

Infectious ulcers: not hurry, worry and curry?

Dave Kelly

Gastric ulcers were once believed to be caused by lifestyle factors. Dave Kelly describes *Helicobacter pylori*, the microbe now known to be the real culprit.

Until about 20 years ago, if the question 'what causes stomach ulcers?' had been put to any self-respecting GP or even a consultant gastroenterologist, the answer would have included stress, diet, smoking or alcohol (particularly if the patient was also overweight). The notion that bacteria could be a cause of gastric ulcers would not have been considered plausible. The major reason for this was, of course, that the hydrochloric-acid-containing stomach was regarded as essentially a sterile organ. All this changed when two Australian scientists, Robin Warren and Barry Marshall, brought to light an association between spiral-shaped bacteria and inflammation of the gastric mucosa (stomach lining) in 1982. In fact, sporadic reports of the presence of spiral bacteria in both human and animal stomachs appeared in the late 19th century, but the realization that these bacteria might be agents of disease had to wait until they could be cultured. This was the crucial advance made by Robin Warren, using the microaerobic growth conditions that had been recently introduced for campylobacters.

Campylobacter. However, 16S rRNA sequence data and additional taxonomic features, such as the presence of the sheathed flagella and a distinct SDS-PAGE protein profile, led to the establishment of the new genus *Helicobacter*. There are now about 20 recognized *Helicobacter* species, many of which are animal pathogens. *H. pylori* has a relatively small genome (1.7 Mb), and in 1997 was amongst the first bacterial pathogens to be sequenced. Many insights are being gained into the biology of the organism from experimental approaches that utilize this genomic information.

● Infection and epidemiology

H. pylori is extremely widespread in humans and it is now regarded as one of the commonest infections. Even famous people are not immune (Table 1)! There seems to be little relationship between *H. pylori* infection and alcohol intake, smoking or gender. Developing countries generally have a much higher overall prevalence (up to 95 % of the population infected in some countries) compared to the Western world (30–50 % infection rates). The pattern of *H. pylori* disease found within a population is determined by the age of acquisition of the infection. Infection in childhood is common in developing countries and leads to a predominance of gastric ulcer and gastric cancer, whereas infection as an adult generally leads to duodenal ulcer and gastric cancer is rarer. Evidence indicates that infection rates are inversely related to socio-economic class. In developing countries, where poverty may prevail, there is overcrowding and poor childhood health. In Japan the change in epidemiology of *H. pylori* as a result of Westernization has been studied. By testing serum banks for anti-*H. pylori* antibody, it was concluded that in 1940 infection was most likely to occur before adulthood. A similar investigation in 1990, i.e. after an improvement in sanitation and healthcare, indicated that individuals were more likely to become infected between the ages of 20 and 40.

● Transmission

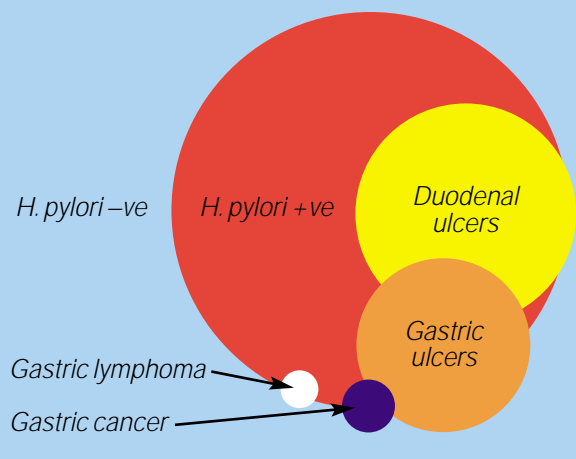
Surprisingly, definitive proof of the exact mode of transmission of *H. pylori* infection is still lacking. The oral–oral route, particularly from mother to child, is the most obvious method of spread, but a large number of studies have produced contradictory data. *H. pylori* has been successfully cultured from human faeces which raises the possibility of a faecal–oral route of transmission. The natural niche for *H. pylori* is the human stomach; it has fastidious nutritional requirements and there is no convincing evidence that it is able to grow or survive for extended periods in an *ex vivo* environment. Some excitement has been generated by controversial reports of possible *H. pylori* reservoirs in sheep, domestic cats and even houseflies, but it seems unlikely that *H. pylori* is transmitted zoonotically.

The now famous story of the (re)-discovery of *Helicobacter pylori* is exceptional for several reasons, not least that within a few years, the field of gastroenterology was literally revolutionized, with the realization that this bacterium was implicated in a range of diseases, including gastritis, gastric and duodenal ulceration and as a risk factor for gastric adenocarcinoma and lymphoma (see Fig. 1). The new insights and treatment

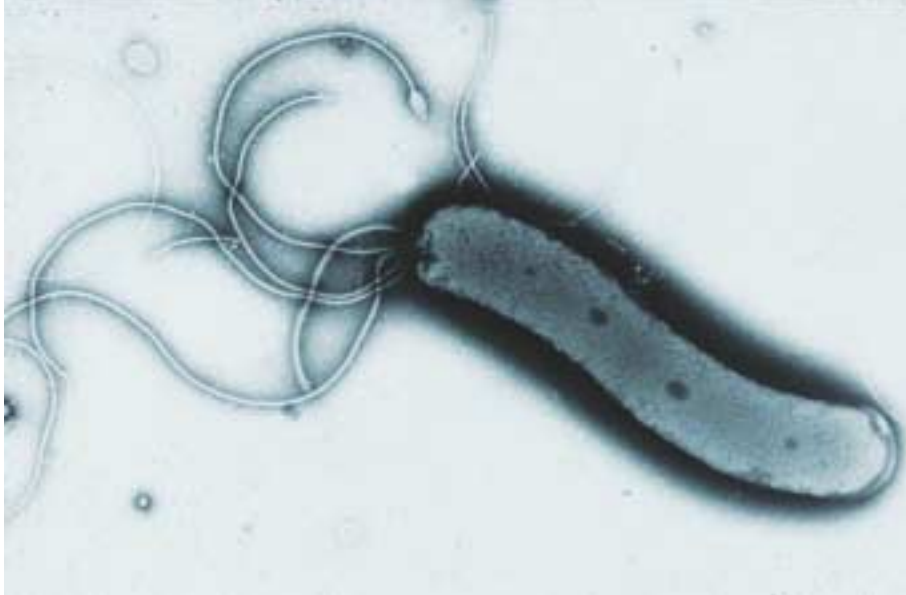
options for these chronic diseases have undoubtedly relieved much suffering in people worldwide. However, to the frustration of Barry Marshall, the medical establishment took some convincing that *H. pylori* really was a causative agent of human disease. This is where an element of drama was introduced into the story, when in 1984 Marshall decided to drink a suspension of the bacteria to demonstrate that gastritis would result. That he was right is surely the most heroic proof of Koch's postulates in the recent history of microbiology!

● The microbe

H. pylori is a Gram-negative, microaerophilic, spiral-shaped bacterium, which is actively motile using five to six sheathed polar flagella (Fig. 2). Coccoid-shaped cells accumulate in older cultures; these are dead, as they do not have a membrane potential. After its initial isolation, the bacterium was classified as a new species in the genus



ABOVE:
Fig. 1. Representation of the association of various diseases with *H. pylori* infection in the population of the USA. The pale blue rectangle represents the *H. pylori*-negative population and the red circle within it represents all those infected with *H. pylori*. About 95 % of duodenal ulcer patients (yellow circle) and about 70 % of gastric ulcer patients (orange circle) are infected with *H. pylori*. Gastric cancer (blue circle) is strongly associated with *H. pylori* infection and with untreated gastric ulcers, while most cases of gastric lymphoma (white circle) occur in *H. pylori*-infected patients.



complex 'type IV' secretion system which functions in the translocation of a protein known as CagA into the host epithelial cell.

Here, CagA becomes phosphorylated and induces rearrangements in the actin cytoskeleton which causes the formation of cup-like structures underneath the attached bacteria. Other PI genes induce production of the chemokine interleukin-8 which mediates the infiltration of neutrophils into the infection site, thus generating a strong inflammatory response in the gastric mucosa.

LEFT: **Fig. 2.** Electron micrograph of *H. pylori*. Note the characteristic curved/spiral morphology and the terminal tuft of flagella with a terminal bulb. COURTESY DR ALAN CURRY, PRESTON PHLS LABORATORY

● Pathogenicity

Some major discoveries have been made in recent years concerning the mechanisms of pathogenicity of *H. pylori*. One of the most obvious questions is how the organism thrives in the acid environment of the stomach. *H. pylori* is certainly not an acidophilic bacterium and prefers to live in the gastric mucosa which is at neutral pH rather than in the lumen (approximately pH 2). Nevertheless, it may be periodically exposed to stomach acid and has several protection systems, one of which involves the production of huge amounts of urease. The alkaline ammonia produced by urea hydrolysis is proposed to be a major acid protectant, although urease has other physiological roles as well. Animal studies have shown that motility, chemotaxis and urease are all essential for colonization. Another question stems from the ability of *H. pylori* to set up a chronic infection which, if not treated, can be life-long, yet is often asymptomatic. How does *H. pylori* avoid clearance by the immune system? Part of the answer lies in the phase variation and molecular mimicry exhibited by its lipopolysaccharide, which contains Lewis X or Y blood-group antigens, allowing immune evasion to occur. Other roles of the lipopolysaccharide in adhesion and tissue damage via auto-antibody formation have also been shown.

One of the most important discoveries concerning the pathogenicity of *H. pylori* was that it possessed a vacuolating cytotoxin (VacA) that can directly damage epithelial cells. VacA inserts into the lysosomal membrane and forms ion channels which lead to massive vacuole formation and eventually cell death. Another important feature of *H. pylori* is the possession of a 40 kb chromosomal region which constitutes a 'pathogenicity island' (PI). These are found in several pathogenic bacteria and can often be recognized by an unusual GC content and codon usage, suggesting horizontal transfer from foreign species. In *H. pylori* the PI encodes a

● Gastric cancer

Long-term infection with *H. pylori* is now a well-established risk factor for the development of gastric cancer, and in 1994 the WHO designated *H. pylori* a group 1 (definite) carcinogen. It is not certain whether *H. pylori* directly produces carcinogens, but it is more likely that long-term infection results in changes in factors such as the cellular apoptosis-proliferation balance, effects on signal transduction pathways and gene expression, mutagenic effects of *H. pylori*-induced oxidative stress, etc., all of which can contribute to neoplastic transformation.

● Treatment

What are the treatments for *H. pylori* infection? As the bacteria are living in a mucus layer, they are not easy to eradicate using systemic antibiotics. Generally, two antibiotics, often amoxicillin and either metronidazole or clarithromycin, are combined with an acid-lowering drug, such as omeperazole, and taken for up to 2 weeks. Although patient compliance can be a problem, variations on this kind of 'triple-therapy' have become the standard treatment to eradicate *H. pylori* and are quite successful. However, resistance to metronidazole is now common and that to clarithromycin is increasing, so there is a need for new therapies to be developed. Vaccines are being developed for *H. pylori*, but this is proving difficult and it is too early to tell how successful this approach to eradication will be.

The discovery of *H. pylori* has largely replaced 'hurry, worry and curry' as the explanation for the major gastric and duodenal diseases in man. It is a fascinating organism which provides lifelong challenges – whether you are infected with it or study it!

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Further reading

The *Helicobacter pylori* Foundation website (<http://www.helico.com>), set up by Dr Barry Marshall, the co-discoverer of *H. pylori*, contains a wealth of information aimed at the general public.

Mobley, H. L. T., Mendz, G. L. & Hazell, S.L. (eds) (2001). *Helicobacter pylori: Physiology and Genetics*. Washington, DC: ASM Press. (An authoritative book covering all aspects of the biology of *H. pylori*.)

Table 1. A few famous people who were or are probably infected with *H. pylori*

■ Ayatollah Khomeini (died from intestinal bleeding)
■ Lorne Greene (the 'Bonanza' actor; had peptic ulcers)
■ James Joyce (died of a perforated ulcer; family history of stomach cancer)
■ George Bush Snr (had a duodenal ulcer in the 1960s)
■ Pope John Paul II (had gastric bleeding in the 1980s)
■ Imelda Marcos (had gastritis and gastric bleeding)

Source: <http://www.helico.com>