Helicobacter pylori in Peptic Ulcer: Have Koch's Postulates Been Fulfilled?

Barry J. Marshall

This brief review considers whether or not Koch's postulates have been fulfilled for *Helicobacter pylori* and peptic ulceration. The histological features of peptic ulcer disease in man are active chronic gastritis with antral predominance, duodenal gastric metaplasia and active duodenitis. Other features are hyperpepsinogenaemia, relative postprandial hypergastrinaemia and basal acid hypersecretion. The macroscopic features are duodenal bulb ulceration or lesser curve and antral gastric ulceration.

At present, gastric colonization with *H. pylori* has been produced in small animal species (rats and mice), but the infection is difficult to establish in immunocompetent animals, and histological gastritis is unconvincing. In larger animals the germ-free pig has been the most reliable model but the gastritis tends to be chronic with little activity.

The best examples of acute infection are in three 'self-administration' experiments in humans. In these cases acute gastritis with hypochlorhydria developed which, when it converted to active chronic gastritis, tended to be asymptomatic. Either the circumstances were incompatible with ulceration, or the experiments were not continued for the many years necessary to develop peptic ulceration. It is concluded that only one of the many steps required for the development of peptic ulceration has so far been fulfilled, i.e. the ability of *H. pylori* to produce histological gastritis in a susceptible host.

Key words: *Helicobacter pylori*; peptic ulcer; gastritis; Koch's postulates.

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Introduction

In order to define a set of rules whereby the pathogenicity of any aetiologic agent could be reasonably proven, Koch developed his four postulates in 1884 (1). At that time many doctors believed his tubercle bacillus was a commensal of the respiratory tract. Similarly, 100 years later in 1984, most physicians believed that *H. pylori* was also a commensal. Koch's four postulates are summarized as follows:

1. The organism, germ, should always be found microscopically in the bodies of animals having the disease and in that disease only; it should occur in such numbers, and be distributed in such a manner as to explain the lesions of the disease.
2. The organism must be able to be grown in pure culture outside the diseased host.
3. After culture outside the animal, organisms from a single colony should be able to reproduce the original disease in a susceptible animal.
4. The germs should be found in the diseased areas so produced in the animal.

In the case of *H. pylori* there are several disease associations of varying strength, particularly gastritis, peptic ulcer and gastric cancer. In this paper I will attempt to address the fulfillment of Koch's postulates as they pertain to *H. pylori* to the first two of these. Gastric malignancy has been addressed fully elsewhere in this volume.

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Koch's Postulates for *H. pylori* and Gastritis

Self-infection

There are three self-administration studies in which scientists studying *H. pylori* were infected with the bacterium. These studies were necessary because successful animal models of *H. pylori* infection took

several years to develop. In 1984, Marshall et al. described the initial human experiment performed at the Fremantle Hospital in Perth Western Australia. A male volunteer was first biopsied to confirm that the gastric mucosa was normal, then was given 10^9 organisms of *H. pylori* (2) after premedication 2 hours previously with 800 mg of cimetidine. The isolate was not well characterized but had come from an elderly man with nonulcer dyspepsia and had been proven to be sensitive to most of the known antibiotics, including metronidazole. The volunteer noticed no symptoms for 3 days, after which time vague gnawing abdominal discomfort and early satiety were noted. On the fifth to the eighth day nausea and vomiting occurred each morning and halitosis was present. Vomitus on day 8 was clear and did not taste acidic (but pH was not measured). Biopsy on day 8 showed heavy colonization with *H. pylori*, infiltration with neutrophils and a degenerating epithelial cell layer. Symptoms decreased after the eighth day and were largely resolved by day 14, when histology showed resolution of the infection (*H. pylori* absent), with near normal gastric mucosal morphology. Seroconversion did not occur.

Arthur Morris, a New Zealander, repeated the experiment in 1985 (3). Morris's experiment was more detailed with baseline and follow-up intragastric pH recordings in parallel with biopsy samples. Morris used a fresh isolate of *H. pylori* and again premedicated with cimetidine, so that the intragastric pH was 7.6 at the time of ingestion. He was asymptomatic for 2 days, then severe nocturnal epigastric pain occurred as well as two vomiting attacks, followed by 3 more days of nausea. After the seventh day he was asymptomatic. Biopsies on the fifth day showed severe neutrophil infiltration of the antral mucosa but not of the corpus. Fasting pH was 7.6 on the eighth and the eleventh day. Endoscopy and biopsy on day 11 showed normal appearance but now a mixed inflammatory infiltrate was present in the antral and the corpus biopsy samples. After taking doxycycline, pH dropped to normal (≤ 2) and inflammation resolved. After ceasing therapy, however, *H. pylori* relapsed and chronic gastritis affecting antrum and body mucosa remained for nearly 3 years (4). Finally, in 1989, the infection was eradicated with triple therapy (bismuth–tetracycline–metronidazole) after which the gastric mucosa returned to normal. Seroconversion of IgG occurred during the fourth week of the infection.

The third 'self' administration was by Dr George Sobala in Leeds, UK (5). The subject had been tested by ^{14}C-urea breath test at an earlier time and was negative for *H. pylori*. An acute illness, characterized by about 1 week of epigastric pain, was recognized as possible *H. pylori* infection and proven to be so by breath test and biopsy. On the fifth day an acute neutrophilic gastritis was noted on biopsy which had become chronic by the 74th day. Achlorhydria was present in the initial week but resolved after that, and for most of the infection the subject was asymptomatic. Seroconversion was noted with an initial IgA and IgM response in the third week and a delayed IgG response after 2 months.

These three reports demonstrate the consistent association between *H. pylori* and a syndrome of epigastric pain, achlorhydria and neutrophilic infiltration of the mucosa. This syndrome has been observed in less detail over the past 100 years and termed 'acute hypochlorhydric gastritis'. In the second two cases above (3, 5), development of chronic gastritis was observed and an antibody response was detected.

Iatrogenic Infection

Other detailed reports of accidental infection with *H. pylori* are available. An epidemic of probable *H. pylori* infection was noted in Dallas, Texas, USA in 1979 (6) and followed up in 1991 (7). In that epidemic, most subjects developed epigastric pain with nausea or vomiting which resolved after 1 week. They remained achlorhydric for several months until corpus inflammation subsided, leaving chronic antral inflammation and normal acid secretion. At 10-year follow-up on 29 of 37 subjects, current age averaging 40 years, it was found that five subjects had chronic indigestion and one of these had developed a prepyloric ulcer. Most of the subjects were well, without epigastric symptoms or ulcers, but with stable chronic antral gastritis and *H. pylori* infection. In 20 subjects tested, acid secretion was normal but two remained hypochlorhydric. Interestingly, three subjects had died, an apparently high attrition rate for such a small group of supposedly normal volunteers.

Numerous other cases in the literature support the above epidemic of hypochlorhydric gastritis, the best of which is a report from Houston (8). The patient, a volunteer in a nonsteroidal anti-inflammatory drug trial, developed epigastric pain, gastritis, transient achlorhydria, then hyperchlorhydria with acute antral ulceration and endoscopic gastritis, before settling into a state of chronic asymptomatic gastritis. He was probably infected by a contaminated endoscope at an initial endoscopy.

Thus it has been proven that *H. pylori* causes an acute illness lasting perhaps 1 week in most cases, associated with neutrophilic infiltration of the gastric mucosa and achlorhydria. After the second week the infection may resolve (rarely), or lead to acute ulceration if acid secretion returns to high levels and aspirin is taken. In the chronically infected state (most people), acid secretion is usually normal and the patient is generally asymptomatic. From this data we can conclude that Koch's postulates have been fulfilled for the relationship between *H. pylori* and chronic gastritis. The natural history of the initial infection is shown in Figure 1.

Koch's Postulates and Peptic Ulceration

Koch's postulates for *H. pylori* have not been fulfilled in the case of peptic ulceration because, at present, no human or animal experimental model has produced peptic ulcer after inoculation with *H. pylori*. Most of the

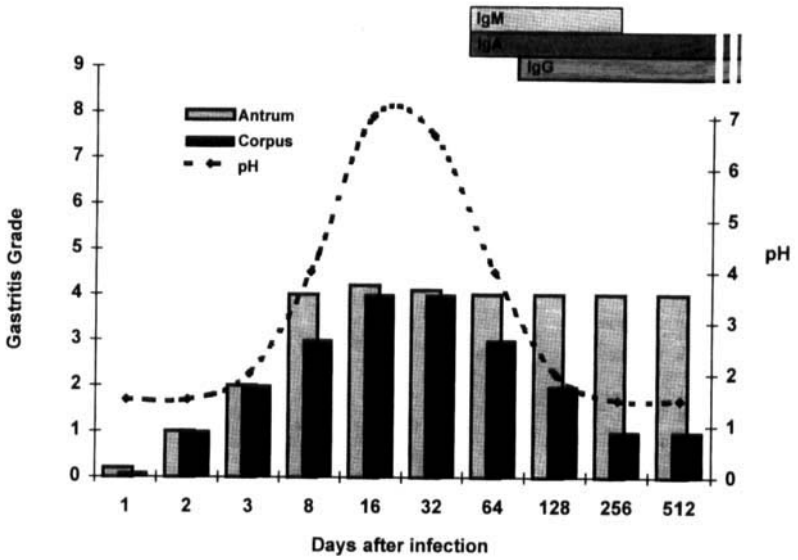

Figure 1. Natural history of acute *Helicobacter pylori* infection. The horizontal axis shows time scale in days over 18 months. The left vertical axis is gastritis grade as represented in the columns showing antral and corpus mucosa inflammation graded 0–4. Right vertical axis shows pH of gastric juice on a scale of 0–7. Note that corpus mucosa inflammation (dark vertical bars) subsides after 3 months whereas antral inflammation remains. As corpus mucosa returns to near normal, acid secretion revives and gastric pH (dotted line) falls to normal acidic levels. Variable early responses are seen in IgA and IgM. IgG is present after the fourth week and remains as the most stable antibody response in nearly all infected people.

evidence that *H. pylori* causes peptic ulceration comes indirectly from treatment studies or from prospective case–control studies in humans. Treatment trials have shown the following effects.

1. Cure of *H. pylori* results in healing of histological gastritis.
2. Healing of gastritis is associated with 80–90% cure of duodenal ulcer.
3. Resolution of the following ulcer associated abnormalities also commonly occurs:

- elevated serum pepsinogen I (9);
- elevated postprandial gastrin response (10);
- elevated basal acid secretion in some studies (11), but not others (12);
- depression (13); and
- mucus thinning (14) and decreased mucus hydrophobicity (15).

Prospective studies have shown that ulcer risk is greater in asymptomatic people infected with *H. pylori*. Logically, because only 10% of the population develops documented peptic ulcer in a lifetime, and about 30% of the population are infected with *H. pylori*, the lifetime ulcer rate for these infected people should not be more than one-third. In support of this number, prospective studies have noted a relative peptic ulcer risk of 3–6-fold in asymptomatic adults followed for periods of 10–20 years (16). This reflects a new peptic ulcer incidence of about 1% per annum in the infected subjects which could translate into 30–50% lifetime incidence as predicted above.

The prerequisites for duodenal ulcer in man are shown in Figure 2. For peptic ulcer to be likely, infection with *H. pylori* must cause gastritis localized to the antrum so that the corpus is spared and continues to

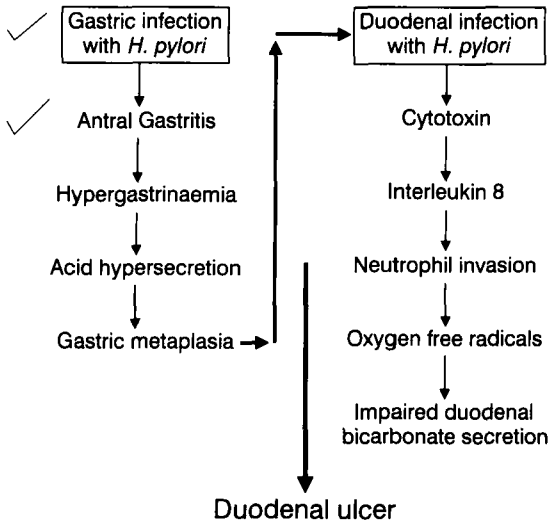

Figure 2. Prerequisite lesions for duodenal ulcer. Check marks (✓) show the degree to which animal models have been able to duplicate the scenario necessary for the development of duodenal ulcer. The development of a high acid secretory state in the presence of colonized gastric epithelial metaplasia in the duodenum might be an absolute prerequisite before Koch's postulates can be fulfilled in this disease.

secrete acid in response to an augmented secretion of gastrin from the antrum. Spontaneously (most likely), or in response to high acid secretion (less likely), gastric metaplasia develops in the duodenum. This may then be colonized with *H. pylori* resulting in acute inflammation (duodenitis). The duodenitis is more severe when the *H. pylori* strain secretes a cytotoxin because IL-8 is produced in the epithelial cells and greater recruitment of neutrophils results. As shown in the diagram, this model might be too complex for

reproduction in an animal model. In any case, the pressing need for such an effort might have passed because, in 1995, diagnostic modalities and effective therapy for *H. pylori* can now cure associated duodenal ulcer disease in most patients.

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