

Review article

Campylobacter pyloridis, gastritis, and peptic ulceration

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SUMMARY *Campylobacter pyloridis* is a spiral bacterium which was seen by histopathologists several years before it was cultured in 1982 in Perth, Western Australia. It has unique cellular fatty acids, predominantly tetradecanoic acid and cis-11, 12 methylene octadecanoic acid. It also has a unique ultrastructure which is different from that of other campylobacters. *C. pyloridis* possesses a powerful urease enzyme and produces large amounts of extracellular catalase. Both these features may be important virulence factors, allowing it to occupy a protected niche in the stomach below the mucus layer but above the gastric mucosa. Specific lesions are found in the gastric mucosa, and ultrastructural studies show the presence of adherence pedestals identical with those found with enteropathogenic *Escherichia coli* of the intestine. Histological examination of gastric biopsy tissue has shown that *C. pyloridis* is strongly associated with active chronic gastritis, when polymorphonuclear leucocytes are present, and is not found on normal mucosa except when a biopsy specimen from elsewhere in the stomach shows active chronic gastritis. When patients with symptoms caused by gastritis are identified dual antibacterial treatment, combining the action of bismuth in the stomach with a systemic antibiotic, can eradicate *C. pyloridis*, with remission of symptoms and restoration of normal epithelial morphology. Most peptic ulcers relapse after modern acid reducing treatment, and antibacterial treatment may be beneficial in preventing relapse.

Until a microbe is cultured and characterised, histopathological observation of the new organism in an unexpected site remains tantalisingly incomplete. In patients suffering from peptic ulceration there have been many reports of bacteria in association with the stomach mucosa,¹⁻³ in contrast to transient bacteria found above the mucus layer. In 1938 Doenges⁴ reported "spirochaetes" in the stomach in necropsy specimens, and Freedberg and Barron in 1940⁵ found "spirochaetes" in 13 of 35 gastrectomy specimens. Steer in 1975⁶ described bacteria closely related to the gastric mucosa under the mucus layer in association with gastritis but absent from the normal stomach. The bacteria were usually "apposed to the mucus-secreting cells," and there was "at least one filament projecting from one end of the bacterium." Ultrastructural illustrations^{6,7} indicated that the bacteria

were spiral, but Steer did not comment on this feature. He provided convincing evidence that these bacteria were not contaminants introduced at the time of biopsy and emphasised that polymorphonuclear leucocytes migrate through the gastric mucosa, presumably in response to the bacteria. Cultures of these endoscopic biopsy specimens yielded *Pseudomonas aeruginosa*,⁷ but this is not a spiral organism and was almost certainly an irrelevant contaminant. In May 1983 Steer submitted an article⁸ with scanning electron microscopic pictures of curved and spiral bacteria in large numbers on the surface of gastric type epithelial cells in the pre-pyloric area of the stomach and in areas of gastric metaplasia in the duodenal bulb, but the bacteria were not associated with the surface of intestinal type epithelial cells. They were found in 73% of patients with duodenal ulceration.

Since 1980 curved and spiral campylobacter like bacteria had been observed by Warren in endoscopic biopsy specimens from patients with gastritis and pep-

tic ulceration at the Royal Perth Hospital in Western Australia; the bacteria stained well by the Warthin-Starry method⁹ but were difficult to see with the haematoxylin and eosin stain. Marshall and Warren initiated a prospective study in 1982 that resulted in the culture from gastric antral biopsy specimens of micro-aerophilic campylobacter like organisms with a smooth coat and sheathed flagella arising from one pole of each organism.¹⁰ The first 34 biopsy specimens were cultured on standard campylobacter media and non-selective media for 48 hours without success. The thirty fifth specimen was incubated during the Easter holiday and was examined after five days, when a heavy growth of campylobacter like bacteria was observed on the non-selective medium. Subsequent specimens yielded these bacteria after three or four days of incubation but only on the non-selective medium; contaminants often covered the plates, so that only 11 isolations were achieved, although the bacteria were often seen in the Gram stain.¹¹ These spiral bacteria were named *Campylobacter pyloridis*,¹¹ and this name has now been validated.¹² *C. pyloridis* was detected histologically in a high proportion of the patients with gastritis and peptic ulcer; Marshall and Warren¹³ presented cogent arguments for the probable clinical importance of *C. pyloridis* in the aetiology of peptic ulcers when not associated with malignancy, or non-steroidal anti-inflammatory drugs.

A careful ultrastructural study of gastritis in 1979 by Fung *et al*¹⁴ included an illustration of curved bacteria, which "abutted directly on to the plasma-membrane of the mucosal lining cells, but were never seen within the cell," and thus were thought not to be clinically important.

In September 1983 a retrospective histological study by Rollason *et al*¹⁵ was accepted for publication; 42% of endoscopic gastric biopsy specimens showed spiral bacteria, undoubtedly associated with gastritis. Thus in 1982 in at least three separate laboratories in Southampton,⁸ Birmingham,¹⁵ and Perth, Western Australia⁹ gastric spiral bacteria were being visualised, but only in Perth were the organisms cultured.¹¹ *C. pyloridis* has now been isolated from patients with gastritis and peptic ulcer in England,^{16,17} Holland,¹⁸ Germany, United States of America, Canada, Japan, and Peru.¹⁹

Unique features of *C. pyloridis*

Campylobacter pyloridis is a fascinating microbe in its own right. The true spiral bacteria, which include *Campylobacter*, *Spirillum*, and *Vibrio* spp must be distinguished from spirochaetes, which have endoflagella or periplasmic fibres²⁰; these spirochaetes also include the human rectal spirochaete²¹ and an organism from

the gut of rodents.²² Analyses of *C. pyloridis* have yielded a DNA base composition of guanosine plus cytosine 35.8–37.1 mol percent,¹¹ which is within the campylobacter range. In contrast to nearly all other campylobacters, however, *C. pyloridis* possesses a powerful urease enzyme present in large amounts.^{18,23} Urea is present in food such as milk, and this would result in the organism surrounding itself with a cloud of ammonia that would effectively insulate it from the lethal effects of stomach acid. *C. pyloridis* also possesses large amounts of extracellular superoxide dismutase and catalase,²⁴ which may confer resistance to the oxidative killing mechanisms of phagocytes. *C. nitrofigilis*²⁵ and some aquatic campylobacters²⁶ possess a weak urease enzyme, and other campylobacters possess smaller amounts of extracellular or intracellular catalase.²⁴ *C. pyloridis* shows strong phosphatase activity in the phenolphthalein test, in which other campylobacters including "GCLO-2", an ordinary campylobacter isolated rarely from the stomach, are negative²⁷; the cellular fatty acid profile of GCLO-2 resembles that of *C. jejuni*,²⁷ and it may be a related biotype of *C. jejuni*.²⁸

Ultrastructural appearances and chemical analyses indicate that there are fundamental differences between *C. pyloridis* and other campylobacters.²⁹ *C. pyloridis* has a smooth surface with four to six unipolar flagella of sheathed type, each with a terminal bulb; it lacks the distinct pit like depression at each pole from which the single flagellum of other campylobacters arises.²⁹ Typically, campylobacters have a rugose cell wall, with unsheathed flagella without terminal bulbs.³⁰ Terminal bulbs have been seen on the flagella of *Vibrio cholerae*,³¹ and it seems inappropriate to designate these terminal structures as "paddles."

It is now accepted that the cellular fatty acid composition of bacteria is important taxonomically.^{32,33} The major cellular fatty acids of campylobacters are hexadecanoic (16:0), octadecenoic (18:1), and hexadecenoic (16:1).³⁴ In contrast, the major cellular fatty acids of *C. pyloridis* are tetradecanoic (14:0) and cis-methylene octadecanoic (19:0Δ), with a very small amount of hexadecanoic.²⁹ Recently, the cis-methylene octadecanoic acid was shown to be cis-11, 12-methylene octadecanoic,³⁵ correcting the original erroneous report of cis-9,10-methylene octadecanoic acid.²⁹ Respiratory quinones are also important chemotaxonomic markers. *C. pyloridis* lacks the methylated menaquinone-6,²⁷ which is found in all other campylobacters.³⁶ Evidence that a new bacterial genus has been discovered will have to await studies of cistron similarities,³⁷ and it is hoped that these will not be delayed too long.

C. pyloridis is very sensitive to most antibiotics; in liquid medium the minimum inhibitory

concentration₉₀ of amoxycillin is 0.25 mg/l, of benzyl penicillin 0.5 mg/l, and of erythromycin 0.25 mg/l.³⁸ *C jejuni* and *C fetus* are 10 to 100 times more resistant to these antibiotics.^{39 40}

Growth of *C pyloridis* in liquid media can be enhanced in many ways. The addition of blood will result in a heavy growth, but high counts can also be obtained in brain heart infusion broth plus 10% horse serum plus 0.25% yeast extract, provided that the depth of liquid is shallow.³⁸ Satisfactory growth can also be obtained in nutrient broth with 5% serum and 0.25% yeast extract in flat sided virus containers, or with shaking.

C pyloridis in vivo

C pyloridis can be isolated readily from endoscopic specimens of the gastric mucosa, but in a study of 103 specimens its distribution was found to be patchy.⁴¹ This observation has a direct bearing on the frequency with which *C pyloridis* has been alleged to occur in patients with duodenal ulcer. Evidence for a negative finding can only be accepted if sufficient specimens have been taken from different areas of the stomach, at least one from the antrum and one from the body. One specimen may not show *C pyloridis* when it is, in fact, present elsewhere in the stomach. A satisfactory medium for the isolation of *C pyloridis* is brain heart infusion agar base (Oxoid) with 7% horse blood and IsoVitalex 1% (BBL Microbiology Systems), vancomycin 6 mg/l, nalidixic acid 20 mg/l, and amphotericin B 2 mg/l; the plates should be undried, but they can be kept in a plastic container at room temperature for up to two weeks.⁴¹ Biopsy specimens can be kept in 0.5 ml 20% glucose at 4°C for at least five hours without loss of viability of *C pyloridis*.⁴¹

The importance of *C pyloridis* in the aetiology of gastritis and peptic ulcer, and the consequent possible value of antibacterial treatment in the resolution of these conditions remains highly controversial, at least in the minds of gastroenterologists. Microbiologists and histopathologists have been greatly impressed by the close association of *C pyloridis* with active gastritis^{13 15-19}; activity is indicated by the presence of polymorphonuclear leucocytes.^{13 42} *C pyloridis* is detected very rarely on normal mucosa and again the importance of taking at least one specimen from the antrum has been shown in a study of 150 patients with biopsy specimens taken from both the body and the antrum of the stomach; when *C pyloridis* was found on normal mucosa in the body the other specimen from the antrum always showed gastritis.⁴³ *C pyloridis* may not be detected due to poor technique by the gastroenterologist, the microbiologist, or the histopathologist; Marshall⁴⁴ warned that false negative findings can result from lignocaine being swal-

lowed before endoscopy, simethicone being given before biopsy, cimetidine in the stomach, which is slightly active against *C pyloridis*³⁸; the patient may have taken bismuth preparations or antibiotic drugs, biopsy forceps may have been contaminated with glutaraldehyde, or the biopsy specimen may contain no epithelium.⁴⁴ If the specimen is kept at room temperature for more than three hours *C pyloridis* may have died; in the laboratory the plates may not be fresh enough or may be too dry, and if primary isolation is attempted in a carbon dioxide incubator the humidity must be greater than 98%.⁴¹ The histopathologist may be unable to detect *C pyloridis* if the specimen contains mainly intestinal metaplasia or acid secreting mucosa, or if the Warthin-Starry stain is poorly prepared.⁴⁴

In one Dutch study of "healthy" volunteers *C pyloridis* was found in some of them, but in every one of these the gastric mucosa showed gastritis while the volunteers without gastritis did not have *C pyloridis*.⁴⁵

NON-ULCER DYSPEPSIA

Non-ulcer dyspepsia may be broadly defined as ulcer like symptoms in the absence of an ulcer crater. Clinicians seem unwilling to subdivide this group of patients into those with histological gastritis and those with a histologically normal mucosa. One reason for their reluctance may be the poor association between histological gastritis and symptoms which may be considered important.⁴⁶ Thus, although *C pyloridis* is associated with histological gastritis and is rarely found in normal mucosa, it may still be difficult to provide convincing evidence that *C pyloridis* is a pathogen, because the organism may be found in people with apparently few symptoms but with histological gastritis; and it may be absent in people who complain of dyspepsia but who have a normal mucosa. On careful questioning of patients, however, a remarkably consistent pattern of symptoms can be detected in patients subsequently found to have histological gastritis and *C pyloridis*. Apart from severe indigestion or abdominal pain, these symptoms are sternal, or epigastric burning or discomfort, reflux, burping, epigastric distension, periodic nausea, flatulence,⁴⁷ and halitosis. Currently, there may be little convincing evidence that gastritis gives rise to the symptoms of the non-ulcer dyspepsia syndrome.⁴⁸ Although there is no proof that duodeno-gastric bile reflux causes non-ulcer dyspepsia,⁴⁹ neither can peptic ulcer be ascribed to such reflux.⁴⁷ The importance of stress in the aetiology of non-ulcer dyspepsia and peptic ulcer is also unclear; patients with non-ulcer dyspepsia seem to suffer no more major life event traumas, such as a bereavement, than controls.⁵⁰ Cimetidine, which inhibits gastric acid secretion, has

been found to be no better than placebo in relieving the symptoms of non-ulcer dyspepsia⁵¹; nor does truncal vagotomy, which reduces acid output, relieve these symptoms.⁵²

Endoscopy is unreliable as a means of detecting histologically florid gastritis.¹⁴ Its main value is to determine whether a gastric or duodenal ulcer is present and to obtain several specimens for histology and microbiological processing. It is to be hoped that definitive studies of the importance of *C. pyloridis* will rely on histological evidence of the presence or absence of active gastritis in the body or the antrum of the stomach and not on endoscopic appearances. There are clear pathophysiological differences between the gastritis that accompanies a chronic erosion, the lesion of pernicious anaemia, the chronic gastritis which is alleged to be associated with increasing age, and the gastritis which is associated with peptic ulcer.⁵³ Non-steroidal anti-inflammatory drugs are notorious for causing haemorrhagic erosions, but these lesions are not necessarily associated with histological active chronic gastritis.

EPIDEMIC GASTRITIS WITH HYPOCHLORHYDRIA

In 1984 one of the authors (BJM) underwent an endoscopy and a gastric biopsy, which showed normal mucosa without bacteria. One month later 10^9 colony forming units of *C. pyloridis* in alkaline peptone water were swallowed, and eight days later a transient achlorhydric gastritis was experienced.⁵⁴ Symptoms included a brief episode of non-acidic vomiting, epigastric distension, malaise, and severe halitosis. On the tenth day biopsy specimens showed active chronic gastritis with polymorphonuclear cell inflammation in the antrum, and large numbers of *C. pyloridis* were seen and cultured. Electronmicroscopy showed that the antral epithelial cells had lost their characteristic pattern of alignment and had developed irregular bulging surfaces with depletion of microvilli and a severe reduction in the numbers of cytoplasmic mucus secretory granules. On the fourteenth day another biopsy specimen was taken; *C. pyloridis* was not found, polymorphonuclear cells were absent, and the ultrastructural changes had partially resolved. On the same day treatment was started with tinidazole 500 mg twice daily, and the symptoms resolved completely within 24 hours of the start of this treatment.

A study in Texas in 1978 of 37 healthy volunteers participating in a study of acid secretion was associated with 17 volunteers becoming rapidly and profoundly hypochlorhydric: nine of these had a mild illness with epigastric pain several days before hypochlorhydria was detected. Gastric mucosal biopsy specimens taken from subjects during the stage of hypochlorhydria showed severe fundal and antral gas-

tritis.⁵⁵ Retrospective analysis of the histological specimens showed that the volunteers with gastritis were infected with *C. pyloridis* (WL Peterson, personal communication). Acid secretion returned to baseline levels in 14 of 17 subjects after a mean of 26 days, and the severity of the gastritis diminished concurrently in seven of 10 subjects on whom biopsy was serially performed. The pH electrode was not sterilised between measurements, and gastric juice was returned to the stomach after being tested. Thus it would be possible for an infective agent to have been transmitted via a contaminated glass electrode. Similarly, in a Canadian study of gastric secretion four out of six previously healthy subjects developed hypochlorhydria after a transient illness: nausea, vomiting, and abdominal pain were reported.⁵⁶ No endoscopic abnormality was seen at one and eight months, but biopsy specimens showed active superficial gastritis, which resolved in one subject and became chronic in two. As in the previous study the pH electrode was not sterilised between measurements, and the gastric juice was returned to the stomach, because this was considered to be essential to avoid aspirating antacid, which might have resulted in loss of buffering effect. Again, analysis of the specimens suggested that in two subjects spiral bacteria were present in the biopsies. In this Canadian report there was a suggestion that the gastritis was a response to the presence of bacteria that colonised the stomach which had previously had a high intragastric pH. Such an argument is refuted by the Texas report⁵⁵ in which the volunteers had a normal stomach pH and then developed gastritis. In general, some authorities assert that the gastritis associated with *C. pyloridis* occurs after cimetidine treatment has raised the intragastric pH. Many patients with peptic ulcer, however, have high acid output and also have gastritis with *C. pyloridis*, and so again the argument is refuted by the facts.

Gastric and duodenal ulceration

The pathogenesis of gastric ulcer that shows malignant change is not clear. Gastritis may possibly precede the malignant ulcer, so that chronic inflammation induced by *C. pyloridis* may be an important factor in the aetiology of such an ulcer. Apart from ulcers due to non-steroidal anti-inflammatory drugs, gastric acid seems to be the main precipitating cause of gastric and duodenal ulcers. When acid secretion is reduced by drugs that act as H_2 receptor antagonists—namely, cimetidine and ranitidine,⁵⁷ or proton pump inhibitors such as omeprazole⁵⁸—healing of the ulcer can be observed by endoscopy. When tissue is taken from healed duodenal ulcers, however, most show evidence of moderate to severe inflammation and gastric epithelial

metaplasia at or adjacent to the site of the ulcer.⁵⁹ Whitehead stated that "ulcer and gastritis are invariably present in the same stomach"⁵³; the gastritis always affects the antrum in prepyloric ulcers and extends to a larger area in body ulcers.⁶⁰ There is some evidence that high gastric ulcers are always associated with gastritis in the area of stomach distal to the ulcer.⁶¹ Active chronic gastritis can be one cause of gastric ulcer,⁶² and gastric ulcers commonly occur in inflamed antral type mucosa.⁶³

The frequency with which *C pyloridis* has been found in patients with duodenal ulceration has varied; even when tissue was taken only from the gastric antrum, 95% of 61 patients were found to have the organism.⁶⁴ In 16 patients additional specimens were taken from the duodenum, stomach, and oesophagus; *C pyloridis* was identified in the duodenal mucosa proximal to the ulcer within the stomach but not in the oesophagus. Ninety four per cent of the patients with peptic ulcer also had associated gastritis.⁶⁴ The skill of the endoscopist in choosing correct areas to biopsy and the strictness with which a peptic ulcer is defined could influence the final percentage of patients with ulcers found to have *C pyloridis*. In one small study in Holland all 15 patients with duodenal ulcer and nine of 10 patients with gastric ulcer were found to have the organism.⁴⁵ In another study in which only two specimens were taken for histology, but not all specimens were cultured, seven of 70 patients with duodenal ulcer did not have *C pyloridis*, neither did 13 of the 40 patients with gastric ulcer.⁴⁴

Until the importance of gastritis in the pathogenesis of gastric and duodenal ulcers is clearly established, the exact place for antibacterial treatment will remain unresolved.⁶⁵

Is *C pyloridis* a commensal, an opportunist, or a primary pathogen?

Firstly, it should be determined whether *C pyloridis* is associated with a specific lesion which can be detected ultrastructurally, and, secondly, whether or not this lesion occurs in the absence of the organism. Specific serum antibodies should be detected in patients from whom *C pyloridis* can be cultured, and IgA antibodies should be found in the gastric juice of patients. These antibodies should be less common and at a lower titre in patients without the organism. Specific antibacterial treatment directed against *C pyloridis* should also reverse the specific lesions and relieve the symptoms of infected patients.

Ultrastructural features of infection with *C pyloridis* and their reversal after treatment with antibiotics

Ultrastructural studies of antral tissue have been per-

formed in the Royal Perth Hospital since 1982.¹² Invariably, the presence of *C pyloridis* has been associated with a specific lesion in which *C pyloridis* is intimately associated with the gastric mucosa.⁶⁵ Such a lesion was found in a 64 year old woman with a history of "nervous dyspepsia," which had started at the age of 18; she did not have a peptic ulcer (Fig. 1). This woman's father had also suffered from life long dyspepsia and two of three brothers had a confirmed duodenal ulcer. Her symptoms included burning epigastric pain after meals associated with acid reflux, a feeling of distension in the stomach after meals, nocturnal pain with burning and nausea, and episodes of colic. (Interestingly, the feeling of distension could be due to the fact that *C pyloridis* produces powerful enzymes, possibly resulting in the liberation of carbon dioxide. A controlled study of patients with duodenal ulcer showed increased partial pressures of carbon dioxide in the duodenum of patients after meals.⁶⁶)

She underwent endoscopy, and culture of the antral tissue yielded *C pyloridis*. Although macroscopically the stomach mucosa seemed to be normal, histology showed the presence of severe active chronic gastritis. The patient was given tri-potassium di-citrate bismuthate (DeNol), one tablet to be chewed an hour before meals and at night time: this is the same dose as is used for the treatment of duodenal ulcer. After 14 days she was able to stop taking the antacid medication and felt well. Endoscopy and biopsy were repeated after four and eight weeks of treatment, and *C pyloridis* was not detected in either of the biopsy specimens. Treatment with DeNol was then stopped, but three weeks later she again developed symptoms. At endoscopy the stomach and duodenum were again normal, but the biopsy specimen showed active chronic gastritis and *C pyloridis*. The patient was then given 28 days of treatment with DeNol supplemented with amoxycillin 500 mg thrice daily from the seventh to the 28th day. Her symptoms resolved in three days. One month and six months after completing the second course of treatment biopsy was performed which showed a histologically normal mucosa; *C pyloridis* could not be cultured. She has remained well for two years, has been able to eat any type of food, and has rarely used antacids.

For the ultrastructural studies on the patient specimens were processed in a manner already described.²⁹ Thin sections of the antral biopsy specimen before treatment with bismuth was started showed considerable abnormalities of the mucosal ultrastructure (Fig. 1). Most notably, the flattened luminal surfaces of normal mucus secreting epithelial cells were replaced by an irregular pattern due to dome like bulging or ragged flap like protrusion of the individual epithelial cells. Partial to complete loss of surface microvilli was also evident. Intracellular mucin gran-

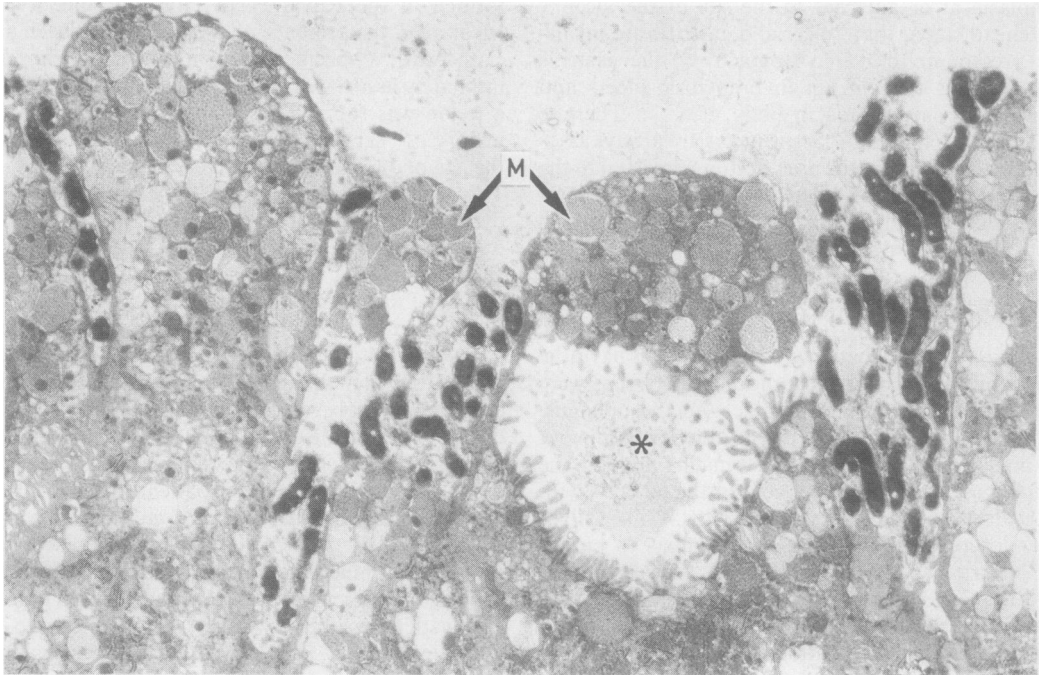


Fig. 1 Luminal surface of antral epithelium before treatment. Clusters of *Campylobacter pyloridis* lie close to bulging membranes of mucus secretory cells. Note retention of microvilli in isolated bacteria free pocket (*). M = mucin granules (Electron microscopy.) $\times 5750$.

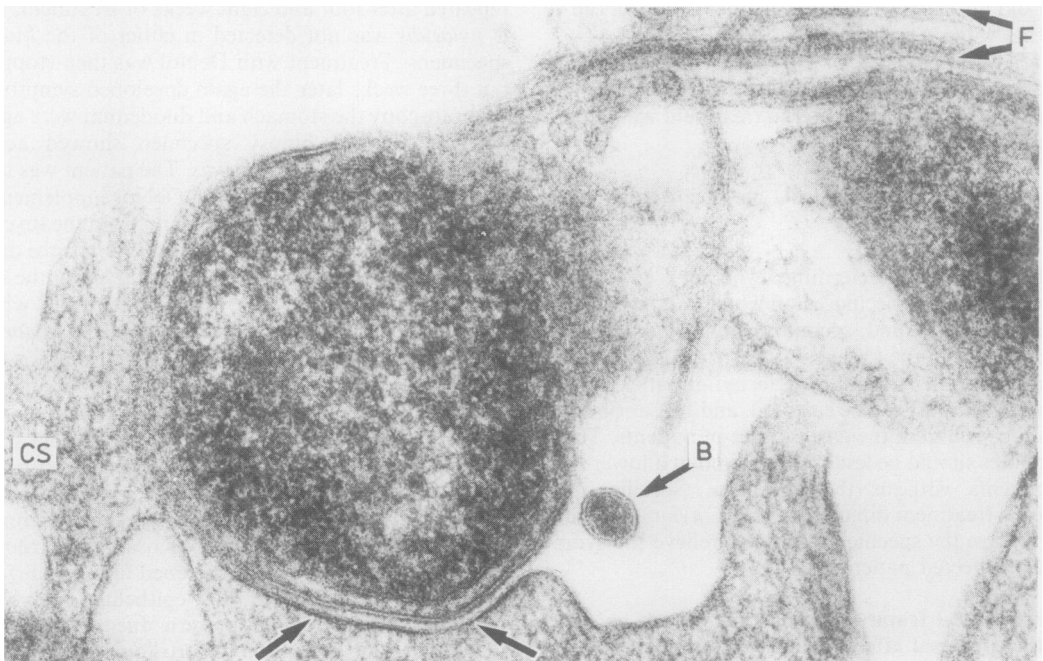


Fig. 2 Higher magnification shows intimate adherence between *Campylobacter pyloridis* and antral cell membrane (arrows). Cellular cytoskeleton (CS) shows random orientation. Sheathed flagellar profiles (F) and sectioned terminal bulb (B) are present. (Electron microscopy.) $\times 110000$.

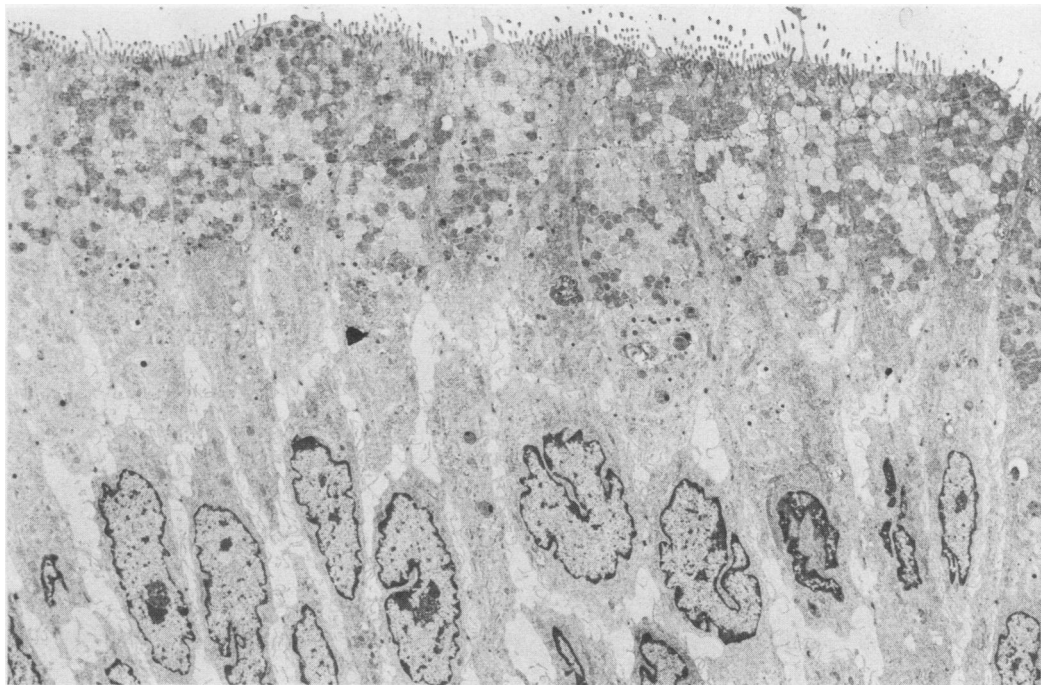


Fig. 3 Restored normal appearance of antral epithelium after four weeks of treatment with bismuth. (Electron microscopy.) $\times 2750$.

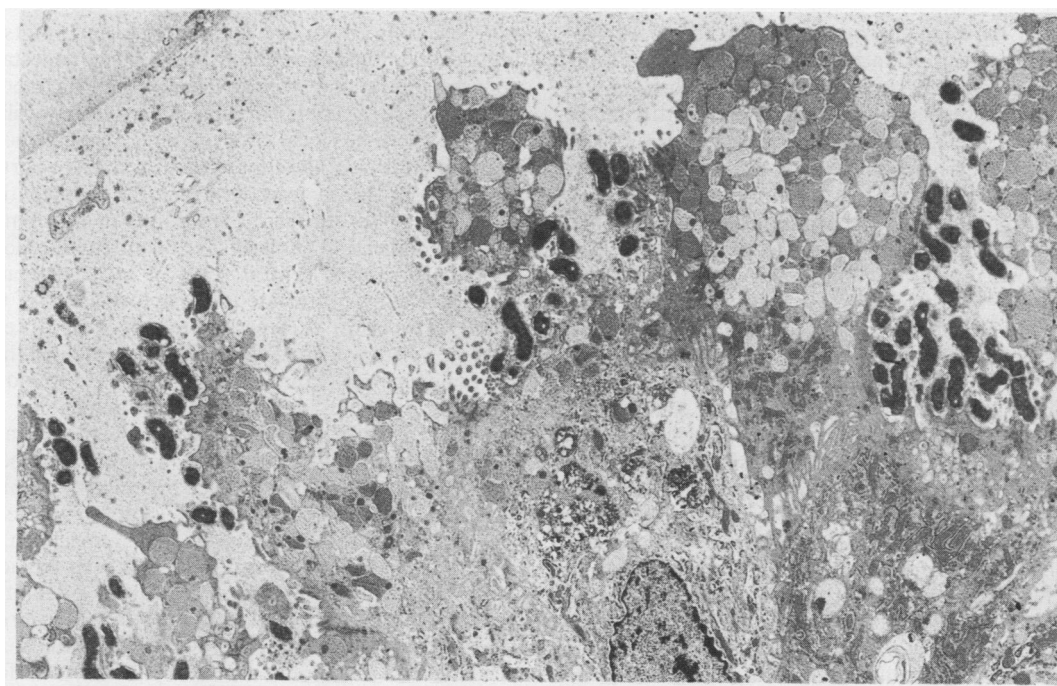


Fig. 4 Ragged flap like cell protrusions and associated *Campylobacter pyloridis* in antral tissue after clinical relapse. (Electron microscopy.) $\times 4500$.

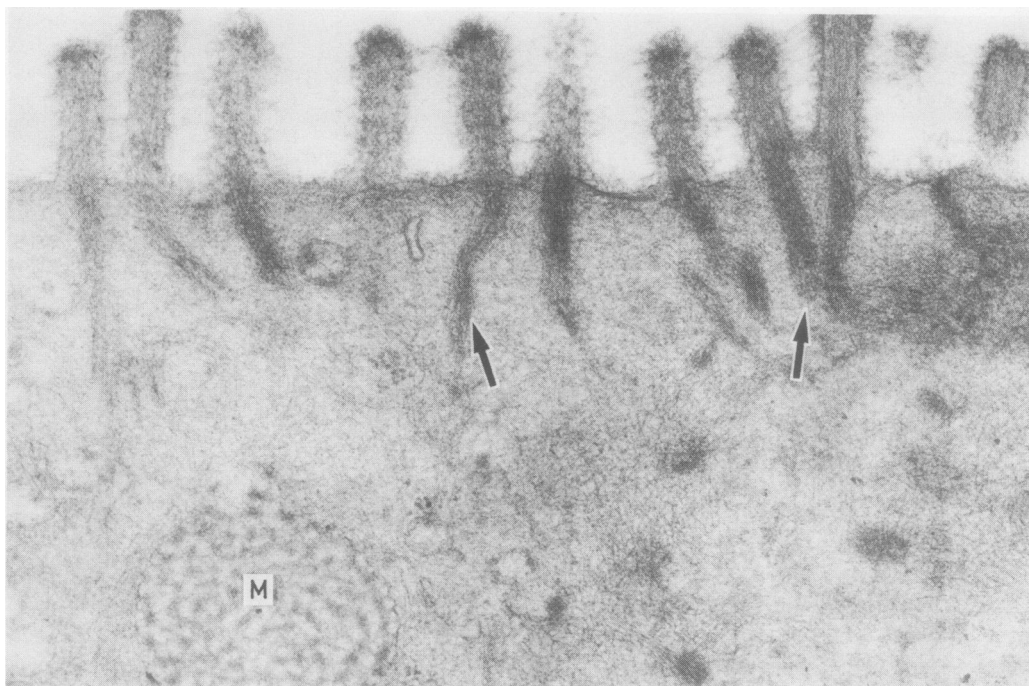


Fig. 5 Detail from antral specimen of normal appearance four months after completion of combined treatment. Restored microvilli have filamentous cores (arrows) entering cytoskeletal web. (Electron microscopy.) $\times 45\,000$.

ules were depleted and often confined to apical cytoplasmic protrusions. Intracellular oedema was prominent, but essential continuity of the epithelium was preserved through junctional complexes bordering the lumen and attachment to an intact underlying basal lamina. Superficial neck cells of the gastric pits were similarly affected, but the tubular glands themselves seemed to be normal. A sparse infiltrate of neutrophil polymorphs and lymphocytes was present in the lamina propria, and occasional neutrophils had crossed the basal lamina to penetrate between the epithelial cells while others lay free on the luminal surface.

Large numbers of curved rod like or spiral bacteria up to $3\,\mu\text{m}$ in length and about $0.5\,\mu\text{m}$ in width, were distributed singly or in clusters over the luminal surface of the epithelium, including the gastric pits. The bacteria had multiple unipolar sheathed flagella, which is characteristic of *C. pyloridis*. They were located deep to the layer of gastric mucus and close to the smooth bulging plasma membranes of the antral epithelial cells, often interspersed with remnants of detached microvilli. The bacteria seemed to be well preserved, and so presumably viable, and included dividing forms; no preferential orientation with respect to the epithelium was apparent; some lay end on and others lengthwise to the cell membranes. Where bacteria were numerous, cellular microvilli

were generally absent or much depleted, and points of intimate membranous adhesion (adherence pedestals) between the outer bacterial cell wall and distinctive concavities of the epithelial surface were clearly visible (Fig. 2). There was local "thickening" of the cell membrane in the area of the adherence pedestal. No particular parts of the bacteria seemed to be participating more fully than others in such points of adherence. High magnification showed loss of microvilli, along with the organised central cores of microfilaments, which normally contribute to the cytoskeleton of the apical cytoplasm. A few isolated pockets of epithelium, which were free of bacteria had retained their surface microvilli (Fig. 1). No profiles were found to suggest bacterial intracellular penetration, or attempts by epithelial cells at phagocytic ingestion of the organisms; but occasional *C. pyloridis* had been ingested by neutrophils, and such organisms appeared degraded and non-viable. A small island of epithelial metaplasia was found within the biopsy specimen, in which mucus secreting antral cells had been replaced by columnar intestinal type cells bearing a definitive brush border. Here infestation with *C. pyloridis* stopped, only to reappear on the far side of the metaplastic zone; the columnar cells showed no surface membrane changes like those of adjacent antral mucus cells. It seems that the organisms have a predi-

lection for adherence to typical mucus secreting antral epithelium.

After treatment with bismuth tablets alone the antral tissue (Fig. 3) showed an essentially normal mucosa without any spiral bacteria. Notable details were even alignment and general flattening of the luminal surfaces, restoration of short microvilli, and a considerable increase in the number of mucin granules in the supranuclear cytoplasm. The specimen obtained after clinical relapse showed reversal of the reparative process, with return of severe epithelial bulging or flap like protrusion and depletion of microvilli; spiral bacteria were again present in profusion (Fig. 4). In contrast, the final specimen taken four months after treatment with bismuth tablets and oral amoxycillin once again showed a normal well aligned epithelium, without any spiral bacteria. Microvilli were fully developed for the antral cell type, each exhibiting a prominent core of microfilaments reaching down into the submembranous cytoskeletal web (Fig. 5).

These ultrastructural studies of sequential specimens illustrate the specific lesion of *C pyloridis* and show that when the bacteria were eliminated the mucosa returned to normal. The pathological changes occurred both in the initial biopsy specimen before treatment and after clinical relapse following inadequate monotherapy. After completion of each treatment schedule there was a reversion to normal epithelial cell alignment and disappearance of the organisms. These observations clearly favour a cytopathogenic role for *C pyloridis*, with mucus secreting cells as the preferential target. An identical lesion was seen in the mucosa of a volunteer who swallowed *C pyloridis*,⁵⁴ and in all our other gastric biopsies this lesion was seen only in association with *C pyloridis*.

As *C pyloridis* affects gastric mucosal cells it is not surprising that the mucus content of the mucosal cells is greatly reduced. It can be envisaged that with a much reduced layer of mucus the mucosal cells might be more susceptible to gastric acid, possibly resulting in an ulcer. Numerous compounds such as alcohol, bile salts, and salicylates directly damage the stomach: these substances increase the permeability of the mucus barrier, allowing diffusion of acid into the mucosa with subsequent development of haemorrhage and mucosal erosion.^{67 68} Whether these compounds pave the way for infection with *C pyloridis* or whether they further weaken the mucosal protection after *C pyloridis* has caused gastritis and allow an ulcer to form is not yet clear. The layer of gastric mucus in the stomach almost certainly has a major role in protecting gastric epithelium from gastric acid.⁶⁹ The depth of mucus gel is an important consideration in terms of mucosal protection, because below a minimum depth luminal acid entering the gel

will overwhelm the bicarbonate secreted by the mucosa.⁶⁹ It is of great interest that *C pyloridis* maintains its motility in highly viscous material such as methyl cellulose, in which *Escherichia coli* becomes immobile.⁷⁰

SIMILARITY BETWEEN LESIONS CAUSED BY *C PYLORIDIS* AND THOSE CAUSED BY ENTEROPATHOGENIC *ESCHERICHIA COLI*

Enterotoxigenic *E coli* produce toxins, and other strains of *E coli* invade the mucosa. The pathogenesis of disease caused by enteropathogenic *E coli*, however, was obscure until Cantey and Blake⁷¹ described a strain of *E coli* (RDEC-1) in 1977, which reliably produced diarrhoea in rabbits without producing toxins or invading the mucosa. Subsequently, a few isolates of enteropathogenic *E coli* (EPEC) were shown to produce a small amount of shiga enterotoxin.⁷² Ultrastructural studies of *E coli* 015 (RDEC-1) infection in rabbits have shown specific lesions associated with the close adherence of the bacteria to the mucosa of the ileum, caecum, and colon. The microvilli are destroyed and disappear, and the bacteria rest on extrusions of epithelial cell plasma membrane, which can be seen to cup the bacteria, and which have been termed "adherence pedestals."⁷³⁻⁷⁵ Although the bacteria do not invade cells, degenerative changes are seen in cells with many adherent bacteria. An identical ultrastructural lesion has been observed in a rectal biopsy specimen from an infant with diarrhoea associated with *E coli* 0119.⁷⁶ Similar adherence pedestals and ultrastructural changes have been reported in gnotobiotic piglets with enteritis due to EPEC⁷⁷; polymorphonuclear leucocytes, plasma cells, and macrophages had infiltrated the mucosa and submucosa. Another organism that produces a similar lesion, and probably associated diarrhoea, is *Cryptosporidium*.⁷²

Our ultrastructural studies of *C pyloridis* here and elsewhere¹² have shown a similar picture, with adherence of *C pyloridis* to the mucosa, depletion of microvilli, disruption of submembranous cytoskeletal supporting microfilaments, and the development of adherence pedestals. The selectivity of the bacterial attachment is shown by sparing of metaplastic intestinal type columnar epithelium surrounded by affected antral mucus secretory cells. There was no evidence of epithelial cytolysis or intracellular parasitism. Mechanisms underlying the cytopathic effects have yet to be determined.

This ultrastructural evidence militates against the hypothesis that *C pyloridis* is associated with gastritis merely by colonising the mucosa after inflammation has occurred. The presence and precise location of *C pyloridis* in intimate relation to antral epithelium showing obvious changes, both at an initial case

presentation and after clinical relapse, together with the reversion to epithelial normality and disappearance of organisms after completion of each treatment schedule, are findings that clearly favour a pathogenic role for this organism. The return of inflammation and bacteria after monotherapy with DeNol would indicate that not all the organisms were eliminated. Support is given to this conclusion by a report from Holland, in which three patients who relapsed after monotherapy with DeNol or an antibiotic were subjected to endoscopic biopsies, and *C pyloridis* was cultured after relapse. The strains were analysed by Hind III restriction endonuclease analysis. Each strain produced a different profile from the other strain, but the isolate obtained after relapse was identical with the isolate obtained before treatment.⁷⁸ This indicated relapse rather than reinfection. In our patient treated concurrently with DeNol and a systemic antibiotic, however, the organism seems to have been completely eradicated and the patient has remained well for two years.

Immune responses to *Campylobacter pyloridis*

Methods of measuring antibodies to *C pyloridis* have varied considerably. Complement fixation titres are higher in patients with gastritis than in patients without gastritis, in blood donors, and in antenatal patients.¹⁷ A passive haemagglutination test has been described briefly.⁷⁹ Using this method 20% (216) of blood donors were found to have antibody to *C pyloridis* and these donors had more abdominal symptoms than the antibody negative donors. Passive haemagglutination, however, is not an easily standardised test and other workers have not found the test reliable (J Eldridge, personal communication). Enzyme linked immunosorbent assay (ELISA) is a well established method, but in some brief published reports the antigen used was a sonicate of *C pyloridis*,⁸⁰ or organisms killed by whole formalin.⁴³ In a study conducted in Melbourne it was reported that IgG antibody to *C pyloridis* was lower in "healthy" people than in patients with peptic ulcer.⁸⁰ In that study, however, histological data were not reported, and commenting on it Rathbone *et al*⁴³ emphasised that *C pyloridis* correlated very strongly with gastritis, but the relation of *C pyloridis* to peptic ulcer was probably due to coexistent antral gastritis. Thus the Melbourne study reported relatively high antibody titres in a few children but no histological data on these patients. Rathbone *et al*⁴³ reported considerably raised IgG and IgA serum antibody titres in patients from whom *C pyloridis* was cultured, but IgM titres were similar in groups positive or negative for the bacteria. They also detected IgA antibody against *C pyloridis* in the gastric juice of most colonised

patients, which was undetectable in normal subjects. If IgA antibody is not present in other transudates such as saliva then the local antibody response in the stomach would provide further evidence for a pathogenic role of the organism in chronic gastritis.

In the case of *C jejuni* ELISA results in infected patients were most reliable when an acid-glycine extract of the organism was used.⁸¹ Such an antigen is difficult to prepare for *C pyloridis* but is now in routine use at the Royal Perth Hospital; in bacteria negative patients very low titres of polyclonal antibody are found, but in most bacteria positive patients high titres are present (authors' personal observations).

Antibacterial treatment directed against *C pyloridis*

Although peptic ulcers are readily healed with acid reducing drugs, after such treatment is stopped the rate of relapse may reach 100% in patients followed up for two years.⁸² Marshall *et al*⁴⁴ showed that *C pyloridis* could be found in inflamed mucosa adjacent to a duodenal ulcer and they presented convincing arguments for the clinical importance of *C pyloridis* in gastritis and peptic ulceration not caused by non-steroidal anti-inflammatory drugs. A study by McClean *et al*⁸³ of the reports of ulcer relapse following different treatments showed that treatment with cimetidine produced higher rates of relapse than treatment with tri-potassium di-citrate bismuthate, or other "mucosal-protection agents". They also suggested⁸⁴ that cimetidine may promote ulcer relapse by raising intragastric pH to provide an ideal growth environment for bacteria.

The response of our patient (Figs. 1–4) showed that bismuth is antibacterial to *C pyloridis* but inadequate on its own to eradicate the organism. Treatment with amoxycillin alone is also usually followed by relapse and reappearance of the organism.⁷⁸ This is not surprising, considering the sequestered niche where *C pyloridis* is found, below the mucus layer but above the gastric mucosa. By using combination treatment, however, similar to that described above, Marshall⁸⁵ was able to eradicate the bacterium in 15 of 17 patients with duodenal ulcer as assessed by repeat biopsy one month after treatment had been stopped. Thus treatment with both bismuth and a systemic antibiotic may be required to eradicate the organism. At present the optimum length of treatment is not known, nor whether *C pyloridis* can develop resistance to an antibacterial drug during treatment. Controlled trials showing healing of the ulcer with antibiotics have already been reported; metronidazole, which was active against 80% of isolates of *C pyloridis* in Perth⁴⁷ has been reported to heal peptic ulcers,⁸⁶ as has furazolidone.^{87 88}

Until the natural history of gastritis and its relation to peptic ulceration is fully understood, it will be impossible to plan the most rational treatment.⁶⁵ Conventional treatment regimens, which concentrate only on the immediate healing of a macroscopic ulcer crater, are clearly defective if they do not cure the disease, in addition to which they must be continued indefinitely. It is also illogical to confine treatment that relieves ulcer type symptoms to patients with ulcer craters. Many patients without an ulcer have identical symptoms associated with an identical histological lesion (active chronic gastritis), affecting large areas of their gastroduodenal mucosa. These patients must be more carefully studied and their symptoms evaluated as part of the spectrum of ulcer disease. Antibacterial treatment of all symptomatic patients with confirmed *C pyloridis* infection and patients with a high titre of antibodies to the organism must be carefully evaluated.

Future developments

C pyloridis has not been cultured from any organ other than the stomach in man, nor from the environment, and such studies will be eagerly awaited. Saliva from 33 patients with gastritis did not yield *C pyloridis* (authors' personal observations). *C pyloridis* is a fascinating new spiral organism that will be studied for its own sake. Already several of its features have been found to be unique—its cellular fatty acids, ultrastructure, and enzyme qualities. A study of cistron similarities should be made to determine whether it should remain in the genus *Campylobacter*, or be the first member of a new genus. The importance of *C pyloridis* as a human pathogen, however, will need to be proved in great detail to satisfy gastroenterologists. We hope that the importance of a histological diagnosis rather than the macroscopic appearance at endoscopy will be accepted as a basis on which to assess the pathogenicity of *C pyloridis*. As the pathogenic mechanisms of enteropathogenic *E coli* are more fully delineated they may indicate which avenues should be studied for *C pyloridis*, which has an identical method of mucosal adherence to that of EPEC. Serological tests of patients and controls must be undertaken with a clearly defined antigen and full assessment of all factors, which might show that a supposed control was, in fact, a patient. The role of antibacterial medicine in the long term treatment of peptic ulceration and gastritis will require double blind placebo controlled prospective trials, which are no doubt already being undertaken around the world. *C pyloridis* could be described as "a galactic intruder into gastroenterology". If and when it is finally accepted as a pathogen by practising clinicians and surgeons then no doubt more microbiology laborato-

ries will be required to isolate this organism from gastric biopsy specimens and perhaps other sources, and advice on antibacterial treatment will be sought. Immunoblot techniques may show the importance of different antigens in patients and healthy contacts, and those antigens which would be candidates for a vaccine may be delineated. *C pyloridis* is to be admired for its parasitism of a unique niche, where it "grazes" on the microvilli of cells which have the capacity for rapid regeneration, thus providing new pasture: because the underlying cells are not invaded the host will continue to live. Possibly, our modern stressful civilisation induces people to develop peptic ulceration, from which a few of the hosts do perish. Modern medicine has been kind to *C pyloridis*, however, in that the current antacids such as cimetidine and ranitidine alleviate the most serious symptoms and concomitantly make the stomach a more pleasant place in which *C pyloridis* can multiply.

Within the symptom complex of gastritis and peptic ulceration more study must be given to the cause of symptoms. Thus some duodenal ulcers give rise to very few symptoms until an episode of bleeding occurs. After acid reducing treatment duodenal ulcers can reappear without symptoms. Are the symptoms of peptic ulcer due to the ulcer itself or to concomitant gastritis? Patients with asymptomatic but bleeding ulcers may have less gastritis than patients with a highly inflamed gastric antrum but no duodenal ulcer.

Studies of acute transient gastritis should include an attempt to detect the presence of *C pyloridis* by biopsy or brushing of the gastric mucosa. Osler described such a condition^{89 54} and we have referred to two small outbreaks.^{55 56} Possibly, acute achlorhydric gastritis may be an unrecognised common minor illness, but if it leads to the more serious disorders associated with chronic gastritis then detailed examination of vomit from such cases, and even gastric biopsy will be warranted.

The presence of *C pyloridis* infection in apparently healthy subjects will continue to be problematical for those who maintain that the bacterium is a pathogen. Like most other chronic infections, however, such as tuberculosis, the success of *C pyloridis* as a pathogen may be partly due to the fact that it often induces a relatively asymptomatic but nonetheless infectious carrier state.

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research on *C. pyloridis* is at an early stage some references are to letters, journals, and abstracts. In several cases, however, we have seen submitted manuscripts that give full details of the studies, and we thank those authors.

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