REVIEW ARTICLE

Helicobacter pylori: bridging the credibility gap

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The earliest descriptions of bacteria colonising the stomach date from the 19th and early 20th century,¹⁻³ but it was not until 1983 that successful culture was achieved.⁴ As is often the case, it was a combination of scientific acumen, luck, and determination that led to the isolation of *Helicobacter pylori*. The organism is slow growing and early cultures were discarded prematurely. Only during the Easter holiday was sufficient time left for colonies to develop.⁵

In retrospect, the intervention of a religious festival seems entirely appropriate. *H. pylori* attracts great loyalty from its devotees. 'Pylorites' accept that the organism causes gastritis, duodenal ulcer, and non-ulcer dyspepsia. In contrast 'Schwartzians,' who attribute all disease to acid, remain sceptical; the undisputed efficacy of the H₂ receptor antagonists being the cornerstone of their credo. Currently, there is the need for a middle ground to bridge the credibility gap. What facts are accepted and in which areas should we focus research?

Epidemiology

H. pylori has been found in all human populations studied to date.⁶⁻¹⁰ In western countries the carriage rate is low among children, but rises progressively through life. At least 50% of those over the age of 50 are positive for *H. pylori*.⁶ In contrast the limited data from the third world suggest that a greater percentage of the population may be colonised in childhood.^{8,10}

The source of infection is unknown. One report suggests that the carriage rate among abattoir workers in close proximity to animals is greater than in their clerical counterparts.¹¹ To date the only animal, other than humans, from which *H. pylori* has been isolated is the rhesus monkey.¹² There are virtually no reports of isolations of helicobacter-like organisms from domesticated animals.¹³ We think that it is more likely that the source of the organism will prove to be other humans.

Diagnostic methods

Contrary to the expectations of many clinicians, *H. pylori* is not difficult to diagnose. Most methods use endoscopic gastric biopsy specimens taken from two sites within the stomach, one of which should be the antrum.¹⁴ The organism can be readily identified by histopathologists provided they are familiar with its characteristic appearance. *H. pylori* can be seen in haematoxylin and eosin stained sections, but a

variety of stains can improve detection.¹⁵⁻¹⁹ Biopsy urease tests, which can be carried out in the endoscopy room, are easily applied and provide a useful addition to histology.^{20,21}

Although the combination of positive histology and a positive biopsy urease test is highly specific for the organism, we would still favour the routine culture of gastric biopsy specimens. The culture of *H. pylori* involves methods that are essentially identical to those used in the culture of *Campylobacter*.²² As *Campylobacter jejuni* is now the most commonly isolated enteric pathogen, the culture of *H. pylori* should not be beyond the capability of any competent microbiological laboratory.

More recently, the urea breath test has been developed, although this remains confined to a number of research centres.^{23,24} Two isotopes of carbon have been used. Carbon 14 is radioactive and easily detected, but is not recommended for use in children or women of childbearing age. Carbon 13 is not radioactive and has no such restrictions, but requires a mass spectrometer for its measurement.²⁵ The advantage of breath tests is that they are non-invasive and allow repeated measurements on the same subject.

Serological diagnostic tests were described remarkably quickly after the discovery of *H. pylori*,^{26,27} and are the subject of continuing development. A number of different laboratory methods have been used including haemagglutination²⁶ and complement fixation,²⁷ but the enzyme linked immunosorbent assay (ELISA) has been most widely adopted for routine use.^{28,29} The more exacting technique of Western blotting³⁰ has given invaluable insights into the diversity of the human systemic antibody response but is impracticable for mass screening.

The choice of antigen for routine diagnostic use remains problematic. Ideally the antigen should be specific but highly immunogenic, easily prepared, and stable on storage.³¹

A number of the earlier antigenic preparations, such as whole cell sonicates, encompassed a broad range of antigens but often included flagella proteins, which are highly immunogenic but are shared with other species, most notably *C. jejuni*.³² Antibodies to this organism are common in the general population, and the net result was tests that were sensitive but lacked specificity. Some early epidemiological data may, therefore, need to be re-examined with more specific techniques.

An acid extractable preparation³³ or the ultra-centrifuged whole cell supernatant are cleaner

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preparations and produce more acceptable results when used in ELISA.³¹

An alternative approach is to use a protein unique to *H. pylori*, such as its urease, as the basis for the assay.³⁴ This produces the required specificity but illustrates a second problem. Western blotting shows a remarkably diverse response among human subjects to each individual antigen, which in turn implies that not all subjects may respond strongly to a single antigen test. Such an assay may be highly specific but have a lower sensitivity than those using multiple antigens.³¹

The solution will probably involve combining a series of highly specific antigens to produce the required sensitivity.

While serology has been invaluable in elucidating the epidemiology of *H. pylori*, its role in clinical screening is at present uncertain and subject to much speculation.^{35,36} It has been suggested that ELISA screening could reduce endoscopy by about one quarter. Patients positive for *H. pylori* by serology would be started on treatment, and only submitted to endoscopy if symptoms persisted. Those negative on serological testing, or in whom gastric carcinoma is suspected, would undergo endoscopy before treatment. We believe that this approach has a number of weaknesses. Firstly, gastric carcinoma is primarily found in patients over the age of 50 years, 50% of whom will be positive for *H. pylori*, and it is frequently not suspected until endoscopy is performed. A few early carcinomas will be missed, and while this will not alter the consequences for most patients, many clinicians may be uneasy about this prospect. Secondly, the strategy entails treating some *H. pylori* positive patients with reflux oesophagitis or irritable bowel syndrome with an unnecessary course of tripotassium dicitratobismuthate. Is this justifiable? Finally, we suspect that the saving in endoscopy time produced by serological screening has been overestimated. In our practice much of our endoscopy time is spent checking for peptic ulcer healing, in sclerotherapy for varices, or investigating anaemia or dyspepsia in patients taking non-steroidal anti-inflammatory drugs. *H. pylori* status is irrelevant under these circumstances.

Serological tests are of limited value after treatment for *H. pylori* has been started, although there is some evidence that titres fall after successful treatment.^{11,37}

We believe that an attempt to make a positive diagnosis should be made before the use of antimicrobials is considered.

Clinical associations

CHRONIC GASTRITIS

There is a strong association between type B chronic gastritis and the presence of *H. pylori*, which is found in between 70% and 92% of patients with this.^{14,38} As unbelievers are quick to point out, however, this is not proof of a causal relation. In the case of type B gastritis, however, there are good reasons for believing that *H. pylori* is more than an innocent bystander.³⁹ Firstly, the association has been found in all populations studied to date. Secondly, there is a relation,

although admittedly a weak one, between the number of organisms and the intensity of the infiltrate, particularly of the polymorph component.^{40,41} Thirdly, a number of groups have shown that successful eradication of the organism is accompanied by resolution of the gastritis, and in turn that recurrence of *H. pylori* is associated with relapse of the gastritis.^{42,43} Finally, two human volunteers have taken live cultures of the organism, and both developed an acute gastritis. In one this proved to be a transient phenomenon and the organism was eliminated before seroconversion occurred.⁴⁴ The second was less fortunate and developed a chronic gastritis that was accompanied by seroconversion.⁴⁵ These experiments are important because they show a clear temporal relation between acquisition of the organism and the subsequent development of gastritis. Both volunteers had normal gastric mucosa before the introduction of *H. pylori*.

Once the gastric mucosa is colonised by *H. pylori*, what mechanisms might explain the onset of gastritis? Hazel and Lee⁴⁶ have argued that urease may act as an important pathogenic mechanism by creating ammonium ions within the mucus-bicarbonate barrier, allowing back diffusion of hydrogen ions. Unfortunately, there is little evidence to support the pivotal role of urease in this respect. Other urease positive organisms found in animals are not associated with inflammatory changes.⁴⁷ *H. pylori* is now known to produce a variety of other extracellular products,⁴⁸ including at least one cytotoxin⁴⁹ which is, as yet, poorly characterised. It seems unlikely that *H. pylori* is entirely innocuous. The aim for the future must be to clarify its aggressive factors and place them in perspective against the more established luminal agents such as pepsin, bile, and gastric acid itself.

DUODENAL ULCER

Duodenal ulcer shows an even stronger association with *H. pylori*, with isolation of the organism occurring in most patients with this disorder. In some reports, up to 100% of all patients with duodenal ulcer have been found to be positive but in a review of 10 published studies the mean carriage rate was 86%.⁵⁰ The association, however, is between duodenal ulcer and carriage of the organism in the gastric antrum, rather than in the duodenum itself. *H. pylori* can be found in the duodenum, but only on areas of gastric metaplasia.⁵¹ The association between *H. pylori* and duodenal ulcer is found worldwide. Less is known about the temporal relation between contracting the infection and the development of duodenal ulcer, and this is potentially of great importance. If the organism is causative it must be acquired before the ulcer develops. Moreover, any attempt to link *H. pylori* and ulcerogenesis must also embrace the established data on acid secretion.

Patients with duodenal ulcer have a higher stimulated mean acid output, parietal cell mass, and nocturnal acid secretion than normal people. It has been recognised for many years, however, that there is considerable overlap between ulcer patients and normal subjects. Wyatt and her

colleagues have suggested that abnormal acid secretion induces gastric metaplasia within the duodenal cap, allowing the bacterium to move from its natural habitat in the gastric antrum into the duodenum. This in turn, initiates duodenitis, which either alone or in conjunction with other factors leads to duodenal ulceration.⁵⁰

The relation between gastric metaplasia and acid secretion is interesting. Metaplasia is said to occur only in patients with a low fasting pH, to be extensive in those with the Zollinger-Ellison syndrome, and to correlate with maximal acid output.⁵⁰ Animal experiments also indicate a link with acid secretion. Some of the data are old, however, and the subject deserves prospective re-evaluation.

Gastric metaplasia is essentially a microscopic diagnosis, and while the determination of its extent within an individual biopsy specimen is straightforward, it is difficult to extrapolate this to the duodenal cap as a whole. The problem of sampling error will always remain.

More importantly, can the hypothesis explain some of the known differences between the epidemiology of duodenal ulcer and the carriage of *H pylori*? Duodenal ulcer is more common in the north of the United Kingdom, affects younger people, and shows a male preponderance. There is no evidence to date that *H pylori* is more common in the north or among men, and its incidence rises progressively with age. Gastric metaplasia is, however, more common in men.⁵²

Levi and colleagues⁵³ have suggested that plasma gastrin values are higher in patients colonised with *H pylori* than in those who are not. It is suggested that the release of urease within the mucous layer leads to a rise in pH and promotes gastrin release. There are important reservations about these data. The presence of *H pylori* was determined by the biopsy urease test and 19% of the duodenal ulcers were negative for the organism. It has been suggested that this figure is higher than might have been expected,⁵⁴ but a similar proportion has been reported previously, admittedly by the same group, using culture and histology as diagnostic criteria.⁵⁵ More importantly, a small study suggests that both basal and stimulated gastrin values fall after treatment designed to eradicate *H pylori* from the stomach, although intragastric and nocturnal acid secretion values did not change.⁵⁶ Only nine patients were investigated, but the findings suggest that the gastrin link should be pursued further. Even more surprisingly, it has been suggested that healing resistant duodenal ulcers with omeprazole can clear the organism from the antral mucosa.⁵⁷ Again, only nine patients were studied and endoscopy was performed immediately after the end of treatment. Confirmation of this finding in larger prospective studies will be required, but it raises further questions about the interaction between *H pylori* and its peculiar environmental niche. Why should an organism that is incapable of growth below pH 4 find omeprazole detrimental, and if the changes in plasma gastrin are genuine are they capable of producing significant alterations in acid output? To add further confusion, there is evidence that acute infections with *H pylori* may lead to hypochlorhydria, although

this is probably only a transient state.⁵⁸ Finally, it is not clear whether *H pylori* associated gastritis influences mucosal prostaglandin values. It has been suggested that 6-keto F_{2α} concentrations are lower in *H pylori* positive patients than in their negative counterparts.⁵⁹ In contrast, there are contradictory findings regarding prostaglandin E₂, a prostaglandin with a more established role in mucosal protection.^{59, 60} The interaction between the infection and host is obviously complex and requires further elucidation.

It has been known for many years that bismuth salts can heal ulcers. The suggestion that duodenal ulcer relapse occurs less frequently after treatment with tripotassium dicitratobismuthate (DeNol) was given greater credibility in 1981 with the publication of a study comparing it and H₂ blockers.⁶¹ The discovery that *H pylori* is sensitive to bismuth in vitro prompted new questions regarding the mechanism of action of tripotassium dicitratobismuthate and the role of *H pylori* in ulcer relapse. A number of studies now suggest that in patients with duodenal ulcer, in whom the organism is successfully eradicated and who remain free of *H pylori* for longer than one month, the ulcer relapse rate is 10–20%.^{62–64} This is significantly lower than in control groups treated with H₂ blockers. Recurrence of the organism seems to predict relapse. The problem remains, however, that *H pylori* may be acting as a marker for other factors operating within the gastric environment. For example, it could be argued that healing the ulcer itself may alter conditions in such a way as to make the upper gastrointestinal tract less hospitable to the bacterium. This seems unlikely because the carriage rate for *H pylori* remains unchanged in patients whose ulcers are healed by H₂ blockers.⁶³ More importantly, the low ulcer recurrence rate may be directly related to tripotassium dicitratobismuthate itself, which is known to have actions unrelated to its bactericidal activity. Tripotassium dicitratobismuthate has been shown to form complexes with mucus,^{65–69} making it more effective as a diffusion barrier to hydrogen ion. It reduces pepsin output and activity⁷⁰ and promotes prostaglandin synthesis.⁷¹ Some bismuth is absorbed during treatment⁷² and this may act as a depot within the gastric mucosa. What is less clear, however, is whether plasma or urine concentrations truly reflect bismuth values within the gastric mucosa, and whether these concentrations would be sufficient to eradicate or suppress the growth of the organism. This seems unlikely in view of the relative inefficiency of tripotassium dicitratobismuthate alone in the eradication of *H pylori*, with rates as low as 5–33% one month after treatment.^{43, 73} It cannot be taken as proved, therefore, that *H pylori* is responsible for the lower duodenal ulcer relapse rate for duodenal ulcer after treatment with tripotassium dicitratobismuthate, but it is certainly possible that it has an important role in this respect.

GASTRIC ULCER

The association with gastric ulcer is less strong with only 65% of these patients being positive for

H. pylori.⁷⁴ Less information is available regarding the outcome of treatment and *H. pylori* status. Interestingly, bismuth has been shown to be as effective in healing gastric ulcer as it is in duodenal ulcer despite their differing associations with *H. pylori*.⁷⁵

NON-ULCER DYSPEPSIA

Attempting to investigate the relation between *H. pylori* and non-ulcer dyspepsia is difficult because there is no universally accepted definition of the condition. Retrospective studies have often classified non-ulcer dyspepsia as occurring in those patients with dyspepsia who have undergone a negative upper gastrointestinal endoscopy. Frequently, the precise symptomatology, the age range of the patients, and details of other investigations are omitted from reports. Not surprisingly, therefore, there is considerable variation in the *H. pylori* carriage rates between studies. Roccas and colleagues found *H. pylori* in 45% of patients with predominantly upper abdominal pain, which was three times higher than in asymptomatic controls.⁷⁶ Similarly, in a study from Leeds, the incidence of antibody to *H. pylori* among patients with non-ulcer dyspepsia was twice that of age matched blood donor controls, for every age group.⁷⁷ A number of controlled studies have been published in which patients with defined symptoms have received treatment designed to eradicate *H. pylori*, with subsequent reassessment.⁷⁸⁻⁸⁰ Elimination of *H. pylori* seems to improve symptoms, with the proviso that these patients may represent only one part of a wider spectrum of non-ulcer dyspepsia and that follow up to date has been short.

Helicobacter pylori in children

Serological studies suggest that *H. pylori* colonisation is rare among asymptomatic children.⁶ Retrospective studies indicate that *H. pylori* is associated with both duodenal ulcer and antral gastritis,^{81,82} but the actual numbers of positive patients is small. Prospective studies on children with non-specific abdominal pain suggest that antral gastritis and *H. pylori* are found more commonly than would be expected in asymptomatic children of a similar age.^{81,83} There is some evidence that treatment will improve symptoms, but numbers again are small.⁸⁴

Children represent a particularly important population group who may help to clarify our understanding of *H. pylori* infection. Their upper gastrointestinal tract is subjected to less self poisoning, with low rates of non-steroidal anti-inflammatory drug usage, little smoking, and only modest consumption of alcohol in comparison to adults. A prospective study of a cohort of children, to determine their rate of acquisition of the organism and subsequent risk of developing peptic ulcer, may help to answer some of the outstanding questions. The ¹³C breath test and serology are minimally invasive and regular monitoring for *H. pylori* is, therefore, feasible.

Treatment of *H. pylori* infection

Initially, it seemed likely that *H. pylori* infection would prove an easy target for treatment because the organism is sensitive to a wide range of antimicrobials, including bismuth salts such as tripotassium dicitratobismuthate. Surprisingly, McNulty's study in 1986 showed that one of the strongest contenders, erythromycin, was little better than placebo.⁸⁵ Moreover, the efficacy of bismuth containing compounds was almost certainly overestimated in early reports because insufficient time was allowed between treatment and repeat biopsy specimen examination. The clearance rate seen immediately after treatment is high, but falls rapidly over the following four weeks as the infection recurs.⁸⁶ This effect may be due to a declining bismuth depot, but may also be related to the organism's ability to produce metabolically inactive 'coccoid' forms.

Amoxycillin is also disappointing when used alone,⁸⁷ and tinidazole produces unacceptably high resistance when employed as a single agent.⁸⁸ Both agents are more effective when combined with tripotassium dicitratobismuthate (De-Nol), and this also applies to metronidazole where promising eradication rates have recently been described.⁸⁹ Triple treatment is also effective, but the cost may be greater side effects.^{90,91} No regime described to date has proved 100% effective.

This prompts the question: which patients should be treated? Duodenal ulcer healing rates with any of the above combinations are broadly comparable with those obtained with H₂ blockers, but the drug combinations may be less acceptable to patients. Eradication of *H. pylori* should now be considered in patients suffering from duodenal ulcer who have one or more recurrences after treatment with H₂ blockers, and may represent an alternative to long term maintenance treatment. To achieve low relapse rates the organism must be eradicated, necessitating repeat biopsy at least four weeks after treatment has stopped. It is not clear what action should be taken if eradication has not been achieved, but culture and sensitivity testing may be helpful if a further course of treatment is being considered. Elimination of *H. pylori* may be another line of treatment worthy of consideration in patients with resistant duodenal ulcers, before surgery. Little data are available, however, on this subject.

Some patients with non-ulcer dyspepsia may also benefit from treatment. It is essential to exclude other organic causes of dyspepsia and to confirm that the patient has *H. pylori* associated gastritis, before beginning treatment.

From the preceding discussion it can be seen that many uncertainties remain, and we would urge clinicians interested in treating *H. pylori* infections to enter their patients into clinical trials.

Summary

In summary, therefore, there are interesting associations between *H. pylori*, duodenal ulcer, and non-ulcer dyspepsia. In type B gastritis there may be enough evidence to suggest a causal role. The relation between gastritis and upper gastro-

intestinal symptomatology, however, remains contentious. The relation between *H pylori* and acid secretion may be more intimate than was previously thought. 'Pylorites' must temper their enthusiasm and provide hard data; 'Schwartzians' must broaden their horizons.

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