

J. W. KONTUREK

DISCOVERY BY JAWORSKI OF *HELICOBACTER PYLORI*
AND ITS PATHOGENETIC ROLE IN PEPTIC ULCER, GASTRITIS
AND GASTRIC CANCER

Department of Gastroenterology, Elbe Klinikum Stade, Stade, Germany

The presence of spiral-shaped micro-organisms in the human stomach was described over 100 years ago by Polish clinical researcher, Professor W. Jaworski at Cracow Jagiellonian University. Their presence was then confirmed in animals by G. Bizzazero, but was not really taken seriously until the late 1970s, when J.R. Warren, a pathologist in Perth, Australia, noted the appearance of spiral bacteria overlaying gastric mucosa, chiefly over inflamed tissue. Warren and B.J. Marshall cultured these organisms in 1982 from 11 patients with gastritis and were able to demonstrate a strong association between the presence of *Helicobacter pylori* (*H. pylori*) and the finding of inflammation in gastric biopsies. People, who did not exhibit gastritis, also did not have the organism, a finding which was confirmed in a number of studies. Originally called *Campylobacter pyloridis*, the name was changed to *Campylobacter pylori*, and then later to *Helicobacter pylori* (*H. pylori*) as specific morphologic, structural, and genetic features indicated that it should be placed in a new genus. Marshall elegantly fulfilled Koch's postulates for the role of *H. pylori* in antral gastritis with the self administration of *H. pylori*, and also showed that it could be cured by use of antibiotics and bismuth salts. Most persons who are infected with *H. pylori* never suffer any symptoms related to the infection; however, *H. pylori* causes chronic active, chronic persistent, and atrophic gastritis in adults and children. Infection with *H. pylori* also causes duodenal and gastric ulcers. Infected persons have a 2- to 6-fold increased risk of developing gastric cancer and mucosal-associated-lymphoid-type (MALT) lymphoma compared with their uninfected counterparts. The role of *H. pylori* in non-ulcer dyspepsia remains unclear. These practical aspects of *H. pylori* were subjects of two international symposia organized by us in 1995 and 1997 in Cracow, helping to promote research and Polish consensus regarding treatment of *H. pylori* infection.

Key words: *Helicobacter pylori*, gastritis, peptic ulcer, gastric cancer, nonsteroidal anti-inflammatory drugs, dyspepsia

INTRODUCTION

Our knowledge about the cause of peptic ulcer disease, the etiology of gastric cancer, and perhaps of some forms of dyspepsia is in a state of permanent evolution. The discovery of the infective organism *Helicobacter pylori* (*H. pylori*) and its involvement in these diseases has begun a dramatic change in our views on how to approach its diagnosis and treatment. As yet, the story is still unfolding. The presence of spiral-shaped micro-organisms in stomach mucosa was described in men more than 100 years ago by Polish clinical researcher, W. Jaworski (1), however, it was not really taken seriously until the late 1970s, when J. R. Warren, a pathologist in Perth, Australia, noted the appearance of spiral bacteria in mucus overlaying gastric mucosa, chiefly over inflamed tissue. Warren and B.J. Marshall cultured these organisms in 1982 from 11 patients with gastritis (2). Originally called *Campylobacter pyloridis*, the name was changed to *Campylobacter pylori* and then later to *H. pylori* as specific morphologic, structural and genetic features indicated that it should be placed in a new genus. The organism is a motile, gram-negative, curved rod which expresses such enzymes as oxidase, catalase, and urease. Marshall and Warren (3) were able to demonstrate a strong association between the presence of *H. pylori* and the finding of inflammation on gastric biopsy. Also, people who failed to exhibit gastritis, did not have the organism, a finding confirmed in a number of studies. Marshall elegantly fulfilled Koch's postulates for the role of *H. pylori* in antral gastritis by the self administration of *H. pylori*, and also showed that it could be cured by the use of antibiotics and bismuth salts. Even so, enough is now known to consider getting some of the fruits of a decade of research into practice - to cure peptic ulcer disease with antimicrobial therapy rather than placing patients on expensive long term acid-suppressing therapies. This section is not intended to give a comprehensive review of all the information that exists on *H. pylori* and its associations with gastric diseases. Rather, it is designed to provide sufficient background information about *H. pylori* pathology, and especially, to present the Polish traces in the history of the *H. pylori* discovery, which is considered by J.B. Kirsner (4) to be one of the major achievements in gastroenterology of 20th century.

The History of Helicobacter pylori

H. pylori is one of the most common bacterial infections in humans that affect most populations throughout the world. The story of *H. pylori* and the recognition of its major role in gastric pathology originated from simple histological observations of the spiral organisms in the gastric mucosa of men and animals. W. Jaworski, Professor of Medicine at the Jagiellonian University of Cracow, Poland was first to describe the spiral organisms in the sediment of gastric washings obtained from humans (*Fig. 1*) (1). He noticed among the other rods, a *bacterium* with a characteristic spiral appearance and named it, *Vibrio rugula*, suggesting for

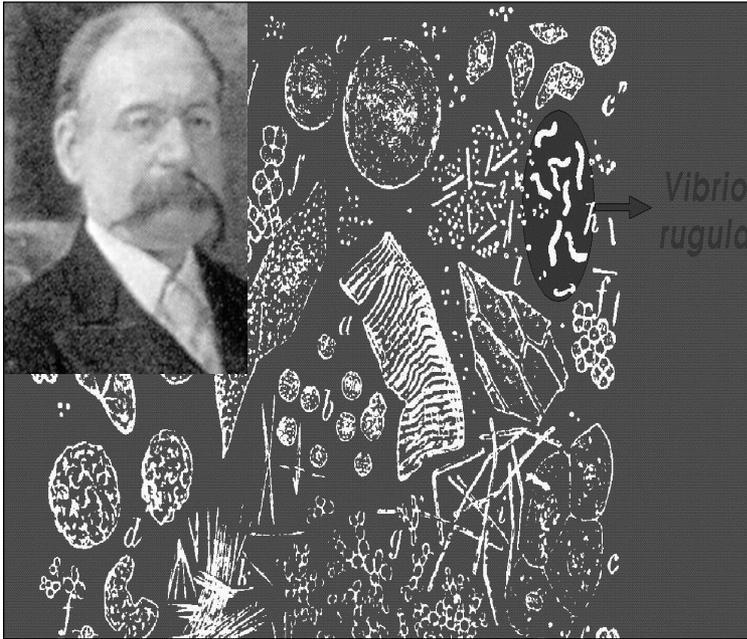


Fig. 1. W. Jaworski discovered in 1886 spiral bacteria in gastric sediment from humans and called them *Vibrio rugula*.

the first time its possible pathogenic role in gastric diseases. His work on gastric bacteria was included into the voluminous "*Handbook of Gastric Diseases*" but it was little known because it was written in Polish until it was "rediscovered" by Konturek *et al.* (5) and then included by Modlin in his excellent GI history book (6). Jaworski should be considered a world pioneer in gastroenterology, particularly in gastric microbiology at the end of the last century, and represents the major Polish trace in the history of gastroenterology.

In animals, Bizzozero (7) was probably first in the second part of the 19th century to report the presence of such organisms in the gastrointestinal tract, but these findings were considered a mere microbiological curiosity. By 1900, Salomon (8) showed that spiral bacteria infecting dogs and cats can be transmitted to mice and this phenomenon is now utilized in the development of immunization against *Helicobacters*. Jaworski's discovery of spiral bacteria in the human stomach was confirmed by Kreinitz in 1906 (9) and then by other reports around 1940. They described spirochetes in about 40% of human stomachs in postmortem examination (10) and in fresh surgical specimens (11). The latter work was important because it indicated that the organisms are not merely postmortem contaminations, but actual gastric pathogens. These studies carried out mostly in Europe, and were not supported by research in America, where Palmer (12) reported in "*Gastroenterology*" in 1954 that he was unable to find any bacteria in suction biopsies from 1180 human stomachs. At this stage the progress in research on gastric *Helicobacters* was dominated by the concept that stomach secretes acid

to keep its lumen sterile and that gastric acid may cause mucosal lesions in accordance to the Schwarz *dictum* in 1910 "no acid, no ulcer" (13).

It is interesting that in 1924, Luck and Seth (14) reported that the human stomach exhibits abundant urease activity, and later, it was found that this activity disappears following the treatment with antibiotics but the connection between this enzyme and gastric spirochetes was not made until 1984 (15). The major obstacle in recognizing the role of spiral bacteria in human gastric pathology was the persistent failure to culture the bacteria from the stomach. For example, in 1975 Steer (16) found spiral bacteria closely attached to gastric surface epithelial cells but cultured only *Pseudomonas aeruginosa*. It was the successful culture of spiral-shaped bacterium during long Easter holiday weekend in 1982 in the microbiology lab of the Royal Perth Hospital by Warren and Marshall (*Fig. 2*) that heralded a new era in basic and clinical gastroenterology (2, 3). The first culture obtained from a gastric biopsy of a duodenal ulcer patient was initially called a *Campylobacter*-Like Organism (CLO) thinking that it was a *Campylobacter* species, but it turned out to be different genus, now named *H. pylori*. The ability of *H. pylori* to colonize the human stomach, to induce acute and then chronic active gastritis and/or chronic atrophic gastritis, and to respond with clearance or eradication to antibiotic therapy, all fulfilled Koch's postulates for *H. pylori* as infection agent (17).

Marshall developed Warren's idea (2) that *H. pylori* infection is associated with gastritis and duodenal ulcers (3) and this was then confirmed independently

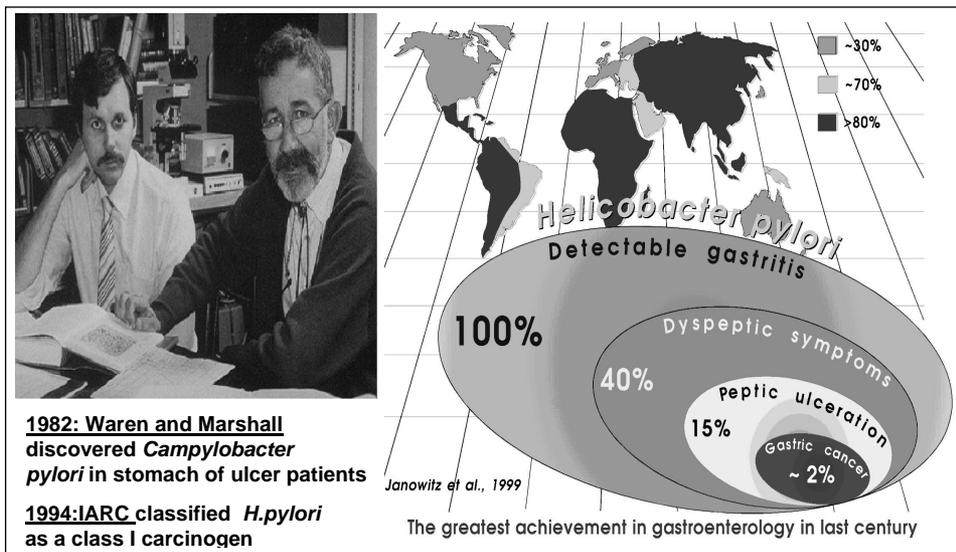


Fig. 2. Rediscovery of *H. pylori* by Warren and Marshall and its prevalence in various parts of the world and related gastric pathologies. (Janowitz, et. al. 1999)

by Rollason *et al.* (18) and Steer, (19) who reported that patients with these diseases were more often infected with spiral bacteria than healthy controls.

Helicobacter pylori and peptic ulcer

There are numerous pieces of evidence that *H. pylori*-induced gastric mucosal infection may lead to gastritis and eventually may be responsible for the development of gastric and duodenal ulcerations, or gastric cancer. The localization of ulcers and the development of cancer depend upon the type and localization of gastritis. Voluntary ingestion of *H. pylori* results in acute then chronic active gastritis, and experimental animals challenged with live bacterium simulate human infection and gastritis, while antimicrobial therapy clears the infection and the gastritis. *H. pylori* only overlies the gastric epithelium and is associated with certain types of gastroduodenal inflammation, that may persist throughout the life of the subject (notably type B gastritis almost universally present in duodenal ulcers), although not all types (20). There is a systemic immune response to gastric *H. pylori* infection and anti-*H. pylori* antibodies diminish with effective antimicrobial therapy, (21) though it may take several months for antibody titer to decline after *H. pylori* eradication. Another compelling piece of evidence comes from the epidemiology of gastritis and *H. pylori* infection. The pattern of *H. pylori* acquisition with age is identical to that of gastritis. Serological tests for *H. pylori* infection (circulating IgG and IgA antibodies measured by immunological methods) show that *H. pylori* infection is low in children, but rises dramatically in the fifth and subsequent decades, and that more than half of the population over 50 years is infected. This seems to be due to a continuous risk of infection (22). As shown by Bielanski, (23) using his original mini-dose capsulated urea breath test (UBT) in a large Polish population, the *H. pylori* prevalence reached about 60-70% in adults, and also increases with their age, while in children it averaged 20-30%. Smoking increases the *H. pylori* prevalence, and this remains in keeping with the associated increased incidence of gastro-duodenal ulcerations.

H. pylori are motile, even in the highly viscous mucus gel layer in which they live. The application of this simple, non-invasive and inexpensive UBT to population studies should be considered an important Polish achievement. This test helped to determine various factors related to the prevalence of *H. pylori* in Poland, including age, gender, smoking, use of non-steroidal anti-inflammatory drugs (NSAID), and various gastric diseases including gastro-duodenal ulcerations, gastritis and gastric cancer.

Gastric *H. pylori* infection allows the organisms to invade the gastric mucosal barrier, including surface epithelial cells and the parietal cells through their intracellular cannalliculi. It has been proven that chronic *H. pylori* infection may lead to duodenal ulcer disease accompanied by an inappropriately high gastrin release due to reduced somatostatin paracrine release, resulting in enhancement of

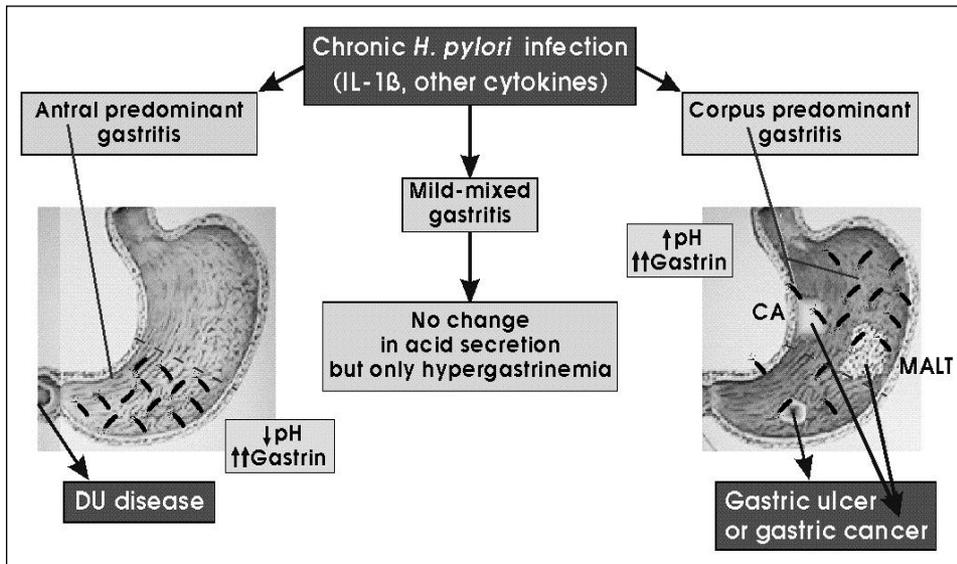


Fig. 3. Ulcerogenic and carcinogenic effects of *H. pylori* depend upon the localization of *H. pylori* infection in humans. (Konturek S.J., et. al. 2000)

gastric acid secretion and gastric emptying rate (Fig. 3). Those changes in hormonal endocrine and paracrine secretions, caused by *H. pylori* infection, are responsible for impairment of the inhibitory effect of cholecystokinin (CCK) on postprandial gastric acid secretion and gastric emptying in patients with *H. pylori* infection, which may also account for key factors involved in the pathogenesis of peptic ulcer disease. As shown previously by our group, the eradication of *H. pylori* restores the inhibitory effect of CCK on acid secretion and gastric emptying (24, 25).

The *H. pylori* organisms seem specifically to overlay gastric-type epithelial cells, whether in the stomach or metaplastic in the duodenum; they do not overlay absorptive-type duodenal cells, even when these are metaplastic in the stomach. Although they are motile, they also may adhere to the gastric mucosa through specific adhesion mechanisms. The release of large amounts of urease by *H. pylori* results in the conversion of any urea in the gastric environment into ammonia - with the result of intensified acidity around the bacterium in the stomach, this may be attenuated by allowing the bacteria to survive in acidic conditions and cause the gastric antrum to release excessive amounts of gastrin from the G cells. The Michaelis constant of *H. pylori* urease is 0.4 mM, making it one of the lowest known for this enzyme, and allowing significant conversion of urea to ammonia at very low urea concentrations and, therefore, to work efficiently in the stomach.

About 50% of *H. pylori* strains produce cytotoxins (Cag) (26), of which, some types such as CagA, have been specifically linked to active gastritis, peptic

ulceration, and gastric cancer. The strains isolated from patients with the most severe disease tend to be more likely to release CagA than strains isolated from asymptomatic patients. These cytotoxins can cause local inflammation, though other secretions by the organism, such as proteases and phospholipases, can attack and damage mucosal cell membranes. Weakening the gastric-mucosal barrier permits back-diffusion of hydrogen ions resulting in further tissue injury, as well as causing local immune responses to the organism due to the inactivation (by *H. pylori*-originating VacA) of receptors for interleukin 2 (IL-2) in the T-cells (which are responsible for the cellular immunity, and constitutes a major defense against infection).

There is also evidence that *H. pylori* infection is responsible for reducing the levels of ascorbic acid in the gastric juice; levels in infected patients were only 25% of those in non-infected subjects (27). Moreover, eradication of *H. pylori* resulted in a large increase in gastric juice ascorbate. The reversible lowering of gastric juice ascorbate may predispose to gastric cancer and peptic ulceration.

Interactions between Helicobacter pylori and NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recognized as one of the most common etiologic factors associated with gastritis and peptic ulceration. How aspirin and other NSAIDs damage the gastroduodenal mucosa, exacerbate existing ulcers, or delay their healing is not clearly understood. Their deleterious effects on gastroduodenal mucosa are mainly attributed to direct damage of mucosal cells and their ability to inhibit cyclooxygenase (COX) and reduce the formation of prostaglandins (PG) (Fig. 4) (28). Although PG exhibit a potent

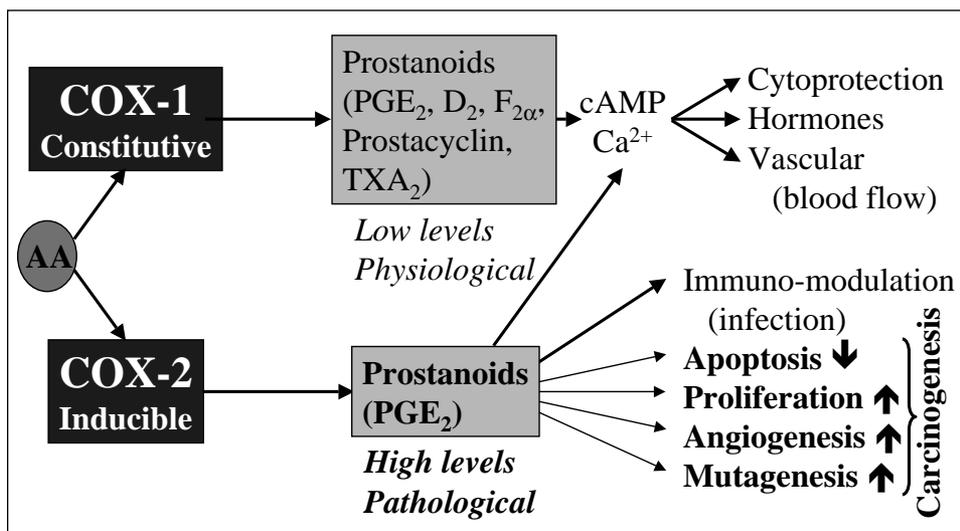


Fig. 4. Actions of cyclooxygenases (COX) in gastric cancerogenesis.

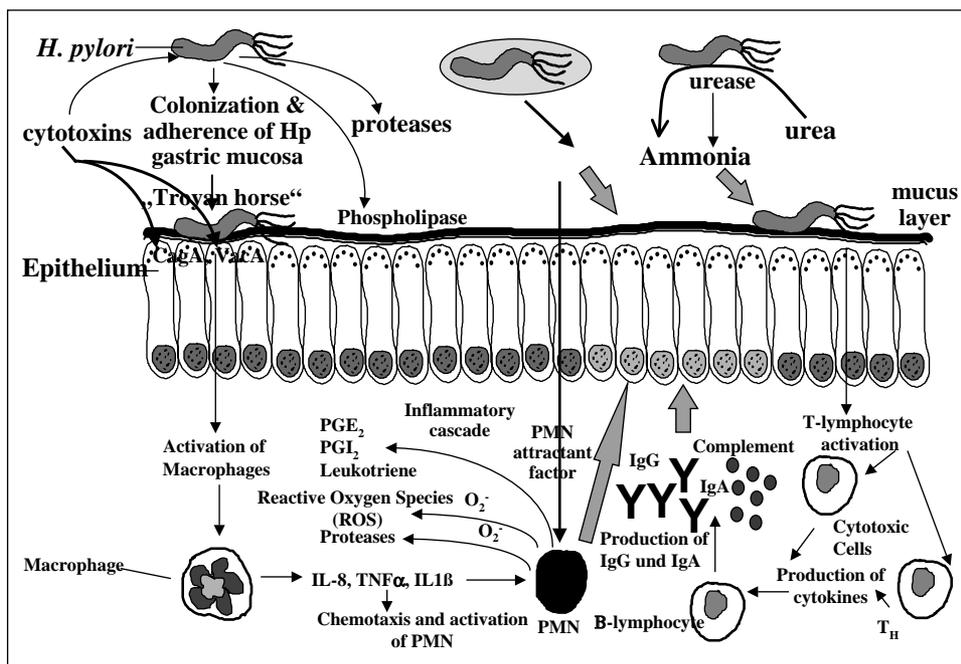


Fig. 5. Colonization of the stomach by *H. pylori* and induction of gastritis.

protective effect on gastrointestinal mucosa and the inhibition of cyclooxygenase-1 (COX-1) activity increases its susceptibility to injury by other irritants, the precise mechanisms of the ulcerogenic action of NSAIDs and the involvement of endogenous PG in mucosal integrity are not clear. Certain NSAIDs, such as ibuprofen or aspirin, inhibit both COX-1 and COX-2, while specific inhibitors of COX-2 including rofecoxib or celecoxib ("coxibs") fail to affect PG release and appear to be less harmful to the gastric mucosa and ulcerogenesis. Furthermore, as shown by our group, growth factors, similar to PG, especially transforming growth factor alpha ($TGF\alpha$), produced in the gastric mucosa, are also capable of preventing acute gastric lesions produced by NSAIDs. It is likely that endogenous growth factors are involved in NSAID-induced damage of gastric mucosa and adaptation of this mucosa to NSAID (29 - 32), but decreased salivary epidermal growth factor (EGF) has been suggested as a possible mechanism for the increased susceptibility of gastric ulceration in patients with rheumatic disease. Vascular and neutrophil etiology of NSAIDs gastropathy have recently been postulated as demonstrated by the ability of these drugs to cause vascular endothelial damage, neutrophil adhesion and thrombus formation, leading to the occlusion of gastric microvasculature and mucosal damage (31). The effects of NSAIDs on mucosal blood flow, an important component of mucosal protection, remain controversial. In some studies

mucosal blood flow was shown to be decreased by aspirin, whereas in others an increase in blood flow of the gastric mucosa was observed. Studies of Eastwood and Quimby (33) revealed that continued exposure to aspirin increases proliferative activity of mucosal cells as measured by ^3H -thymidine uptake. Other studies, showing elevated DNA synthesis in gastric mucosa during chronic NSAID administration and increased mitotic activity of mucosal cells after chronic ingestion of these drugs, support the suggestion that higher turnover rate of gastric mucosa could be one of the mechanisms underlying gastric adaptation to these drugs (29 - 32).

The interaction between *H. pylori* and NSAIDs is a controversial issue and its relationship in ulcerogenesis has been established. According to Hawkey, *H. pylori* infection in humans does not act synergistically with NSAIDs on ulcer healing, therefore, there is no need to eradicate the germ. This notion is supported by the finding that the eradication of *H. pylori* does not affect NSAID-induced gastropathy treated with omeprazole and that *H. pylori* infection induces a strong COX-2 expression resulting in excessive biosynthesis of gastroprotective prostaglandins, which should in turn counteract NSAID-induced gastropathy and heal the existing ulcer. In contrast, other investigators claim that *H. pylori* infection act synergistically with NSAIDs on ulcerogenesis, therefore, *H. pylori* should be eradicated, particularly at the onset of long-term NSAID therapy. Impaired gastric adaptation to NSAIDs in healthy humans, as well as duodenal ulcer patients, may be one of the key factors supporting this view (Fig. 5) (29 - 32). Maastricht 2-2000 consensus also recommends eradication prior to NSAID treatment but this does not appear to accelerate ulcer healing or prevent the recurrent ulcers in NSAID users. The effects of *H. pylori* infection on NSAID-provoked ulcers and its complication, particularly bleeding, appear to be affected by the concomitant use of a potent gastric acid suppressant such as proton pump inhibitors (PPI). *H. pylori* was found to increase the risk for gastroduodenal ulcers in patients who do not use PPI (36), suggesting that the mucosal damaging action of *H. pylori* can be overcome by acid inhibition. On the other hand, active *H. pylori* infection is known to increase gastric inhibitory efficacy of PPI because of an increased number of active proton pumps of oxyntic cells in the *H. pylori* infected mucosa. In the large trials, OMNIUM or ASTRONAUT carried out by Hawkey (37, 38) to compare the efficacy in NSAID-induced ulcers of gastric inhibitors (omeprazole versus ranitidine and by misoprostol versus omeprazole), ulcer relapse at 6 months occurred in 75% in *H. pylori* positive and only in 60% in *H. pylori* negative patients. This suggests that *H. pylori* in the absence of gastric acid (due to administration of potent gastric inhibitors) appears to increase the NSAID-related ulcers, while opposite effects were observed in the stomach with acid suppression. The results of the ASTRONAUT and OMNIUM are difficult to interpret regarding the interaction of NSAID and *H. pylori* infection in gastroduodenal mucosa because of the above mentioned reduction of the ulcer risk by PPI in NSAID-induced gastric ulceration. Therefore, the assessment of impact of *H. pylori* on NSAID-induced ulcerogenesis

requires further studies in patients not taking PPI or other potent gastric inhibitors. Our Polish experience based on UBT and endoscopy in about 6000 patients examined in the same university unit shows clearly that *H. pylori* infection, NSAID use, smoking, and age play a major role in the pathogenesis of peptic ulcerations in dyspeptic patients. There is a negative interaction between *H. pylori* and NSAID on duodenal ulcers suggesting that *H. pylori* reduces the development of these ulcers in NSAID users, possibly due to expression of COX-2 and excessive release of protective PG. In contrast, *H. pylori* infection tends to enhance gastric ulcers in NSAID users suggesting that local mucosal injury by the germ and NSAID play a more predominant role than the expression of PG. The *H. pylori* prevalence and the ulcer risk are significantly higher in smokers than in non-smokers. Finally, about 20% of peptic ulcers in the Polish population are unrelated to *H. pylori* and NSAID use. This study is based on the largest published group to date of ulcer patients tested in one unit, which probably expresses the present situation regarding NSAID and *H. pylori* relationship in the Polish population and may constitute an important Polish trace in gastrointestinal history (39).

The role of Helicobacter pylori infection in dyspepsia

At present, there is no satisfactory information on which, if any, conclusions could be drawn about whether *H. pylori* has some causative role in dyspepsia, or whether eradication of *H. pylori* results in clinically significant improvements. Despite methodological limitations and different outcome measurements in several studies on this regard, a metaanalysis published in 1996 (38) for the first time reported that symptom improvement was more pronounced in dyspeptic patients in whom *H. pylori* was eradicated, than in those in whom the infection persisted. Since this publication, a number of studies were performed in order to confirm or disaffirm those findings producing even more conflicting results and exacerbating the uncertainty about the association between *H. pylori* infection and nonulcer dyspepsia. Recently, Laheij *et al.* (39) performed an analysis of previous meta-analyses and were able to show that eradication of *H. pylori* appears to have a beneficial effect on dyspeptic symptoms but a significant relation in this matter involves only a very small number of patients treated for this infection. *H. pylori* infections impair gastric emptying, which may in turn underlie at least in part some of dyspeptic symptoms. About 70% of patients with dyspepsia and impaired gastric emptying show improvement of their symptoms following successful eradication of *H. pylori* (41). In the vast majority of dyspeptic patients there is no strong direct causal relation between infection by this bacterium and the presence of nonulcer dyspepsia. Several unanswered questions and concerns remain and should be investigated. Additional studies should be undertaken to verify which patients with nonulcer dyspepsia benefit most from curing *H. pylori*.

Is Helicobacter pylori involved in gastric carcinogenesis?

Gastric cancer is the fourth most common cause of death from cancer in Poland (after lung, colorectal and breast cancer) and accounts for about 10,000 deaths each year. Five year survival after resection is not particularly good, being perhaps 5% for all patients and 20% for those having a potentially curable resection. Because of that, we focus our research on the role of *H. pylori* in gastric cancerogenesis and the possible mechanism of cancer development.

H. pylori is the major environmental contributory factor in the development of gastric cancer which still remains a major health problem worldwide. Almost 10 years ago, *H. pylori* was classified by the World Health Organization (WHO) as a group 1 carcinogen (42). Support for this view has been mainly provided by epidemiological studies (43, 44). A number of studies, including our own, showed the prevalence of *H. pylori* and CagA in gastric cancer patients is significantly higher than in age- and gender-matched controls (Fig. 6). Individuals with previous *H. pylori* infection have significantly increased risk of gastric cancer (4 to 6 folds) (43, 44) and the risk of development of gastric cancer is clearly related to the CagA expression by infecting *H. pylori* and the duration of *H. pylori* infection accounting in part for the increasing rates of gastric cancer in older individuals.

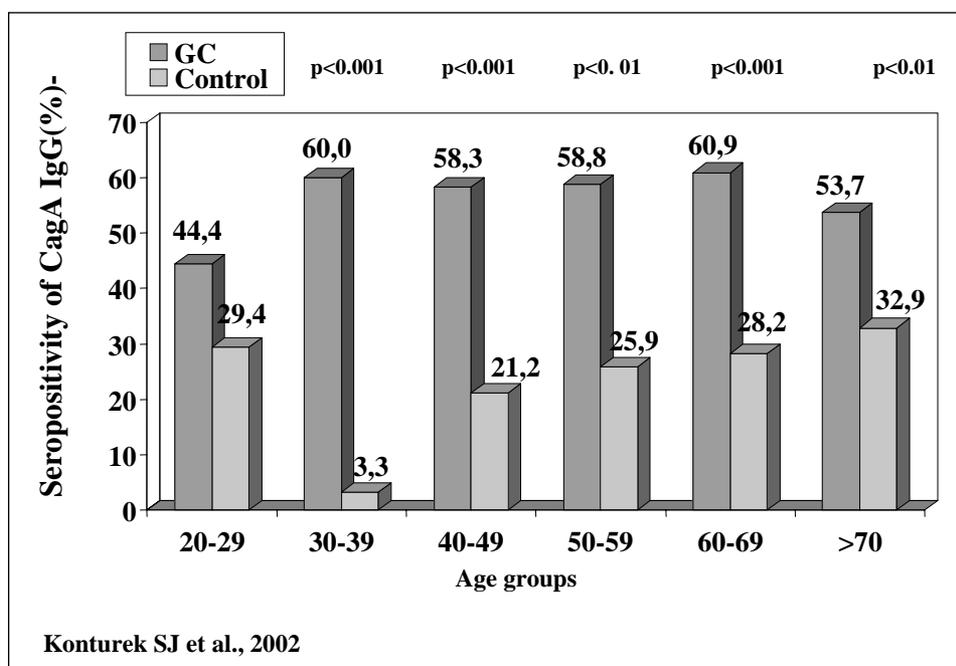


Fig. 6. CagA seropositivity in various age groups in gastric cancer and controls.

An important finding of our studies was the discovery of a very high expression of gastrin and its precursor, progastrin, by cancer cells combined with upregulation of COX-2 and anti-apoptotic proteins. These changes in molecular biology of gastric cancer appear to decline following the eradication of *H. pylori* and the use of specific COX-2 antagonists, suggesting that the removal of the infecting germ and/or the biochemical consequences of infection may be of value in the treatment of gastric cancer (45). Whether this signifies an important Polish trace in the history of gastroenterology requires confirmation, but some reports are in agreement with the above mentioned notion.

There is also significant geographic relation between gastric cancer mortality rates and the *H. pylori* prevalence. Countries with increased *H. pylori* prevalence also exhibit higher rates of gastric cancer. The decline in gastric cancer involving the antrum during the last century concerns predominantly those parts of the world in which the rate of *H. pylori* prevalence is also declining (Fig. 7). The only exception, which seems to contradict the above mentioned rule, is Africa, where despite high *H. pylori* prevalence, the rate of gastric cancer remains low, so called "African Enigma". The high parasite infestation and ingestion of plant food with higher content of antioxidants in this part of the world may somehow protect the stomach from development of gastric cancer. Also in our country, the region with the highest *H. pylori* infection rate (almost 100%), is among Tatra Mountain shepherds and their families (46), but the rate of gastric cancer appears quite low. This phenomenon could, however, be explained by the overuse of certain

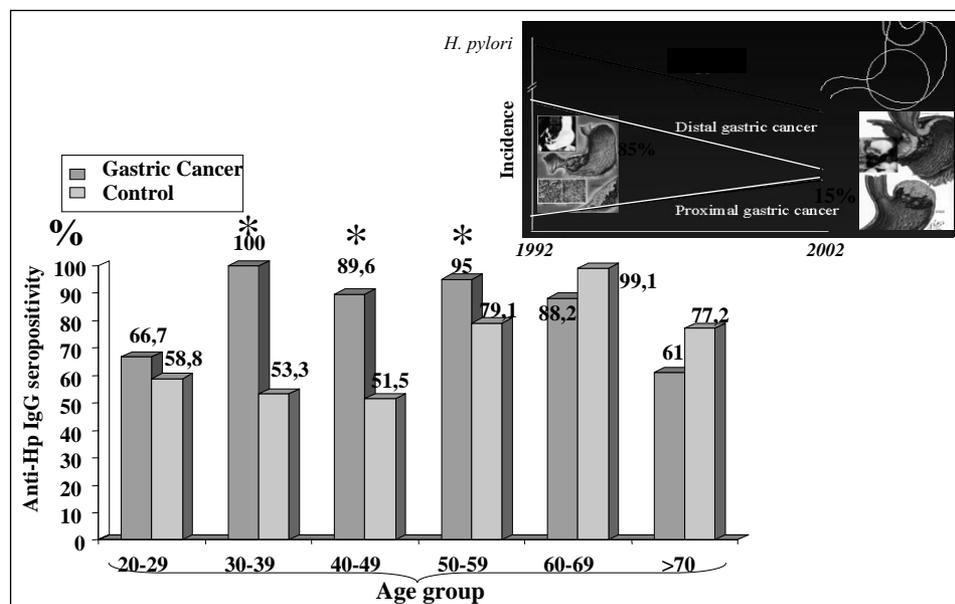


Fig. 7. Hp IgG seropositivity in GC patients (N = 440) and controls 9N = 460 in various age groups (Konturek S.J. et. al., 2002)

alcoholic beverages, especially red wines with spices, possessing anti-*H. pylori* effects due to their phenolic compounds (47, 48) exhibiting antioxidant, cancer suppressing and stimulating effect on the synthesis of nitric oxide, which has been shown to protect the mucosa against damage and to stimulate the mucosal repair and healing of mucosal inflammation, erosions and ulcerations. On the other hand, despite an assumption that *H. pylori* infection plays a crucial role in the pathogenesis of gastric cancer, only a small proportion (1 - 2%) of infected patients develops gastric cancer. Thus, the *H. pylori* infection may be important but neither essential nor wholly responsible for the process of malignant transformation. The majority of *H. pylori* infected patients do not develop gastric cancer, while a number of *H. pylori*-seronegative patients do develop it (up to 20%). Therefore, in addition to *H. pylori* other environmental and host factors are likely to be important. Following the occurrence of gastric atrophy, usually the *H. pylori* detection becomes difficult despite of the obvious premalignant changes in the gastric mucosa. Simply the *H. pylori* disappears from the stomach with marked atrophic changes perhaps due to lack of nutrients for this germ. In addition, as shown recently by Semino-Mora *et al.* (48), the bacteria may hide themselves within the mucosal cells without causing alteration in immunological system (*H. pylori* serology negative) and without producing urease in the stomach lumen (urea breath test negative). There is little doubt, that, at least one type of tumor, gastric lymphoma of mucosa-associate lymphoid tissue (MALT lymphoma) is causally related to *H. pylori* infection, as it is acquired in gastric mucosa almost in 100% in association with *H. pylori* infection (49). Clinical studies have shown that the eradication of *bacterium*, at least from early lesions, results in tumor regression in 60%-92% (50).

From a pathological point of view, the development of intestinal-type gastric cancer in *H. pylori*-infected stomach involves progression through a well-defined series of histological steps, initiated by the change of normal mucosa to chronic superficial gastritis, followed by the appearance of atrophic gastritis and intestinal metaplasia, then dysplasia and finally adenocarcinoma preceded and accompanied by numerous changes in molecular biology of mucosa cells, particularly in the regeneration zone of gastric glands from which all gastric cancers originate. These subsequent pathological changes from gastritis to gastric dysplasia and gastric cancer was recognized by Correa (51) long before the *H. pylori* was discovered as major gastric pathogen by Marshall and Warren and this sequence is called Correa's cascade. Following discovery of *H. pylori*, Correa included this pathogen in his cascade and ascribed to it the major role in gastric cancer pathogenesis (*Fig. 8*).

It is now clear that patients with pangastritis are prone to the development of gastric atrophy and progression to gastric cancer. In contrast, gastritis predominantly located in the antrum (antrum-predominant gastritis) that is associated with hypergastrinemia and hyperchlorhydria may result in duodenal ulcerations that somehow "protect" the stomach from development of gastric

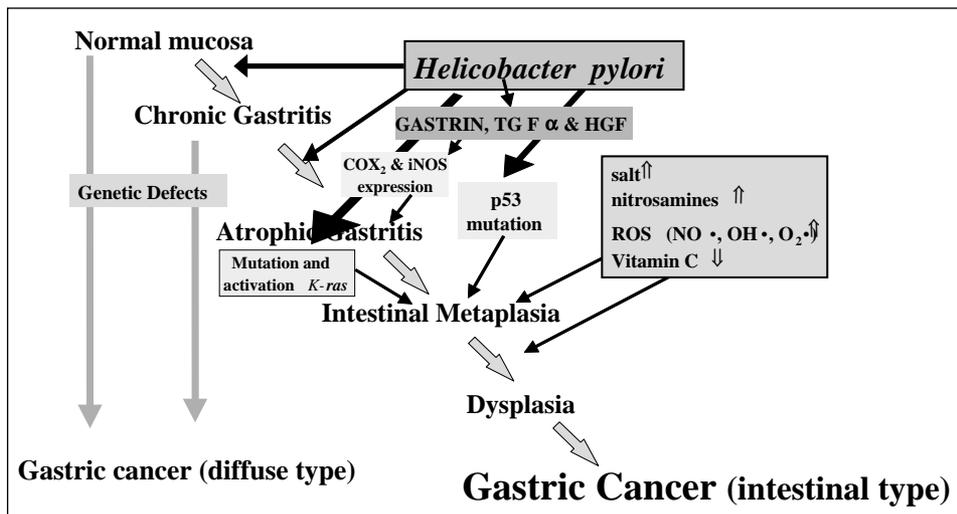


Fig. 8. Correa cascade modified by including *H. pylori* in gastric cancerogenesis.

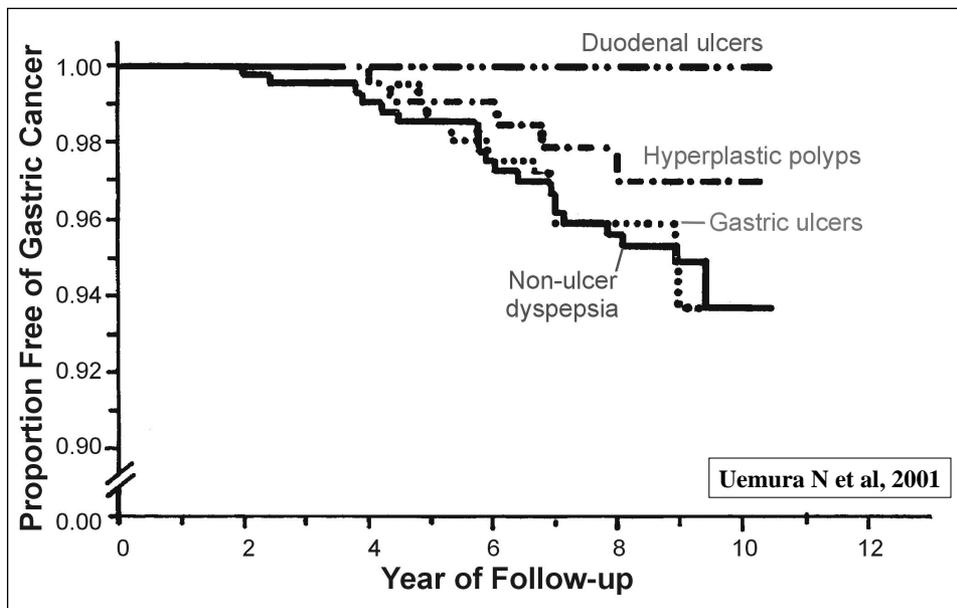


Fig. 9. *H. pylori* and gastric cancerogenesis: prospective study.

cancer (Fig. 9). In contrast, "corpus-predominant gastritis", though similarly accompanied by hypergastrinemia due to decrease of gastric acid and the removal of acid-controlled suppression of antral somatostatin, tends to progress into metaplasia, atrophy, dysplasia, and gastric cancer. The strongest evidence for the association between *H. pylori* infection and gastric cancer development was

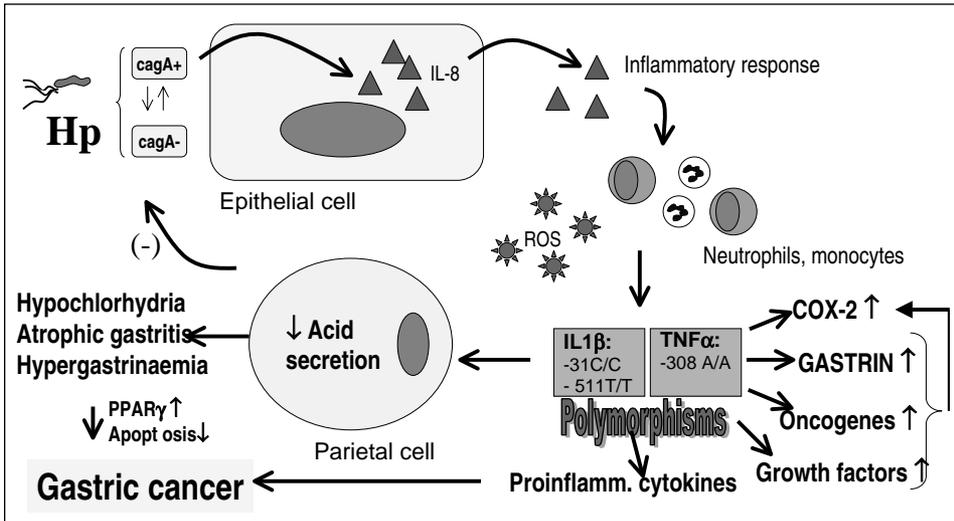


Fig. 10. Interaction between *H. pylori* and its host leading to gastric cancer.

shown in the prospective study by Uemura *et al.* (52). In this study a large number of patients with *H. pylori* infection were followed with serial endoscopic examinations. Over time, gastric cancer was not diagnosed in negative patients or in patients who had duodenal ulcer. In contrast, the risk for gastric cancer was highly increased in *H. pylori* positive patients with gastric ulcers, hyperplastic polyps and non-ulcer dyspepsia. The same group of investigators revealed that in patients with early gastric cancer subjected to endoscopic mucosal resection but without *H. pylori* therapy, new gastric cancer was found in 13% as opposed to only 1% of gastric cancer relapse during 4 - 7 years in similar group of patients subjected to mucosectomy of gastric cancer combined with eradication of *H. pylori*. The difference in gastric cancer occurrence between eradication group (N = 65) and non-treated group (N = 67) was highly significant. It is of interest that such eradication in early gastric cancer group was followed by the improvement of gastric acid secretion, remission of corpus-gastritis and decrease of nitrous compounds associated with gastric carcinogenesis. These studies indicate that *H. pylori* positive patients with gastric cancer should be eradicated even before the surgery to reduce the progression of ongoing gastric carcinogenesis.

It appears that the increased risk for the development of gastric cancer in *H. pylori* infected patients depends on both microbial and host factors. Among microbial factors, especially the gene expression for Cag pathogenicity island (PAI) (a large region of the genome containing approximately 30 genes), is an important determinant of gastric cancer development in *H. pylori* infected patients. Some of the genes of the Cag PAI have close similarities to a type IV secretion system. This system provides the mechanisms for a direct transfer of bacterial cytotoxic proteins into eucaryotic host cells. The CagA was shown to be

translocated from adherent bacterial cell to epithelial cell. This leads to phosphorylation of CagA on the tyrosine residue by cellular kinases. This induces cell morphological changes including actin polymerization and pedestal formation, possibly by activating N-WASP. It may also trigger a signaling cascade via MAP pathway, which may induce the transcription of nuclear genes (Fig. 10). It is postulated that CagA, by still not completely understood mechanisms, activates the NF κ B signaling system leading to the increased production of cytokines such as IL-8. It is possible that increased IL-8 may result in a greater degree of gastritis, ultimately predisposing to the development of cancer, but exact mechanism involved in CagA-IL-8 promotion of cancerogenesis remains to be elucidated, but there is little doubt that CagA positive *H. pylori* infection remarkably raises the risk of gastric cancer. Another important virulence factor is a vacuolating cytotoxin (VacA) (53). A vacA gene is present in virtually all of the *H. pylori* strains examined. However, strains vary considerably in the production of vacuolating cytotoxin. This is attributed to the variation in vacA gene structure. Also, factors responsible for the attachment of *H. pylori* to gastric epithelium (blood group antigen binding adhesin BabA encoded by babA or sialic acid binding adhesin) are important microbial factors associated with an increased risk for gastric cancer development (53). Concerning the host answer, multiple pathways are involved in the gastric carcinogenesis including chronic inflammatory response with predominant lymphocyte Th 1 answer, increased cell proliferation due to activation of protooncogenes, increased expression of mucosal growth factors and hypergastrinaemia with overexpression of COX-2. Finally, polymorphisms of host genes for inflammatory cytokines such as IL-1 β and TNF α , excessive production of prostaglandins and upregulation of PPAR γ with subsequent alteration in apoptosis lead to cancer development (51).

Concluding remarks

1. There are several distinct Polish traces in the history of *H. pylori* infection starting with the first description by W. Jaworski over 100 years ago of spiral bacteria in the gastric sediment from patients with gastric diseases.
2. With the increased knowledge of the pathogenicity of *H. pylori*, we were the first to develop a simple and highly efficient testing of active *H. pylori* infection without the necessity of performing costly gastroscopy, using the mini-capsulated urea breath test (UBT) in the largest epidemiological study in the world on the prevalence of *H. pylori*. Using this technique we found that the *H. pylori* infection rate in Poland is about twice as high as in Western countries, reaching about 60-70% in adult and 30-40% in children population.
3. Concerning the *H. pylori*-induced gastric pathology, it was found for the first time that the prevalence of *H. pylori*, especially expressing CagA cytotoxin, is significantly higher in gastric cancer patients than in age- and

gender-matched controls and accompanied by higher expression and release of growth factors such as progastrin, gastrin and TGF α as well as certain COX-2, apoptotic protein, cytokines such as interleukin 1 and 8.

4. It was found that gastric MALT lymphoma is in almost 100% infected with *H. pylori* and eradication results in complete regression of the tumor. In *H. pylori*-related gastric cancer the eradication of *H. pylori* and/or application of potent COX-2 inhibitors may be beneficial in terms of the control of spread of gastric cancerogenesis.

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Author's address: Prof. J.W. Konturek, M.D., Department of Gastroenterology, Elbe Klinikum Stade, Bremervörderstr. 111, 21682 Stade, Germany. Tel.: +49/4141/971400; Fax: +49/4141/971402; E-mail: j.konturek@elbekliniken.de