Pyloric campylobacter infection and gastroduodenal disease

(see also page 431)

Barry J. Marshall, David B. McGechie, Peter A. Rogers and Ross J. Glancy

ABSTRACT In 1982, a new spiral Gram-negative bacterium which was similar to those of the genus *Campylobacter* was isolated from the gastric mucosa of 11 patients with gastritis. From then on, the organism was isolated in a further 114 of 267 patients who underwent antral biopsy in Fremantle Hospital between January 1983 and September 1984. During 1984, the bacterium was cultured from 88% of patients in whom it was detected histologically, and was not cultured from any patient with histologically normal gastric mucosa. The new bacterium, pyloric campylobacter, grew in three days on brain–heart infusion blood-agar at 37°C in an atmosphere with added CO_2. All isolates tested were sensitive to penicillin, erythromycin, tetracycline, cephalosporins, gentamicin and bismuth citrate; 80% of isolates were sensitive to metronidazole or tinidazole. It is suggested that pyloric campylobacter infection is a major factor in the causation of dyspeptic disease and peptic ulceration. Antibacterial regimens directed against the bacterium may provide a permanent cure for these chronic disorders.

(Med J Aust 1985; 142: 439-444)

After Warren observed that campylobacter-like organisms inhabited the gastric epithelium of patients with gastritis,[1] a study which was conducted between April and June 1982 in the Royal Perth Hospital led to the isolation of a new, Gram-negative spiral bacterium, pyloric campylobacter (PC). The bacterium was present in 57 of 100 patients who underwent gastroscopy, including all 13 patients with a duodenal ulcer and 14 of 18 patients with a gastric ulcer.[2-4] The new organism was very uncommon in patients with histologically normal mucosa, but was found in 38 of the 40 patients who were found to have polymorph infiltration of the mucosa representative of active disease. It appeared to inhabit the deeper (alkaline) layers of the antral mucus and, thus, was protected from the luminal gastric acid.

Because of the investigatory nature of the original work, the new bacterium was isolated only from 20% of the biopsy specimens in which it was evident on histological examination. The taxonomic status of the new bacterium was uncertain, and it could not be isolated reliably. This research was continued in Fremantle hospital, and, in January 1983, isolation methods suitable for routine use were developed and the original observations of Warren[1] and Marshall[2] were confirmed.

The purpose of this paper is to communicate our preliminary data, so that others may test the validity of our observations. We found that pyloric campylobacter can be easily isolated in a standard clinical microbiology laboratory. The organism is associated with biopsy-proven gastritis and is rarely found in gastric biopsy specimens which show no evidence of inflammation. We postulate that pyloric campylobacter is a common and important gastrointestinal pathogen.

Patients and methods

The patients were seen by B.J.M. at a joint endoscopy session with a gastroenterologist during 1983, and at a dyspepsia research clinic established by B.J.M. in 1984. In 1983, biopsies were performed only in patients with ulcers. When microbiological techniques became sufficiently advanced, biopsy specimens were taken also from patients with normal findings at gastroscopy, so that histologically normal samples of gastric mucosa could be obtained. These specimens were cultured to see if pyloric campylobacter were present as a commensal of normal tissue, perhaps in numbers too small to be visible in histological sections.

In 1984, most of the patients who underwent biopsy came from the dyspepsia research clinic, and were referred specifically to have the diagnosis of pyloric campylobacter infection excluded after other investigations had failed to provide a diagnosis. Patients with known duodenal ulcer disease were also referred for investigation after reports of the new bacterium appeared in the local press. The 1984 group of patients represented a consecutive series in which data were complete, and these data were analysed separately.

At the time of writing, antral biopsy specimens for histological examination had been obtained from 350 patients; in 267 of these the material was also sent for culture. Microbiological data were entered onto a computer database. A brief recording of the endoscopy findings was made at the time of the examination. Gastric ulcers were defined as those which were visible from within the stomach and which did not have their major portion within the pyloric canal. Duodenal ulcers, therefore, included nearly all pyloric canal ulcers. The findings in all other patients, except those with carcinoma, were recorded as "dyspepsia, no ulcer". No records were kept of patients in whom a biopsy was not performed.

Analysis of data

The data were analysed to find the answers to the following three questions: What proportion of patients with peptic ulceration had pyloric campylobacter infection?; In patients without pyloric campylobacter infection, what other factors could be indentified which might predispose to ulceration?; How efficient were the microbiological techniques in use?

Names of patients with ulcers were obtained from the endoscopy record book. The microbiology record was then examined and pa-

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tients with ulcers in whom PC was found (by means of either culture or Gram-staining) were detected. In the remaining patients with ulcers, detailed examination of haematoxylin–eosin-stained sections (for gastritis) and silver-stained sections (for bacteria) was undertaken. For the purposes of this study it was assumed that all patients with pyloric campylobacter infection had gastritis. This assumption was made on the basis of the study of Marshall and Warren who found that the prevalence of gastritis in PC-infected patients was 96% in a single antral biopsy.[3] Gastritis and PC infection may be patchy, so if two or more biopsy specimens are taken (as we now do), the prevalence of gastritis in patients with positive results of investigations for PC approaches 100%.

The isolation rate was determined using the data from all patients in whom gastroscopy was performed by B.J.M. between January and September 1984. "PC-negative" patients were defined as those in whom the bacterium was not detected by means of Gram-staining, or culture, or haematoxylin–eosin or silver-stained histological sections. Only the results of the initial biopsy specimen examination were used for analysis, as in many patients a biopsy was repeated after treatment and no organisms were then isolated in culture. (Detailed clinical and histological findings of treated patients will be reported when an adequate follow-up period has elapsed.)

Endoscopy and biopsy

Patients were fasting and received no ulcer therapy for at least four hours before endoscopy. Simethicone was not administered before the procedure. The patients gargled with (but did not swallow) 5 mL of 2% lignocaine (Xylocaine viscous) in 10 mL of water. (In-vitro tests have shown that high concentrations of simethicone [Mylicon], lignocaine [Xylocaine], ranitidine and cimetidine inhibit the growth of PC [B.J.M., unpublished observations]).

The biopsy forceps were sterilized after each patient by soaking in a 2% solution of glutaraldehyde (Aldecyde) and allowing them to dry. They were rinsed in tap water before the first biopsy specimen was taken. Three antral biopsy specimens were taken from each patient, the first one for microbiological examination and two others for histological studies. Biopsy specimens were taken from mucosa within 5 cm of the pylorus — the culture specimen from the greater curve (the site was not critical), one histology specimen from the greater curve and the other from the lesser curve. It was not necessary to obtain red mucosa to demonstrate either bacteria or gastritis. The tissue was removed from the forceps with a sterile needle and placed in a single drop of transport solution (three parts of normal saline, one part of 50% dextrose) in a sterile Petri dish. The specimen was either examined in the laboratory within an hour or was refrigerated.

Two biopsy specimens were necessary for histological examination to ensure that at least some antral-type epithelium was presented to the pathologist. Areas of intestinal metaplasia, if included, were found not to contain bacteria. Histological specimens were fixed in buffered formol saline and stained with haematoxylin–eosin, periodic acid–Schiff (PAS), and Warthin–Starry silver.

Microbiological investigations

While still in the Petri dish, the specimen was finely minced with two scalpel blades. One-quarter of the minced specimen was spread on a glass slide and Gram-stained. The remaining tissue was smeared onto two plates — a non-selective brain–heart infusion agar (BHIA) plate with 7% horse blood, and a selective BHIA blood plate containing amphotericin (2 μg/mL) trimethoprim (5 μg/mL), nalidixic acid (10 μg/mL) and vancomycin (3 μg/mL). Moisture was an important prerequisite for growth, so the plates were stored in an airtight container within 24 hours of pouring. Media were incubated after inoculation at 37°C in a microaerophilic "campylobacter" atmosphere (Oxoid BR56) or in a 10% carbon-dioxide incubator (Forma Scientific 3336). Culture was continued for six days before it was considered to be "negative" if no growth had occurred. To maintain viable colonies, PC were subcultured every five days onto fresh media. Isolates were vacuum-dried from the liquid state after the suspension of a three-day growth in a solution of glucose (250 g/L) in brain–heart infusion broth, and stored at −20°C (D.I. Annear, personal communication).

Biotyping was performed by P.A.R., using the methods of Cowan and Steel.[5] Where growth in broth was required, the plate biopsy method of Phillips was used instead.[6] Hippurate hydrolysis was carried out by the method of Harvey.[7] Growth in glycine and in a 3.5% solution of sodium chloride was tested by incorporating the test substance into BHIA with 7% horse blood.

False-negative findings

The possible causes of false-negative findings are listed as follows:

Endoscopy
- Lignocaine swallowed.
- Simethicone given before biopsy.
- Patient taking bismuth preparations or antibiotic drugs.
- Cimetidine or ranitidine tablet in the stomach.
- Biopsy forceps contaminated with gluteraldehyde.
- Biopsy specimen contains no antral epithelium.

Microbiology
- Specimen kept at room temperature for more than three hours.
- Plates not fresh enough or too dry.
- Incubator not sufficiently humid.

Histology
- Specimen contains mainly intestinal metaplasia.
- Specimen contains mainly acid-secreting mucosa.
- Low numbers of bacteria and poor silver stain.

Results

Microbiological findings

PC were the predominant bacteria seen in Gram-stained gastric mucosa (Figure 1). The characteristically curved Gram-negative rods were so distinctive that, in some cases, a positive identification could be made on the basis of a single organism.

On the media described, PC grew in transparent, 1 mm diameter, weakly beta-haemolytic colonies, which were visible after three to six days of incubation (Figure 2) and were usually the only colonies on the selective medium.

When grown on artificial media, the bacteria did not have the typical "campylobacter" shape, but were present as curved

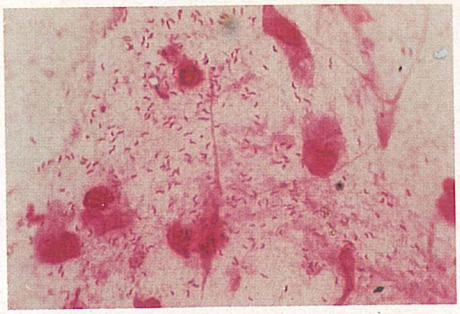


FIGURE 1: Large numbers of PC organisms in smeared mucus from the antral biopsy specimen of a 56-year-old woman with undiagnosed dyspepsia. (Gram stain; original magnification × 900.)

FIGURE 2: Heavy growth of PC from the antral biopsy specimen of a 20-year-old man with duodenal ulcer after four days' incubation. The transparent colonies are best viewed by reflected light. The larger white colonies are commensal flora of the mouth. (Non-selective BHIA+7% horse blood medium.)

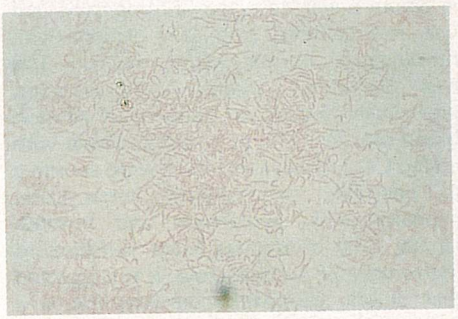


FIGURE 3: A three-day culture of PC. The bacteria are longer, are rarely of the typical shape, and often are U-shaped. (Gram stain; original magnification × 900.)

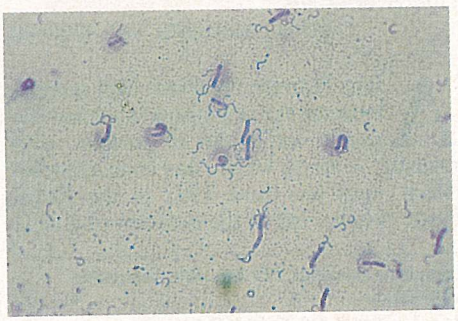


FIGURE 4: A three-day culture of PC. Most well-preserved organisms have flagella at one end, which rarely number more than four. Longer and dividing organisms have flagella at both ends. (Flagellar stain; original magnification × 1000.)

rods or U-shapes (Figure 3) — an appearance caused by the absence of separation of dividing organisms from their daughter cells.

Flagellar staining[8] showed up to four flagella, usually at one end (Figure 4). In older cultures, PC formed flagellated coccoid bodies, similar to those seen with *Campylobacter jejuni*.

Isolation rate. The isolation rate during 1984 is indicated in Table 1, in which the microbiological findings in the initial biopsy specimens taken from all patients who underwent gastroscopy by B.J.M. are recorded. There were 75 patients, of whom PC was demonstrated by Gram-staining or culture in 50 and by silver-staining alone in two. Culture was successful in 88% of biopsy specimens in which the bacteria were shown to be present by one or other method.

TABLE 1: PC isolation rate 1984*

	PC-positive	False-negative†	True-negative‡
Gram-staining	+ − +	−	−
Culture	− + +	−	−
Duodenal ulcer (n = 17)	0 4 11	0	2
Gastric ulcer (n = 9)	1 2 4	0	2
Dyspepsia, no ulcer (n = 49)	3 5 20	2§	19

* The results of the initial biopsies performed by B.J.M. in all patients during 1984. Antral gastritis was present in all patients with PC (52/52) and in two patients without PC (2/23).
† PC was found in silver-stained sections.
‡ No PC found by any method.
§ Both patients had undergone Billroth II partial gastrectomies.

Attempts to isolate PC from other sites. PC could not be isolated by culturing on the selective medium the nasopharyngeal swabs of five patients with proven PC infection and gastritis; routine faecal specimens (40% paediatric) from 60 patients; and urethral and vaginal swabs from 50 patients attending a venereal diseases clinic.

Biotyping and sensitivity to antibiotic agents. PC were (by definition) Gram-negative, oxidase-positive and catalase-positive bacteria. Detailed testing was carried out initially on 13 isolates. Optimal growth was obtained in a humid atmosphere with 10% carbon dioxide at 37°C. Biotyping and growth characteristics are summarized as follows (numbers of isolates tested in parentheses):

Oxidase (114)	+
Catalase (30)	+
Indole (13)	−
Nitrate reduction (20)	−
Hydrogen sulphide (13)	+
Hippurate hydrolysis (10)	+
Urease (13)	+
Glucose (acid) (13)	−
Growth	
In air (13)	−
Anaerobically (13)	−
Anaer. with 1% NO_3 (13)	−
10% CO_2 (114)	+
"Campy" (Oxoid BR56) (20)	+
Candle jar (5)	+
42°C (13)	+6, −7
25°C (13)	−
BHIA + 7% serum (13)	+
Skirrow's medium (13)	+
Chocolate agar (10)	+ (slow)
Blood agar (10)	+ (slow)
Nutrient agar (3)	+ − (v. slow)
1% glycine (13)	−
3.5% NaCl (13)	−

Antibiotic disc sensitivities are listed in Table 2; these were read after 72 hours' incubation, because growth was not visible before that time. A zone radius of less than 10 mm was taken as "resistant", except in the case of rifampicin. Penicillin zones varied down to 12 mm in two isolates, for one of which the minimum inhibitory concentration (MIC) was 0.1–1.0 μg/mL when tested by an agar plate dilution method. In 10 other isolates which were tested by the agar plate dilution method for sensitivity to ampicillin, MICs of 0.1 μg/mL and lower were observed. Sensitivity to metronidazole paralleled that to tinidazole, so we did not carry out testing of both drugs as a routine. Zones for tinidazole and metronidazole were either large or non-existent. The MIC for metronidazole was less than 1.0 μg/mL for six sensitive isolates tested by the agar plate dilution method. Bismuth citrate solution was found to have an antibacterial activity equal to that of liquid tripotassium dicitrato bismuthate (De-Nol). Ten PC isolates had plate MICs of less than 25 μg/mL for bismuth citrate or De-Nol. Rifampicin was included in the range of antibiotic agents tested, because it is concentrated up to a hundredfold in bile, which may make it more active in vivo than in vitro.[9] About 50% of isolates gave zones greater than 8 mm with a 2-μg rifampicin disc.

TABLE 2: Sensitivities to antimicrobial drugs

Drug	Disc content (μg)	Sensitivity	Usual zone radius (mm)
Penicillin	1.5	100% (53/53)	25
Erythromycin	15	100% (53/53)	30
Tetracycline	10	100% (53/53)	30
Tinidazole	5	70% (28/39)	25
Metronidazole	5	90% (11/12)	25
Gentamicin	10	100% (13/13)	25
Cephalothin	30	100% (13/13)	25
Bismuth citrate	50	100% (30/30)	25
Rifampicin	2	50% (15/30)	8

All 13 isolates tested were resistant to nalidixic acid, trimethoprim, and vancomycin.

Associations with disease

Duodenal ulcer. Data were available for 70 patients with duodenal ulcer (DU), of whom 63 (90%) had PC. Six of the seven patients in whom PC was not isolated had histologically normal antral mucosa. Two of these six patients were elderly and were taking non-steroidal anti-inflammatory drugs (NSAIDs); one had a pancreatic carcinoma attached to the base of a small pyloric ulcer; and one suffered from chronic alcoholism. The remaining two patients were women, one of whom had a small aphthous duodenal ulcer (3 mm in diameter). The other, who had both prepyloric and duodenal ulceration, had been noted to have histologically confirmed gastritis in 1982, after which De-Nol had been prescribed; however, she had not been taking this drug for several months.

The seventh patient in whom PC was not found had moderately severe chronic gastritis, but specimens for culture were not obtained.

Gastric ulcer. Antral biopsies were obtained from 48 patients with benign gastric ulcers (GU). Of these, eight patients had both DU and GU and were included in the DU group. Of the remaining 40 patients, PC infection was found in 27 (68%).

Of the 13 patients with GU in whom PC infection was not demonstrated, only one had gastritis, and no specimen for microbiological investigation was obtained from this subject. The 12 patients who did not have gastritis comprised nine with a recent history of NSAID ingestion; one who had taken cytotoxic drugs for non-gastric malignant disease and two who appeared to have no evidence of predisposing ulcerogenic factors.

Gastric carcinoma. Adequate antral type mucosal specimens were obtained in five patients with malignant gastric ulcers. Four of these patients (three with ulcers situated on the lesser curve and one with an ulcer on the greater curve) had histologically confirmed antral gastritis and PC was found on microbiological studies. The fifth patient had neither gastritis nor PC.

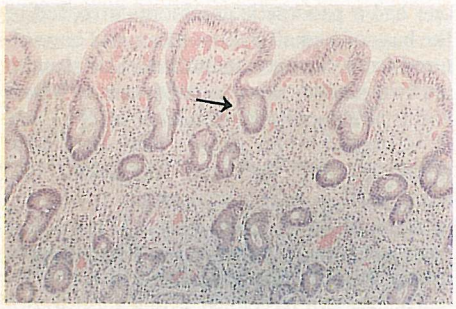
A biopsy was performed in four other patients with extensive gastric carcinoma, but "typical" gastric epithelium was not available for analysis. Pyloric campylobacter was not detected in these four patients, and the presence of antral gastritis could not be ascertained.

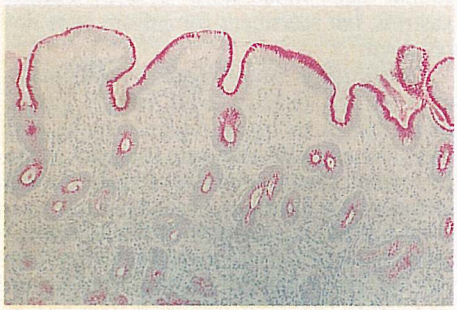
Patients without ulcers. Only the 1984 group of patients was analysed as it represented a consecutive series of patients in whom endoscopies were performed and could, therefore, be compared with other en-

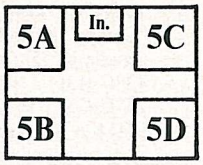
TABLE 3: Endoscopic findings in 49 patients without ulcers*

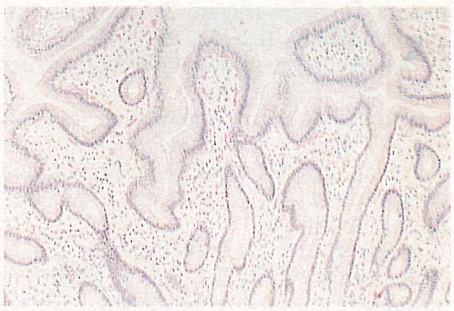
Finding	Total	PC-negative	PC-positive (any method)
Normal	24	10	14
Hiatus hernia or oesophagitis	9	3	6
Gastritis/duodenitis or minor erosions	6	2	4
Previous gastric surgery	10	4†	6‡

* 1984 group of patients (Table 1).
† Billroth II partial gastrectomy.
‡ Billroth II partial gastrectomy, 5 patients; highly selective vagotomy, 1 patient.









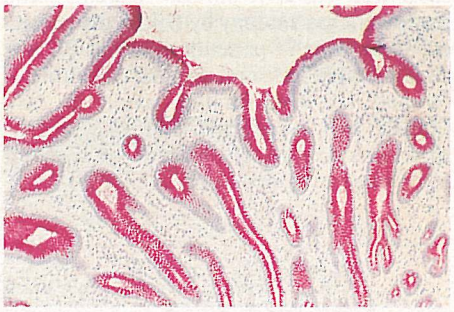


*FIGURE 5: Antral mucosa before and after eradication of pyloric campylobacter. **A.** Same patient as in Figure 1. Polymorphonuclear neutrophil leucocytes, lymphocytes, and plasma cells invade the lamina propria (haematoxylin–eosin stain; original magnification × 100). Inset: High-power view of gland (arrowed) shows PC organisms (original magnification × 900). **B.** PAS-stained section indicates mucus depletion of the surface and glandular epithelium (PAS stain; original magnification × 100). **C.** Mucosa after eradication of PC (De-Nol, one tablet three times a day before meals, and erythromycin 500 mg four times a day before meals, for 28 days). No polymorphonuclear cells are present, but a minor excess of mononuclear cells persists (haematoxylin–eosin stain; original magnification × 100). **D.** PAS-stained section shows normal mucus content of the epithelial cells (PAS stain; original magnification × 100).*

doscopy populations. The diagnosis made at gastroscopy (including "normal" findings) could not be related to the histological state of the mucosa or to the presence of pyloric campylobacter infection. The bacteria were common in patients without abnormality, as well as in those with oesophagitis and post-gastrectomy syndromes. It is worth noting that histological evidence of gastritis was not found in the four patients with a Billroth II gastrectomy who did not have PC infection (Table 3).

Discussion

The taxonomic status of the organism which we have called "pyloric campylobacter" has yet to be determined. The new bacterium does not reduce nitrate, and has a more complex structure than do the known campylobacters, which do not have multiple sheathed flagella and also lack many of the proteins and lipids present in PC.[10,11] However, the new organism resembles those of the genus *Campylobacter* in that it inhabits the gastrointestinal mucus; has a similar shape; is Gram-negative and oxidase-positive; grows best in an atmosphere with reduced oxygen and added carbon dioxide; has a DNA base pair ratio in the *Campylobacter* range (G+C = 36%);[3] and is unable to metabolize sugars. Our tests indicate a pattern of sensitivities to antibiotic agents which is similar to that of other campylobacters, including its susceptibility to metronidazole — an unusual feature in a bacterium which is not a strict anaerobe.[12]

The new bacterium may be the prototype for a new genus, but, for the present, its inclusion in the genus *Campylobacter* has practical advantages. Much of the expertise gained from studies on *C. jejuni* can be usefully applied to PC. The proposed taxonomic name, *Campylobacter pyloridis*, conveys the information necessary to recall its major characteristics and the diseases with which it is associated.[4]

It is known that the zones of inhibition obtained with disc-testing of slow-growing bacteria are only an approximate guide to MICs of antibiotic agents as determined by more accurate methods.[13] However, we used a disc sensitivity test as a practical laboratory alternative to the time-consuming agar plate dilution methods. These results seem to correlate with in-vivo studies. In limited clinical studies, we have eradicated PC with amoxycillin, tinidazole, metronidazole or erythromycin, usually administered concurrently with De-Nol tablets. Therapy with any of these agents, whether administered separately or together, leads to the resolution of gastritis (Figure 5).

Our results support the findings of other workers who have noted the association between PC bacteria and antral gastritis.[3,14-20] As noted in Table 1, in the patients in whom a biopsy was performed during 1984, the frequency rate of gastritis was 100% in the patients with PC (52/52), but this rate was only 8% (2/23) in the patients in whom PC was not detected.

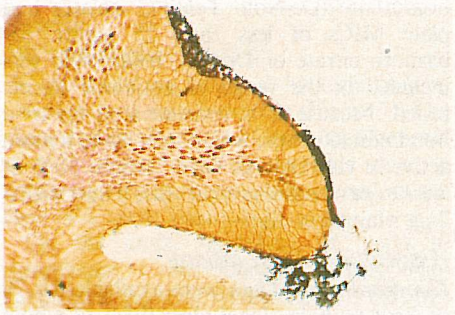


FIGURE 6: This biopsy specimen was taken from the proximal border of an ulcer in the mid duodenal cap. A thick black layer of adherent PC is seen. The mucosal cells are of gastric epithelial type. (Warthin–Starry silver stain; original magnification × 250.)

Marshall and Warren proposed that antral gastritis was caused by PC organisms and that the subsequent mucosal damage predisposed their patients to acid and peptic digestion (ulceration) by interfering with the mucus barrier.[3] This was supported by the observation that gastric ulcers most commonly occur in antral type mucosa affected by gastritis.[21] It is our contention also that this mucosal damage results from PC infection.

As an extension to the "antral gastritis" hypothesis, it seems reasonable to propose that PC also damages the duodenal epithelium, and is responsible for the duodenitis which is almost always present in patients with DU,[22] and which the usual ulcer remedies (except De-Nol) do not heal.[23] Duodenal ulcers usually occur at the junction between gastric (antral-type) epithelium and intestinal (duodenal-type) epithelium.[21] We propose that this mucosal junction is either ill-defined or more distal (that is, located in the duodenal cap) in patients with a familial tendency to duodenal ulceration. It was demonstrated by James in 1964 and by Patrick in 1974 that antral-type epithelium is commonly present in the duodenal cap of patients with duodenitis, and in duodenal ulcer borders.[24,25] Earlier investigators proposed that this "ectopic" antral-type mucosa was secondary to the hyperacidity present in patients with DU.

We suggest that antral-type epithelium in the duodenal cap is the primary phenomenon which, when colonized by PC organisms, leads to duodenitis and to subsequent ulceration. Colonization of this "antral-type" mucosa in duodenal ulcer borders by PC organisms has been

demonstrated by Gregory et al.,[26] and Sousha et al. have demonstrated this in patients with duodenitis.[27] Because it adjoins the antrum, the proximal border of a duodenal ulcer should be the more heavily colonized if PC are present. Unfortunately, a biopsy of the proximal DU border is often difficult to carry out with any accuracy. In most distal DU borders, however, antral epithelium with small numbers of adherent PC organisms can still be detected. Figure 6 shows the silver-stained section from a heavily colonized duodenal ulcer border.

We have paid particular attention to patients with peptic ulcers in whom PC organisms were not detected, because an alternative mucosal defect to gastritis may be operating in these patients. In the group of patients with duodenal ulcers, six patients did not have gastritis; in four of these there may have been a reason for mucosal damage, that is, intake of NSAIDs (two patients), carcinoma (one patient), and intake of alcohol (one patient).

The association between gastric ulcers and PC infection was less obvious, possibly because the stomach is exposed to ulcerogenic agents more than the duodenum. MacDonald noted the occurrence of gastric ulcers in histologically normal antral mucosa when patients were taking aspirin.[28] Of our 13 patients with GU in whom no PC was found, 12 had normal antral mucosa. Nine of these were taking NSAIDs at the time ulcers developed. It appears likely that ulcers which occur in the absence of gastritis and PC infection are directly related to the ingestion of NSAIDs.

Marshall and Warren observed that gastritis and PC infection were common, even in patients in whom no ulcer was found at endoscopy.[3] Although not all endoscopies are performed for the investigation of dyspepsia, many such PC-positive patients have the syndrome of "non-ulcer dyspepsia (NUD)" — at present a "non-diagnosis" for patients without any proven cause of their symptoms.[29] The frequency rate of antral gastritis is known to approach 50% in dyspeptic patients without an ulcer, regardless of the concurrent presence of other disorders, for example, oesophagitis.[3,30,31] It can be seen from Tables 1 and 3 that more than half our "no-ulcer" patients had PC infection and antral gastritis. Greenlaw et al. proposed that patients with antral gastritis, duodenitis, and peptic ulceration formed a continuum with identical histological changes in their mucosa and with similar symptoms.[32] He called the disease "gastroduodenitis". PC infection of the gastroduodenal mucosa might explain Greenlaw's observations. As shown in Figure 5B, mucus production is deficient in patients with pyloric campylobacter infection, possibly allowing even normal levels of acid secretion to penetrate the mucosa. When the bacteria are no longer present, mucus production (as evidenced by PAS-stained sections) returns to normal (Fig. 5D).

The presence of antral gastritis in patients with reflux oesophagitis may also be more than coincidence. Peptic damage to the oesophageal mucosa is related to the volume of the oesophageal reflux and its frequency. Both these factors will intensify when the stomach is full. Two recent studies have demonstrated impaired antral motility,[33] and delayed gastric emptying,[34] in patients with reflux oesophagitis, thus justifying the use of metoclopramide in the treatment of this disorder.[33] If individual patients are studied, it may be that only those with antral gastritis and pyloric campylobacter infection will be found to be suffering from gastric retention. If this is so, then reflux oesophagitis in a significant proportion of patients (60%) should respond to therapy with agents such as De-Nol or antibiotic drugs.

Previous research into the aetiology of duodenal ulceration has emphasized the role of acid rather than an underlying mucosal defect. As a consequence, the therapy has been directed towards a reduction of acidity, either by medical or surgical means. The "no acid, no ulcer" dictum of Schwartz[35] has also held true for gastric ulcer, although a mucosal defect has been given more consideration in the aetiology of this disorder. Nevertheless, most patients with either GU or DU have normal levels of acid secretion,[36] which implies that a mucosal defect must be of primary importance in both disorders.

A bacterial aetiology for gastritis and duodenitis could be applicable in most patients with peptic ulceration, and possibly also in a proportion of patients with non-ulcer dyspepsia. If pyloric campylobacter is the cause of the antral gastritis which is present in these conditions, it will be necessary to review the prevailing attitudes towards their management. In dyspeptic patients with proven pyloric campylobacter infection, the presence or absence of an ulcer crater may become irrelevant if therapy directed against pyloric campylobacter can be proven to heal ulcers and to prevent their relapse. In young patients with serological evidence of pyloric campylobacter infection, barium meal and endoscopic examinations may become unnecessary. A serological test for this infection is already in regular use in our hospital,[37] and in one centre overseas.[20]

Acknowledgements

We gratefully acknowledge the help of Dr I. G. Hislop who performed many of the procedures and who revised the text; we also thank Sandra Bierwirth, Meredith Poore, Deena Le-Page, Helen Tilley, Stephanie Myers and Fiona Reid for assistance with the many biopsies; Dr H. P. Lee for referrals; G. Francis for the cultures; and J. E. Holdsworth for the preparation of the silver-stained sections.

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(Received October 12; accepted December 12, 1984)

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