Helicobacter pylori[1] (formerly Campylobacter pyloridis/pylori) 1986–1989: A review

A C Maddocks

Introduction

In 1986 a clear and prescient review, "*Campylobacter pyloridis* gastritis and peptic ulceration," by Goodwin, Armstrong, and Marshall was published in this Journal.[2] What has happened since then? This short review mentions some evolving areas and new discoveries.

"Current interest worldwide is explosive," stated Tytgat,[3] but has the flow of new facts continued? Looking back at the review by Goodwin *et al*, it is striking that the information gained about *H pylori* between the early 1980s and 1985 was considerable. The organism and its chemical and ultrastructural characteristics were being explored and restriction endonuclease analysis had been used to investigate relations among isolates. Immunological, serological, and epidemiological studies had been done and some also related to the use of antibiotics. A firm association with "chronic active gastritis" was established and the problems raised by lack of visible macroscopic change at endoscopy noted. Treatment of duodenal ulcers with bismuth plus systemic antibiotics was already beginning to reduce the relapse rate (albeit with assessment at one month). It was recognised that gastritis was present in the stomach of patients with duodenal ulcers, although it was noted that the association between gastritis and the pathogenesis of ulcers had yet to be established. There was even a prototype of the "leaking roof" argument published by Goodwin in 1988.[4]

What has happened since 1986?

The rapid advances made by the pioneers was followed by a period of a much wider but slower and more amorphous growth of research. Recently, there has been a strong impetus towards the synthesis and clarification of this research. There were various interesting comments made by Goodwin *et al* in their section on future developments, including one remark which has proved prophetic: "The importance of *C pyloridis* as a human pathogen, however, will need to be proved in great detail to satisfy gastroenterologists." The development of two polarised groups of believers and sceptics who found antibiotic treatment, "intuitively offensive", has been a feature of the period commented on by Bartlett[5] and others.[6] Although understandable, this schism (most pronounced in the United States of America) probably hindered acceptance of the hypothesis (that *H pylori* is a human pathogen causing disease rather than a mere coloniser of damaged tissue) by clinicians and the well organised investigations needed to make further advances in the clinical field.

Other suggestions made by Goodwin *et al* in their review and which have been followed up are serological testing with clearly defined antigens with careful assessment of "supposed controls" and double blind placebo controlled prospective trials. The form "supposed controls" highlights the fact that some work published before wide experience had been gained produced false negative results. This provided ammunition for the sceptics. Most of the problems related to the patchy distribution of the organisms which was poorly understood, small numbers in samples, and the other causes of false negative results listed by Goodwin *et al*.[1] It is also, of course, possible to find positive histology and serology in those who claim to have no digestive problems. This invites speculation on the host-parasite relation.

There have been complaints that work on *H pylori* appeared only in abstracts and conference proceedings. This has now changed for the better. Over the past 12 months there has been a crystallisation of information and ideas in a monograph,[7] reviews,[3] and papers.[8–10]

Diagnostic techniques

Serology, histology, and bacterial culture are essential for research into the natural history of the infection and the validation of other diagnostic techniques. For ordinary clinical diagnosis it is hoped that non-invasive, rapid, and cheaper tests will be developed which would also be helpful for epidemiological studies. Obviously there will always be a need for endoscopy and biopsy in some patients to exclude malignancy, but rapid screening, and easy treatment follow up are very desirable goals.

TECHNIQUES USING UREASE PRODUCTION

Methods detecting the urease produced by *H pylori* offer rapid and virtually specific techniques for diagnostic use in outpatients and the possibility of non-invasive treatment and follow up (by breath tests). These are described in detail by Rathbone and Heatley.[7] These tests depend on the release of labelled carbon dioxide from labelled urea.

13C urea breath test

Described by Graham,[11] it was the first of this group. It has the major advantage that it is non-invasive and does not contain radioactive material. The disadvantage is that fewer hospitals have the relatively expensive isotope ratio mass spectrometer needed to perform it.

Department of Bacteriology, Wright Fleming Institute, St Marys' Hospital Medical School, Paddington, London W2 1PG
A C Maddocks

Correspondence to:
Dr A C Maddocks

Accepted for publication
8 November 1989

14C urea breath test[12-14]
This test uses a liquid scintillation counter which is much more widely available but the material is, of course, radioactive. Even though the dose is safe and very small, the radioactivity makes this a less attractive test for follow up repeats etc.

Apart from being non-invasive the other advantage of these tests in a notoriously "patchy" condition is that they investigate the entire mucosa rather than the small area provided by a biopsy specimen.

ENDOSCOPIC BIOPSY-UREASE TEST
McNulty's observation that there is enough preformed urease present in a biopsy specimen to give a rapid result when it is placed in a urea solution[15] has been followed by variants from many other workers. These modifications allow the test to be carried out in the endoscopy clinic in less and less time. Commercial tests can be bought in (CLO-test), but are considerably more expensive at £2.00 per test than the £0.05 per test for home made urease.[16]

ANTIGENS FOR SEROLOGY: A NEW GENERATION
Although relatively crude, whole organism antigens and lysates gave interesting early serological results, and it became obvious that there were some crossreactions with other bacteria, notably *C jejuni*. This could be particularly misleading in third world countries where *C jejuni* infections are very common. Although changing the ELISA cut off value and adsorbing sera have been tried, it is thought that better results could be obtained by using more highly purified antigens (second generation antigen). The urease is an obvious candidate and urease rich antigens have been successfully used by Bolton and Hutchinson[8] and Evans *et al*[9] and are recommended by the former to determine IgG antibody as a pre-endoscopy screening test.

Gastritis
Although the association between cultured *H pylori* and histological chronic active gastritis is accepted, there have always been occasional discrepancies which have upset the "gold standards". Bayersdörffer *et al* produced a study of the topographic association which must convince all but the most sceptical.[10] They studied 1000 biopsy specimens obtained from 10 sites in 50 patients and showed that the area of *H pylori* colonisation was larger than the area of gastritis. They suggest that two biopsy specimens will detect *H pylori* and that four should detect active chronic gastritis.

Oderda *et al* investigated gastritis and upper abdominal pain in children by biopsy, antibody, and serum pepsinogen 1 studies and showed that serum IgG concentrations and serum pepsinogen 1 could predict gastritis.[17]

Duodenal ulcers, duodenitis, and gastric metaplasia
The association between gastritis and duodenal ulcers is now well recognised, as is the restriction of *H pylori* colonisation to gastric type epithelial cells. The questions that arise next are, how does *H pylori* antritis relate to disease in the duodenum? What is the relation between gastric metaplasia, duodenitis, and duodenal ulcers? Johnston *et al* showed that *H pylori* can be seen by light microscopy in 96% of cases of duodenitis associated with duodenal ulcers.[18] Wyatt *et al*[19] and Carrick *et al*[20] explored the relation between *H pylori* duodenitis and ulcer formation and gastric metaplasia and heterotopic gastric mucosa. In a microscopic study of multiple duodenal and antral biopsy specimens from 137 subjects Carrick *et al* found that the presence of duodenal *H pylori* infection was a strong risk factor for the development of duodenal ulcers; cigarette smoking, age, sex and use of non-steroidal anti-inflammatory drugs were not significant risk factors. Carrick *et al* also postulated a synergic role for duodenal *H pylori* and endogenous acid production in the development of duodenal ulceration. (Functioning acid producing tissue could be found most often at the edge of duodenal ulcers but was also found in subjects without ulcers). They also suggested that most of the acid producing tissue would be destroyed by the time the ulcer was formed.

The multifactorial aetiology duodenal ulcers is now emphasised by several groups[21,22] and seems to be a theory more likely to appeal to clinicians trained on the premise of "no acid, no ulcer" than a heavy emphasis on *H pylori* infection alone. Goodwin's "leaking roof" theory is also a persuasive argument for multiple causation and "mending the roof"—that is, killing the bacteria, which cause the damage, which lets in the acid, which causes the ulcer.

TREATMENT
Reports on therapeutic trials of the type suggested by Goodwin *et al* are emerging and are in line with the hypothesis that continuing *H pylori* infection causes conditions which allow peptic ulcers to relapse.[23,24] Incidentally, the use of the word "eradicated" to mean "not detectable" is an unfortunate and misleading feature of many articles in this area, which could well be avoided.

HOST-PARASITE RELATION
There are several factors now being studied which may contribute to the pathogenicity of *H pylori*. Some relate to the organism, such as adherence factors and cytotoxin, and some to the host defences, such as mucus, prostaglandins, and plasma gastrin concentrations which overlap with classic gastroenterology.

Cytotoxins have been described by Leunk *et al*,[25] who found intracellular vacuolisation when they tested *H pylori* supernatant on tissue culture cells. Figura *et al* studied the association between cytotoxin production and ulcers.[26] Other cytotoxins have been obtained by sonication etc, but their role is uncertain. Urease presumably exerts some toxic effect, although its role may be more concerned with protection from the acid environment of the lumen, or

possibly, obtaining nutrients from the intercellular mucus. The enzyme seems to be associated with the bacterial outer membrane and periplasm.[27]

Mucinase, a protease which proteolyses gastric mucin, was investigated by Slomiany *et al*.[28] The action of this enzyme weakens the mucous gel and thins the barrier defending the epithelium from the luminal gastric acid.

The organism agglutinates red cells, and a fibrillar haemagglutinin was described by Evans *et al*,[29] found only in bacteria cultured on solid media. The characteristic adhesion sites, whose appearance is variously described as cup or pedestal, may be associated with a cell receptor glycolipid.

Lingwood *et al* described a substance in the lipid of red cells, human and pig stomach tissue, and HEp-2 cultured cells which was specifically recognised by whole *H pylori* organisms when separated by thin layer chromatography.[30] The substance is thought to be a novel glyceroglycolipid. It was present in the human stomach antrum to a greater extent than in the fundus and there was less in infant tissue than adult.

Although antibody dependent phagocytosis takes place, the organism also directly activates the classical complement pathway. Bernatowska *et al* suggest that this may explain the inflammatory reaction produced in the tissue, although there is no bacterial invasion.[31] Antibody seems to have little protective effect, and patients with severe hypogammaglobulinaemia are not particularly prone to attack by *H pylori*.

Work on host reponses is still at an early stage and reports are conflicting but the picture is beginning to take shape.

Mucin

Degradation of mucus and damage to the protective mucous coat are described by Slomiany *et al*,[28] who investigated enzymic degradation, and by Shida *et al*[32] and Tsuju *et al*,[33] who looked at histological changes in mucus in *H pylori* infections. Thomsen *et al* studied infected mucus and the possibility of H+ ion back diffusion.[34]

Prostaglandins

Tissue prostaglandins are thought to have a protective role in maintaining epithelial integrity. Tissue concentrations are lowered in some *H pylori* infections, and although findings are variable, it is agreed that in patients with duodenal ulcers prostaglandins are lowered.[35]

Gastrin

Plasma gastrin is raised in healthy subjects with positive *H pylori*, serology as well as in subjects with duodenal ulcer and antral colonisation.[36] Levi *et al* put forward "the gastrin link" between *H pylori* and duodenal ulcers as a unifying hypothesis.[37] They contended that *H pylori* stimulates gastrin release in duodenal ulcer disease, and this causes the well known increased gastric acid secretion. They propose testing their results by following up treated cases. Wagner *et al* contested this view because they did not find excess acid in patients who only had *H pylori* gastritis.[38]

Other "gastric spirals"

Work on *H pylori* has opened up other areas of research, particularly other mucus related spiral organisms in man and animals. In man "*Gastrospirillum hominis*,"[39] a tightly coiled gimlet-like organism (3·5–7·5 μm), was found in cases of chronic active gastritis, mainly in the gastric pits, not attached to the epithelium. It produces a powerful urease. The organism has not been cultured on artificial media. It is much rarer than *H pylori*, occurring about once for every 1000 *H pylori*. Other similar tightly coiled spirals are found in cats, dogs, and apes. *Campylobacter mustelae*, an organism similar to *H pylori*, is found in many ferrets' stomachs and infection can be associated with ulcers.

The studies by Lee of the mucosal and mucus associated bacterial flora[40] are well worth reading in the originals or in the beautifully illustrated chapter in the book by Rathbone and Heatley.[7] The spiral shape and urease production are shared by these mucus colonising bacteria. Many of these organisms are found in apparently healthy animals and the *H pylori* and *C mustelae* are unusual in that they produce some minor pathological changes, although they do not invade. For this reason Lee has referred to the group as "almost" normal flora.

The missing links

The mode of spread of *H pylori* is still problematic, although there are many pointers towards person to person spread by mouth. In addition to spread by electrodes during experiments, endoscopy and biopsy equipment have been incriminated.[41,42] This implies that adequate quantities of equipment and sterilising facilities to carry out endoscopy lists safely are essential. An elusive coccoid[43] form of the organism is thought to be relatively resistant and may be involved in faecal-oral spread, but evidence is so far lacking. The mode of spread is probably the single most important area for new research as it holds the key to prevention, as well as being microbiologically fascinating.

1 Marshall BJ, Goodwin CS. Revised nomenclature of Campylobacter pyloridis. *Int J Systemat Bacteriol* 1987; **37**:68.
2 Goodwin CS, Armstrong JA, Marshall BJ. Campylobacter pyloridis, gastritis, and peptic ulceration. *J Clin Pathol* 1986;**39**:353–65.
3 Tytgat Guido NJ. Campylobacter pylori: recent developments. *Eur J Gastroenterol Hepatol* 1989;**1**:3–41.
4 Goodwin CS. Duodenal ulcer, Campylobacter pylori, and the "leaking roof" concept. *Lancet* 1988;ii:1467–9.
5 Bartlett JG. Campylobacter pylori: Fact or fancy? *Gastroenterology* 1988;**94**:229–38.
6 Peterson WL. Antimicrobial therapy of duodenal ulcer? Hold off for now! (selected summary) reply by Marshall BJ. *Gastroenterology* 1989;**97**:508–10.
7 Rathbone BJ, Heatley RV, eds. "*Campylobacter pylori and gastroduodenal disease*". Oxford: Blackwell Scientific Publications, 1989.
8 Bolton FJ, Hutchinson DN. Evaluation of three Campylobacter pylori antigen preparations for screening sera from patients undergoing endoscopy. *J Clin Pathol* 1989;**42**:723–6.
9 Evans DG Jr, Evans DG, Graham DY, Klein PD. A sensitive and specific serological test for detection of Campylobacter pylori infection. *Gastroenterology* 1989; **96**:1004–8.
10 Bayerdorffer E, Oertrel H, Lehn N, *et al*. Topographic association between active gastritis and Campylobacter pylori colonisation. *J Clin Pathol* 1989;**42**:834–9.

11 Graham DY, Klein PD, Evans DJ, *et al. Campylobacter pyloridis* detected by the 13C -urea test. *Lancet* 1987;i:1174–7.
12 Bell GD, Weil J, Harrison G, *et al.* 14C—urea breath analysis, a non-invasive test for Campylobacter pylori in the stomach. *Lancet* 1987;i:1367–8.
13 Marshall BJ, Surveyor I. Carbon—14 urea breath test for the diagnosis of Campylobacter pylori associated gastritis. *J Nucl Med* 1988;**29**:11–16.
14 Rauws EAJ, Tytgat GNJ, Langenberg W, Royen EV. Experience with 14C Urea breath test in detecting C pylori. In: Menge H, Gregory M, Tytgat GN, Marshall BJ, eds. *Campylobacter pylori*. Berlin: Springer-Verlag, 1988:151–6.
15 McNulty CAM, Wise R. Rapid diagnosis of Campylobacter—associated gastritis. *Lancet* 1985;i:1443–4.
16 McNulty CAM, Dent JC, Uff JS, Gear MWL, Wilkinson SP. Detection of Campylobacter pylori by the biopsy urease test: an assessment in 1445 patients. *Gut* 1989;**30**:1058–62.
17 Oderda G, Vaira D, Holton J, Dowsett JF, Ansaldi N. Serum pepsinogen 1 and Ig G antibody to Campylobacter pylori in non-specific abdominal pain in childhood. *Gut* 1989;**30**:912–16.
18 Johnston BJ, Reed PI, Ali MH. Prevalence of Campylobacter pylori in duodenal and gastric mucosa—relationship to inflammation. *Scand J Gastroenterol* 1988;**23** (suppl 142):69–75.
19 Wyatt JI, Rathbone BJ, Dixon MF, Heatley RV. Campylobacter pyloridis and acid induced gastric metaplasia in the pathogenesis of duodenitis. *J Clin Pathol* 1987;**40**:841–8.
20 Carrick J, Lee A, Hazell S, Ralston M, Daskalopoulos G. Campylobacter pylori duodenal ulcer and gastric metaplasia: possible role of functional heterotopic tissue in ulcerogenesis. *Gut* 1989;**30**:790–7.
21 Graham DY. Campylobacter pylori and peptic ulcer disease. *Gastroenterology* 1989;**96**:615–25.
22 Wyatt JI. Campylobacter pylori duodenitis and duodenal ulceration. In: Rathbone BO, Heatley RV, eds. *Campylobacter pylori* and *Gastroduodenal disease*. Oxford: Blackwell Scientific, 1989:117.
23 Marshall BJ, Goodwin CS, Warcon JR, *et al.* Prospective double blind trial of duodenal relapse after eradication of Campylobacter pylori. *Lancet* 1988;ii:1437–42.
24 Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. Campylobacter pyloridis-associated chronic active antral gastritis. A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. *Gastroenterology* 1988;**94**:33–40.
25 Leunk RD, Johnson PT, David BC, Kraft WG, Morgan DR. Cytotoxic activity in broth culture filtrates of Campylobacter pylori. *J Med Microbiol* 1988;**26**:93–9.
26 Figura N, Guguelmetti P, Rossolini A, *et al.* Cytotoxin production by Campylobacter pylori strains isolated from patients with peptic ulcers and from patients with chronic gastritis only. *J Clin Microbiol* 1989;**27**:225–6.
27 Bode G, Malfertheiner P, Nilius M, Lehnhardt G, Ditschunheit H. Ultrastructure localisation of urease in outer membrane and periplasm of Campylobacter pylori. *J Clin Pathol* 1989;**42**:1578–9.
28 Slomiany BC, Bilski J, Sarsiek, *et al.* Campylobacter pyloridis degrades mucin and undermines gastric mucosal integrity. *Biochim Biophys Res Commun* 1987;**144**:307–14.
29 Evans DG, Evans DJ Jr, Moulds JJ, Graham DY. N-acetylneuraminyl lactose binding fibrillar haemagglutinin of Campylobacter pylori: a putative colonization factor antigen. *Infect Immun* 1988;**56**:2896–906.
30 Lingwood CA, Law H, Pellizzari A, Sherman P, Drumm B. Gastric glycerolipid as a receptor for Campylobacter pylori. *Lancet* 1989;ii:238–41.
31 Bernatowska E, Jose P, Davies H, Stephenson M, Webster D. Interaction of campylobacter species with antibody complement and phagocytes. *Gut* 1989;**30**:906–11.
32 Shida Y, Yoshida I, Inoto I, Suzuki S. Campylobacter pylori infection and mucin production of the gastric mucosa. *Gastroenterology* 1989;**96**:A466.
33 Tsuju M, Kawano S, Sato N, Kamada T. Campylobacter pylori infection decreases the intracellular mucin of human gastric mucosa. *Gastroenterology* 1989;**96**:A517.
34 Thomsen L, Tasman-Jones C, Morris A, Wiggin T, Lee S. Campylobacter pylori infected mucus presents a barrier to hydrogen ion movement—ammonia is important. *Gastroenterol Int* 1988;**1** (suppl 1):759.
35 Taha AS, McKinlay AW. Uphadhyay R, Kelly R, Russell RJ. Prostaglandins and Campylobacter pylori. *Lancet* 1989;ii:800–1.
36 Smith JTL, Founder RE, Evans DJ, Graham DY, Evans DG. Inappropriate 24 hour hypergastrinaemia in asymptomatic C pylori infection. *Gut* 1989;**30**:A732–3.
37 Levi S, Haddad G, Ghosh P, *et al.* Campylobacter pylori and duodenal ulcers: the gastrin link. *Lancet* 1989;i:1167–8.
38 Wagner S, Schuler A, Gebel M, Freise J, Schmidt FW. Campylobacter pylori and acid secretion. *Lancet* 1989; ii:562.
39 Anonymous. Gastrospirillum hominis. [Editorial.] *Lancet* 1989;ii:252–3.
40 Lee A, Hazell SL. Campylobacter pylori in health and disease; an ecological perspective. *Microb Ecol Health Dis* 1988;**1**:1–16.
41 Karim QN, Rao GG, Taylor M, Baron JH. Routine cleaning and elimination of Campylobacter pylori from endoscopic biopsy forceps. *J Hosp Infect* 1989;**13**:87–90.
42 Rokkas T, Pursey C, Uzoechina E, *et al.* Non-ulcer dyspepsia and short term De-Nol therapy: a placebo controlled trial with particular reference to the role of Campylobacter pylori. *Gut* 1988;**29**:1386–91.
43 Mégraud F. Campylobacter pylori: recent developments. Microbiological characteristics of Campylobacter pylori. *Eur J Gastroenterol Hepatol* 1989;**1**:5–12.