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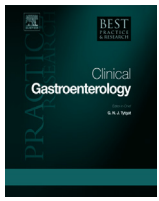

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Helicobacter pylori: The balance between a role as colonizer and pathogen

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A B S T R A C T

The isolation of *Helicobacter pylori* from the human stomach produced significant changes in how gastroenterologists, immunologists, epidemiologists, pathologists and microbiologists have approached gastro-duodenal diseases in the last half of the XX century. However, research of this organism has progressed greatly in the first decade of this century, evidence suggest that *H. pylori* is associated with disease only in humans older than 40 years, while, the lack of *H. pylori* colonization is associated with the emergence of new diseases, particularly in younger individuals. These differing effects of *H. pylori* colonization have created two contrasting concepts: the 'bad' and the 'good' Helicobacter. Following from renewed interest in the normal human microbiome, we need to reconsider our definitions and perhaps recognize that *H. pylori* might be a normal member of the human gastric microbiome in ancient humans that gradually, as results of the improvement in our environment, is disappearing.

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Historical concepts

Helicobacter pylori is a Gram negative, spiral shaped, flagellated bacteria that colonizes the human gastric mucosa [1]. Currently it is estimated that half the world hosts this bacterium [2,3].

For many years the stomach was thought to be a sterile organ without a normal resident microbiota and with only a transient microbiota. In fact, it was thought that due to the acidic gastric secretions of the stomach, no microorganism could survive the highly acidic environment.

The first observations of bacteria in the stomach were presented in 1875, when two German researchers, Bottcher and Letulle [4], discovered bacteria in the stomach of patients with gastric ulcers. Thus, they suggested that ulcers could be caused by bacteria. However, as they were unable to cultivate the bacteria, the scientific community ignored their results. Several years later, in 1893, Bizzozero [5] reported a display of spiral shaped bacteria in the stomach of dogs and cats. However, their findings were not associated with the early reports describing similar organisms in humans.

Salomon, in 1896, after confirming the earlier findings in animals, also found the same spiral bacteria in the human stomach. In the same year, Jaworski [6], a polish researcher, describes spiral bacteria in gastric sediment obtained from humans and called them *Vibrio rugula*. Furthermore, Jaworski suggested a possible pathogenic role of these spiral bacteria, associated with gastric diseases. This work was included in the *Handbook of Gastric Diseases*, but because it was published in Polish, the knowledge did not become widespread [6].

In 1906 Krienitz found the same type of microorganisms in the mucosa of stomachs of patients with gastric cancer [7].

In the twentieth century, Doenges conducted the first systematic study searching for helical bacteria in human stomachs, and published the first work relating these microorganisms to gastric ulcers [8].

However, in 1954, Palmer [9] published a widely accepted study in which no bacteria were found in the human stomach, and concluded that earlier discoveries were a result of microbial contamination of the mouth.

From that moment, it was assumed that the stomach was a sterile environment in which no organism could survive, and could not therefore cause any gastric pathology.

For the next 20 years conventional thought considered the etiological agents of gastric ulcers to be stress and spicy foods. In 1975, with the introduction of the electronic microscopy, investigators observed spiral shaped microorganisms in patients with gastric ulcer and again associated this organism with inflammatory response in the gastric mucosa [10].

In 1979, the bacterium was observed by an Australian pathologist Robin Warren. Later, an Australian physician, Barry Marshall, joined in the investigation of this spiral microorganism. In 1981, Marshall and Warren began a prospective study in Royal Perth Hospital, looking to culture this microorganism for the first time. They followed the methodology used by Martin Skirrow [11] for the isolation and culture of *Campylobacter* species, due to the morphological similarities of the two species. After numerous unsuccessful attempts, the bacteria was finally isolated from the stomach of a patient, and they succeeded in visualizing colonies in 1982, when they unintentionally left Petri dishes incubating for five days over a long Easter weekend. This scientific event marks a revolution in medicine, bacteriology, and gastroenterology, proving clearly for the first time that live bacteria colonize the gastric epithelium in the stomach and in particular in the gastric mucosa.

At that moment, it was reckoned that this bacterium could be a new species in the genus *Campylobacter* due to their appearance in the Gram stain and microaerobic requirements. Thus *C. pyloridis* was the initial name of the bacterium, it was renamed *C. pylori* to correct a Latin grammar error [12]. In 1989, 16S ribosomal RNA gene sequencing showed that the bacterium did not belong in the genus *Campylobacter*; therefore it was placed in its own genus, *Helicobacter*.

The changes in gastric concepts

Early theories on the causes of gastric ulcers were related to direct or primary pathogenic factors such as gastric acid in hypersecretory patients and secondary factors such as stress, alcohol, smoking,