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LETTERS TO THE EDITOR

This year's Nobel Prize to gastroenterology: Robin Warren and Barry Marshall awarded for their discovery of *Helicobacter pylori* as pathogen in the gastrointestinal tract

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TO THE EDITOR

Peptic ulcer disease is a major health care concern in the society today, in view of personal suffering as well as economical health care costs.

Before *Helicobacter pylori* (*H pylori*)

During the last century peptic ulcer research was much focused on the understanding of the relationship of peptic ulcers to acid secretion. The dictum of Karl Schwarz: "No acid - no ulcer" provided the framework for ulcer research.

Surgery aiming at reducing gastric acid secretion is a common treatment of choice, as drugs such as anticholinergics and antacids are not good enough in achieving a reliable treatment response. The surgery involves selective and proximal vagotomy of the parietal cell mass, removal of the gastrin-producing antrum, or combinations of the two. The most extensive operations carried out are the Billroth I and Billroth II operations which regularly remove the antrum, alone or in combination with vagotomy and gastroenteroanastomosis. Both operations involve major surgery and often postoperative complications.

Since the invention of the histamine H_2-receptor antagonists in 1974, the peptic ulcer research field has been even more emphasized and the drug industry has converged on its power on the inhibition of gastric acid secretion as a cure for peptic ulcer disease. This was further encouraged by the 1988 Nobel Prize in physiology or medicine for important principles in drug treatment. The principles that were awarded have resulted in the development of drugs with antagonist action, the acid-inhibitory H_2-receptor antagonist cimetidine is among them.

Along this line even more efficient acid inhibitors that block the H^+,K^+-ATPase, the proton pump, have been developed. To mention one, omeprazole was the first to surface on the arena at the World Congresses of Gastroenterology in 1982, yet some years before taken to the clinic. This compound was later shown to be able to bring down acid secretion to nil and heal ulcers more rapidly than H_2-receptor antagonists. To conclude, the "no acid, no ulcer" concept is consolidated among gastroenterologists as the problem of peptic ulcer appears to be resolved with chronic administration of antisecretory drugs. However, when treatment is withdrawn the ulcers recur. Since then, the recurrence has been considered an effect of receptor up-regulation after long-standing H_2-receptor blockade or persistent hypergastrinemia after treatment with a proton pump inhibitor[1].

Infectious etiology of peptic ulcer disease

An association between gastritis and peptic ulcer disease has been known since the 1940s. Efforts to culture these bacteria however have failed. The Australian histopathologist Robin Warren, in Perth, being unaware of the earlier findings has made similar observations but also the observation that the appearance of these bacteria is similar to the *Campylobacter* genus and preliminary named the bacterium *Campylobacter pylori*[2].

Barry Marshall, being a trainee in internal medicine working in Stewart Goodwin´s Laboratory in Perth, Australia, was with serendipity successful in culturing the bacteria. Over the Easter holiday the Petri dishes with bacterial cultures were inadvertently left in the incubator in five, instead of two days, as recommended for *Campylobacter*. When the dishes were examined after the holidays, small colonies with a shiny appearance were detected. This is the first successful culture and isolation of a bacterium from the stomach of a patient with gastritis. The findings were presented at a Campylobacter meeting 1983[3]. Initially the reports of an association between the bacterium and gastritis were met with great scepticism from the established scientific community. The findings were later published in the Lancet[3].

One major question is whether the bacterium is the cause of gastritis or simply an innocent bystander that happens to colonise a damaged mucosa. In order to rule this out, Barry Marshall and Arthur Morris decided to inoculate themselves by drinking a solution containing vast amounts (10^9) of the bacterium under acid suppression with cimetidine. Both developed signs of an acute gastric "flu"-like illness, with gastric distension, nausea and vomiting. After 10 days endoscopy revealed contraction of *H pylori* and chronic gastritis[4], which gradually subsided over the next

two weeks. Renewed endoscopy could not disclose the organism and the gastritis was healing. In the case of Morris the symptoms remained as a common gastritis. These cases are the ones to confirm the Koch´s postulate that the bacterium itself indeed is the cause of disease[5].

Clinical trials in order to eliminate the bacterium from the stomach showed that treatment with antibiotics could reduce the symptoms and severity of gastritis. Studies also showed that eradication of *Helicobacter* could prevent the relapse of peptic ulcer disease[6]. This has generated a continuing flow of research from the scientific community, which emanated in the acceptance of gastritis and peptic ulcers as basically infectious diseases. The cause of ulcer disease has previously been hidden by a dual false premise that the stomach is sterile and ulcers are caused by stress. This dogma is so deep in scientific thinking that it has taken more than a decade of research and repeat replication of results by scientists to have this fact accepted.

H pylori causes life-long infection

H pylori is a spiral-shaped Gram-negative bacterium that colonizes the stomach. In countries with high socioeconomic standards infection is considerably less common than in developing countries where virtually everyone may be infected.

Infection is typically contracted in early childhood, frequently by transmission from mother to child, and the bacteria may remain in the stomach for the rest of the person's life. This chronic infection is initiated in the antrum of the stomach. As first reported by Robin Warren, the presence of *H pylori* is always associated with an inflammation of the underlying gastric mucosa as evidenced by an infiltration of inflammatory cells[2].

The infection is usually asymptomatic but can cause peptic ulcer

The severity of this inflammation and its location in the stomach are of crucial importance for diseases that can result from *H pylori* infection. In most individuals *H pylori* infection is asymptomatic. However, about 15% of infected individuals will some time develop peptic ulcer disease. The current view is that the chronic inflammation in the distal part of the stomach caused by *H pylori* infection results in an increased acid production from the non-infected upper corpus region of the stomach. This will predispose for ulcer development in the more vulnerable duodenum. After the discovery of *Helicobacter* as the pathogen, a 7-day course of antibiotics in conjunction with acid suppression may heal a previously chronic disabling disease.

Malignancies associated with H pylori infection

H pylori can also infect the corpus of the stomach. This results in a more widespread inflammation that predisposes not only to gastric ulcers in the corpus, but also to stomach cancer. Globally, this cancer has decreased in incidence in many countries during the last 50 years but is still ranked as number two in the world in terms of cancer deaths after lung cancer. Mucosa associated lymphoid tissue (MALT) lymphoma is a specific type of lymphatic neoplasm in the stomach that has been associated with *H pylori*. Curiously, MALT lymphomas regress when *H pylori* is eradicated by antibiotics, why the bacterium seems to play an important role in the development of this tumour.

Microbial origin of chronic inflammatory conditions in general?

The discovery that one of the most common diseases of mankind, peptic ulcer disease has a microbial cause, has stimulated the search for microbes as possible causes of other chronic inflammatory conditions. Even though no definite answers are at hand, recent data clearly suggest that a dysfunction in the recognition of microbial products by the human immune system can result in disease development. The discovery of *H pylori* opens the possibility of an increased understanding of the connection between chronic infection, inflammation and cancer.

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