HELICOBACTER PYLORI AND ITS INVOLVEMENT IN GASTRITIS AND PEPTIC ULCER FORMATION

Modern gastroenterology started in early 19th century with the identification by W. Prout of the inorganic (hydrochloric) acid in the stomach and continued through 20th century with the discoveries by I.P. Pavlov of neuro-reflex stimulation of gastric secretion for which he was awarded first Nobel Prize in 1904. When concept of nervism or complete neural control of all digestive functions reached apogee in Eastern Europe, on the other side of Europe (in United Kingdom), E. Edkins discovered in 1906 that a hormone, gastrin, may serve as chemical messenger in stimulation of gastric acid secretion, while L. Popielski revealed in 1916 that histamine is the most potent gastric secretagogue. K. Schwartz, without considering neural or hormonal nature of gastric secretory stimulation, enunciated in 1910 famous dictum; “no acid no ulcer” and suggested gastrectomy as the best medication for excessive gastric acid secretion and peptic ulcer. In early 70s, J.W. Black, basing on earlier L. Popielski’s histamine concept, identified histamine-H2 receptors (H2-R) and obtained their antagonists, which were found very useful in the control of gastric acid secretion and ulcer therapy for which he was awarded in 1972 second Nobel Prize in gastrology. With discovery by G. Sachs in 1973 of proton pumps and their inhibitors (PPI), even more effective in gastric acid inhibition and ulcer therapy than H2-R antagonists, gastric surgery, namely gastrectomy, practiced since first gastric resection in 1881 by L. Rydygier, has been considered obsolete for ulcer treatment. Despite of the progress in gastric pharmacology, the ulcer disease remained essentially “undefeated” and showed periodic exacerbation and relapses. The discovery of spiral bacteria in the stomach in 1983 by B.J. Marshall and R.J. Warren, Australian, clinical researches, awarded in 2005 the Nobel Prize for the third time in gastrology, has been widely considered as a major breakthrough in pathophysiology of gastritis and peptic ulcer, which for the first time can be definitively cured by merely eradication of germ infecting stomach. This overview presents the mechanism of induction of gastritis and peptic ulcer by the H. pylori infection and describes accompanying changes in gastric acid and endocrine secretion as well as...
the effects of germ eradication on gastric secretory functions and gastroduodenal mucosal integrity

**Key words:** gastrology, vagal nerves, gastrin, histamine, peptic ulcer, *Helicobacter pylori*

**INTRODUCTION**

Failure of understanding of anatomy and physiology of the digestive system prevented any progress in gastroenterology for thousand years of antiquity and medieval time, when major remedies for digestive problems involved diverse prayers to gods, sacrifices and, at best, herbal medicine. The *alpha* and *omega* of medicine were dogmas coined by ancient Galen and Hippocrates, who believed that food in the digestive system undergoes ordinary boiling before assimilation by the body. Modern gastroenterology started with the discovery by W. Prout (1) in 1823 of the presence of inorganic hydrochloric acid (HCl) in the stomach and with ingenious observations by W. Beaumont (2) in 1822 of gastric secretory functions in Alexis St. Martin, a French Canadian traveler, with the permanent post-shot-gastric fistula that served to Beaumont as a precious “human guinea pig” for experimentation on gastric secretion. Since then it became generally accepted that gastric HCl (and pepsin) secretion is present in the stomach to contribute to food digestion as proposed for the first time by Spallanzani (3). Further studies on animals and humans, confirmed that gastric acid secretion is required for normal digestion and that it results from the interplay of stimulatory and inhibitory influences on the gastric parietal cells as suggested before by Beaumont (2).

*Gastric acid secretion in healthy stomach and infected by Helicobacter pylori (H. pylori)*

The first impressive basic research related to the physiology of gastric HCl secretion originated at the end of 19th and beginning of 20th century from the experiments performed in St-Petersburg by I. P. Pavlov’s team on “sham-fed” dogs prepared with special vagally innervated gastric pouches or gastric fistulas and with esophageal fistulas (4). Pavlov demonstrated that gastric HCl secretion starts almost immediately after presentation to hungry animal of appetizing food or feeding such animals without allowing the food to enter the stomach (“sham-feeding”). Pavlov proposed the concept of *nervism* or entirely neural control of gastric secretion (as well as salivary and pancreatic) and this raised wide interest including Nobel Foundation at the Karoliska Institute, which offered financial support for Pavlov (and closely collaborating with him Polish chemist M. Nencki) and then awarded Pavlov first in gastroenterology Nobel Prize in 1904 (*Fig. 1*). The importance of vagal nerves in sham-feeding induced secretion
**Short history of gastric discoveries**

*W. Prout* discovered in 1823 the presence of HCl in human stomach and *W. Beaumont* described its alteration after feeding;

*Neural reflex stimulation of gastric and pancreatic secretion discovered by I.P. Pavlov* and awarded Nobel prize in 1904,

*J.S. Edkins* in 1906 found that chemical messenger, gastrin mediates gastric secretion;

*K. Schwartz’s dictum „No acid no ulcer” provided basis for use of gastrectomy performed already in 1881 by L. Rydygier*;

*Histamine, a humoral substance, present in stomach is potent gastric HCl stimulant discovered by L. Popielski in 1916*;

*J. Fibiger „discovered” Spiroptera carcinoma as a cause of gastric carcinoma and got wrong Nobel prize for it in 1926*;

*J.W. Black* identified H₂-receptors (H₂-R) and synthesized their antagonists, awarded Nobel prize in 1972, while proton pump inhibitors (PPI) were obtained by G. Sachs in 1980, strong inhibitors of HCl and effective anti-ulcer drugs;

*Discovery of epidermal growth factor (EGF) in salivary glands by S. Cohen* awarded Nobel prize in 1986;


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*Fig. 1. Historical background of major discoveries in gastrology without and with (stars) Nobel prize awards*

...documented by showing that vagotomy in dogs eliminated such neurally stimulated gastric acid secretion and, later on, by L. Dragstedt (5), who pioneered in using *vagus* section in humans to treat acid-pepsin disorders in peptic ulcer. The K. Schwarz’s (1910) *dictum “no acid no ulcer” initiated gastric resections to treat peptic ulcer starting in 1881 with first gastrectomy carried out by Polish surgeon from Chelmo, L. Rydygier, then professor of *Alma Mater Jagiellonica*, and almost concomitantly by Austrian surgeon from Vienna, T. Billroth. With discovery by J.S. Edkins in 1906 of antral hormone, gastrin (6), confirmed about half century later by isolation and synthesis of gastrin peptides (17-aminoacid “little gastrin” and 34-aminoacid “big gastrin”) by R. Gregory and H. Tracy (7), the novel neuro-hormonal concept of gastric secretory mechanism was formulated, indicating that, in addition to vagal nerves, also gastric hormones are involved in stimulation of gastric HCl secretion. The discovery in 1916 by L. Popielski, Polish pharmacologist at the Lvov University, a former assistant of Pavlov and fervent supporter of his *nervism*, that histamine (8), a non-nervous factor, produced the most powerful gastric acid stimulation opened an alternative, humoral, concept of oxyntic cell stimulation and became an important
contribution to the development of gastric physiology, apparently depreciating the role of nerves and hormones, but favoring histamine as natural gastric secretagogue, the concept championed later on by C.F. Code (9). Further studies (10, 11) revealed that vagal excitation by sham feeding increased not only gastric HCl secretion but also enhanced release of gastrin (9,10) as well as histamine (12, 13), the former being released, at least in part due to the activation of the neuronal gastrin-releasing peptide (GRP), acting on the G-cells and the latter due to the excitation of enterochromaffin-like (ECL)-cells situated in close vicinity of parietal cells to stimulate in paracrine fashion histamine-2 receptors (H2-R) of parietal cells (Fig. 2). It is of interest that *H. pylori* infected stomach contains unusual form of histamine such as N-alpha-methyl histamine, produced by N-methyl transferase expressed in such *H. pylori*-infected stomach and being a potent stimulant of gastrin release from antral G-cells (14), thus, there is a complex vagus-gastrin-histamine interaction, a self-stimulating loop, acting in positive feedback mechanisms to stimulate gastric acid secretion, particularly

![Diagram](image_url)
excessive in subjects with chronic \textit{H. pylori} infected antral portion of the stomach. An important role in maintenance of the balance between the release of gastrin from G-cells and histamine from ECL-cells is played by somatostatin (SST), released from the D-cells, present in close vicinity of the G-cells in antral mucosa to exert a tonic inhibitory influence on gastrin release. Whenever the intraluminal pH drops below 4.0, the H\textsuperscript{+} ions activate the D-cells to release of somatostatin, that in turn reduces gastrin release via SST receptors\textsuperscript{2} (SSTR\textsubscript{2}) on D-, ECL and parietal cells (15) (Fig. 3). This complex mechanism controlling gastrin and histamine release involving SST, normally released by D cells in close vicinity of G cells, effectively prevents excessive histamine release and subsequently gastric acid secretion. This mechanism is deeply impaired by \textit{H. pylori} infection, that suppresses the D cell activity leading to hypergastrinemia and subsequently increases gastric acid secretion observed in \textit{H. pylori}-infected

\begin{center}
\textbf{Fig. 3.} Relation between the activity of vagal nerves and enteric cholinergic and GRP-releasing neurons and gastrin released from the G-cells (A) in intact and \textit{H. pylori} infected mucosa. Meal and IV injection of gastrin-releasing peptide (GRP) induces gastric acid secretion via releasing gastrin and subsequent stimulation of the parietal cells to secrete acid that in turn inhibits further release of antral hormone by stimulating the D-cells and releasing somatostatin (SST). The latter peptide inhibits gastrin release via SST receptors (SSTR\textsubscript{2}) and thus attenuates gastric acid secretion (modified from 36)
\end{center}
patients with antrum-predominant gastritis. *H. pylori* may, also act directly on the ECL-cells to release histamine that increases the secretory activity of the parietal cells. When, however, *H. pylori* infection involves oxyntic gland area and so called corpus-predominant gastritis develops, the bacteria acts directly on the oxyntic cells to down-regulate the expression of the subunits of the proton pumps or H⁺/Na⁺-ATPase, resulting in hypochlorhydria characteristic for acute *H. pylori* infection and for chronic corpus-predominant gastritis. The overall changes in gastric secretory activity regarding gastrin–histamine–somatostatin interaction on parietal cells in intact and *H. pylori*-infected stomach are presented on Fig. 4. Thus, usual localization of *H. pylori* infection in gastric antrum leads to gastric acid hypersecretion due to hypergastrinemia, eventually resulting in duodenal ulcer, particularly when islets of gastric metaplasia appear in the duodenum, whereas corpus-predominant *H. pylori* infection, leading to atrophic gastritis, is

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**Fig. 4.** Interrelationship between gastrin, histamine and somatostatin in control of gastric acid secretion. Luminal acid directly inhibits the G-cells and gastrin release but stimulates the D-cells to release somatostatin which by paracrine pathway inhibits gastrin release from the G-cells and indirectly reduces gastric acid secretion. The *H. pylori* infection of antral mucosa increases gastrin release by acting on the G-cells through Nα-methyl-histamine produced by infected mucosa and increase the release of proinflammatory cytokines that stimulate the G-cells to release gastrin and ECL-cells to release histamine, both leading to increased gastric acid secretion.
accompanied by low acid secretion and high plasma gastrin due to lack of normal acid-dependent inhibition of the G-cells and stimulation of D-cells. Under such conditions, the atrophic gastritis without or with intestinal metaplasia may develop and the risk of gastric neoplasia becomes very high so such *H. pylori*-infected patients require periodical checking (gastroscopy and biopsy) to detect the possible progression towards the cancerogenesis (Fig. 5).

**Pharmacological control of gastric acid secretion and ulcer healing**

One of the first agents used in the pharmacotherapy of gastritis and peptic ulcers were extracts of *Atropa belladonna*, which eventually resulted in the isolation at the end of 19th century of active principle, atropine. The extracts of *belladonna* and atropine are known to inhibit gastric acid secretion, especially when induced by vagal stimulation (4, 15) but, unfortunately it is accompanied by unpleasant side-effects such as dry mouth, blurred vision or bladder dysfunction. Novel highly specific muscarinic M₁-receptor antagonists (M₁-RA) such as

![Divergent mucosal and secretory responses to *H. pylori* infection](image)

*Fig. 5.慢性胃炎*Helicobacter pylori* infection results either in antral predominant gastritis with hypergastrinemia and hyperchlohydria leading to duodenal or gastric peptic ulceration, while corpus predominant *H. pylori*-induced atrophic gastritis leads to hypochlohydria and increased gastrin release, resulting in the cancerogenesis. Most of infected patients (~80%) show only mild mixed gastritis and normal gastric acid secretion without significant gastric diseases (modified from 36).*
pirenzepine and telenzepine became available for treatment of acid-pepsin disorders but their clinical usefulness was later found rather limited, particularly that the target parietal cells are equipped with M$_3$-R, rather than M$_1$-R and that they fail to affect histamine-induced gastric acid secretion. Pharmacological studies initiated by J.W. Black et al. (16), who modulating chemically the structure of histamine, succeeded in development of specific H$_2$R antagonists, which were found to cause not only potent and side-effect free gastric acid inhibition, but also to be effective in acceleration of ulcer healing that brought to their inventor, Black, a second Nobel prize in gastrology within last century. It should be noticed that Black’s pioneering studies were carried on the assumption, originally proposed by L. Popielski (8, 9) that histamine plays a key role in gastric acid secretory mechanism, the concept that was challenged by Johnson’s (17), stating in 1971, few month before synthesis of H$_2$-R antagonists that there is “no room for histamine” in gastric secretory mechanisms, presumably because of ubiquity of this amine in various organs of the body and failure of inhibiting gastric secretion by suppressing histidine decarboxylase (HDC) activity in rats. Interestingly, these new agents, H$_2$-R antagonists, such as burimamide, metiamide and then cimetidine or ranitidine, were found to inhibit gastric secretion not only induced by histamine, but also by other stimulants of parietal cells including ordinary meal and even vagal excitation (17, 18). These results were initially explained by the interaction of H$_2$R with others such as M$_3$-R and gastrinic (CCK$_2$-R) receptors at the oxyntic cell membrane and this was supported, at least in part, by in vitro studies on isolated oxyntic cells by Lloyd and Soll (19). The discovery of H$_2$-R and their specific antagonists should be considered as the major breakthrough in the physiology of gastric secretion, reinforcing previous Popielski’s and Code’s assumption concerning significant role of histamine in the regulation of gastric secretion as the “final common chemostimulator” of oxyntic cells (9,17) (see Fig. 4). More recent achievements in pharmacological research led to discovery by G. Sachs and his associates (20) of Na$^+$/K$^+$/ATPase (proton pump) existing in inactive form in cytoplasmic tubulo-vesicles that following excitation of oxyntic cells and an increase of intracellular mediators such as cyclic AMP (histamine) or Ca$^{2+}$ ions (acetylcholine or gastrin) and subsequent increase in protein kinase activity, are incorporated into the membrane of intracellular cannaliculi of oxyntic cells resulting in the stimulation of gastric acid secretion. The discovery of specific proton pump inhibitors (PPI), such as omeprazole, polprazole, lanzoprazole, pantoprazole, esoprazole and others that were found to be the most powerful inhibitors of gastric acid secretion, acting independently of the mode of oxyntic cell stimulation and clinically extremely useful in controlling of gastric acid secretion due to higher gastric acid inhibitory efficacy than that of H$_2$-R antagonists (20-22). Moreover, their biological (gastric inhibitory) half life was found to be remarkable longer, ranging from 14 h for lanzoprazole to 46 h for pantoprazole, when compared to that for histamine H$_2$-R antagonists. These discoveries apparently undermined, at least from practical
point of view, the significance of both vagal nerves, as well as gastrin in the in the concepts of the gastric secretory stimulation (Fig. 5).

Secretion of gastric acid, constituting major “parietal” component of gastric juice (17) results from the interaction of numerous stimulatory and inhibitory neuro-hormonal factors, acting on parietal cells after ingestion of food. It should be mentioned at this point that already A. Vesalius in 1543 (23) identified the unusually “wandering” (vagal) nerves among various intra-abdominal structures. The question was then raised what functions could be attributed to these “wandering” nerves in gastric secretion and food digestion. Pavlov (4) showed experimentally that vagally stimulated gastric acid secretion induced by e.g. sham feeding (cephalic phase) or provoked by ordinary feeding can be, at least in part, reduced by vagotomy introduced later on into clinical practice by Dragstedt (5). With the use of microscopy, it was demonstrated that the gastric glands comprise the parietal (oxyntic – acid producing) as well as peptic (pepsinogen producing) cells. R. Heidenhain (24) of Breslav University, characterized a “third” type of cells, which adhere to the external surface of epithelial cells, later identified as ECL-cells and found to express the histidine decarboxylase (HDC), the important enzyme responsible for the biosynthesis in the oxyntic mucosa of histamine, the major stimulus of parietal cells. Naturally, in addition to vagus and histamine, gastrin was considered as major player in the mechanism of gastric acid secretion.

All the above mentioned gastric secretagogues stimulate “parietal” component of gastric juice secreted by parietal cells, which are exposed to extremely high acid concentration, reaching within intracellular cannaliculi, about 170 mmol/L. The possible cell damage by this highly concentrated acid is prevented by locally released prostaglandins (PG) released due to constitutively expressed COX-2 in these cells (25). Non-parietal secretion originating from other than parietal cells of gastric mucosa contributes to the mucus-alkaline secretion, protecting surface epithelium that appears to be mediated by COX-1-PG system existing in normal mucosa to exert gastroprotection and to maintain mucosal integrity (25-32).

The role of H. pylori infection in the development of gastro-duodenal ulcers

The spiral bacterium, has been identified for the first time in gastric sediment and depicted under microscope in humans with various gastric diseases by W. Jaworski, professor of Cracow Academy in his Handbook of Gastric Diseases (in Polish) over 100 years ago and due to their curved forms named by him Vibrio rugula (33) (Fig. 6). Definitive microbiological characterization of this spiral bacteria named initially by mistake Campylobacter pylori, but then properly identified as H. pylori should be attributed to Australian clinical researchers, R. J. Warren, pathomorphologist, and B. J. Marshall, gastroenterologist (34), who in early 1980s proved that bacterium is pathogenic by fulfilling all three Koch’s criteria (isolation of germ, its culture and demonstration of it pathogenicity). Marshall used his own stomach to prove pathogeneity of bacteria by drinking
their pure culture and documenting endoscopically and histologically the development of acute gastritis cured with antibiotics and bismuth salts. Numerous studies in various countries showed that the stomach of more than 50% of world adult population contains \textit{H. pylori} (35, 36) that exhibits an ability to induce gastritis in all infected subjects and peptic ulcers in about 10-15% of them. \textit{H. pylori} is mobile germ due to the presence of flagella and easily moves within thick mucus layer covering the gastric mucosa to reach the apical membrane of surface epithelial cells and to bind by its adhesin molecules to mucosal glycolipid receptors at this membrane (Fig. 7). Bacterial genome is now well-studied structure and shown to contain about 1300 genes. More toxic bacteria are capable of expressing the cytotoxins such as CagA encoded by \textit{cagA} and VacA encoded by \textit{vacA}. The bacterium adhering to mucous cell membrane, is capable to “inject” into cytoplasm of mucosal cells its cytotoxins acting there like “Trojan horse” to induce inflammation (CagA) or to damage its mucosal cell surface and causing its

**The 2005 Nobel Prize in Physiology or Medicine, October 2005**

The Nobel Assembly at Karolinska Institute has today decided to award the Nobel Prize in Physiology or Medicine for 2005 jointly to Barry J. Marshall and J. Robin Warren for their discovery of

“the bacterium \textit{Helicobacter pylori} and its role in gastritis and peptic ulcer disease”

Fig. 6. Nobel laureates in physiology and medicine in 2005. B.J. Marshall and J.R. Warren receiving prize for the discovery of \textit{Helicobacter pylori} and its role in gastritis and peptic ulcer disease. W. Jaworski (upper panel), who described spiral bacteria in the human stomach 100 years before Marshall and Warren should be considered a real discoverer of these bacteria.
vacuolization (VacA) (36, 37). Furthermore, the cytotoxins turn on the mucosal immunological system, resulting in enhanced expression and release of proinflammatory cytokines, including interleukin-8 (IL-8), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Fig. 8). It is of interest that *H. pylori* infection interferes with ghrelin releasing cells (Gr-cells), present mainly in oxyntic mucosa to decrease usual fasting rise in plasma ghrelin and the appetite as well as to retard the growth of infected children (38,39). Following eradication of *H. pylori* the plasma and gastric corpus mucosa content of ghrelin were restored accompanied by the improvement of appetite and reduction in dyspeptic symptoms.

The infection strongly affects gastric acid secretion by altering the gastrin-somatostatin ratio as well as damaging the mucus-alkaline coat at the mucous surface and the quality of adherent mucus gel, resulting in acute and then chronic gastritis and ulcerations (Fig. 9). The induction of COX-2-PG system by this *bacterium* may limit the mucosal cell damage due to released PG, but the *H. pylori* infection results also in the generation of proinflammatory substances,
including reactive oxygen species (ROS), that, unlike PG belong to damaging proinflammatory “team”. It becomes evident that the eradication of the bacterium restores, at least in part, the disturbed mucosal integrity and reverses the course of gastritis. Administration of mucosal barrier breaker such as aspirin or ethanol usually results in bleeding erosions or exacerbation of chronic gastric ulcerations (30,32). Considering duodenal mucus-alkaline secretion in response to topical H⁺, delivered into duodenal bulb by H. pylori infected stomach, it should be emphasized that the duodenal mucosa behaves somehow differently than gastric mucosa in response to topical acid. Isenbergh and his colleagues (31, 40) and Kaunitz and Akiba (26) using chambered human or animal duodenum, confirmed earlier proposal that, unlike gastric mucosa, where tight epithelial cells constitute the main component of gastric mucosal barrier against H⁺, in the duodenum, H⁺ easily penetrates the duodenocytes, but does not damage them, though transiently decreases their intracellular pH (pH). This strongly activates the basolateral Na⁺-HCO₃⁻ cotransporters, allowing for massive inward movement through basolateral membrane of HCO₃⁻ from the extracellular space, leading to activation of the HCO₃⁻/Cl⁻ exchangers in apical membrane of duodenocytes and resulting in a marked stimulation of HCO₃⁻ secretion together with mucus gel that is capable of

Fig. 8. The activation and expression of Helicobacter pylori cytotoxins (CagA and VacA) and expression of other genes (oipA, dupA an babA) result in mucosal cell damage and proinflammatory cytokine formation.
neutralization of H\(^+\) ions entering the duodenal lumen, thereby securing duodenal mucosal neutrality and integrity (Fig. 10).

Sjoblom and Flemstrom (41) provided evidence that, neurally released melatonin and neuronal VIP, participate in the mechanism of the stimulation of duodenal mucus-alkaline secretion by topical H\(^+\)-activating the vago-vagal reflexes and their brainstem centers, also essential for the control of gastric, duodenal or pancreatic secretion (32, 42). The neuronal pathway involved in activation of gastro-duodenal mucus-alkaline secretion with the contribution of melatonin was confirmed by Reiter et al. (43), just reinforcing Sjoblom and Flemstrom (41) idea implicating melatonin in gastro-duodenal protective system. As shown by Isenberg et al (40), the *H. pylori* infection reduces duodenal HCO\(_3\) mucus secretion (despite of increasing mucosal PGE\(_2\) generation) and this allows for excessive penetration of gastric H\(^+\) and other irritants into the mucosa, causing damage of duodenocytes with subsequent formation of gastric metaplastic islets in duodenum. This mechanism leads to the formation of the “*locus minoris*
"resistentiae" for duodenal *H. pylori* infection and, finally, to the ulcer development in duodenum. This occurs when *duodenitis*, combined with disorders of duodenal mucus-alkaline secretion caused by *H. pylori* infection, takes place and when complex mechanism controlling this secretion is deeply altered by this infection (Fig. 10).

As shown on Figs 11, the prevalence of *H. pylori* infection estimated by W. Łaszewicz (35) on about 18 000 subjects and Bielanski’s studies including about 20 000 subjects of southern part of Poland (46-48), reached similar values. The infection rate shows similar trends regarding the influence of the age, but in Bielanski’s studies extending up to 80 years of age, some tendency of the infection rate to decline at age above 50 years and this could be due either to the development in these patients of atrophic gastritis and/or the translocation of the bacteria from the gastric surface into the mucosal cells without showing *H. pylori* positivity in UBT or CLO (46).

It is of interest that the prevalence of *H. pylori* infection in Poland decreased by about 30% during last 10 years when the eradication procedure has been widely applied in ulcer therapy. At the same time, the incidence of ulcers without *H. pylori* infection or the use of non-steroidal anti-inflammatory drugs (NSAID) also tended

*Fig. 10. Mechanisms controlling the duodenal alkaline secretion.*
to increase so that the ratio of these “idiopathic” ulcers to total number of ulcer significantly increased (47, 48). Despite of the decline in *H. pylori* prevalence, the rate of ulcer complications such as bleeding and perforation did not change dramatically as compared to the period when no eradication therapy has been applied. According to the opinion of Blaser (49) the fall in *H. pylori* prevalence occurs all over the world due to improvement of living standard levels, but it is accompanied by the increase in the occurrence of gastro-esophageal reflux disease (GERD), Barrett’s esophagus and esophageal carcinoma (Fig. 12).

The *H. pylori* infection appears to interfere with the expression and release from the oxyntic mucosa of ghrelin, and this may result in the decrease of appetite and retardation of the growth in children (38, 39). Following the eradication of the *H. pylori* the release of ghrelin has been restored and this was accompanied by the improvement of appetite and decrease of dyspeptic symptoms (Fig. 13).

Concerning the risk of *H. pylori* infection, numerous conditions increase such risk including the low socio-economic status, poor sanitary conditions, unclean water and smoking as well as the direct exposure nurses to endoscopic instruments or gastric contents (51).
Brain-gut axis in gastroduodenal mucosal damage caused by H. pylori, NSAID and other irritants

The question remains whether H. pylori-induced gastric and duodenal mucosal damage is merely a local phenomenon or whether it also involves the extragastric, namely neuro-hormonal mechanisms. To answer this question, several tools were employed in experimental animals: 1) inactivation of sensory afferent nerves that serve to signal the brain the changes occurring in the gastrointestinal tract by using animals injected with large neurotoxic dose of capsaicin; 2) surgical vagotomy to eliminate the transmission of signals from the GI tract to central nervous system (CNS) through the sensory vagal fibers, which constitute over 90% of total vagal fibers, and which supply the gastro-duodenal area that is crucial for the H. pylori-induced inflammatory changes and ulcerogenesis; 3) intracerebral application of various hormonal substances to determine whether the CNS centers can influence the gastric H⁺-secretory pattern and gastro-duodenal mucus-HCO₃⁻ responses to topical irritant application such as H. pylori or aspirin and 4) determination of expression of cFOS in intrinsic and

Fig. 12. During last decades the H. pylori prevalence and the occurrence of distal gastric cancer are declining, while there is an increase in the gastro-duodenal reflux disease (GERD), esophagitis and cancer of the proximal part of the stomach.

Modified from Blaser, 2005
extrinsic neurons involved in the transmission of gut-brain-gut signals (30). Using such wide spectrum of physiological and pharmacological tools, several researchers, including our group, were able to reveal that the gastro-duodenal mucosa is equipped with a variety of neuronal sensors that respond to the action of luminal irritants such as \textit{H. pylori} produced cytotoxic substances, especially cytotoxin CagA, VacA and ammonia, luminal acid, ethanol, various drugs e.g. NSAID or even physiological changes such as chemical ingredients of food, its osmolarity and pH as well as motility and tension of the GI tract wall. Through activation of chemo-, osmo-, mechano- and noci-receptors of gastro-duodenal mucosa, the afferent nerves may mediate short local or intramural and long, vago-vagal or extramural (axonal and spinal or cerebral) reflexes triggered by luminal \( \text{H}^+ \) or \textit{H. pylori} and affecting, among others, also the mucus-HCO\(_3^-\) secretion, the gastro-duodenal mucosal barriers, and mucosal integrity as well as mucosal

**Fig. 13.** The gastric infection with \textit{H. pylori} results in the decrease in the expression and the release of ghrelin, gastric hormone stimulating appetite and enhancing the body growth.
microcirculation (30). The space limitation of this review does not allow for the detailed presentation of the evidence, obtained, in part, from animal experimentations, supporting the involvement of extragastric neuro-reflexes in the maintenance of gastro-duodenal mucosal integrity but it is of interest that e.g. experimental chronic gastric ulcers in rats infected with *H. pylori* or with gastric mucosal damage by acidified aspirin or ethanol are greatly augmented following capsaicin-induced inactivation of afferent sensory nerves or vagotomy. This could be interpreted that both sensory afferent and vagal efferent nerves are involved not only in the pathogenesis of gastro-duodenal mucosal lesions but also are required for normal course of their healing and for the maintenance of mucosal integrity (30). In humans with *H. pylori* infected stomach, the course of post-eradication ulcer healing probably also involves the long vago-vagal reflexes initiated by activation of gastric mucosal sensors by *H. pylori*-released cytotoxins and inflammatory products such as the reactive oxygen species (ROS) as well as
various growth factors including EGF, TGFα, bFGF, VEGF generated in gastric mucosa under the influence of H. pylori infection but enhancing mucosal regeneration and ulcer healing. Also the clot filling the ulcer niche is rich source of various growth factors produced by platelets as well as by microphages and interacting with the damage by ulcer mucosa to enhance its regeneration and ulcer healing (Fig. 14). Also the development and subsequent repair of aspirin- and ethanol-induced gastric mucosal lesions may involve the brain-gut axis, starting with the irritation of mucosal chemo-receptors by noxious chemicals and their mucosal toxic products such as ROS (32). This is supported by experimental evidence that inactivation of sensory afferent fibers with capsaicin or subdiaphragmatic vagotomy, eliminating the activity of both afferent and efferent vagal pathways, greatly delays ulcer healing and worsens the lesion induced by various local irritants (30-32). Mucosal lesions and ulcerations induced either by H. pylori infection and aspirin, ethanol or ischemia-reperfusion, have been thought to involve predominantly local mechanism related to the activation of COX-2-PG system and various growth factors assuring spontaneous healing of gastric lesions (Fig. 14). However, based on studies with ulcer healing after inactivation of afferent sensory fibers with neurotoxic dose of capsaicin or by vagotomy, it is tempting to assume that brain-gut axis is involved in pathogenesis of H. pylori induced ulcer formation and in healing of these ulcers via neural mediation of local mucosal changes including gastric blood flow at ulcer area (30). This does not to exclude the contribution in mucosal repair processes of local anti-ulcer and protective humorals such as COX-2-PG, growth factors, gastrin, somatostatin, ghrelin, melatonin etc., that may modify the final outcome of H. pylori-induced ulcer healing, and repair processes involving both local factors and neural brain-gut axis (32).

Concluding remarks

1. H. pylori infection interferes with the release and action on parietal cells of basic secretagogues such as histamine, gastrin and somatostatin, resulting in gastric acid hypersecretion, when the infection is localized in gastric antrum, or in hypochlorhydria when such infection involves gastric corpus, resulting in corpus-predominant chronic gastritis.

2. Duodenal ulcer, which is causally related to the H. pylori infection in antral mucosa, is usually accompanied by hyperchlorhydria caused by an excessive release of gastrin from the G-cells due to deficient somatostatin release from the antral D-cells as well as due to excessive histamine release from the ECL-cells caused by their stimulation by endogenous gastrin induced by the action on Nα-methyl histamine, present in H. pylori infected stomach.

3. Gastric ulcer is usually accompanied by reduced corpus mucosal integrity and altered mucosal barrier as well as reduced gastric acid secretion caused by down-regulation of the expression of compound units of the proton pumps and reduced acid secretory activity of oxyntic cells. Following H. pylori eradication,
gastric acid tends to increase depending upon the improvement of the mucosal integrity and secretory activity of oxyntic cells.

4. Neuro-hormonal pharmacology of the stomach and duodenum succeeded in discovery and clinical use of potent inhibitors of gastric acid secretion such as H₂-R antagonists and PPI, that abolish all modes of gastric secretory stimulation but, concomitantly, result in hypergastrinemia that stimulates the growth of *H. pylori* promoting spreading the infection towards the proximal part of the stomach with subsequent development of corpus-predominant atrophic gastritis and cancerogenesis.

4. The eradication of *H. pylori* abolishes hyperchlorhydria and hypergastrinemia in duodenal ulcer patients and is successful in healing and prevention of ulcer recurrence as well as in prevention of the *H. pylori*-related gastric cancerogenesis.

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