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Abstract

The story of gastric acid secretion had begun with early ideas on gastric secretion (Spallanzani and de Reaumur, 17th century) and with first descriptions of food digestion (Dupuytren and Bichat, Beaumont, early 18th century), followed by proof that gastric juice contained acid (Prout, early 18th century). The research continued with first descriptions of gastric glands as the source of gastric acid and its changes upon digestive stimulus (Purkinje and Golgi, mid and late 19th century). The theory of "nervism" – the neuro-reflex stimulation of gastric secretion by vagal nerve (Pavlov, early 20th century) was contrasted by histamine mediated concept of gastric secretion (Popielsky and Code, mid 20th century). Thus, gastric acid and pepsin (Schwann, early 19th century) were found to be essential for food digestion and studies also pointed to histamine, being the most potent final common chemostimulator of oxyntic cells. The discoveries in etiopathogenesis of mucosal injury were marked by famous dictum: "No acid, no ulcer" ("Ohne saueren Magensaft kein peptisches Geschwuer", Schwarz, 1910) that later induced the term of "mucosal defence" and notion that the breaking of "gastric mucosal barrier" represents the initial step in the process of mucosal injury (Davenport, Code and Scholer, mid 20th century). The prostaglandins were shown to influence all major components of gastric mucosal barrier, described with term "cytoprotection" (Vane, Robert and Jacobson, 1970s). Beginning in the latter half of 19th century, the studies on gastric bacteriology that followed enabled discovery of association between *Campylobacter (Helicobacter) pylori* and peptic ulcers (Warren and Marshall, 1980s) thal led to worldwide major interventions in treating peptic ulcer disease. Surgical approach to peptic ulcer had been outlined by resection procedures (Billroth, Pean, Moynihan, late 19 century) and vagotomy, with or without drainge procedures (Jaboulay, Latarjet, Dragstedt, mid 20th century). Antacids, protective agents, anticholinergics, and later gastrin antagonists and prostaglandins were used for decades in treatment of peptic ulcer, with differing effects. The advent of the concept of H_2 receptor antagonists (Black, 1970s) and discovery of acid (proton) pumps in parietal cells (Ganser, Forte and Sachs, late 1970s) paved the way for potent (H_2 antagonists) and profound acid inhibition (proton pump inhibitors) that revolutionized the treatment of acid related disorders, including peptic ulcer disease. Worldwide, peptic ulcer and its complications remain the cause of significant morbidity, especially in older age groups, representing a major burden for ambulatory and hospital healthcare resources.

"Have we reached the zenith in our understanding of gastric acid physiology and the development of pharmacology treatment for acid peptic disorders?
We do not think so.
This disorders remain prominent, and there is much still to be discovered by future clinical and basic investigators."

Mitchell L. Schubert and David A. Peura
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Historic path to gastroenterology

Peptic ulcer has been a disease of animals and humans since the acid producing organs were the means of preparing the food for absorption. In mammals, digestion and passage of food to be absorbed in the intestines was enabled by acid producing organs that had specialized epithelial cells, musculature and innervation. On the path through the hystory of civilisation we could observe views and perspectives of food digestion that were introduced by contemporary philosophers, physicians, experts and scientists, differing from era of agriculture, over the era of industrialization to modern times of electronic technology and computers.

Hippocrates (5th century B.C.) introduced the term of *pepsys* to denote that the food was "cooked" and converted to four humors: blood, phlegm, yellow and black bile.[1] (Figure 1) This view prevailed for nearly two thousands years, a time span in which almost nothing was done to clear the mystery of food digestion in the stomach. Teofrastus Bombastus von Hohenheim (Paracelsus, 1493 - 1541), a professor of medicine in Basel who also taught at Freiburg and Strasbourg, beleived the human diseases were caused by chemical changes governed by chief *archeus* that represented the ultimate forces of energy that governed the universe.[2] Thus, the historic path to modern gastroenterology represented a long way from these early philosophical observations, over the identification of gastric acidity and studies of gastric function in 19th century to Ismar Boas (1858 – 1938), the founder of gastroenterology as a specialty and the editor of the first medical journal for digestive diseases.

It is almost an impossible task to describe the whole history of concepts in gastric pathophysiology and discoveries in etiopathogenesis of peptic ulcer disease, mentioning the single role of each anatomist, physiologist, researcher or clinician who contributed to revealing of the mechanisms of gastric acid secretion and therapy of acid related diseases.

The authors have tried to point out the most important steps in understanding the workings of the stomach – from early ideas to modern concept of molecular mechanisms of gastric acid secretion and mucosal protection in order to diagnose and treat peptic ulcer disease (Table 1).

Pathophysiogical concepts in gastric acid secretion

In regard to the role of nerves in gastric acid secretion, it was A. Vesalius (1543) who described vagal nerves, "wandering" to different abdominal organs and structures.[3] The story of gastric acid secretion had begun with early ideas on gastric secretion and process of digestion, described by Lazzaro Spallanzani (1729 - 1799), the Italian physiologist and Rene de Reaumur (1683 - 1757), the French scientist. After series of experiments conducted on animals and himself, Spallanzani proposed his "theory of chemical solution"(1784) by which the solvent called "gastric juice" (1793) was entirely neutral.[4] In contrast, Reaumur concluded (1752) that gastric juice was acidic.[5] He conducted the experiments on buzzard, a prey bird that was known to eject indigestible food form its stomach, and his experiments showed that the juice extracted form regurgitated pieces of sponge out of buzzard's stomach were capable of digesting meat. The experiments of Reaumur paved the way for William Prout, the English physiologist who provided the chemical analysis, showing the gastric juice contained acid – termed "muriatic acid" - that was later identified to be hydrochloric acid.[6]

The first descriptions of gastric physiology of food digestion were made by French scientists Dupuytren and Bichat (1801) in Paris, who observed gastric fistula of Madeline Gore, after she fell down stone stairs at age 20 years; and William Beaumont, the US Army surgeon, who studied Alexis St. Martin's gastric fistula (1823 – 1833), acquired after a gunshot wound, in 1822.[7] During 19th century and early 20th century, the investigation of the morphology and fine structure of the stomach answered the question of the source of gastric acid: Johannes Purkinje gave the first description of gastric glands and principal cell types (light microscopy, 1837), Camillo Golgi noted the marked change of glands and parietal cells by digestive stimulus (1893 / 1895) and Dalton and colleagues documented the fine structure of gastric epithelial cells, including parietal cells (1951) (Figure 2).[8,9]

Almost paralleling the investigations of stomach glands' morphology and acidic nature of gastric juice were the studies on physiological concepts of gastric secretion, in late 19th and early 20th century. In St. Petersburg, I.P. Pavlov was the first to demonstrate that gastric acid secretion in fasted dogs starts following exposure to appetizing food even without the passage of this food into the stomach, using eosophageal and gastric fistulas in dogs ("sham-feeding", 1895).[10] For his theory of "nervism" - the neuro-reflex stimulation of digestive secretion by n. vagus - he was awarded Nobel prize in 1904. The works of L.

Popielski, a Polish pharmacologist at the Lvov University (1920) and C.F. Code (1956) revealed the histamine mediated concept of gastric secretion, as an alternative to "nervism".[11,12] The discovery of gastrin by J. S Edkins (1905) and its isolation and synthesis by R. Gregory and H. Tracy (1964) was followed by experiments of B. Uvnas and L. Olbe, demonstrating the role of gastrin in acid secretion by the fact that removal of gastric antrum – the major source of gastrin – greatly attenuated gastric secretory response to sham-feeding.[13,14,15] Theodor Schwann at Berlin described a water-soluble factor in gastric juice that was capable of digesting egg-white (1836), and he called it "pepsin", after the Greek word for digestion.[16] The possible existence of a pro-enzyme, pepsinogen was formally postulated by Epstein and Grutzner (1854) and, in a series of publications (1879 – 1882) J.N. Langley at Cambridge established the basic morphology and secretory characteristics of the pepsin-forming glands in the stomach that contained pepsinogen.[17] Langley also coined the term "oxyntic" to identify the role of the acid secreting cells in gastric mucosa. R.P Heidenhein, a professor of physiology at Breslau continued the study of pepsin (1878) and also described a "third" type of cells, which adhered to external surface of epithelial cells, that 100 years later would be identified as enterochromaffine-like cells (ECL), responsible for biosynthesis of histamine.[18] These discoveries have shown that gastric acid and pepsin are essential for process of food digestion in the stomach, and also pointed to histamine, being the most potent gastric acid secretagogue and final common chemostimulator of oxyntic cells. In addition, it was found that histamine is released from ECL cells upon stimulation by food and other gastric secretagogues, such as gastrin. However, there existed the unresolved questions of regulation and mechanisms of acid secretion or "how does it happen", and physiologic gastric secretion profile or "how does it look like". Preceeded by A. Kay of Glasgow who developed the augmented histamine test, W. Card and I.N. Marks of the Western General Hospital in Edinburgh (1960) were able to establish that maximal acid output correlated with parietal cell mass.[19] Gerhard Katsch of Greiswald introduced quantitative function tests with caffeine / histamine in order to evaluate gastric secretory capacity for hydrochloric acid (1925) [20]

By 1960s a long list of antihistaminic agents had been proposed and studied, without identification of an agent effective in the inhibition of acid secretion.

Following the pioneering work of Sir Henry Dale in isolation and function of histamine, Sir James Black, a pharmacologist working for Smith Kline and French in England proposed that there existed a homogenous population of non-H_1 receptors in gastric mucosa that he chose to term "H_2" receptors, and announced that compound burimamide (1972), which posessed an imidazole ring with side chain was capable to inhibit the secretion of gastric acid.[21] These new H_2-receptor antagonists were found to inhibit histamine-induced gastric secretion, as

well as the gastric secretion provoked by meal or vagal excitation.[22] Development of the concept of H_2 receptor antagonists and their therapeutic utility was major factor in gaining Sir James Black the Nobel prize for Medicine or Physiology in 1988.

Still, the key question was unanswered: how does the stimulation by vagal nerves, gastrin or histamine, acting via the membrane receptors and intracelullar mediators provoke the gastric acid secretion? The experiments on bullfrog oxyntic cells by A.L. Ganser and J.G Forte in USA were able to demonstrate the existence of a unique enzyme in the parietal cell: a potassium – stimulated adenosine triphosphatase (K^+-ATPase) which was later identified, also in mammals and humans as the final step in acid secretion – the acid pump.[23] In studies that followed, G. Sachs and coworkers elucidated that there are about 1 billion (10^9) parietal cells in the healthy stomach, being characterised by a large number of mitochondria that provide ATP to drive acid secretion process, and having tubulovesicles and secretory canaliculi, as well. They have also shown that upon activation of parietal cell much of tubulovesical membrane is inserted into secretory canalicular membrane, carrying with it many acid pumps and greatly increasing acid secretion by activation of the proton or acid pump (H^+,K^+-ATPase): for each H^+ ion pumped out of the cell, a K^+ ion is pumped in, resulting in a significant pH gradient – from pH 7.3 inside the parietal cell cytosol to pH 1.0 in the secretory canaliculi.[24] When the parietal cell is stimulated, an increase in permeability of the apical membrane for chloride (Cl^-) ions occurs and diffusion of chloride ions into secretory canaliculi takes place, but unlike K^+ ions, the chloride ions are not pumped back into parietal cell.[24] The discovery of location, nature and molecular structure of the acid pump led to development of products that acted directly on the acid pump: CMN 131 (pyridylmethylthioacetamide) in 1971 and its derivative timoprazole in 1974, picoprazole in 1976 and ultimately to omeprazole in 1979.[25] Omeprazole is a prodrug and a weak base with high affinity for acidic space close to the acid pump where it is rapidly converted into sulphenamide, which forms a covalent complex with the acid pump enzyme that results in effective acid inhibition, irrespective of the type of stimulus acting on parietal cell.[26] Following the first discoveries, the human energy and resources of many pharmaceutical companies were focused on development of compounds that would rapidly end effectively act on acid pump enzyme, outlining the group of potential proton pump inhibitors, of which many were thrown to healthcare market and have been used for treatment of patients with acid related disorders.

Discoveries in etiopathogenesis of mucosal injury and peptic ulcer disease

Dragutin (Carl) Schwarz (Varazdin, Croatia 1868 – Vienna, Austria 1917) was the unique figure in clinical research in regard to the role of gastric acid in etiopathogenesis of peptic ulcer disease. With his works as a surgeon, he contributed to surgical therapy and pathology of penetrating gastric ulcer.[27] However, in regard to historical impact to drive research in peptic ulcer disease Schwarz has been remembered for his famous dictum: "No acid, no ulcer" ("Ohne saueren Magensaft kein peptisches Geschwuer", 1910), that has been strongly influencing peptic ulcer research till nowdays.[28]

At the beginning of 20th century, it was believed that the stomach wall harbours an intrinsic property that was capable of resisting digestion with gastric acid, the so-called "vital spirit", and that the breakdown of a such vital force is responsible of mucosal damage and ulcer formation.[29] In the early 1930s, T. Teorell proved that surface epithelial cells and adherent mucus containing bipolar phospholipids prevent the ionized mineral acids, such as hydrochloric acid, from back-diffusing from gastric lumen into the mucosa, due to high polarity of phospholipids.[30] On the contrary, the unionized organic compounds, such as byle salts or aspirin, with a relatively low pKa, can rapidly reach surface mucosal cells by non-ionic diffusion to accumulate in their interior, dissociate in neutral surroundings and to cause mucosal damage.[30] This observations suggested that mucosal injury occurs regularly, but does not lead to clinically significant disruption of the function, implicating that "mucosal defense" consists of several components or "layers", with secondary components becoming more important when more superficial components are breached. H. Davenport and C. Code are responsible for coining the term "gastric mucosal barrier" (1955) , and together with J. F. Scholer they proposed that breaking of the barrier represents the initial step in the process of mucosal injury.[31,32]

Untill 1970s, peptic ulcer was believed to be the result of corrosive effects of gastric acid, and in 1980s and 1990s the term of "mucosal defence" was delineating various factors and components that permit the gastric mucosa to remain intact despite its frequent exposure to substances with wide range of temperature, pH, and osmolarity, as well as to substances with detergent or cytotoxic action, and bacterial products capable of causing local and systemic inflammatory reactions.[33] The works of J.R. Vane and A. Robert documented that prostaglandins (a group of fatty acids first isolated from seminal fluids by Von Euler, in 1936) modulate virtually every aspect of gastric mucosal defence.[34] Vane, who was later awarded the Nobel prize, described the finding that aspirin and other NSAIDs inhibited the synthesis of prostaglandins in the gastric mucosa (1971) and Robert (1976) documented that prostaglandins, in doses well below those necessary for inhibiting gastric acid secretion showed the protective effect against oral administration of necrotizing agents.[35,36] Later on, the prostaglandins were shown to influence major components of gastric mucosal barrier: they maintain the integrity of epithelium and mucosal blood flow, also being the potent

inhibitors of leukocyte adherence to endothelium in mucosal inflammation, as well as the promotors of ulcer healing. They enhance bicarbonate and mucus secretion and decrease gastric mucosal barrier permeability and acid back-diffusion.[37] This remarkable ability of prostaglandins to reduce the gastric mucosal injury was described with term "cytoprotection", that was coined by A. Robert, at the suggestion of E. Jacobson.

Beginning in the latter half of 19th century, the studies on gastric bacteriology that followed paved the way for discovery of association between *Campylobacter (Helicobacter) pylori* and peptic ulcers by Robin Warren (1979) and Barry Marshall (1982). German scientists G. Bottcher and French scientist M. Letulle demonstrated bacterial colonies in the ulcer floor and its mucosal margins (1875), being first to postulate the causation of ulcers to the bacteria which they could demonstrate, followed by W. Javorski at Cracow, who discovered and postulated a pathogenic role for the spiral organism (Vibrio rugula) he found in gastric contents (1896), and I. Boas at Berlin, who co-discovered the Oppler-Boas bacterium, which he tought was implicated in etiology of gastric carcinoma.[38] Almost paralleling the research of gastric bacteria, the importance of vagal nerve in gastric pathophysiology was widely accepted, especially after Dragstedt's pionerring work on the role of vagotomy in the treatment of peptic ulcers.[39] Interestingly, in his first paper that was published in 1917, in the same year when C. Schwarz died in Austria, Dragstedt described the bacterial model of gastric and duodenal ulcers, revealing the posibility of growing bacteria from these ulcers.[40] Further studies of A. Kussmaul (1869), C. Golgi (1893), K. Shiga (1898), Krienitz (1906), Hoffman (1925), Saunders (1930), Freedberg and Barron (1941) and Gorham (1940s) were all speaking of bacteria in the stomach, that subsequently led to the study of E.D. Palmer on gastric samples from 1180 subjects, using standard histological techniques (1950s) that failed to demonstrate the presence of bacteria in the stomach.[38] Palmer concluded that the results of all previous authors were the sequels of *post mortem* colonization of the gastric mucosa with oral cavity organisms.

Robin Warren, a pathologist at the Royal Perth Hospital and a young gastroenterology fellow Barry Marshal described the association of S-shaped Campylobacter-like organism and histological changes in 135 gastric biopsy specimens (1983), and by fulfilling the requirements of four Koch's postulates demonstrated the infectious nature of provoked gastritis.[41] With this discovery began the modern *Helicobacter* era leading to the fact that *H. pylori* represents a major etiopathogenetic factor for gastroduodenal pathology: acute and chronic gastritis, peptic ulcer, gastric cancer and MALT lymphoma. The notion that the prevalence of *H. pylori* associated gastritis and its sequels should be regarded as an

infectious disease led to worldwide major interventions, such as use of antibiotics in eradication therapy for *H. pylori* and attempts in vaccine development, as well.

Old and new therapies: modalities of acid inhibition

Beside chalk and pearl juleps, throughout 17th century and in early 19th century there was no record on specific remedies for gastric diseases. Cruveilhier at Paris had written extensively on the pathology of peptic ulcer disesae, but in those times little specific therapy apart form dietary adjustments or homeopatic remedies were apparent. Glycerrhetinic acid, a constituent of liquorice was used as a folk remedy for peptic ulcer disease, and in the latter half of 19th century physicans were treating peptic ulcer by using the extract of beladona, containing atropine, a nonselective muscarinic antagonists with intolerable side-effects, such as blurred vision, dry mouth and bladder dysfunction.[42] B Sippy (1915) and R. Doll introduced bland diets in the treatment of patients with peptic ulcer, augmented with the addition of neutrilizing compounds and antacids. However, such regimens lead to significant decline in the quality of life and significant side effects that even surgery became a reasonable option.[43]

Surgical approach to peptic ulcer had been confounded for years by the problems related to sepsis and lack of anesthesia, problems of perioperative morbidity and mortality, as well as the problems of "post gastrectomy syndromes". Nevertheless, the resection procedures, devised by Billroth (1881), Pean, Moynihan and Ridiger were capable of removing the ulceration, also providing relief of pain, bleeding, perforation and stenosis. However, alternative strategies to decrease secretion of acid were developed: M. Jaboulay of France performed the first vagotomy in a human patient (late 19th century), later combining vagotomy with a gastrojejunostomy to promote gastric emptying, followed by M.A. Latarjet in Lyons (1921) and L. Dragstedt (1943), in Chicago.[44]

Antacids, protective agents, anticholinergics, and later gastrin antagonists and prostaglandins were used for decades in treatment of peptic ulcer, with differing effects. The advent of the concept of H_2 receptor antagonists in late 1970s denoted the end of "before cimetidine" era, due to the results of clinical studies that documented that these drugs were effective for pain relief of ulcer pain and for ulcer healing, as well as in continued use being effective in reducing the ulcer recurrence.[45] A standard single dose of an H_2 antagonists taken at bedtime (e.g. cimetidine 800 mg, ranitidine 300 mg, , famotidine 40 mg, or nizatidine 300 mg) would be expected to heal about 80% of duodenal ulcers after 4 weeks, a proportion that increases to 95% after a total of 8 weeks.[46] Healing of gastric ulcers with H_2 receptors usually takes longer: 65% to 70% after 4 weeks and 85% to 90% after 8 weeks.[47] However, the development of pharmacologic tolerance to all available H_2 antagonosts in prolonged

therapy had been observed in early 1990s, especially limiting the use of these drugs in maintenance therapy for acid related disorders.[48]

The proton pump inhibitors (the irreversible inhibitors of the enzyme H^+/K^+-ATPase) were associated with higher rates and faster duodenal ulcers healing (90% after 4 weeks), as well as higher rates and faster gastric ulcers healing (approximately 90% after 4 weeks), providing a greater degree of inhibition of gastric acid secretion than did conventional doses of the H_2 antagonists.[49] In addition, PPIs have been proven to be a successfull treatment in patients with Zollinger-Ellison syndrome, and in healing of gastric ulcers in patients who continue to use NSAIDs.[50] Noteworthy, inhibiton of acid secretion with PPIs is never complete because new molecules of acid pump are constantly being synthesized, and therefore, PPIs do not induce achlorhydria.[51] Early concerns in regard to formation of carcinoid tumors, derived from ECL cells in rats on prolonged use of high doses of PPIs had not been encountered in routine clinical use of PPIs.[52] Thus, H_2 antagonists had been proven to be more effective in inhibiting acid secretion in basal state (fasting or overnight), than in response to food digestion, and PPIs offered strong reduction of basal and stimulated acid output, beeing effective to maintain gastric juice in pH >3 to pH >5, in duration of 8 – 16 hours, providing optimal treatment for acid related disorders.[53]

The role of endoscopy

The low prevalence of peptic ulcer that had been documented during 19th century may be atributed to an inability at the time to diagnose uncomplicated peptic ulcer during the patient's life: the statistics were mostly based on autopsy studies.[54] Adolf Kussmaul (1822 – 1902) at University of Freiburg performed the first gastroscopy ever (1868), by introducing his endoscope into the stomach of the sword swallower.[55] Nevertheless, from 1910 to 1970, the methods of radiology were superior to endoscopy in diagnosing peptic ulcer. Using the side-viewing endoscope, devised by Elsner (1910 / 1911), Rudolf Schindler successfully performed gastroscopies that resulted in his first published book on gastroscopic diagnosis ("Lehrbuch und Atlas der Gastroskopie", 1923).[56] In 1932, Schindler introduced the semiflexible Wolf-Schindler gastroscope into clinical practice, but still, there was a problem of difficulty of passage, limitations of viewing, and continuing risk of injury.[57] In 1954, the dicoveries of image transmission through a flexible bundle of oriented glass fibers - termed a "fiberscope" - by Hopkins and Kapany, followed by development of Hirschowitz's prototype of first fiberscope for clinical use (1957), enabled the commercial production of gastroduodenal fiberscope by American Cystoscope Makers, Inc. (ACMI), in 1960.[58] Since the 1970s, the endoscopy has been the gold standard for diagnosing ulcer, healing and relapse in a

multitude of clinical trials of ulcer treatment. Further development of electronic video technology enabled the advent of videoendoscopy (Welch-Allyin Inc, 1983), that revolutionized the methods of teaching in gastrointestinal endoscopy.[59]

The burden of peptic ulcer in the society may be outlined by its association with the prevalence of *H. pylori* in a certain population, the prevalence of comorbid conditions and chronic medication, as well as the risk factors, making the patients prone to development of peptic ulcer. Nowdays, we have witnessed the new techniques and methods of endoscopy and endosonography that have been brought into clinical practice, highlighting the possibility of imaging beyond white light and beyond mucosal layer, as well.

Society and Healthcare

The burden of peptic ulcer in the society may be outlined by its association with the prevalence of *H. pylori* in a certain population, the prevalence of comorbid conditions and chronic medication, as well as the other risk factors, making the patients prone to development of peptic ulcer. Nevertheless, the lifetime risk for peptic ulcer in patients with *H. pylori* infection is 3% to 25%, the overall risk being greater in NSAID users (OR 6.1) than in NSAID users without *H. pylori* infection (OR 4.8).[60] There has also been some data, pointing out to possible association of peptic ulcer to other conditions with significant impact on the society: anxiety disorder (OR 3.43), panic disorder (OR 3.11), dysthymia (OR 3.59) and bipolar disorder (OR 2.91).[61] However, nicotine and alcohol dependence seems to play a substantial role in explaining the link of these disorders to peptic ulcer disease. Interestingly, the Italian authors even observed a significant reduction in sperm motilitiy with increased systemic levels of TNFα levels in CagA- positive infertile patients with *H. pylori* infection, but it seems these results need further clarification.[62]

Peptic ulcer remains a common condition, although reported incidence and prevalence is decreasing, and this decrease may be due to decrease in *H. pylori* associated peptic ulcer disease.[63] However, the 1-year prevalence of peptic ulcer has been reported ten times greater in patients aged 75-84 years (0.40%) than in patients aged 0-35 years (0.04%).[64] A Danish study reported a decrease of overall incidence of peptic ulcer that was accompanied by an increase of peptic ulcers potentially related to NSAID use from 39% in 1993 to 53% in 2002 ($p < 0.01$), and a study from The Netherlands documented that admission rates for complications of PUD remained fairly stable in men and increased slightly in women, over the period 1980 – 2003.[65,66] In the USA (2004), peptic ulcer was first-listed diagnosis at hospital discharge in 37% of cases, and nearly 80% of deaths related to peptic ulcers occurrred among people aged ≥ 65 years.[67] In regard to total costs of digestive diseases in the USA (2004), the total costs of both, PUD and GERD were leveling to about 60% of total

costs for all digestive cancers and, interestingly, PPIs represented 50.6% of prescriptions and 77.3% of costs of retail pharmacy sales for all digestive diseases.[67] Worldwide, peptic ulcer and its complications thus remain the cause of significant morbidity, especially in older age groups, representing a major burden for ambulatory and hospital healthcare resources. Never to be forgotten, all our efforts as gastroenterologists have been aimed to well being of our patients, throughout patients' journey in the circles of diagnosis and treatment (Figure 3). If it is not possible to cure the disease entirely, our task is the improvement of patient's health-related quality of life.

Conclusions and "A view to the future"

Being an interface to "outer world", the gastroduodenal mucosa has been under constant attack during the era of human civilization, and its homeostasis is essential for living a healthy life. The history of medicine has taught us that gastric acid secretion plays a major role in pathophysiology of PUD. During past 50 years we have witnessed the major discoveries in etiopathogenesis of PUD, as well as the advent of potent acid inhibitors and advances in methods and techniques of upper GI endoscopy. Just to mention the few, the open questions that remain are do we need the special approach for cohorts of parients, who are at special risk for PUD and do we need the more powerful / prolonged acid inhibition. Maybe, the study of genetics and epigenetics would lead to improved protocols for eradication of *H. pylori* infection and to effective prevention of gastric atrophy. Looking back, we should realize that there is at least so much to learn in front of us, as there was behind.

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Table 1 Major historical impacts to drive research in peptic ulcer disease

EARLY OBSERVATIONS	**Hippocrates** (5th century B.C.): *pepsys* : the food was "cooked" in the stomach **Paracelsus** (1493-1541): *archei*:ultimate forces of enery governing humans and universe **A. Vesalius** (1543): first description of vagal nerves
PATHOPHYSIOLOGICAL CONCEPTS IN GASTRIC ACID SECRETION	
Early ideas: gastric juice and gastric acid	**R. de Reaumur** (1752): acidic nature of gastric juice **L. Spallanzani** (1793): gastric juice as chemical solvent **W. Prout**: "muriatic acid" in stomach contents, later identified to be hydrochloric acid
Gastric phyisiology of food digestion	**Dupuytren and Bichat** (1801) and **W Beaumont** (1823): accidentally acquired gastric fistulas as "a window" to observe the process of food digestion
Morphology and fine structure of stomach glands	**J Purkinje** (light microscopy, 1837): first description of gastric glands **C. Golgi** (1893): marked changes of stomach glands upon digestive stimulus **Dalton** (1951): fine structure of gastric parietal cells
Phisyological concepts of gastric secretion	**I.P Pavlov** (1895): neuro-reflex stimulation of gastric secretion by vagal nerve **L. Popielski** (1920) and **C.F. Code** (1956): histamine mediated concept of gastric secretion **J.S. Edkins** (1905): the discovery of gastrin **T. Schwann** (1836): the discovery of pepsin
DISCOVERIES IN ETIOPATHOGENESIS OF MUCOSAL INJURY AND PEPTIC ULCER	
Gastric acid and gastric mucosal barrier	**D.K. Schwarz** (1910): dictum "No acid, no ulcer" **T. Teorell** (1930s): "back-diffusion" of acid causes mucosal damage **H. Davenport / C. Code / J. Scholer** (1955): the concept of "gastric mucosal barrier"
Prostaglandins (PGs) and "gastric cytoprotection"	**J.R Vane** (1971) and **A. Robert** (1976): PGs modulate the gastric mucosal defence **A. Robert** and **E Jacobson** (1970s): PGs reduce gastric mucosal injury – "cytoprotection"
Bacteria in the stomach	**G. Bottcher and M. Letulle** (1875): documented bacterial colonies in ulcer floor and mucosal margins **W. Jaworski** (Vibrio rugula, 1896) and **I. Boas** (Oppler-Boas bacterium): postulated a pathogenic role of bacteria in gastric ulcer and gastric carcinoma **E.D. Palmer** (1950s): failed to demonstrate the presence of bacteria in the stomach **R. Warren** and **B. Marshall** (1983): the discovery of Helicobacter (Campylobacter) pylori in gastric mucosa
OLD AND NEW THERAPIES: MODALITIES OF ACID INHIBITION	
Old therapies	**17th to early 19th century**: no record on specific remedies for gastric diseases **19th century physicians**: use of extract of beladona (atropine) for treating peptic ulcer, with intolerable side-effects **B. Sippy** (1915) and **R. Doll**: introduced bland diets and antacids in treatment of peptic ulcer **20th century**: use of anticholinergics, gastrin antagonists and PGs in peptic ulcer treatment, with differing effects
Surgical approach to treating of peptic ulcer	**Billroth** (1881), **Pean**, **Moynihan**, **Ridiger**: gastric resection procedures **M. Jaboulay** (late 19th century): first vagotomy in human patient **M. Jaboulay**, **M.A. Latarjet** (1921), **L. Dragstedt** (1943): vagotomy with gastrojejunostomy to promote gastric emptying
Advent of potent inhibitors of gastric acid secretion	**Sir J. Black** (1972): the concept of H_2-receptor antagonists as potent inhibitors of gastric secretion **A.L. Ganser** and **J.G. Forte** (1970s): the discovery of K^+-ATPase in bullfrog oxyntic cells **G. Sachs** and coworkers (1970s and 80s): dicovery of location, nature and molecular structure of acid pump / synthesis of first PPIs

Figure 1

By term *pepsys* Hippocrates (5th century B.C.) denoted that food was "cooked" in the stomach

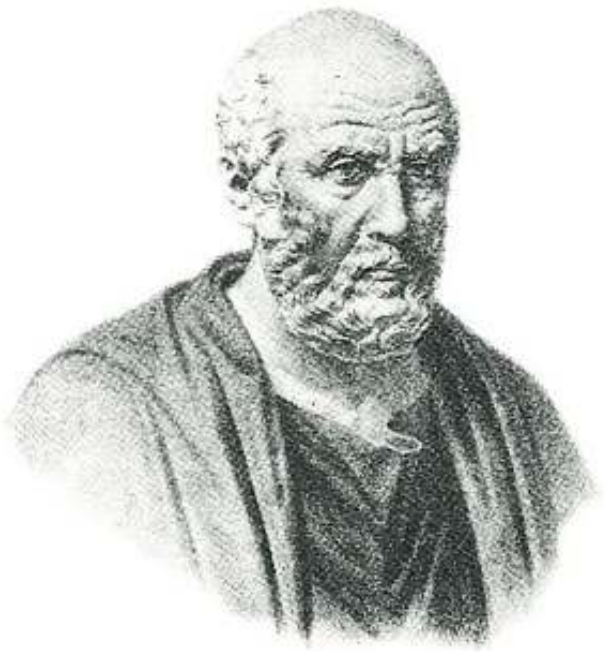

Figure 2

Camillo Golgi noted the marked change in appearance of gastric glands upon stimulation (1893 / 1895): resting gland (a) and stimulated gland (b)

a **b**

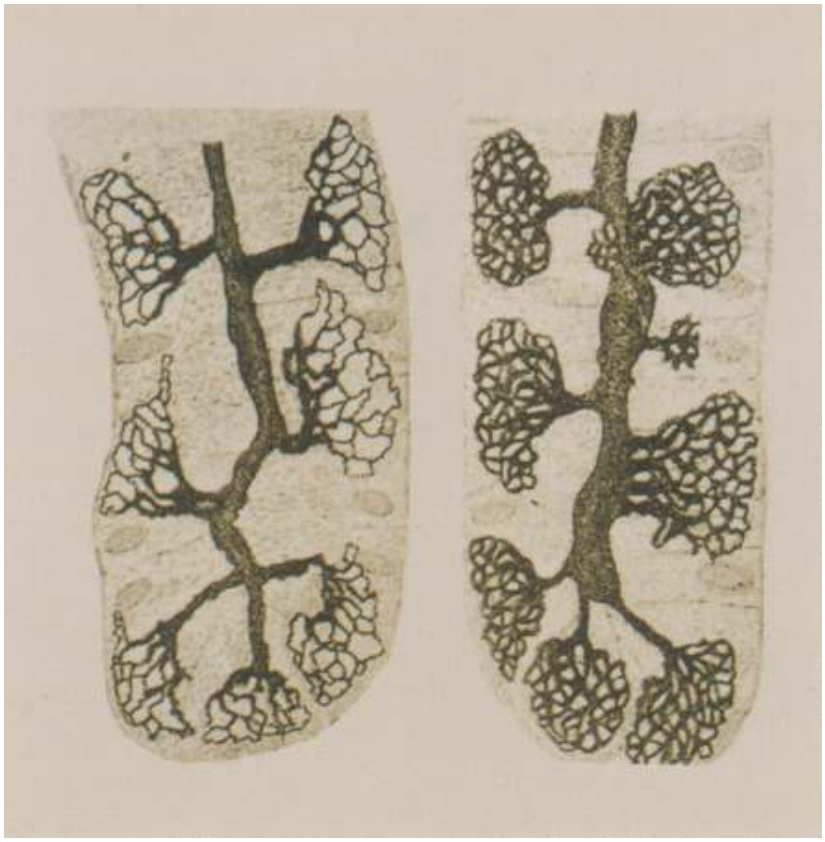

Figure 3

The patients' "Journey"