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Leading article

Helicobacter pylori and peptic ulcers: the present position

We are currently at a curious point in the evolution of treatment for peptic ulcer. On one hand it has been discovered that eradication of *Helicobacter pylori* offers an excellent solution to the problem of duodenal ulcer relapse. On the other hand most clinicians still choose to treat ulcers with regimens that do not offer this benefit. This could be dismissed as 'natural conservatism' or 'healthy scepticism' but the issue seems to be more profound. A doctor wishing to accept that *H pylori* and its eradication are important is immediately confronted with unresolved problems. Firstly, we have come to expect rational explanations, but some information on *H pylori* seems confused and in particular there is no consensus on how it causes ulcers. Secondly, there is no general agreement on how *H pylori* should be eradicated. This review discusses some of these problems and how they may be resolved.

The discovery: eradication of *H pylori* prolongs remissions

In 1981 Martin *et al* were surprised to find that duodenal ulcers stay healed for considerably longer after treatment with tri-potassium di-citrato bismuthate (De-Nol) than after H_2 antagonists.[1] *H pylori* was first cultured in 1983[2,3] and was identified in about 90% of patients with duodenal ulcer disease compared with a minority of control subjects.[4] Furthermore, De-Nol had anti-*H pylori* activity both in vivo[5,6] and in vitro.[7] For some time, the connection between these observations was not generally accepted. It was noted that some bismuth remained in the body for up to four months after De-Nol treatment[8] and that bismuth produces non-*H pylori* related benefits such as prostaglandin mediated cytoprotection.[9] Another idea was that H_2 antagonists might actually shorten remission by producing rebound hypersecretion of acid/pepsin, but there is little evidence to support this.[10] Recent findings have established that *H pylori* does have a major effect on relapse. The addition of antibiotics to De-Nol increases eradication from about 20% to about 80% and produces a futher considerable prolongation of remission.[11,12] Remissions last a year or more if *H pylori* is eradicated compared with only about four months if it is not.[11] Furthermore, recurrence after eradication is almost always preceded by recolonisation with *H pylori*.

Unresolved aspects of *H pylori* and duodenal ulcer disease

WHAT ARE THE RESPECTIVE ROLES OF *H PYLORI* AND ACID/PEPSIN?

Recurrence of duodenal ulcer disease is prevented by either eradication of *H pylori* or suppression of acid secretion. Apparently both acid/pepsin and *H pylori* are required to cause duodenal ulcers. Ulcers result where luminal attack exceeds mucosal resistance, but this may be an over simplification. Acid/pepsin clearly provides the luminal attack and *H pylori* probably reduces mucosal resistance, but the bacteria may also directly attack the epithelium.

HOW DOES *H PYLORI* CAUSE ULCERS IN THE DUODENUM?

Theories are broadly divided according to whether the proposed mechanism starts in the duodenum itself or in the stomach. While considering how *H pylori* causes ulcers, it is also important to consider why it does not have this effect in most people? The prevalence of *H pylori* increases with age, but at any time of life it is considerably above that of duodenal ulcer disease. For example, by the age of 50 years most of the population have *H pylori* but only about 10% have duodenal ulcers. This discrepancy may be viewed in terms of 'the seed or the soil' – are there ulcerogenic strains of *H pylori*, susceptible individuals, or both?

Duodenal mechanisms

It was initially difficult to understand how *H pylori*, which only colonised gastric type epithelium, might cause local damage within the duodenum. This is explained by the presence of patches of gastric metaplasia in the duodenum of patients with duodenal ulcer disease.[13] It has been estimated that gastric metaplasia is present in about 90%, and is colonised with *H pylori* in about 50% of patients with duodenal ulcer disease,[11] but only present in 5 to 30% of non-ulcer *H pylori* colonised persons.[14,15] This raises the question of what causes gastric metaplasia? In man it is associated with acid hypersecretion[15] and may be reduced after prolonged suppression of acid.[16] In animals it has been induced experimentally by chronic stimulation of gastric acid secretion.[17,18] However, gastric metaplasia is probably a non-specific response to injury. A similar phenomenon occurs in Crohn's disease, in association with local epidermal growth factor production[19] so an as yet unidentified insult could be responsible for gastric metaplasia in duodenal ulcer disease. Patches of metaplasia may well reflect the sites of previous ulcers[20] but what causes the first ulcer?

Having colonised the duodenum, *H pylori* may cause ulcers by provoking inflammation or by releasing an ulcerogenic toxin. The nature of the inflammatory response in the duodenum has so far received little attention. Prostanoids and platelet activating factor may be involved.[21] Some results support the idea that certain types of *H pylori* are more

ulcerogenic than others. Preliminary observations suggest that strains specifically associated with duodenal ulcer disease have a different DNA finger print.[22] During culture in vitro, some strains of *H pylori* produced a toxin that resulted in vacuoles in cultured cells – the 'vacuolating toxin' – whereas other strains did not.[23] Moreover, antibodies to a protein thought to be the toxin were present in 100% of duodenal ulcer patients with *H pylori* compared with 61% of patients with *H pylori* but no ulcer.[24] However, studies of *H pylori* derived toxins have produced different results in different laboratories: in one laboratory the toxin proved to be *H pylori*'s enzyme urease itself.[25] Collaboration is inhibited by the possibility of patenting specific assays.

Thus, whether an ulcer forms in the duodenum may depend on the presence of gastric metaplasia, the vigour of ulcerogenic immunological responses, whether the particular strain of *H pylori* produces a toxin, and also on individual susceptibility.

Gastric mechanisms

It remains a paradox that while most *H pylori* are located in the stomach, the clinical disease it most obviously causes is in the duodenum. The stomach causes duodenal ulcer disease by harbouring *H pylori* as well as by secreting acid/pepsin and these two roles are related. The stomach is the site where *H pylori* infection first occurs and thereafter probably acts as a reservoir from which the duodenum becomes colonised. After first infection, which decreases acid secretion,[26] *H pylori* thrives in an acidic environment. Its prevalence is significantly less in patients who secrete no acid because of atrophic gastritis,[27 28] and it is suppressed by omeprazole therapy.[29] Acid may neutralise the alkali generated by *H pylori*'s urease or suppress the growth of competing bacteria.

We have published work which indicates that *H pylori* alters gastric physiology in a way that may promote duodenal ulceration. Duodenal ulcer patients tend to have higher peak stimulated acid output (PAO) and peak postprandial plasma gastrin values than normal subjects.[30 31] Both of these measurements were greater in duodenal ulcer patients with a positive urease test for *H pylori*, than in the few duodenal ulcer patients who have a negative urease test, indicating that colonisation with *H pylori* is light or absent.[32] Suppression of *H pylori* led to a fall in gastrin but no change in PAO.[33] Other groups have confirmed these findings.[34 35] It is surprising that eradication consistently reduces circulating gastrin but has little or no effect on acid secretion rates or intragastric hydrogen ion concentrations (acidity). This is perhaps because gastrin was not the major determinant of acid secretion or acidity under the conditions of the studies. For example, PAO is measured during maximal stimulation with pentagastrin. In addition, intragastric acidity may depend more on intragastric buffering capacity than on acid secretion, because acidity goes down rather than up after a meal. Another possibility is that the sensitivity of the acid secreting parietal cells to gastrin is increased by eradication of *H pylori* so that smaller gastrin concentrations are then required to produce equivalent acid secretion.

There has been a tendency to regard gastric acid secretion from a purely physiological point of view as a function of the stimulatory and trophic effects of factors like gastrin on parietal cells whose sensitivity and number were otherwise determined genetically. It is now clear that the number of parietal cells and aspects of their function, including sensitivity to stimulation, is variable[31 36] and is possibly affected by infective and immunological events.

The idea that hypersecretion is inherited was based on the familial clustering of hyperpepsinogenaemia I, which was used as a marker of hypersecretion.[37] This concept now has to be re-examined because eradication of *H pylori* reduces circulating group I pepsinogens.[38] Although *H pylori* infection is associated with increased basal and peak acid output,[32] *H pylori* itself produces a factor that inhibits gastric acid secretion[39] which may suppress acid during first infection.[26] Atrophic gastritis is an important determinant of acid secretion in the general population because it leads to loss of parietal cells. Atrophy is notably absent in duodenal ulcer patients[40] and it is entirely possible that this is why they secrete more acid.

An open mind must be kept about the factors that may affect circulating gastrin concentrations in duodenal ulcer disease. The original observation that *H pylori* increases gastrin values in duodenal ulcer disease[32] was prompted by the idea tht *H pylori* might alkalinise the antral microenvironment. It has now been confirmed that the pH of the antral mucus layer is indeed more alkaline in the presence of the bacteria.[41 42] This may be the result of urease releasing ammonia, but could be caused by other mechanisms such as damaged epithelium leaking bicarbonate. The difference in pH between *H pylori* positive and negative patients is 0·3–0·8, which is not great, but we have no idea of the magnitude of change in the pH of the antral mucus layer that is required to affect gastrin release. McColl's group have shown that inhibition of *H pylori*'s urease does not change gastrin release, at least in the short term.[43] Immunological rather than physiological events may be more important in the increased gastrin release. *H pylori* provokes both humoral and cell mediated immune responses and is associated with an increased expression of MHC class II antigens on gastric epithelial cells.[44] This is accompanied by the release of several inflammatory mediators including interleukins 1[45] and 6,[46] tissue necrosis factor α,[46] and platelet activating factor.[47] In vitro some proinflammatory cytokines have been shown to release gastrin from antral preparations, including interleukin 1,[48] 2,[49] and γ interferon[49] and the leukotrienes C_4 and D_4.[50] Wyatt *et al* found increased basal gastrin values in two patients with non-*H pylori* antral gastritis.[51] This may be the result of the inflammation produced by pyloric reflux of bile, which was observed in a group of hypergastrinaemic patients.[52] Antral inflammation may have produced the increased sensitivity of G cells to weak stimulants of gastrin release that was observed in these patients.[53]

Duodenal ulcer – a self healing disease

To date there has been little discussion of how *H pylori* might contribute to the highly characteristic tendency of duodenal ulcer disease to relapse and remit. One possibility is that it triggers a sequence of immunological events that lead to a progression through ulceration and healing to a period of resistance to further damage. Another possibility is that ulceration clears *H pylori* locally by destroying the relevant patch of gastric metaplasia. The next ulcer would not occur until healing has generated another patch of metaplasia and this has become recolonised with the bacteria.

Clinical strategies

HOW BEST TO DIAGNOSE *H PYLORI* INFECTION?

At present the diagnosis of *H pylori* can easily be made either at endoscopy or by using non-invasive methods. The various tests have been reviewed in detail elsewhere.[54 55] A patchy distribution of *H pylori* within the antrum occasionally leads to tests on biopsy specimens being false negative. However, the biopsy urease test is sufficiently sensitive for most purposes and very simple to perform. Sensitivity may be increased by examining a further biopsy specimen histologically for *H pylori*, which compares favourably with the more

technically demanding bacterial culture.[55] The latter method has the advantage of indicating antibiotic sensitivity, although it is still not clear how best to treat the metronidazole resistant strains, which are present in about 15% of British patients with *H pylori* infection. Retesting should be performed about four weeks after the end of the eradication regimen because of the tendency of *H pylori* to 'lurk and revive'.[5 56] The urea breath tests are particularly good for confirming eradication because they sample the whole stomach. They may be performed cheaply using radioactive ^{14}C[57] or, more expensively using the non-radioactive ^{13}C.[58] Serological tests are also available. These are generally satisfactory but it can take six months for titres to fall when *H pylori* has been eradicated. A rapid serological test for use in outpatient clinics and general practice at the initial presentation would be helpful.

The variety of eradication regimens reflects their incomplete clinical success. The best currently eradicate *H pylori* from about 80% of patients, but are still not widely used. An international working party has agreed an effective regimen. This consists of De-Nol, 120 mg four times daily (30 minutes before meals and at night), metronidazole 400 mg three times daily, and tetracycline hydrochloride (or amoxycillin) 500 mg four times daily, all for two weeks.[59] Success depends on compliance[60] and resistance to metronidazole.[61] The former requires careful instruction and a calendar eradication pack would help. Metronidazole resistance develops rapidly if the drug is given without bismuth.[62] Consequently, resistance is present in about 15% of colonised women in the UK and in about 80% of colonised men and women in parts of Africa.[61]

Further progress will be made through clinical studies examining, for example, the interesting possibility that antibiotics could be made more effective by combining them with drugs that suppress acid secretion. It is to be hoped that pharmacological science will now address the important questions that have been raised, highlighted by the major discrepancies between the effects of antibiotics in vivo and in vitro. How do drugs reach the mucus microenvironment; from the lumen or from the bloodstream? Can delivery be improved? This may depend on hydrophobicity, which is in turn determined by dissociation of charged groups on the drug at the prevailing pH. For example, penetration of the basic drug clindamycin is enhanced by suppression of acid secretion.[63] Increasing the intragastric pH might also improve the effectiveness of other agents that are less potent in acid or it might, through encouraging bacterial overgrowth, add to the problem of resistance by plasmid mediated exchange.[62] How do available agents act? It is not clear how bismuth kills *H pylori*. Metronidazole may be bioreduced to produce compounds which kill by binding to the DNA of the microorganisms. Metronidazole resistance might be caused by a failure of bioreduction or of penetration of the drug into the organism. It has not been established whether metronidazole resistance is transmitted to *H pylori* by plasmids.

Gastric ulcer

The prevalence of *H pylori* colonisation in gastric ulcer disease is greater than in the general population, but not by much.[64] Gastric ulcers are strongly related to the presence of gastritis,[65] which may be caused by *H pylori* infection, non-steroidal anti-inflammatory drugs, or pyloric reflux in different patients. An interesting study in the Far East showed that remission of gastric ulcer disease was prolonged by a cephalosporin.[66] Aetiological theories of gastric ulceration currently focus on damage to the mucus layer and changes in gastric mucosal hydrophobicity[67] which might be caused by the organism itself or by the inflammation that it produces.[68 69]

Aspects of the spread of *H pylori*

How is *H pylori* transmitted? There is no known animal reservoir and prevalence is increased with increasing age[70 71] and probably by social deprivation.[72] The effect of age may simply reflect more opportunities for infection to have occurred, or be the result of an epidemic of *H pylori* in the past, perhaps during the depression of the 30s. Serological studies have shown noticeable clustering in families in Toronto[73] and in a mental institution in Australia.[74] In one high prevalence area mothers premasticated food before giving it to their babies.[75] Therefore *H pylori* probably spreads 'person to person,' largely in families, and via a route that depends on suboptimal hygiene. Although *H pylori* cannot usually be cultured from saliva it has been detected in saliva by the polymerase chain reaction.[76] In one individual, the same strain of *H pylori* was cultured from both stomach and dental plaque.[77] Transmission from patient to patient after endoscopy has also been described.[78] *H pylori* has never been isolated from faeces but oral-oral spread does not explain how in one village its presence was limited almost exclusively to people who drank municipal water as opposed to water from private wells, irrespective of social class. Finally, the high incidence of serological positives in abattoir workers[79] may be caused by the animals' bacteria possessing common antigens.

Conclusions

All but the most perverse now accept the abundant evidence that *H pylori* plays an important role in relapse of duodenal ulcer disease and that eradication regimens offer striking benefits in prognosis. Clinicians and patients would be more inclined to accept this approach if eradication regimens were more user friendly – why no blister eradication – pack? In addition, both marketing and scientific curiosity call for studies to determine how *H pylori* does, or in most individuals does not, cause peptic ulcers.

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1 Martin D, May S, Tweedle D, Hollanders D, Ravenscroft M, Miller J. Differences in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitratobismuthate. *Lancet* 1981; i: 7–10.
2 Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; i: 1273–5.
3 Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; i: 1273.
4 Dooley CP, Cohen H. The clinical significance of *Campylobacter pylori*. *Ann Intern Med* 1988; **108**: 70–9.
5 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 anti-bacterial and anti-ulcer treatment. *Gastroenterology* 1988; **94**: 33–40.
6 McNulty CAM, Gearty JC, Crump B, *et al*. *Campylobacter pyloridis* and associated gastritis: investigator-blind placebo-controlled trial of bismuth salicylate and erythromycin ethylsuccinate. *BMJ* 1986; **293**: 645–9.
7 McNulty CA, Dent J, Wise R. Susceptibility of clinical isolates of *Campylobacter pylori* to 11 anti-microbial agents. *Antimicrob Agents Chemother* 1985; **28**: 837–8.
8 Gavey CJ, Szeto M-L, Nwokolo CU, Sercombe J, Pounder RE. Bismuth accumulates in the body during treatment with tripotassium dicitrato bismuthate. *Aliment Pharmacol Therap* 1989; **3**: 21–8.
9 Hall DWR. Review of the modes of action of colloidal bismuth subcitrate. *Scand J Gastroenterol* 1988; **24** (suppl 157): 3–6.
10 Chiverton SG, Hunt RH. Initial therapy and relapse of duodenal ulcer: possible acid secretory mechanisms. *Gastroenterology* 1989; **96**: 632–9.
11 Marshall BJ, Goodwin CS, Warren JR, *et al*. Prospective double blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* 1988; **2**: 1437–42.
12 Rauws EA, Tytgat GNJ. Cure of duodenal ulcer associated with eradicaton of *Helicobacter pylori*. *Lancet* 1990; **335**: 1233–5.
13 Goodwin CS. Duodenal ulcer, *Campylobacter pylori*, and the 'leaking roof' concept. *Lancet* 1988; ii: 1467–9.
14 Fitzgibbons PL, Dooley CP, Cohen H, Appleman MD. Prevalence of gastric metaplasia, inflammation and *Campylobacter pylori* in the duodenum of members of a normal population. *Am J Clin Pathol* 1988; **90**: 711–4.

15 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.
16 Wyatt JI, Rathbone BJ. Gastric metaplasia in the duodenum and *Campylobacter pylori*. *Gastroenterol Clin Biol* 1989; **13**: 78–82B.
17 Rhodes J. Experimental production of gastric epithelium in the duodenum. *Gut* 1964; **5**: 454–8.
18 Gaskin RJ, Gad A, Barros AAJ, Jeffe SN, Baron JM. Natural history and morphology of secretagogue-induced ulcers in rats. *Gastroenterology* 1975; **69**: 903–10.
19 Wright NA, Pike C, Elia G. Induction of a novel epidermal growth factor-secreting cell lineage by mucosal ulceration in human gastrointestinal stem cells. *Nature* 1990; **343**: 82–5.
20 Fullman H, Van Deventer G, Schneidmann D, Walsh J, Elashoff J, Weinstein W. 'Healed' duodenal ulcers are histologically ill [Abstract]. *Gastroenterology* 1985; **88**: 1390.
21 Ackerman Z, Karmelli F, Ligumsky M, Rachmilewitz D. Enhanced gastric and duodenal platelet-activating factor and leukotriene generation in duodenal ulcer patients. *Scand J Gastroenterol* 1990; **25**: 925–34.
22 Yoshimura HH, Evans DG, Graham DY. *Helicobacter pylori* strains from duodenal ulcer patients differ at the genomic level from those from patients with simple gastritis [Abstract]. *Rev Esp Enferm Digest* 1990; **78** (suppl 1): 6.
23 Leunk RD, Johnson PT, David BC, *et al.* Cytotoxic activity in broth-culture filtrates of *Campylobacter pylori*. *J Med Microbiol* 1988; **26**: 93–9.
24 Cover TL, Dooley CP, Blaser MJ. Characterisation of and human serological response to proteins in *Helicobacter pylori* broth culture supernatants with vacuolizing cytotoxin activity. *Infect Immun* 1990; **58**: 603–10.
25 Xu JK, Goodwin CS, Cooper M, Robinson J. Intracellular vacuolization caused by the urease of *Helicobater pylori*. *J Infect Dis* 1990; **161**: 1302–4.
26 Graham DY, Alpert LC, Lacey-Smith J, Yoshimura HH. Iatrogenic Campylobacter infection is a cause of epidemic achlorhydria. *Am J Gastroenterol* 1988; **83**: 971–80.
27 Flejou J-F, Smith AC, Stockbrugger RW, Rode J, Price AB. Pernicious anaemia and gastric campylobacter-like organisms; is the gastric antrum resistant to colonisation? *Gut* 1989; **30**: 60–4.
28 Fong T-L, Dooley CP, Dehesa M, *et al.* *Helicobacter pylori* infection in pernicious anaemia: a prospective controlled study. *Gastroenterology* 1991; **100**: 328–32.
29 Mainguet P, Delmee M, Debongnie J-C. Omeprazole, *Campylobacter pylori* and duodenal ulcer. *Lancet* 1989; ii: 389–90.
30 Blair AJ, Feldman M, Barnett C, *et al.* Detailed composition of basal and food-stimulated gastric acid secretion and serum gastrin concentrations in duodenal ulcer patients and normal subjects. *J Clin Invest* 1987; **79**: 582–7.
31 Lam SK, Isenberg JI, Grossman MI, *et al.* Gastric acid secretion is abnormally sensitive to exogenous gastrin released after peptone test meals in duodenal ulcer patients. *J Clin Invest* 1980; **65**: 552–62.
32 Levi S, Beardshall K, Haddad G, Playford R, Ghosh P, Calam J. *Campylobacter pylori* and duodenal ulcer; the gastrin link. *Lancet* 1989; i: 1167–8.
33 Levi S, Beardshall K, Swift I, *et al.* Antral *Helicobacter pylori*, hypergastrinaemia and duodenal ulcers: effect of eradicating the organism. *BMJ* 1989; **299**: 1504–5.
34 McColl KE, Fullarton GM, El Nujumi AM, *et al.* Lowered gastrin and gastric acidity after eradication of *Campylobacter pylori* in duodenal ulcer. *Lancet* 1989; ii: 499–500.
35 Graham DY, Opekun A, Lew GM, Evans DJ Jr, Klein PD, Evans DG. Ablation of exaggerated meal stimulated gastrin release in duodenal ulcer patients after clearance of *Helicobacter (Campylobacter) pylori* infection. *Am J Gastroenterol* 1990; **85**: 394–8.
36 Lam SK, Koo J. Gastrin sensitivity in duodenal ulcer. *Gut* 1985; **26**: 485–90.
37 Rotter JI, Sones JQ, Samloff IM, *et al.* Duodenal ulcer disease associated with elevated serum pepsinogen 1. An inherited autosomal dominant disorder. *N Engl J Med* 1979; **300**: 53–5.
38 Graham DY, Opekun AR, Lew GM, Malfertheiner P. Is serum pepsinogen I a genetic marker for duodenal ulcer or a surrogate marker for HP infection? *Gastroenterology* 1990; **98**: A53.
39 Cave DR, Vargas M. Effect of a *Campylobacter pylori* protein on acid secretion by parietal cells. *Lancet* 1989; ii: 187–9.
40 Kekki M, Sipponen P, Siurala M. Progression of antral and body gastritis in active and healed duodenal ulcer and duodenitis. *Scand J Gastroenterol* 1984; **19**: 382–8.
41 Kelly SM, Crampton J, Hunter JO. *Helicobacter pylori* increases the pH of the gastric mucosa in vivo. *Gut* 1990; **31**: A1177–8.
42 Beardshall K, Adamson D, Gill J, Unwin R, Calam J. *Helicobacter pylori* raises the pH in the juxtaepithelial region of the mucus layer of the gastric antrum and body. *Gut* 1991; **32**: A569.
43 El Nujumi AM, Dorrian CA, Chittajallu RS, Neithercut WD, McColl KEL. Effect of inhibition of *Helicobacter pylori* urease activity by acetohydroxamic acid on serum gastrin in duodenal ulcer subjects. *Gut* 1991; **32**: 866–70.
44 Engstrand L, Scheynius A, Pahlson C, Grimelius L, Schwan A, Gustavsson S. Association of *Campylobacter pylori* with induced expression of class II transplant antigens on gastric epithelial cells. *Infect Immun* 1989; **57**: 827–32.
45 Mai UEH, Perez-Perez GI, Wahl LM, Wahl SM, Blaser MJ, Smith PD. Inflammatory and cytoprotective responses by human monocytes are induced by *Helicobacter pylori*: possible role in the pathogenesis of type B gastritis. *Gastroenterology* 1990; **98**: A662.
46 Crabtree JE, Shallcross TM, Heatley RV, Wyatt JI. Mucosal tumour necrosis factor α and interleukin-6 in patients with *Helicobacter pylori* associated gastritis. *Gut* 1991; **32**: 1473–7.
47 Denizot Y, Sobhani I, Rambaud JC, Lewin M, Thomas Y, Benveniste J. Paf-acether synthesis by *Helicobacter pylori*. *Gut* 1990; **31**: 1242–5.
48 Teichmann RK, Kramling HJ, Merkle T, Merkle R. Opposite effects of interleukin-1 on gastrin and bombesin release in cell suspensions of antral mucosa. [Abstract]. *Digestion* 1990; **46** (suppl 1): 114.
49 Teichmann RK, Pratschke E, Grab J, Hammer C, Brendel W. Gastrin release by interleukin-2 and gamma-interferon in vitro. [Abstract]. *Can J Physiol Pharmacol* 1986; **64** (suppl): 62.
50 Teichmann RK, Utz E, Becker HD. Leukotrienes release gastrin and somatostatin from human antral mucosa in vitro. [Abstract]. *Digestion* 1990; **46** (suppl 1): 114.
51 Wyatt JI, Rathbone BJ, Green DM, Primrose J. Raised fasting serum gastrin in chronic gastritis is independent of *Campylobacter pylori* status and duodenal ulceration. *Gut* 1989; **30**: A1483.
52 Calam J, Tracy HJ. Pyloric reflux and G-cell hyperfunction. *Lancet* 1980; ii: 918.
53 Cooper RG, Dockray GJ, Calam J, Walker RJ. Acid and gastrin responses during intragastric titration in normal subjects and duodenal ulcer patients with G cell hyperfunction. *Gut* 1985; **26**: 232–6.
54 Barthel JS, Everett ED. Diagnosis of *Campylobacter pylori* infections; the 'gold standard' and the alternatives. *Rev Infect Dis* 1990; **12** (suppl 1): S107–14.
55 Deltenre M, Glupczynski Y, DePrez C, *et al.* The reliability of urease test, histology and culture in the diagnosis of *Campylobacter pylori* infection. *Scand J Gastroenterol* 1989; **24** (suppl 160): 19–24.
56 Weil J, Bell GD, Jones PH, Gant P, Trowell JE, Harrison G. 'Eradication' of *Campylobacter pylori*: are we being misled? *Lancet* 1988; ii: 1245.
57 Bell GD, Weil J, Harrison G, *et al.* ^{14}C urea breath analysis, a non-invasive test for *Campylobacter pylori* in the stomach. *Lancet* 1987; i: 1367–8.
58 Graham DY, Klein PD, Evans DJ Jr, Evans DG, Alpert LC, Opekun AR, *et al.* *Campylobacter pylori* detected noninvasively by the ^{13}C urea breath test. *Lancet* 1987; i: 1174–7.
59 Anonymous. Gastroenterologists in Sydney: histology and helicobacter. [Editorial]. *Lancet* 1990; **336**: 779–80.
60 Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ, Alpert LC, *et al.* Factors affecting the eradication of *Helicobacter pylori* infection with triple therapy. [Abstract]. *Rev Esp Enferm Digest* 1990; **78** (suppl 1): 117.
61 Glupczynski Y, Burette A, De Koster E, Nyst JF, Deltenre M, Cadranel S, *et al.* Metronidazole resistance in *Helicobacter pylori*. *Lancet* 1990; **335**: 976–7.
62 Glupczynski Y, Burette A. Drug therapy for *Helicobacter pylori* infection: problems and pitfalls. *Am J Gastroenterol* 1990; **85**: 1545–51.
63 Westblom YU, Duriex DE. Enhancement of antibiotic concentrations in gastric mucosa by H2-receptor antagonist. *Dig Dis Sci* 1991; **36**: 25–8.
64 O'Connor HJ, Axon ATR. Campylobacter pylori, gastric ulceration and the post-operative stomach. In: Rathbone BJ, Heatley RV, eds. *Campylobacter pylori and gastroduodenal disease*. Oxford: Blackwell, 1989: 125–38.
65 Gear MWL, Truelove SC, Whitehead R. Gastric ulcer and gastritis. *Gut* 1971; **12**: 639–45.
66 Tatsuta M, Ishikawa H, Iishi H, Okuda S, Yokota Y. Reduction of gastric ulcer recurrence after suppression of *Helicobacter pylori* by cefixime. *Gut* 1990; **31**: 973–6.
67 Spychal RT, Goggin PM, Marrero JM, Saverymuttu SH, Yu CW, Corbishley CM, *et al.* Surface hydrophobicity of gastric mucosa in peptic ulcer disease. Relationship to gastritis and *Campylobacter pylori* infection. *Gastroenterology* 1990; **98**: 1250–4.
68 Younan F, Pearson J, Allen A, *et al.* Changes in the structure of the mucous gel on the mucosal surface of the stomach in association with peptic ulcer disease. *Gastroenterology* 1982; **82**: 827–31.
69 Sidebotham RL, Baron JH. Hypothesis: *Helicobacter pylori*, urease, mucus, and gastric ulcer. *Lancet* 1990; **335**: 193–5.
70 Perez-Perez GI, Dworkin BM, Chodos JE, Blaser MJ. *Campylobacter pylori* antibodies in humans. *Ann Intern Med* 1988; **109**: 11–7.
71 Graham DY, Klein PD, Opekun AR, Boutton TW. Effect of age on the frequency of active Campylobacter infection diagnosed by the ^{15}C urea breath test in normal subjects and in patients with peptic ulcer disease. *J Infect Dis* 1988; **157**: 777–80.
72 The gastrointestinal physiology working group. *Helicobacter pylori* and gastritis in Peruvian patients: relationship to socioeconomical level, age and sex. *Am J Gastroenterol* 1990; **85**: 819–23.
73 Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. Intrafamilial clustering of *Helicobacter pylori* infection. *N Engl J Med* 1990; **322**: 359–63.
74 Berkowicz J, Lee A. Person-to-person transmission of *Campylobacter pylori*. *Lancet* 1987; ii: 680–1.
75 Albenque M, Tall F, Dabis F, Megraud F. Epidemiological study of *Helicobacter pylori* transmission from mother to child in Africa. *Rev Esp Enferm Digest* 1990; **78** (suppl 1): 48.
76 Gobert B, Labigne A, DeKorwin DJ, Conroy MC, Bene MC, Faure GC. Polymerase chain reaction for *Helicobacter pylori*. [Abstract]. *Rev Esp Enferm Digest* 1990; **78** (suppl 1): 4.
77 Shames B, Krajden C, Fuksa M, Rabida C, Penner JL. Evidence for the occurrence of the same strain of *Campylobacter pylori* in the stomach and dental plaque. *J Clin Microbiol* 1989; **27**: 2849–50.
78 Langenberg W, Rauws EA, Oudbier JH, Tytgat GNJ. Patient-to-patient transmission of *Campylobacter pylori* infection by fibreoptic gastroduodenoscopy and biopsy. *J Infect Dis* 1990; **161**: 507–11.
79 Vaira D, D'Anastasia CD, Holton J, *et al.* *Campylobacter pylori* in abattoir workers: is it a zoonois? *Lancet* 1988; ii: 725–6.