

The bacterium that could cause cancer

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For decades clinicians the world over took it for granted that bacteria could not live and grow in the stomach because of the acid pH of its lumen. It was, therefore, a great surprise when Barry Marshall and Robin Warren reported in *The Lancet*¹ in 1984 that bacteria resembling campylobacter could be found beneath the gastric mucus layer that lines the surface epithelium of the stomach, and that their presence was associated with gastritis, and gastric and duodenal ulcers. In fact, the same authors had already reported their finding of "unidentified curved bacilli on gastric epithelium in active chronic gastritis", which they set out a year earlier in two letters to *The Lancet*.^{2,3} Indeed, similar bacteria had been described repeatedly during the previous century, but had been overlooked partly because they could not be seen with conventional stains.

In the 4 years following Marshall and Warren's report, it was established that *Campylobacter pylori* infection caused an acute histological gastritis that could become chronic, that it was the causative agent in type-B gastritis, that it was often found in patients with peptic ulcer disease, and that the eradication of the organism was associated with the healing of gastritis and a lower relapse rate in duodenal ulcer disease.⁴ The idea that peptic ulcer disease was related to gastric hypersecretion, stress, smoking, or alcohol was abandoned, and the dictum "no acid, no ulcer" was replaced with "no bacterium, no ulcer".

By 1993 (10 years after the first report) it had been shown that half of the world's population were infected with *C pylori*, that the mode of transmission was probably fecal-oral, and that its prevalence increased with age and was higher in lower socioeconomic groups. Infection with *C pylori* could be diagnosed using serology, breath testing, biopsy, and culture. Effective therapies had been established, and many double-blind trials had shown that eradicating the bacterium, by then known as *Helicobacter pylori*, usually cured duodenal ulcer disease.

These were significant achievements, but of even greater importance from a biological viewpoint was the link between *H pylori* and cancer. Before Marshall and Warren's discovery, no factors had been shown to be causally linked with gastric cancer, although a link between several types of food and drink and gastric cancer had been tentatively suggested. Pivotal work demonstrated that *H pylori* was related to gastric malignancies,⁵ and further studies led the International Agency for Research on Cancer to classify the bacterium as a class I carcinogen in 1994. This was a landmark biological discovery: the first time it had been shown that a bacterium could cause cancer.

It is now clear that *H pylori* infection is the main risk factor for the development of non-cardia, intestinal-type gastric cancer, and that it has a role in mucosa-associated lymphoid tissue non-Hodgkin lymphomas. However, the mechanisms by which *H pylori* causes cancer remain to be fully elucidated, since *H pylori* colonisation is usually asymptomatic, and tumour progression only occurs in a subset of individuals. Host response and genetic variation of the bacterium are thought to have a role in determining whether colonisation leads to cancer.

Given the importance of their discovery, it is not surprising that in 2005 Warren and Marshall were awarded the Nobel Prize in Medicine.

Conflicts of interest

The authors declared no conflicts of interest.

References

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Key findings of the paper

- Biopsy specimens were taken from intact areas of antral mucosa in 100 consenting consecutive patients presenting for gastroscopy at the Royal Perth Hospital, Perth, Australia
- Spiral or curved bacilli were found in biopsy specimens from 58 patients
- The bacteria were usually found in close contact with the mucosa, often in grooves between cells, within acinus-like infoldings of the epithelium, or within the mucosal pits
- Gram-negative, flagellate, microaerophilic bacilli cultured from 11 biopsy specimens seemed to be a new species related to the genus campylobacter
- The bacteria were sensitive to tetracycline, erythromycin, kanamycin, gentamicin, and penicillin, and were resistant to nalidixic acid
- The bacteria were present in almost all patients with active chronic gastritis, duodenal ulcer, or gastric ulcer. Therefore, they might be an important causal factor in these diseases

