. Animal Model

There is, as yet, no good animal model of C. pyloridis-induced antral gastritis. Campylobacter like organisms have been isolated from gastric epithelium of the ferret (136,137), and C. pyloridis will colonize and remain in the

gastric mucosa of the gnotobiotic pig for up to 4 weeks (S. Krakowka, personal communication).

2. NSAID-induced C. pyloridis gastritis

In our study of healthy volunteers comparing the gastric mucosal response to indomethacin versus placebo (29), we made the following observations:

a) There was a strong association between acute antral gastritis and the presence of C. pyloridis (Table 7).

b) C. pyloridis was found in the fundus of 15/23 (65%) of our subjects, most often in normal mucosa (Table 7).

c) Acute antral gastritis was found only in subjects who harbored C. pyloridis in their fundus (Table 11).

Table 11. Relationship between fundic C. pyloridis and acute antral gastritis (29).

		No. With Acute Antral Gastritis
Fundic organisms Present	(N=15)	9
Fundic organisms Absent	(N=8)	0

d) Indomethacin "predisposed" our subjects with fundic C. pyloridis to develop acute antral gastritis (Table 12).

Table 12. Proportion of subjects with fundic C. pyloridis who had acute antral gastritis. (Subjects without fundic C. pyloridis were never found to have acute gastritis - See Table 11).

	C. pyloridis present in fundus (N=15)	
	Placebo (N=9)	Indomethacin (N=6)
No. of subjects with acute antral gastritis after placebo or indomethacin	3 (33%)	6 (100%)
	($p<0.05$)	

If these data can be confirmed by further studies, it would suggest that the administration of NSAID may, by depleting endogenous prostaglandins, predispose C. pyloridis residing in the fundus to enter the antrum and induce acute antral gastritis (Figure 38).

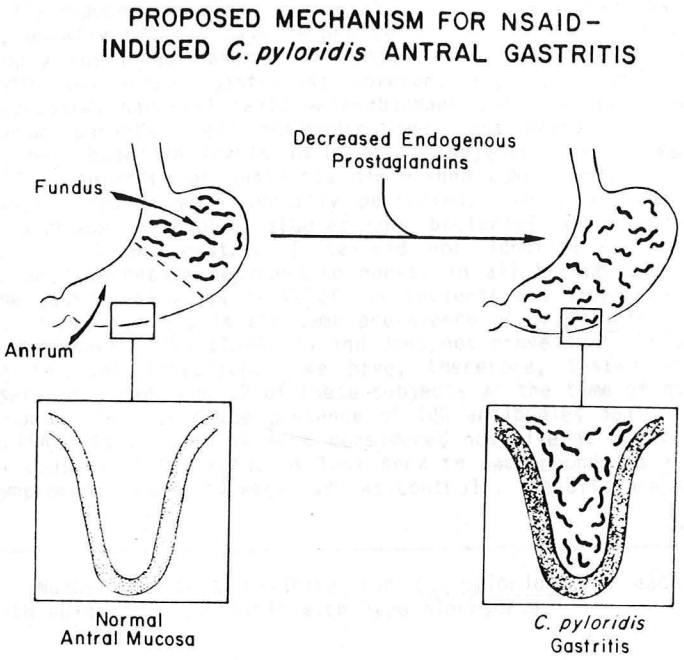


Figure 38.

3. Human Challenge Studies

Two investigators have now challenged themselves with inocula of C. pyloridis (138-141). In the first case, Dr. Barry Marshall (41,42,66,82,114,118,126) ingested 10^9 CFU of C. pyloridis 3 hours after a dose of cimetidine 600 mg. Endoscopic gastric biopsies taken 1 month earlier had shown normal mucosa. Seven days after ingestion of the organisms he developed a mild illness characterized by nausea, epigastric distress, and one episode of vomiting. Endoscopic biopsies at day 10 disclosed acute gastritis and numerous spiral bacteria. Culture disclosed C. pyloridis. By day 14, repeat biopsies showed clearing of the organisms, absence of acute inflammation, but continued abnormal cellular structure. He then began a 7 day course of tinidazole and noted that "his symptoms resolved completely within 24 hours of the start of therapy" (138). In the second case, in addition to documentation of antral gastritis, there was noted the development of fundic gastritis with fasting hypochlorhydria (141).

These self-inoculation experimerts suggest that C. pyloridis can induce antral and fundic gastritis. Additionally, an illness characterized by hypochlorhydria was noted in the second subject. This phenomenon is similar to an illness seen in an epidemic occurring in our laboratory from October 1976 to October 1977 (142) (see below) and in two other laboratories (143,144).

4. Epidemic Gastritis With Hypochlorhydria

In our epidemic, 17 of 37 healthy volunteers participating in studies of acid secretion and 1 patient with Zollinger-Ellison syndrome became rapidly and profoundly hypochlorhydric. A mild illness with epigastric pain occurred in 9 subjects, usually several days before detection of hypochlorhydria. Gastric mucosal biopsy specimens taken from subjects during hypochlorhydria revealed severe fundic and antral gastritis; however, even when acid secretion was severely depressed, parietal cells were abundant and appeared normal histologically. Serum parietal cell antibodies were not present. Acid secretion returned to near baseline levels in 14 of 17 subjects after a mean of 126 days (range 53-235); severity of gastritis diminished concurrently in 7 of 10 subjects in whom biopsies were serially performed. An infectious etiology was suspected, although serologic studies and bacterial and conventional viral cultures of stool and gastric juice did not identify a candidate agent. Ultimately, acid secretion returned to normal in all 17 subjects. We have now reviewed the gastric biopsies of 12 of our subjects and have found C. pyloridis in 8 (67%). However, this is the same prevalence of C. pyloridis as we find in our normal volunteers (29) (Table 7) and does not prove that the organisms were responsible for the infection. We have, therefore, tested acute and convalescent sera obtained from 12 of these subjects at the time of diagnosis and a mean of 6 months later for the presence of IgG antibodies against C. pyloridis using an ELISA (145). Samples were considered positive at a given dilution if the optical density (O.D.) ratio of test sera to background was $\geq$ 3.5. Samples from 10 asymptomatic subjects were used as controls. Results are shown in Table 13.

Table 13. Number of sera positive for C. pyloridis at each dilution in subjects with epigastric gastritis with hypochlorhydria.

	Serum Dilution				
	<1:200	1:200	1:400	1:800	1:1600
Gastritis: Acute	6	1	2	2	1
Gastritis: Convalescent	0	0	7	4	1
Control	4	2	3	0	1

Mean O.D. ratios at 1:200 were Control=5.5$\pm$1.9, Gastritis: Acute=5.3$\pm$1.2 (p=N.S. compared to Control, and Gastritis: Convalescent=7.8$\pm$0.7 ($p<0.05$ compared to Acute). Antibody titers rose during convalescence at least one dilution in 9/12 gastritis patients. These results suggest that C. pyloridis played a role in this epidemic of gastritis.

5. Response of C. pyloridis-Associated Gastritis to Therapy

C. pyloridis is sensitive in vitro to a number of agents (Table 14), while relatively resistant to several antibiotics (sulfamethoxazole, trimethaprim, and vancomycin) and most "ulcer" medications (cimetidine, ranitidine, sucralfate, and carbenoxolone) (42,52,146-150).

Table 14. In vitro sensitivities of C. pyloridis to several agents (from references 52,146-150).

Drug	Range of MIC	MIC_{50}	MIC_{90}
Penicillin	0.002-1.0	0.02-0.06	0.03-0.3
Cefoxitin	0.02-0.5		
Tetracycline	0.1-0.3	0.1	0.1-0.3
Ampicillin			0.1
Erythromicin	0.2-0.5		
Gentamycin	0.1-1	0.1	0.3-1
Cephalothin	0.5-2	0.5	2
Metronidazole	0.5-8	0.5-1	4-8
Chloramphenicol	2-8	4	8
Tinidazole	0.5-32		
DeNol®	4-32	8	16
Bismuth Citrate	<2-16	8	16

Several studies, most with small numbers of patients, have now assessed to ability of therapeutic agents to a) eradicate C. pyloridis and b) reduce the amount of inflammation present in antral mucosa. Patients are those who have concomitant duodenal or gastric ulcers or who have antral gastritis in conjunction with "non-ulcer dyspepsia". There is, in almost every instance, a close parallel between resolution of gastritis and "eradication" of C. pyloridis. The question, of course, is which comes first.

a. H_2-receptor antagonists

Studies with cimetidine have shown neither an improvement in gastritis nor eradication of C. pyloridis (150-156). This is true even if a concomitant peptic ulcer is noted to heal. However, one study reported that 10/24 patients with duodenal ulcer treated with ranitidine had resolution of antral inflammation with no C. pyloridis present after 6 weeks of therapy (156). Since ranitidine has no bactericidal effect on C. pyloridis, these data would suggest that healing of gastritis led to "eradication" of the organism.

b. Sucralfate

In two studies, sucralfate neither improved gastritis nor eradicated C. pyloridis (155,156).

c. Bismuth compounds

DeNol (tripotassium dicitrato bismuthate) has been used as an ulcer therapeutic agent in countries outside the United States for many years, although its mechanism of action was unknown. Its ability to inhibit growth of C. pyloridis in vitro has prompted renewed interest in the compound. Results from 6 studies suggest that treatment with De Nol results in eradication of C. pyloridis and improvement in gastritis in 50 to 75% of patients (150-152,154,156,156a). Similar results have been shown with colloidal bismuth subcitrate (155). In this latter study, C. pyloridis was eradicated in about 40% of patients (compared to 0% of patients treated with placebo, cimetidine, or sucralfate) and gastritis score was significantly reduced. However, relapse was rapid and frequent, with return of an organism which, by restriction endonuclease analysis, appeared to be the same as the organism present before treatment. Finally, recent studies have suggested that Pepto-Bismol (bismuth subsalicylate) can produce potentially bactericidal tissue levels of bismuth (157) and is effective in eradicating C. pyloridis (125,158). Results of one such study are shown in Table 15 (158).

Table 15. Comparison of Pepto-Bismol, Erythromycin, and Placebo in the Treatment of "symptomatic" C. pyloridis-Associated Gastritis (From reference 158).

	Pepto-Bismol[a]	Erythromycin[b]	Placebo	
Organism Cleared	14/18	1/15	0/17	$p<0.001$
Gastritis Resolved	13/16	3/13	0/16	$p<0.001$
Symptoms Improved	13/15	9/14	10/15	(p=NS)

[a] 30 ml qid x 3 weeks
[b] Erythromycin ethyl succinate 500 mg qid X 2 weeks

In this study symptoms improved in 11/12 (92%) subjects in whom organisms were eradicated compared to 21/32 (66%) of those in whom C. pyloridis remained (p=0.05-0.10).

While these studies with bismuth compounds are intriguing, it cannot yet be concluded that eradication of C. pyloridis led to improvement in histology. It remains possible that bismuth has some inherent ability to reduce inflammation and that the organisms may disappear if the gastritis is resolved or that the two phenomena are unrelated. This hypothesis seems less likely and would be difficult to prove unless a) some other form of therapy is found which heals gastritis but has no inherent bactericidal effect on C. pyloridis, or b) a form of therapy is found which is bactericidal for C. pyloridis but has no known effect on inflamed tisue per se (see next section).

d. Amoxicillin

This antibiotic has been shown to eradicate C. pyloridis in almost 3/4 of patients treated, with a substantial reduction in gastritis score (155). This is the strongest evidence to date that primary eradication of the organism leads to resolution in gastritis, rather than the other way around, since amoxicillin appears to be nothing more than an antibiotic. As with bismuth compounds, however, relapse is frequent.

e. Combination Therapy

Several investigators have suggested that a combination of an antibiotic (eg. amoxicillin or tinidazole) plus a bismuth compound results in more frequent eradication of C. pyloridis (with associated improvement in mucosal histology) than with either drug alone (102,155,159). In addition, such treatment may be associated with less frequent relapses. Further studies are needed to confirm these provocative data.

Campylobacter pyloridis

- Its Role in Peptic Ulcer -

A substantial proportion, perhaps the majority, of patients with duodenal and gastric ulcer have C. pyloridis-associated antral gastritis. While the presence of gastritis in antral tissue may predispose to the development of gastric and duodenal (in metaplastic gastric tissue?) ulcer, there is no proof this is the case. There are some reports of metronidazole or furazolidone promoting the healing of peptic ulcer, but such reports are unconvincing (160-163). DeNol, a bismuth compound, clearly promotes the healing of duodenal and gastric ulcer, and has even been reported to heal cimetidine-resistant ulcers (164-166). For example, in one study of ulcers unhealed after 4 weeks of cimetidine, 17/20 healed under further treatment with DeNol compared to 6/15 treated with continued therapy using higher doses of cimetidine (165). However, these data are just as compatible with the possibility that bismuth has inherent ulcer healing properties independent of its bactericidal effect on C. pyloridis.

Of interest are recent reports comparing the recurrence of duodenal ulcer after healing with either DeNol or an H_2-receptor antagonist (167-170). While one study suggested no difference in relapse rates (170), the other three demonstrated a significantly lower incidence of recurrence in patients whose ulcer had been healed with DeNol when compared to those whose ulcer healed while the patient took cimetidine or ranitidine (167-169). Recurrence after 12 months occurred in an average of 86% of patients healed with an H_2-blocker compared to 51% of patients healed with DeNol. Moshal has demonstrated that duodenal epithelium is more "normal" histologically after healing with DeNol than healing with cimetidine (171), perhaps leaving the latter more susceptible to recurrences. Whether this "better healing" and reduced relapse rate is due to eradication of C. pyloridis remains unanswered (172).

Unpublished data from Perth, Western Australia (B. Marshall, personal communication) suggests that reduced relapse is indeed related to clearance of C. pyloridis. Patients with duodenal ulcer and C. pyloridis gastritis (N=100) were randomly assigned to 8 week therapy with cimetidine or DeNol. In addition, half of each of these 2 groups received tinidazole for the first 10 days and half received placebo. Ulcers healed overall in about 65% of patients, with no significant differences among the four treatment groups. Clearance of C. pyloridis occurred in none of the cimetidine/placebo group, 4% of the cimetidine/tinidazole group, 30% of the DeNol/placebo group, and 74% of the

DeNol/tinidazole group. Patients whose ulcer had healed were then followed up to one year. There were 5 symptomatic recurrences (2 documented ulcer) in 24 (21%) patients in whom C. pyloridis had been eradicated at the time of initial healing compared to 33 recurrences in the 41 (80%) patients in whom C. pyloridis had remained despite initial ulcer healing.

Campylobacter pyloridis

- Its Role in Non-Ulcer Dyspepsia -

Antral mucosal biopsy of patients with non-ulcer dyspepsia will frequently show an active inflammatory process (130,173) and C. pyloridis will be found in perhaps 50% of such patients (see page 33). It may be incorrect, however, to assume that C. pyloridis-associated gastritis is the cause of these patients' ulcer-like symptoms. Support for this statement is as follows: 1) antral gastritis, even associated with C. pyloridis, is found in many healthy, asymptomatic subjects (29,50,94,174) especially with increasing age; and 2) not all patients with non-ulcer dyspepsia have antral gastritis (130). Although there are several reports that C. pyloridis - gastritis can be improved with bismuth and/or antibiotic therapy, there is only one report of a significant improvement in dyspeptic symptoms when compared to placebo therapy (156a).

Summary

1) Campylobacter pyloridis while probably not a "true" Campylobacter, has many of the characteristics of a typical Campylobacter.

2) The organism may be identified relatively easily with proper culture and staining techniques.

3) C. pyloridis is probably a pathogen producing fundic (epidemic gastritis with hypochlorhydria) and antral gastritis.

4) Non-steroid anti-inflammatory agents may predispose certain individuals to C. pyloridis-associated antral gastritis.

5) Presence of C. pyloridis is correlated with increasing age, peptic ulcer disease, and non-ulcer dyspepsia. Such correlation may be primarily related to the high prevalence of antral gastritis in these conditions.

6) A role of C. pyloridis gastritis in the pathogenesis of peptic ulcer disease or ulcer-like symptoms (non-ulcer dyspepsia) has not been proven.

Acknowledgements

I wish to acknowledge Bobbie Bullard for typing this protocol, Patricia Ladd for medical illustration, the Medical Media Service of the Dallas Veterans Administration Medical Center, the UTHSCD library staff, and the UTHSCD Medical Illustration Service. This presentation could not have been accomplished without their superb efforts.

References

1. Konturek, S.J. Gastric cytoprotection. Scand. J. Gastroenterol. 1985;20:543-53.

2. Hawkey, C.J. and Rampton, D.S. Prostaglandins and the gastrointestinal mucosa: Are they important in its function, disease or treatment? Gastroenterology 1985;89:1162-88.

3. Miller, T.A. Protective effects of prostaglandins against gastric mucosal damage: Current knowledge and proposed mechanisms. Am. J. Physiol. 1983;245:G601-23.

4. Robert, A., Schultz, J.R., Nezamis, J.E., and Lancaster, C. Gastric antisecretory and antiulcer properties of PGE_2, 15-methyl PGE_2, and 16,16-dimethyl PGE_2. Intravenous, oral and intrajejunal administration. Gastroenterology 1976;70:359-70.

5. Ippoliti, A.F., Isenberg, J.I., Maxwell, V., and Walsh, J.H. The effect of 16,16-dimethyl prostaglandin E_2 on meal-stimulated gastric secretion and serum gastrin in duodenal ulcer patients. Gastroenterology 1976;70:488-91.

6. Peterson, W., Feldman, M., Taylor, I., and Bremer, M. The effect of 15(R)-15-methyl prostaglandin E_2 on meal-stimulated gastric acid secretion, serum gastrin, and pancreatic polypeptide in duodenal ulcer patients. Dig. Dis. Sci. 1979;24:381-84.

7. Robert, A., Nezamis, J.E., Lancaster, C., and Hanchar, A.J. Cytoprotection by prostaglandins in rats: prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl, and thermal injury. Gastroenterology 1979;77:433-43.

8. Robert, A., Lancaster, C., Davis, J.P., Field, S.O., and Nezamis, J.E. Distinction between antiulcer effect and cytoprotection. Scand. J. Gastroenterol. 1984;19(Suppl 101):69-73.

9. Robert, A. Cytoprotection by prostaglandins. Gastroenterology 1979;77:761-67.

10. Robert, A., Lancaster, C., Hanchar, A.J., and Nezamis, J.E. Mild irritants prevent gastric necrosis through prostaglandin formation: Histological study (abstract). Gastroenterology 1978;74:1086.

11. Isenberg, J.I., Hogan, D.L., Koss, M.A., and Selling, J.A. Human duodenal mucosal bicarbonate secretion. Gastroenterology 1986;91:370-78.

12. Silen, W. and Ito, S. Mechanisms for rapid re-epithelialization of the gastric mucosal surface. Am. Rev. Physiol. 1985;47:217-29.

13. Redfern, J.S. Unpublished observations

14. Malagelada, J-R., Ahlquist, D.A., and Moore, S.C. Defects in prostaglandin synthesis and metabolism in ulcer disease. Dig. Dis. Sci. 1986;31(Suppl 2):205-75.

15. Rachmilewitz, D., Ligumsky, M., Fich, A., Goldin, E., Eliakim, A., and Karmeli, F. Role of endogenous gastric prostanoids in the pathogenesis and therapy of duodenal ulcer. Gastroenterology 1986;90:963-69.

16. Isenberg, J.I., Selling, J.A., Hogan, D.L., and Koss, M.A. Impaired proximal duodenal mucosal bicarbonate secretion in patients with duodenal ulcer. N. Engl. J. Med. 1987;316:374-79.

17. Selling, J.A., Hogan, D.L., Aly, A., Koss, M.A., and Isenberg, J.I. Indomethacin inhibits duodenal mucosal bicarbonate secretion and endogenous prostaglandin E_2 output in human subjects. Ann. Int. Med. 1987;106:368-71.

18. Redfern, J.S. Effect of indomethacin on gastric mucosal prostaglandins in humans. Correlation with mucosal damage. Gastroenterology 1987;92:969-77.

19. Duggan, J.M. Aspirin in chronic gastric ulcer: an Australian experience. Gut 1976;17:378-84.

20. Piper, D.W., McIntosh, J.H., Ariotti, D.E., Fenton, B.H., and MacLennan, R. Analgesic ingestion and chronic peptic ulcer. Gastroenterology 1981;80:427-32.

21. McIntosh, J.H., Byth, K., and Piper, D.W. Environmental factors in aetiology of chronic gastric ulcer: a case control study of exposure variables before the first symptoms. Gut 1985;26:789-98.

22. Duggan, J.M., Dobson, A.J., Johnson, H., and Fahey, D. Peptic ulcer and non-steroidal anti-inflammatory agents. Gut 1986;27:929-33.

23. Schrager, J., Spink, R., and Mitra, S. The antrum in patients with duodenal and gastric ulcers. Gut 1967;8:497-508.

24. Whitehead, R., Truelove, S.C., and Gear, M.W.L. The histological diagnosis of chronic gastritis in fibreoptic gastroscope biopsy specimens. J. Clin. Pathol. 1972;25:1-11.

25. Gear, M.W.L., Truelove, S.C., and Whitehead, R. Gastric ulcer and gastritis. Gut 1971;12:639-45.

26. Tatsuta, M., Iishi, H., and Okuda, S. Location of peptic ulcers in relation to antral and fundal gastritis by chromoendoscopic follow-up examinations. Dig. Dis. Sci. 1986;31:7-11.

27. Cohen, M.M. and MacDonald, W.C. Mechanism of aspirin injury to human gastroduodenal mucosa. Prostaglandins and Leukotrienes in Medicine 1982;9:241-55.

28. MacDonald, W.C. Correlation of mucosal histology and aspirin intake in chronic gastric ulcer. Gastroenterology 1973;65:381-89.

29. Peterson, W.L., Lee, E.L., and Feldman, M. Gastric campylobacter-like organisms in healthy humans (abstract). Gastroenterology 1986;90:1585.

30. Rosenow, E.C. and Sandford, A.H. The bacteriology of ulcer of the stomach and duodenum in man. J. Infect. Dis. 1915;17:210-26.

31. Draser, B.S. and Hudson, M.J. Spiral organisms in intestinal disease. In: Reeves, D. and Geddis, A., eds. Recent Advances in Infection. Churchill Livingstone, Edinburgh, 1979;1:41-53.

32. Palmer, E.D. Investigation of the gastric spirochetes in the human. Gastroenterology 1954;27:218-20.

33. Kasai, K. and Kobayashi, R. The stomach spirochete occurring in mammals. J. Parasit. 1919;6:1-11.

34. Doenges J.L. Spirochaetes in gastric glands of Macacus rhesus and of man without related disease. Arch. Path. 1939;27:469-77.

35. Freedburg, A.S. and Barron, L.E. The presence of spirochetes in the human gastric mucosa. Am. J. Dig. Dis. 1940;7:443-45.

36. Lockard, V.G. and Boler, R.K. Ultrastructure of a spiraled micro-organism in the gastric mucosa of dogs. Am. J. Vet. Res. 1970;31:1453-62.

37. Steer, H.W. and Colin-Jones, D.G. Mucosal changes in gastric ulceration and their response to carbenoxolone sodium. Gut 1975;16:590-97.

38. Steer, H.W. Ultrastructure of cell migration through the gastric epithelium and its relationship to bacteria. J. Clin. Pathol. 1975;28:639-46.

39. Fung, W.P., Papadimitriou, J.M. and Matz, L.R. Endoscopic, histological and ultrastructural correlations in chronic gastritis. Am. J. Gastroenterol. 1979;71:269-79.

40. Warren, J.R. Unidentified curved bacilli on gastric epithelium in active chronic gastritis (letter). Lancet 1983;1:1273.

41. Marshall, B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis (letter). Lancet 1983;1:1273-74.

42. Marshall, B.J., Royce, H., Annear, D.I., Goodwin, C.S., Pearman, J.W., Warren, J.R. and Armstrong, J.A. Original isolation of Campylobacter pyloridis from human gastric mucosa. Microbios. Lett. 1984;25:83-8.

43. Anonymous. Validation of publication of new names and new combinations previously effectively published outside the IJSB. Int. J. Syst. Bacteriol. 1985;85:223-5.

44. Steer, H.W. Surface morphology of the gastroduodenal mucosa in duodenal ulceration. Gut 1984;25:1203-10.

45. Rollason, T.P., Stone, J. and Rhodes, J.M. Spiral organisms in endoscopic biopsies of the human stomach. J. Clin. Pathol. 1984;37:23-6.

46. Kasper, G. and Dickgiesser N. Isolation of campylobacter-like bacteria from gastric epithelium. Infect. 1984;3:179-80.

47. Goodwin, C.S., Blincow, E.D., Warren, J.R., Sanderson, C.R., and Easton, L. Evaluation of cultural techniques for isolating Campylobacter pyloridis from endoscopic biopsies of gastric mucosa. J. Clin. Pathol. 1985;38:1127-31.

48. Bolton, F.J., Holt, A.V., and Hutchinson, D.N. Urease-positive thermophilic campylobacters (letter). Lancet 1985;1:1217-18.

49. Lior, H. and Johnson, W.N. Catalase, peroxidase and superoxide dismutase activities in campylobacter spp. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, E., eds. Campylobacter III: proceedings of the third international workshop on Campylobacter infections. London: Public Health Laboratory Service 1985:226-7.

50. Langenberg, M.L., Tytgat G.N.J., Schipper, M.E.I., Rietra, P.J.G.M., and Zanen H.C. Campylobacter like organisms in the stomach of patients and healthy individuals (letter). Lancet 1984;1:1238.

51. Owen, R.J., Martin, S.R. and Borman, P. Rapid urea hydrolysis by gastric campylobacters (letter). Lancet 1985;1:111.

52. Goodwin, C.S., Blake, P., and Blincow, E. The minimum inhibitory and bactericidal concentrations of antibiotics and anti-ulcer agents against Campylobacter pyloridis. J. Antimicrob. Chemother. (in press)

53. Shanker, S. and Sorrell, T.C. Susceptibility of Campylobacter jejuni to twenty-three antimicrobial agents. Pathology 1983;15:61-3.

54. Chow, A.Q., Patten, V., and Bednorz, D. Susceptibility of Campylobacter fetus to twenty-two antimicrobial agents. Antimicrob. Agents Chemother. 1978;13:416-8.

55. Goodwin, C.S., McCulloch, R.K., Armstrong, J.A., and Wee, S.H. Unusual cellular fatty acids and distinctive ultrastructure in a new spiral bacterium (Campylobacter pyloridis) from the human gastric mucosa. J. Med. Microbiol. 1985;19:257-67.

56. Pead, P.J. Electron microscopy of Campylobacter jejuni. J. Med. Microbiol. 1979;12:383-5.

57. Curry, A., Jones, D.M., Eldridge, J., and Fox, A.J. Ultrastructure of Campylobacter pyloridis - not a campylobacter? In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, E., eds. Campylobacter III: proceedings of the third international workshop on Campylobacter infections. London: Public Health Laboratory Service 1985:195.

58. Curtis, M.A. Cellular fatty acid profiles of campylobacters. Med. Lab. Sci. 1983;40:333-48.

59. Hudson, M.J. and Wait, R. Cellular fatty acids of Campylobacter species with particular reference to Campylobacter pyloridis. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, E., eds. Campylobacter III: third international workshop on Campylobacter infections. London: Public Health Laboratory Service 1985:198-9.

60. Goodwin, S., Blincow, E., Armstrong, J., McCulloch, R., and Collins D. Campylobacter pyloridis is unique: GCLO-2 is an ordinary campylobacter (letter). Lancet 1985;2:38-9.

61. Pearson, A.D., Bamforth, J., and Booth, et al. Polyacrylamide gel electrophoresis of spiral bacteria from the gastric antrum (letter). Lancet 1984;1:1349-50.

62. Fox, A.J., Eldridge, J., and Jones, D.M. Analysis of the antigens of Campylobacter pyloridis by SDS-PAGE and immunoblot techniques. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, E., eds. Campylobacter III: proceedings of the third international workshop on Campylobacter infections. London: Public Health Laboratory Service 1985:196.

63. Megraud, F., Bonnet, F., Garnier, M., and Lamouliatte, H. Characterization of "Campylobacter pyloridis" by culture, enzymatic profile, and protein content. J. Clin. Microbiol. 1985;22:1007-10.

64. Kasper, G. and Dickgiesser N. Isolation from gastric epithelium of campylobacter-like bacteria that are distinct from 'Campylobacter pyloridis' (letter). Lancet 1985;1:111-2.

65. Pinkard, K.J., Stockman, K.A., Davidson, A., and Lambert J.R. Campylobacter-like organisms from the human stomach - detection, characterisation and in vitro susceptibilities. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, E., eds. Campylobacter III: proceedings of the third international workshop on Campylobacter infections. London: Public Health Laboratory Service 1985:171.

66. Marshall, B.J., McGechie, D.B., Rogers, P.A., and Glancy, R.J. Pyloric campylobacter infection and gastroduodenal disease. Med. J. Aust. 1985;142:439-44.

67. Spira, W.M. and the Gastrointestinal Physiology Working Group. Rapid identification of pyloric campylobacter in peruvians with gastritis. Dig. Dis. Sci. 1986;10:1089-94.

68. Warthin, A.S. and Starry, A.C. A more rapid and improved method of demonstrating spirochaetes in tissues. Am. J. of Syphilis 1920;4:97-103.

69. Walters, L.L., Budin, R.E., and Paull, G. Acridine-orange to identify Campylobacter pyloridis in formalin fixed paraffin-embedded gastric biopsies (letter). Lancet 1986;1:42.

70. Pinkard, K.L., Harrison, B., Capstick, J.A., Medley, G., and Lambert, J.R. Detection of Campylobacter pyloridis in gastric mucosa by phase contrast microscopy. J. Clin. Pathol. 1986;39:112-3.

71. McNulty, C.A.M. and Wise, R. Rapid diagnosis of campylobacter associated gastritis (letter). Lancet 1985;1:1443-4.

72. Morris, A., McIntyre, D., Rose, T., and Nicholson, G. Rapid diagnosis of Campylobacter pyloridis infection (letter). Lancet 1986;1:149.

73. Graham, D.Y., Klein, P.D., Evans, D.G., Opekun, A.R. Jr., Evans, D.G. Jr., Alpert, L.C., Lobb, K.W., and Boutton, T.W. Rapid noninvasive diagnosis of gastric campylobacter by a ^{13}C urea breath test (abstract). Gastroenterology 1986;90:1435.

74. Phillips, A.D.,Hine, K.R., Holmes, G.K.T., and Woodings, D.F. Gastric spiral bacteria (letter). Lancet 1984;2:100-1.

75. Meyrick-Thomas, J., Poynter, D., and Gooding, C., et al. Gastric spiral bacteria (letter). Lancet 1984;2:100.

76. Steer, H.W. The gastro-duodenal epithelium in peptic ulceration. J. Pathol. 1985;146:355-62.

77. Johnston, B.J., Reed, P.I., and Ali, M.H. Campylobacter like organisms in duodenal and antral endoscopic biopsies: relationship to inflammation. Gut 1986;27:1132-37.

78. Wyatt, J.I., Rathbone, B.J., and Heatley, R.V. Local immune response to gastric Campylobacter in non-ulcer dyspepsia. J. Clin. Pathol. 1986;39:863-70.

79. Buck, G.E., Gourley, W.K., Lee, W.K., Subramanyam, K., Latimer, J.M., and DiNuzzo, A.R. Relation of Campylobacter pyloridis to gastritis and peptic ulcer. J. Infect. Dis. 1986;153:664-69.

80. McNulty, C.A.M. and Watson, D.M. Spiral bacteria of the gastric antrum (letter). Lancet 1984;1:1068-9.

81. Burnett, R.A., Forrest, J.A.H., Girdwood, R.W.A., and Flicker, C.R. Campylobacter-like organisms in the stomach of patients and healthy individuals (letter). Lancet 1984;1:1394.

82. Marshall, B.J. and Warren, J.R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311-4.

83. Jones, D.M., Lessels, A.M., and Eldridge, J. Campylobacter like organisms on the gastric mucosa: culture, histology, and serological studies. J. Clin. Pathol. 1985;37:1002-6.

84. Lambert, J.R., Hansky, J., Eaves, E.R., Korman, M.G., Pinkard, K., and Medley, G. Campylobacter like organisms (CLO) in human stomach (abstract). Gastroenterology 1985;88:1463.

85. Price, A.B., Levi, J., and Dolby, J.M., et al. Campylobacter pyloridis in peptic ulcer disease: microbiology, pathology, and scanning electron microscopy. Gut 1985;26:1183-8.

86. Rawles, J.W., Paull, G., Yardley, J.H., Hendrix, T.R., Ravich, W.J., Walters, L.L., Dick, J.D., and Margolis, A. Gastric camylobacter-like organisms (CLO) in a U.S. hospital population (abstract). Gastroenterology 1986;90:1599.

87. Rathbone, B.J., Wyatt, J.I., Worsley, B.W., Shires, S.E., Trejdosiewicz, L.K., Heatley, R.V., and Losowsky, M.S. Systemic and local antibody responses to gastric Campylobacter pyloridis in non-ulcer dyspepsia. Gut 1986;27:642-47.

88. Rokkas, T., Pursey, C., Simmons, N.A., Filipe, M.I., and Sladen, G.E. Campylobacter-like organisms in 'non-ulcer dyspepsia' (abstract). Gut 1986;27:A1238.

89. Morris, A., Arthur. J., and Nicholson, G. Campylobacter pyloridis infection in Auckland patients with gastritis. N. Zealand Med. J. 1986;99:353-5.

90. Booth, L., Holdstock, G., Macbride, H., Hawtin, P., Gibson, J.R., Ireland, A., Bamforth, J., DuBoulay, C.E., Lloyd, R.S., and Pearson, A.D. Clinical importance of Campylobacter pyloridis and associated serum IgG and IgA antibody responses in patients undergoing upper gastrointestinal endoscopy. J. Clin. Pathol. 1986;39:215-9.

91. Drumm, B., O'Brien, A., Cutz, E., and Sherman, P. Campylobacter pyloridis are associated with primary antral gastritis in the pediatric population (abstract). Gastroenterology 1986;90:1399.

92. Czinn, S.J., Dahms, B., Jacobs, G., Kaplan, B., and Rothstein, F.C. Campylobacter-like organisms (CLO) in association with symptomatic gastritis in children. J. Pedi. 1986;109:80-3.

93. Cadranel, S., Goossens, H., DeBoeck, M., Malengreau, A., Rodesch, P., and Butzler, J-P. Campylobacter pyloridis in children (letter). Lancet 1986;1:735.

94. Barthel, J.S., Westblom, T.U., Havey, A.D., Gonzalez, F.J., and Everett, E.D. Pyloric campylobacter-like organisms (PCLOs) in asymptomatic volunteers (abstract). Gastroenterology 1986;90:1338.

95. O'Connor, H.J., Axon, A.T.R., and Dixon, M.F. Campylobacter-like organisms unusual in type A (pernicious anaemia) gastritis (letter). Lancet 1984;2:1091.

96. Lambert, J.R., Dunn, K.L., Eaves, E.R., Korman, M.G., and Hansky, J. Campylobacter pyloridis in diseases of the human upper gastrointestinal tract (abstract). Gastroenterology 1986;90:1509.

97. Dixon, M.F., O'Connor, H.J., Axon, A.T.R., King, R.F.G.J., and Johnston, D. Reflux gastritis - a distinct histopathological entity? J. Clin. Pathol. 1986;39:524-30.

98. O'Connor, H.J., Wyatt, J.I., Dixon, M.F., and Axon, A.T.R. Campylobacter like organisms and reflux gastritis. J. Clin. Pathol. 1986;39:531-34.

99. O'Connor, H.J., Wyatt, J.I., Ward, D.C., Dixon, M.F., Axon, A.T.R., Dewar, E.P., and Johnston, D. Effect of duodenal ulcer surgery and enterogastric reflux on campylobacter pyloridis. Lancet 1986;2:1178-81.

100. Chen, X.G., Correa, P., Offerhaus, J., Rodriguez, E., Janney, F., Hoffman, E., Fox, J., Hunter, F., and Diavolitsis, S. Ultrastructure of the gastric mucosa harboring campylobacter-like organisms. Am. J. Clin. Pathol 1986;86:575-82.

101. Hazell, S.L., Lee, A., Brady, L., and Hennessy, W. Campylobacter pyloridis and gastritis: association with intercellular spaces and adaptation to an environment of mucus as important factors in colonization of the gastric epithelium. J. Infect. Dis. 1986;153:658-63.

102. Goodwin, C.S., Armstrong, J.A., and Marshall, B.J. Campylobacter pyloridis, gastritis, and peptic ulceration. J. Clin. Pathol. 1986;39:353-65.

103. Shousha, S., Bull, T.B., and Parkins, R.A. Gastric spiral bacteria (letter). Lancet 1984;2:101.

104. Lee, A., O'Rourke, J.L., Barrington, P.J., and Trust, T.J. Mucus colonization as a determinant of pathogenicity in intestinal infection by Campylobacter jejuni: a mouse cecal model. Infect. Immun. 1986;51:536-46.

105. Takeuchi, A., Inman, L.R., O'Hanley, P.D., Cantey, J.R., and Lushbaugh, W.B. Scanning and transmission electron microscopic study of Escherichia coli 015 (RDEC-1) enteric infection in rabbits. Infect. Immun. 1978;19:686-94.

106. Cantey, J.R., Lushbaugh, W.B., and Inman, L.R. Attachment of bacteria to intestinal epithelial cells in diarrhea caused by Escherichia coli strain RDEC-1 in the rabbit: stages and role of capsule. J. Infect. Dis. 1981;143:219-30.

107. Cantey, J.R. The rabbit model of Escherichia coli (strain RDEC-1) diarrhea. In: Boedeker E.C., ed. Attachment of organisms to the gut mucosa. Florida: CRC Press, 1984:40-7.

108. Rothbaum, R.J., McAdams, A.J., Giannella, R., and Partin, J.C. A clinicopathologic study of enterocyte adherent Escherichia coli: a cause of protracted diarrhea in infants. Gastroenterology 1982;83:441-54.

109. Lee, A. Neglected niches. The microbial ecology of the gastrointestinal tract. In: Marshall, K.C. (ed.), Advances in microbial ecology, Vol. 8. Plenum Publishing Corp., New York, 1984:115-62.

110. Lee, A. Normal flora of animal intestinal surfaces. In: Bitton, G. and Marshall, K.C. (ed.), Absorption of microorganisms to surfaces. John Wiley & Sons, Inc., New York, 1980:145-173.

111. Lee, A., Logan, S.M., and Trust, T.J. Demonstration of a flagellar antigen shared by a diverse group of spiral-shaped bacteria that colonize intestinal mucosa. Inf. and Immun. 1987;55:828-31.

112. Luck, J.M. and Seth, T.N. Gastric urease. Biochem. J. 1924;18:1227-31.

113. Dullava A.M., Markley, K., and Davies, R.E. The absence of gastric urease in germ-free animals. Biochim. Biophys. Acta. 1968;151:646-50.

114. Marshall, B.J. and Langston, S.R. Urea hydrolysis in patients with Campylobacter pyloridis infection (letter). Lancet 1986;1:965-6.

115. Rathbone, B.J., Johnson, A.W., Tompkins, D., Heatley, R.V., and M.S. Losowsky. Gastric ammonia production by Campylobacter pyloridis (abstract). Gut 1986;27:A1237.

116. Hazell, S.L. and Lee, A. Campylobacter pyloridis, urease, hydrogen ion back diffusion, and gastric ulcers (letter). Lancet 1986;2:15-7.

117. McNulty, C.A.M., Crump, B., Gearty, J., Davis, M., Donovan, I.A., Melikian, V., and Wise, R. The distribution of and serological response to Campylobacter pyloridis in the stomach and duodenum. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;174-5.

118. Marshall, B.J., McGechie, D.B., Francis, G.J., and Utley, P.J. Pyloric campylobacter serology (letter). Lancet 1984;2:281.

119. Lambert, J.R., Dunn, K.L., Pinkard, K., and Kaldor, J. Campylobacter pyloridis antibodies in human serum (abstract). Gastroenterology 1986;90:1509.

120. Skoglund, M.L., Whalen, J., Krajden, S., Bohnen, J., and Matlow, A. Detection of campylobacter pyloridis infection in a Toronto population with a simple, non-invasive assay of serum IgG antibodies (abstract). Am. J. Gastro. 1986;81:850.

121. Morris, A., Nicholson, G., Lloyd, G., Haines, D., Rodger, A., and Taylor, D. Seroepidemiology of Campylobacter pyloridis. N. Zealand Med. J. 1986;99:657-9.

122. Jones, D.M., Eldridge, J., Fox, A.J., Sethi, P., and Whorwell, P.J. Antibody to the gastric campylobacter-like organism ("Campylobacter pyloridis")--clinical correlations and distribution in the normal population. J. Med. Microbiol. 1986;22:57-62.

123. Steer, H.W. and Newell, D.G. Immunological identification of Campylobacter pyloridis in gastric biopsy tissue (letter). Lancet 1985;2:38.

124. Hui, W.M., Lam, S.K., Ho, J., Chau, P.Y., Lui, I., Lai, C.L., Lok, A., and Ng, M.M.T. Campylobacter-like organisms (CLOS) do not affect the healing of gastric ulcers (GU) (abstract). Gastroenterology 1986;90:1468.

125. Lanza, F.L., Rack, M.F., and Peterson, D.F. Eradication of campylobacter pyloridis with bismuth subsalicylate (abstract). Am. J. Gastroent. 1986;81:853.

126. Marshall, B.J., Whisson, M., Francis, G., and McGechie, D. Correlation between symptoms of dyspepsia and Campylobacter pyloridis serology in Western Australian blood donors (abstract). In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;188-9.

127. Skoglund, M.L. Personal communication.

128. Kaldor, J., Tee, W., McCarthy, P., Watson, J., and Dwyer, B. Immune response to Campylobacter pyloridis in patients with peptic ulceration (letter). Lancet 1985;1:921.

129. Kaldor, J., Tee, W., Nicolacopolous, C., Demirtzoglou, K., Noonan, D., and Dwyer, B. Immunoblot confirmation of immune response to Campylobacter pyloridis in patients with duodenal ulcers. Med. J. Aust. 1986;145:133.

130. Greenlaw, R., Sheahan, D.G., DeLuca, V., Miller, D., Myerson, D., and Myerson, P. Gastroduodenitis: a broader concept of peptic ulcer disease. Dig. Dis. Sci. 1980;25:660-72.

131. Rathbone, B.J., Wyatt, J.I., Worsley, B.W., Trejdosiewicz, L.K., Heatley, R.V., and Losowsky, M.S. Immune response to Campylobacter pyloridis. Lancet 1985;1:1217.

132. Hutchinson, D.N., Bolton, F.J., Hinchliffe, P.M., and Holt, A.V. Distribution in various clinical groups of antibody to Campylobacter pyloridis detected by ELISA, complement fixation and microagglutination tests. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;185.

133. Graham, D.Y., Klein, P.D., Opekun, A.R., Alpert, L.C., Klish, W.J., Evans, D.J., Evans, D.G., Michaletz, P.A., Yoshimura, H.H., Adam, E., and Boutton, T.W. Epidemiology of Campylobacter pyloridis infection (abstract). Gastroenterology 1987;92:in press.

134. Siurala, M. and Varis, K. Gastritis. In: W. Sircus and A.N. Smith (eds). Scientific Foundations of Gastroenterology. W. B. Saunders, Philadelphia, 1980, pp. 357-69.

135. Siurala, M., Sipponen, P., and Kekki, M. Chronic gastritis: dynamic and clinical aspects. Scand. J. Gastroenterol. 1985;20(suppl 109):69-76.

136. Fox, J.G., Edrise, B.M., Cabot, E.B., Beaucage, C., Murphy, J.C., and Prostak, K.S. Campylobacter-like organisms isolated from gastric mucosa of ferrets. Am. J. Vet. Res. 1986;47:236-39.

137. Cave, D.R., Taylor, N., Tuczynski, C., and Fox, J.R. Campylobacter-like organisms (CLO) from man and ferret: Towards an animal model of CLO induced disease (abstract). Gastroenterology 1986;90:1368.

138. Marshall, B.J., Armstrong, J.A., McGechie, D.B., and Glancy, R.J. Attempt to fulfil Koch's postulates for pyloric campylobacter. Med.J. Aust. (editorial). 1985;142:436-39.

139. Piper, D.W. Bacteria, gastritis, acid hyposecretion and peptic ulcer. Am. J. Austr. 1985;142:431.

140. Pyloric campylobacter finds a volunteer (editorial). Lancet 1985;1:1021-22.

141. Morris, A. and Nicholson, G. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH. Am. J. Gastroenterol. 1987;82:192-99.

142. Ramsey, E.J., Carey, K.V., Peterson, W.L., Jackson, J.J., Murphy, F.K., Read, N.W., Taylor, K.B., Trier, J.S., and Fordtran, J.S. Epidemic gastritis with hypochlorhydria. Gastroenterology 1979;76:1449-57.

143. Wiersinga W.M. and Tytgat, G.N. Clinical recovery owing to parietal cell failure in a patient with Zollinger-Ellison syndrome. Gastroenterology 1977;73:1413-7.

144. Gledhill, H., Leischester, R.J., Lightfoot, N., Barnard, J., Viney, N., Darkin, D., and Hunt, R.H. Epidemic hypochlorhydria. Br. Med. J. 1985;290:1383-8.

145. Peterson, W.L., Lee, E., and Skoglund, M. The role of campylobacter pyloridis in epidemic gastritis with hypochlorhydria (abstract). Gastroenterology 1987;92:in press.

146. Goodwin, S. and Bincow. Cimetidine and ranitidine activity against Campylobacter pyloridis and other campylobacters. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;167-9.

147. McNulty, C.A., Dent, J., and Wise, R. Susceptibility of clinical isolates of Campylobacter pyloridis to 11 antimicrobial agents. Antimicrob. Agents Chemother. 1985;28:837-8.

148. Czinn, S., Carr, H., and Aronoff, S. Susceptibility of Campylobacter pyloridis to three macrolide antibiotics (Erythromycin, Roxithrombycin [RU 28965], and CP 62,993) and Rifampin. Antimicrob. Agents Chemother. 1986;30:328-9.

149. Pinkard, H.J., Stockman, K.A., Davidson, A., Lambert, J.R. Campylobacter-like organisms from the human stomach - detectom, characteristics, and in-vitro susceptibilities. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;171-2.

150. Lambert, J.R., Hansky, J., Davidson, A., Pinkard, K., and Stockman, K. Campylobacter like organisms (CLO) - in vivo and in vitro susceptibility to antimicrobial and antiulcer therapy. Gastroenterology 1985;88:1462.

151. Lambert, J.R., Dunn, K.L., Turner, H., and Korman, M.G. Effect on histological gastritis following eradication of campylobacter pyloridis (abstract). Gastroenterology 1986;90:1509.

152. Humphries, H., Dooley, C., O'Leary, D., Bourke, S., McKenna, D., Power, B., Keane, C., Sweeney, E., and O'Morain, C.A. Effect of therapy on Campylobacter pyloridis - a randomised trial (abstract). Gut 1986;27:A611.

153. Wyatt, J., Rathbone, B.J., and Heatley, R.V. Campylobacter pyloridis and cimetidine (abstract). Gut 1986;27:A607.

154. Jones, D.M., Eldridge, J., Whorwell, P.J., and Miller, J.P. The effects of various anti-ulcer regimens and antibiotics on the presence of Campylobacter pyloridis and its antibody. In: Pearson, A.D., Skirrow, M.B., Lior, H. eds. Campylobacter III. Proceedings of the Third International Workshop on Campylobacter Infections. London: Public Health Laboratory Service, 1985;161.

155. Langenberg, M.L., Rauws, E.A.J., Schipper, M.E.I., et al. The pathogenic role of Campylobacter pyloridis studied by attempts to eliminate these organisms. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London. Public Health Laboratory Service, 1985;162-3.

156. Johnston, B.J., Reed, P.I., and Ali, M.H. The influence of treatment on campylobacter-like organism (CLO) presence and duodenal ulcer healing (abstract). Gastroenterology 1986;90:1480.

156a. Lambert, J.R., Borromeo, M., Korman, M.G., and Hansky, J. Role of Campylobacter pyloridis in non-ulcer dyspepsia - a randomized controlled trial (abstract). Gastroenterology 1987;92:in press.

157. Skoglund, M., Watters, K., and Taulbee, J. Bismuth concentration at site of campylobacter pyloridis colonization (abstract). Gastroenterology 1987;92:in press.

158. McNulty, C. M., Gearty, J.C., Crump, B., Davis, M., Donovan, I.A., Melikian, V., Lister, D.M., and Wise, R. Campylobacter pyloridis and associated gastritis: investigator blind, placebo controlled trial of bismuth salicylate and erythromycin ethylsuccinate. Br. Med. J. 1986;293:645-49.

159. Marshall, B.J., McGechie, D.B., Armstrong, J.A., and Francis, G. The antibacterial action of bismuth: early results of antibacterial regimens in the treatment of duodenal ulcer. In: Pearson, A.D., Skirrow, M.B., Lior, H., Rowe, B. eds. Campylobacter III: Proceedings of the Third International Workshop on Campylobacter Infections. London: Public Health Laboratory Service, 1985:165-6.

160. Shirokova K.L., Filomonov, R.M., and Poliakova, L.V. Metronidazole in the treatment of peptic ulcer. Klin. Med. (Mosk) 1981;59(2):48-50.

161. Zheng, Z.T., Wang, Z.Y., Chu Y.X. et al. Double-blind short-term trial of furazolidone in peptic ulcer (letter). Lancet 1985;1:1048-9.

162. Zhoa, H-Y, Li, G., Guo, J., et al. Furazolidone in peptic ulcer (letter). Lancet 1985;2:276-7.

163. Diaz, M.Q. and Escobar, A.S. Metronidazole versus cimetidine in treatment of gastroduodenal ulcer (letter). Lancet 1986;2:907.

164. Pounder, R.E. Duodenal ulcers that will not heal. Gut 1984;25:697-702.

165. Lam, S.K., Lee, N.W., Koo, J., Hui, W.M., Fok, K.H., and Ng M. Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose of cimetidine. Gut 1984;25:703-06.

166. Bianchi-Porro, G.B., Parente, F., Lazzaroni, M., and Ardizzone, S. Tripotassium dicitrato bismuthate versus two different dosages of cimetidine in the treatment of resistant duodenal ulcers (abstract). Gut 1986;27:A613.

167. Martin, D.P., May, S.J., Tweedle, H.D., Ravencroft, M.M., Miller, J.P. Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium cicitrato bismuthate. Lancet 1981;1:7-10.

168. Lee, F.I., Samloff, I.M., and Hardman, M. Comparison of tripotassium cicitro bismuthate tablets with ranitidine in healing and relapse of duodenal ulcers. Lancet 1985;1:1299-301.

169. Hamilton, I., O'Connor, H.J., Wood, N.C., Bradbury, I., and Axon, A.T.R. Healing and recurrence of duodenal ulcer after treatment with tripotassium diditrato bismuthate (TDB) tablets or cimetidine. Gut 1986;27:106-10.

170. Kang J.Y. and Piper, D.W. Cimetidine and colloidal bismuth in treatment of chronic duodenal ulcer. Comparison of initial healing and recurrences after healing. Digestion 1982;23:73-9.

171. Moshal, M.G., Gregory, M.A., Pillay, C., and Spitaels, J.M. Does the duodenal ulcer ever return to normal? A comparison between treatment with cimetidine and denol. Scand. J. Gastroenterol. 1979;14(Suppl 54):48-51.

172. McLean, A.J., Harrison, P.M., Ioannides-Demos, L., Byrne, A.J., McCarthy, P., and Dudley, F.J. The choice of ulcer healing agent influences duodenal ulcer relapse rate and long-term clinical outcome. Aust. NZ J. Med 1985;15:367-74.

173. Toukan, A.U., Kamal, F., Amr, S.S., Arnaout, M.A., and Abu-Romiyeh, A.S. Gasroduodenal inflammation in patients with nonulcer dyspepsia. Dig. Dis. Sci. 1985;30:313-20.

174. Kreuning, J., Bosman, F.T., Kuiper, G., v.d. Wal, A.M., and Lindeman, J. Gastric and duodenal mucosa in 'healthy' individuals. J. Clin. Path. 1978;31:69-77.