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GASTRIC SECRETION - FROM PAVLOV'S *NERVISM* TO POPIELSKI'S HISTAMINE AS DIRECT SECRETAGOGUE OF OXYNTIC GLANDS

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Gastric acid and pepsin secretions result from the interplay of neurohormonal factors with stimulatory and inhibitory actions on oxyntic glands. At the turn of XIX century, the notion of nervism or entire neural control of digestive functions, developed by Pavlov prevailed. However, in the second part of XX century, hormonal control has been thought to play a major role in the mechanism of gastric secretion, especially gastrin, which was isolated and synthesized in 1964 by Gregory. Polish traces in gastroenterological history started with the discovery of histamine, a non-nervous and non-gastrin compound in oxyntic mucosa by L. Popielski in 1916, who found that this amine is the most potent and direct stimulant of gastric acid secretion. This histamine concept was supported by leading American gastroenterologists such as A.C. Ivy, championed later by C.F. Code, and clinically applied for testing gastric secretion by K. Kowalewski. Recently, it received a strong support from pharmacological research when J. Black designed H₂-receptors antagonists, which were first discovered by M.I. Grossman and S.J. Konturek to inhibit not only histamine-, but also meal- and vagally-induced gastric acid secretion, thus reinforcing the notion of the crucial significance of histamine in the control of gastric secretion as the final common chemostimulator. In conclusion, Polish traces appear to be substantial in gastric history due: 1) to discovery by Popielski that histamine is a major, direct stimulus of gastric secretion; 2) to clinical application of this agent by Kowalewski in testing maximal gastric secretory activity; and 3) to clinical use of histamine H₂-antagonists in control of gastric acid secretion and treatment of peptic ulcers.

Key words: *Histamine, gastrin, Pavlov, Popielski, nervism, gastric secretion, mucosal barrier*

DISCOVERY OF GASTRIC HYDROCHLORIC ACID

Gastric acid (H^+) secretion results from the interplay of stimulatory and inhibitory neurohormonal mechanisms activated by the ingestion of food and the presence of nutrients in the upper GI lumen. In antiquity, the stomach (*ventriculus*) was equated with the belly (*venter*) and most often characterized as gluttony or the pluck (1). Following detailed description by Vesalius in 1543 of intra-abdominal structures, including the stomach and "wandering" (vagal) nerves (2), the questions have been raised what functions, besides passage of food can be ascribed to GI organs during food assimilation. It required almost three centuries before the identification by W. Prout in 1824 (3) of hydrochloric acid in the gastric juice of men and other species, and four centuries before the start of studies on regulation of gastric secretion. Pavlov, in the 1880s, discovered the functional significance of nerves in this regulation of gastric and pancreatic secretion (4). With the introduction of microscopy, C. Golgy (1) demonstrated that the gastric glands include oxyntic (acid producing) and peptic (pepsinogen producing) cells. R. Heidenhain, of Breslav University, characterized a "third" type of cell, which adhered to the external surface of epithelial cells, and later identified as enterochromaffin-like cells (ECL-cells) (5).

Prout presented scientific evidence for the presence of hydrochloric acid (called also muriatic acid) in the gastric juice. This coincided with the ingenious observations by W. Beaumont in 1822 on gastric functions of Alexis St. Martin, a French Canadian traveller, who accidentally shot himself in the left upper abdomen and after a fortunate recovery, lived many years with a gastric fistula which served for Beaumont as a precious "human guinea pig" for gastric secretion studies (6). Beaumont wrote in 1833 in his famous book, *Experiments and Observations in Gastric Juice and the Physiology of Digestion*, that having such an opportunity as his unexpected patient, he "considered himself but a humble inquirer after the truth - simple explorer". Despite Beaumont's findings regarding gastric acid secretion, digestion, motility and blood flow, the famous German gastroenterologists, K. Ewald and I. Boas, of the later part of the XIX century, insisted that an empty stomach secretes lactic acid, but after a meal it is gradually replaced by hydrochloric acid (7).

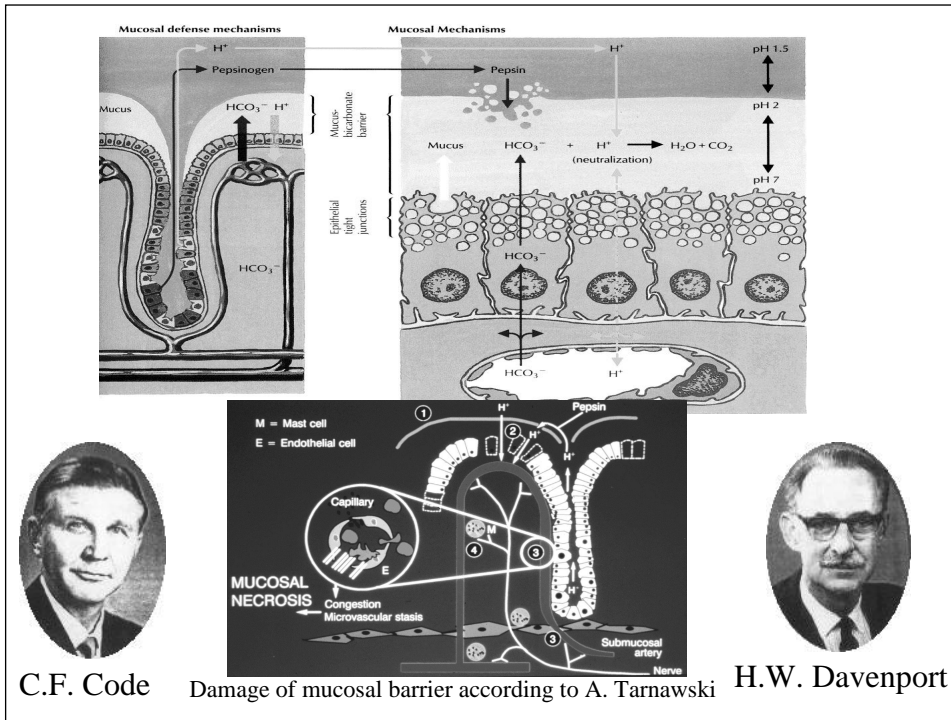
The discovery of gastric acid and pepsinogen initiated numerous investigations regarding various aspects of this secretion, particularly: 1. the mucosal barrier preventing acid and pepsin from aggressive damage of the mucosa; 2. the mechanism underlying the gastric secretory activity; and 3. pathological implication of this secretion. The question arises what Polish traces, if any, could be detected in the area of gastric secretion in health and diseases.

Mucosal barrier

The question of autodigestion of the stomach while digesting a variety of food including meat and even living organisms, such as a frog placed in a dog's stomach

via a fistula by L. Dragsted (8), was pondered in XVII century by Archibald Pitcairn. The existence of putative vital forces in gastric wall was initially proposed, however, it was soon recognized that gastric and duodenal mucosa, exposed to such highly concentrated HCl, must exhibit specific mechanisms responsible for its mucosal protection against acid-pepsin aggression. In the early 1930s, T. Teorell (9) suggested that the presence of acid in the stomach results in small acid back-diffusion into the mucosa in exchange for Na⁺ ions that define the permeability characteristics of the gastric mucosa. It has been proposed that the gastric mucosal surface, which is covered by a mucus gel, secretes bicarbonates into this adherent mucus layer to neutralize luminal H⁺ ions diffusing towards the mucous epithelial cells, thus preventing their damaging action. Tight junctions between adjacent epithelial cells, constant secretion of mucus-HCO₃⁻ producing a continuous protective "blanket" of 200-300 μm thickness on their surface and abundant blood flow in the mucosa form together so called, "mucosal barrier". Teorell proved, that due to the high polarity of surface epithelial cells and adherent mucus containing bipolar phospholipids, ionized mineral acids, such as HCl, do not diffuse, but unionized organic compounds such as bile salts or acetylsalicylic acid (aspirin), with a relatively low pKa, rapidly disappear from the gastric lumen by unionic diffusion into the mucosa and damage it. The barrier concept was further developed by H.W. Davenport (10) and C.F. Code (of Rochester, Minnesota, USA), who published a series of papers related to the significance of the protective gastric mucosal barrier (11). They proposed that breaking the barrier represents an initial step in the process of mucosal injury with a subsequent cascade of liberation of histamine and histamine-like substances, overt mucosal bleeding, and acute gastritis. This is similar to what is observed after exposure of the mucosa to acidified aspirin or ethanol, which is a widely used model of gastric damage for studying gastro-protective efficacy of various drugs in animals and humans (*Fig. 1*).

The history of the mucosal barrier can be traced to several Polish notables. G.J. Glass, a Polish immigrant, who was deported during WW II to Siberia and then resettled to New York, became professor of medicine and Director of the GI Research Lab. at New York Medical College. At this very active research center, he studied the pre-epithelial and epithelial components of the gastric mucosal barrier, particularly the mucus and its characteristics in health and stress conditions (12). He and his colleagues, especially Professors B. Slomiany and A. Slomiany and then Sarosiek (13), excellent biochemists, originated from and studied in Poland before joining Glass in New York. They applied biochemical techniques to examine the major components of mucus gel, including sulphated and non-sulphated glycoproteins. They also quantitatively characterized the mucus layer produced and released by surface epithelial cells, its permeability to diffusing H⁺, and pepsin and mucus disintegration by proteases and phospholipases originating from infecting *Helicobacter pylori* (*H. pylori*) and various irritants such as non-steroidal anti-inflammatory drugs, ethanol,



C.F. Code

Damage of mucosal barrier according to A. Tarnawski



H.W. Davenport

Fig. 1. Gastric mucosal barrier against acid-pepsin damage and its pioneers. (Konturek S.J. et al., 2003)

hypertonic salt, bile salts, etc. Their important contribution explained the mucosal damage following stress in humans (e.g. soldiers wounded in the Vietnam war), in gastric ulcer patients, and in animals. Several Polish centers, especially the Department of Gastroenterology in Bialystok led by Prof. A. Gabryelewicz (14) and our Institute of Physiology in Cracow (15), directly collaborated with the Slomianys in the GI Research Center in New York on studies concerning mucosal alterations with peptic ulcers, following administration of growth factors and various gastro-protective agents, such as sucralfate.

Another skilful investigator of Polish background is A. Tarnawski. Tarnawski was born in Cracow, and earned his medical degree from the Cracow Medical Academy and also received his habilitation there in 1966, and afterwards moved to the USA to work at the Columbia Medical Center with Dr Ivey, and later independently as a professor of medicine at the University of California at Irvine (16, 17). He provided the first evidence that the mucosal barrier in rats changes during gastric secretion, which is strengthened during active stimulation of gastric acid production by various secretagogues, such as gastrin. Furthermore, Tarnawski reported that the mucosal barrier also exists in the proximal duodenum which is occasionally exposed to pulses of concentrated gastric acid emptied by

the stomach. His major achievements are, however, related to the mechanism of maintenance of gastric mucosal integrity, the healing of acute and chronic ulcerations, the role of various growth factors and autacoids, intracellular mediators in epithelial cells involved in mucosal restitution, proliferation and repair (17).

We found (18) that unlike the gastric barrier with its tight epithelial cell surface, the duodenal barrier consists of leaky epithelial cells (duodenocytes), which is maintained by an excessive duodenal HCO_3^- -mucus secretion, particularly in response to topical application of HCl in the proximal duodenum. This is where peptic ulcers usually develop. The highly effective pre-epithelial barrier activated by H^+ with prolonged mucus-alkaline secretion exists in the proximal duodenum as a result of the upregulation of COX-1 and an excessive release of prostaglandins (PG), especially PGE_2 , the overexpression of nitric oxide (NO) synthase (NOS) which releases NO from L-arginine, and activation of capsaicin-sensitive afferent nerves releasing calcitonin-gene related peptide (CGRP) (Fig. 2).

Like the Slomianys, our Institute of Physiology in Cracow has also reported that several anti-ulcer and gastro-protective drugs including sucralfate, bismuth salts (e.g. De-Nol), antacids (e.g. Maalox), and exogenous PGE analogs are highly effective in the stimulation of gastro-duodenal bicarbonate secretion and that this may be one of the mechanisms of their therapeutic (anti-ulcer) efficacy

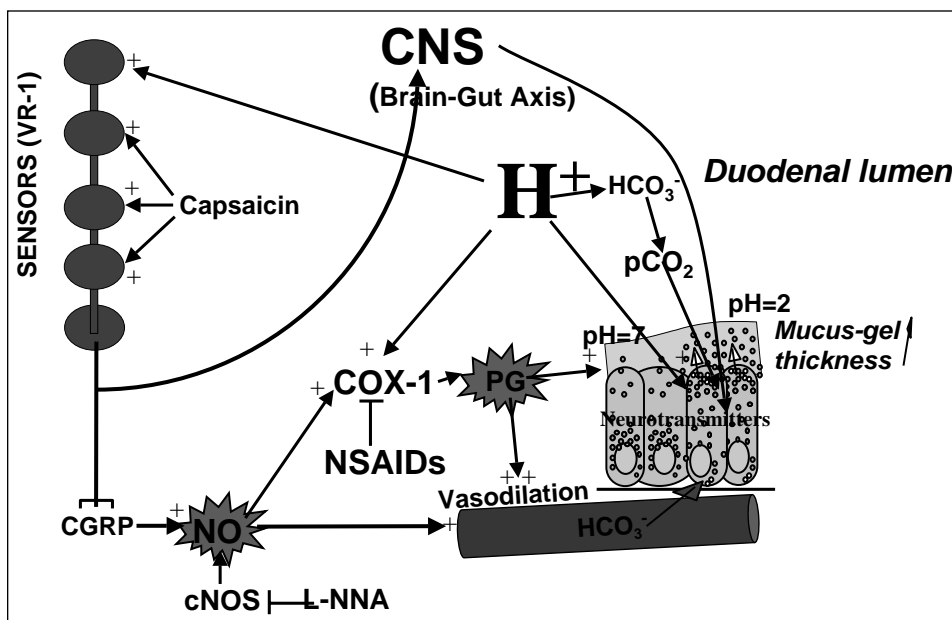


Fig. 2. H^+ -induced duodenal mucus- HCO_3^- secretion involves COX-1-PG activation combined with sensory nerve terminal stimulation and release of CGRP and activation of NOS-NO system. (Konturek S.J. et. al., 2003)

(19). Considering duodenal mucus-alkaline secretion in response to topical acid, Isenberg and his colleagues used human duodenum (20) and Kaunitz et al. (21) employed a chamber with either gastric or duodenal mucosa. They found that, unlike the stomach where tight epithelial cells constitute the main protective barrier against H^+ , the concentrated H^+ delivered in pulses on the duodenum, easily penetrates into the duodenocytes, but does not cause their damage, though transiently decreases their intracellular pH (pH). This strongly activates the basolateral $Na^+-HCO_3^-$ cotransports allowing for massive inward movement of HCO_3^- from the extracellular space, and then for activating HCO_3^-/Cl^- exchangers in apical membrane, resulting in marked stimulation of HCO_3^- secretion and neutralization of remaining (not infusing) H^+ ions in the duodenal lumen to secure its neutrality.

The breaking of the mucosal barrier plays an important role in gastric mucosal damage, gastritis and ulcer formation by non-steroidal anti-inflammatory drugs (NSAID) such as aspirin or *H. pylori* infection. As the bacterium inoculates the stomach of more than 50% of world adult population (in our country the rate of infection reaches about 60%), the germ and its cytotoxins appear to damage surface gastric epithelial cells, that disturbs the mucosal cell immunological resistance to damage and interferes with their HCO_3^- secretory activity as well as affects the quality of adherent mucus gel leading to acute and then chronic gastritis. As shown by Isenberg et al. (20) in the duodenum, *H. pylori* infection also reduces HCO_3^- -mucus secretion (despite of increasing mucosal PGE_2 generation) allowing for excessive penetration of gastric H^+ and other irritants into the mucosa, damaging duodenocytes with subsequent induction of gastric metaplastic loci that become known as the "*locus minoris resistentiae*" and the place of infection with *H. pylori* and, finally, ulcer formation. Upon the eradication of *H. pylori*, there is a restoration of basal and acid-induced duodenal mucosal alkaline secretion despite a reduction in mucosal PG generation (20).

GASTRIC ACID SECRETION AND ITS CONTROL

Regulation of gastric acid secretion

After the discovery of hydrochloric acid in the stomach, attempts were first made to identify the glands producing this inorganic acid, and then to explain the mechanisms of its control. Studies of C. Golgy, working with G. Bizzozero of Padva in the second half of XIX century (1), described the parietal (oxyntic) cells with their characteristic intracellular cannalculi that change upon secretory stimulation by increasing their number and surface due to incorporation of ($Na^+ - K^+$) ATPase-containing plasmatic vesicular membrane.

The mechanism of H^+ stimulation in gastric glands was first attributed to the predominant influence of vagal nerves as proposed and documented by I. P. Pavlov and his school at St. Petersburg Military Medico-Chirurgical Academy

and called *nervism* as described in Pavlov's book "*The Work of the Digestive Glands*" (4).

Neural control

As pointed out by Pavlov himself *nervism* was "a physiological theory which tried to prove that the nervous system controls the greatest possible number of bodily activities". Accordingly, Pavlov proved that neural regulation of gastric and pancreatic secretion is mediated entirely through the vagal nerves which were described earlier by Vesalius in his famous "*De Fabrica Humani Corporis*" (2). After analysis of previous studies in this area, Pavlov, being a very skilful operator, prepared dogs with an esophageal fistula and fully innervated pouches fashioned from the oxyntic gland area in such a way that they reflected the secretory activity of the main stomach without interfering with its homeostasis. Pavlov learned the technique of vagally denervated gastric pouch preparation when he visited the Department of Physiology at University of Breslau chaired by of L. Heidenhain. After returning to St. Petersburg and becoming director of Department of Experimental Medicine at Military Medico-Chirurgical Academy, he surgically prepared a pouch of an oxyntic gland area separating the main stomach by its double layer of mucosa in such a resourceful manner that this separation did not affect vagal innervation of the pouch and the main stomach. This pouch allowed Pavlov to examine the secretory effects of sham-feeding, which is the best physiological stimulus of vagal nerves, on gastric secretion before and after subdiaphragmatic vagotomy. Since sham-feeding induced copious gastric (and pancreatic enzyme) secretion, and this was dramatically reduced by subdiaphragmatic vagotomy, Pavlov concluded that this secretion is entirely vagally-mediated (*Fig. 3*).

Pavlov believed that the sham-feeding effect is transmitted by "numerous channels" to the gastric glands. Subsequent reproduction of the effect of vagotomy on gastric secretion induced by electrical excitation of vagal nerves was considered as the final confirmation of the crucial role of vagal nerves in the control of gastric secretion. The scientific recognition of the importance of neural innervation in gastric secretory studies secured Pavlov international acclaim and the Nobel Prize in 1904 in physiology and medicine for his outstanding discoveries in gastric physiology, especially the preparation of his gastric pouch. Pavlov shared the support from Nobel Foundation with his Polish colleague, M. Nencki, who was a professor of chemistry, first at the University of *Vilnius*, and then later at St. Petersburg University, for his chemical discoveries.

The Medico-Chirurgical Academy in St. Petersburg had a modern department of physiology with an excellent operation theatre, and a large animal supply, was uninterrupted even during Russian Revolution and WWI. These facilities combined with Pavlov's remarkable surgical skills and brilliant thinking considerably facilitated Pavlov's experimental studies on the neuro-regulatory

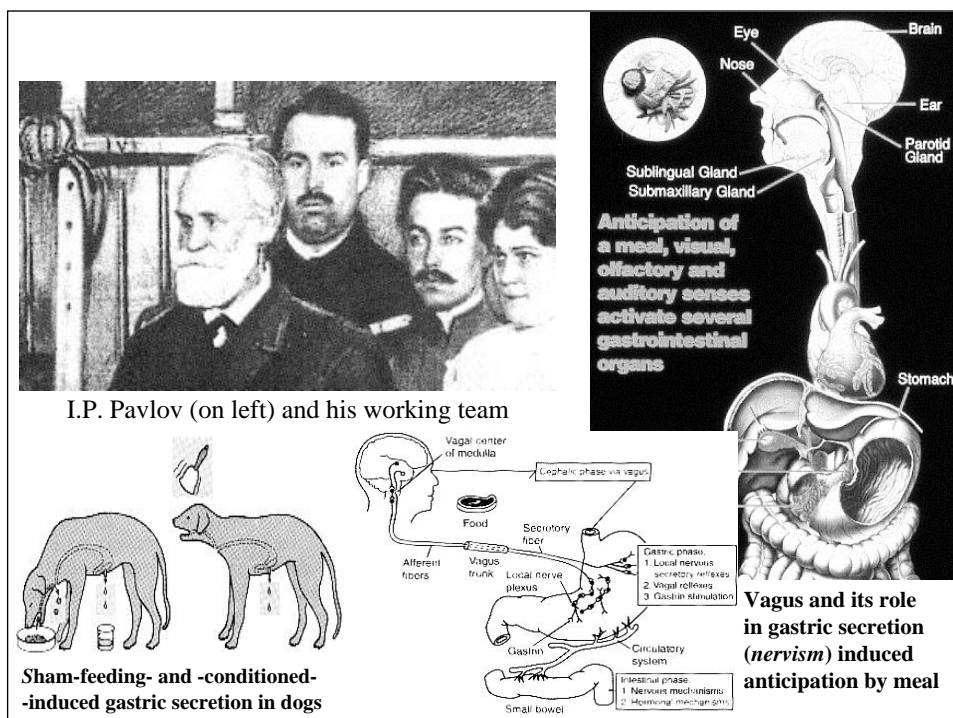


Fig. 3. Pavlov concept of stimulation of gastric acid secretion mediated entirely by vagal reflexes (*nervisms*).

control of gastric and pancreatic secretion and rightly awarded him the title of *princeps physiologorum mundi* by the scientific community gathered in 1935 in Moscow at the World Congress of Physiology just few months before his death. Unfortunately, Pavlov at the end of his career, discouraged by undeniable evidence of humoral control of gastric and pancreatic secretion, left GI physiology (Fig. 4).

Hormonal control

After the first discovery of the hormone, secretin, in the duodenal mucosa by W.M. Bayliss and E.H. Starling in 1902, and then another hormone - gastrin in the *antrum* by J.S. Edkins in 1906 and their publication in the Journal of Physiology (23), Pavlov initially disdained the importance of these discoveries, but then ordered their verification in his lab. Under his supervision, one of his pupils, V.V. Savich, repeated and confirmed the Bayliss and Starling discovery concerning the hormonal contribution to the regulation of exocrine pancreas (23). Similar verification of the "Edkins hypothesis" led him to accept, reluctantly, the importance of hormonal control of gastric and pancreatic secretion, and this was

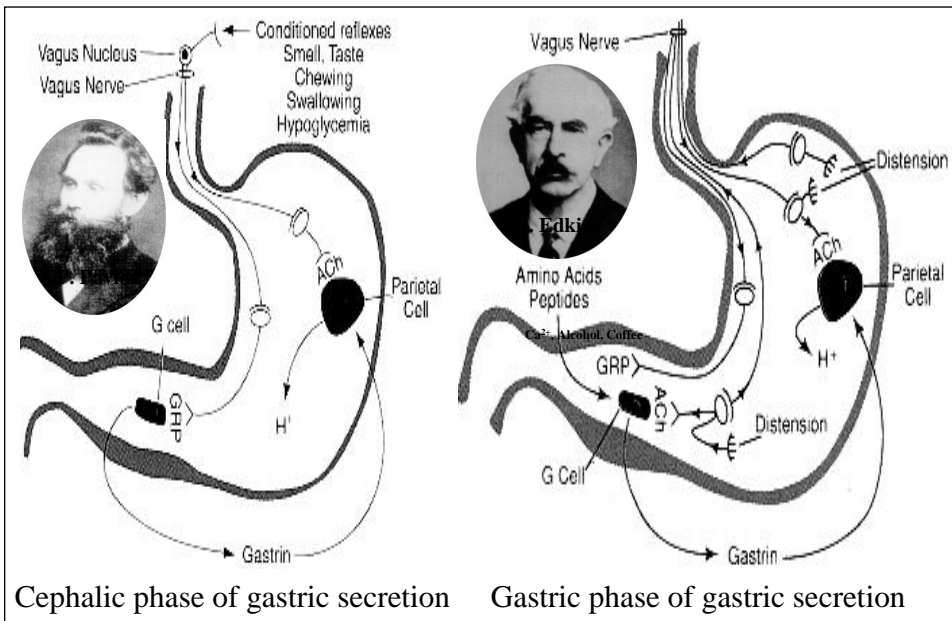


Fig. 4. Neural (cephalic phase) and hormonal (gastric phase) control of gastric acid secretion and its proponents.

probably the major reason of his departure from GI physiology to research of conditioned reflexes (Fig. 4).

With the confirmation in his lab of the results of Bayliss and Starling, and then those of Edkins, Pavlov radically, but perhaps too hastily changed his opinion about the mechanism controlling the exocrine pancreas during the period 1902-1903. As mentioned by B.P. Babkin (23), a former pupil of Pavlov, and chairman of the Department of Physiology at McGill University in Toronto, Pavlov declared "of course, they are right. It is clear that we did not take out an exclusive patent for the discovery of truth". It is a paradox of history that after a century of intensive investigations both neural and hormonal concepts have been proved to be right (see Fig. 4). Cephalic phase that has been entirely attributed by Pavlov to vagal stimulation, appears to involve also gastrin release through the excitation of postsynaptic gastrin-releasing peptide (GRP) nerves. Gastric phase that according to Edkins supposes to be mediated by hormonal (gastrin) stimulation is mediated also by short and long vago-vagal reflexes initiated by the distention of the stomach by food and chemical irritation of gastric receptors by products of food digestion. Moreover, neither vagal nerves nor gastrin are major direct stimulants of gastric glands but this role is played by humoral substance, histamine which, as described in next subchapter, is released by ECL-cells under the influence of vagal and gastrin stimulation.

Popielski and discovery of histamine secretagogue activity

L. Popielski, born into a Polish family at Sosnierzany, first finished mathematical faculty of St. Petersburg University and then completed his medical education at this university to join Pavlov team in which two Poles, Nencki and Tarchanow, already worked under Pavlov's chairmanship. In 1904, Popielski with help of Pavlov, was appointed chairman of the Department of Pharmacology in Lvov (Lemberg) in the eastern part of Galicia (which belonged to Poland before its partition in XVIII and after its restoration after WWI). While in the Pavlov Lab, Popielski was assigned to study nervous connections between the upper intestinal mucosa and the pancreas by cutting the spinal cord below the medulla with and without preservation of vagal and sympathetic nerves (25). Since acid instilled into the duodenum stimulated pancreatic secretion, he concluded that the control of pancreatic secretion is a neural reflex in nature as to apply the dogma of Pavlov's *nervism* (25) His conclusion that pancreatic secretion is mediated by a peripheral reflex or "chemical reflex" is considered by some to be totally erroneous. Popielski's opinion, and recent finding, that the blockade of muscarinic receptors with atropine causes a decrease of pancreatic response to exocrine and endocrine secretin (26) and the observation of Chey and his colleagues (27) that the release of secretin-releasing factor (S-RF) from duodenocytes is under vagal-cholinergic control indicate that despite the Bayliss and Starling discovery of exclusive hormonal (secretin) control of pancreatic response to duodenal acid, there is also place for a neural component proposed by Popielski in this control of pancreatic secretion by duodenal acidification. Unlike Pavlov, Popielski based this on his own research and never withdrew from his already published position.

The greatest and original accomplishment of Popielski (and Polish physiology, in general) came after his appointment as professor of Department of Pharmacology at Lvov University where he met Polish colleagues, famous gastric surgeon L. Rydygier, chairman of Department of Surgery and A. Beck, chairman of Department of Physiology, both offered their positions at the Jagiellonian University in Cracow. According to the grandson of Popielski, Dr. L. Popielski working at the Department of Laryngology of Jagiellonian University, professor Popielski was a close personal friend with the famous Polish surgeon, L. Rydygier, who performed the first gastrectomy in man (28). Popielski focused his attention on the physiology of the GI tract, pathophysiology of autonomic nerves, and most importantly on biologically active substances, especially "vasodilatin" and histamine. His interest in these substances was preceded by their identification by H. H. Dale at the Wellcome Physiological Laboratories in the UK, however, Dale failed to look for the possible effect of these substances on gastric acid secretion. Dale working together with G. Berger, identified the base as beta-imidazoleethyl-amine or simply called "Beta-i or β i" and compared it with an authentic sample, which had been obtained by histidine purification. The

name "histamine" was used for the first time in approximately 1913 when Dale carried out extensive research on its effect on smooth muscle of the uterus and vessels identifying its potent vasodilating action.

Popielski, upon leaving Pavlov's laboratory was testing the vasodilating action of Witte's peptone (a peptic digest of fibrin) and found its powerful vasodilating effect, hence its name, vasodilatin. Popielski thought this was a component of Witte's peptone, different from either histamine or choline. The influence of vasodilatin on heart and vessels has been later used to explain the pathogenesis of cardio-vascular shock. In further studies using extracts from various tissues, Popielski often observed hypotension, attributing it to the above mentioned vasodilatin (30). Popielski initially rejected the view of Dale and Laidlow that both substances (vasodilatin and histamine) represent the same compound but, finally, in 1916, Popielski accepted the concept that vasodilatin is, in fact, histamine.

With respect to the mechanism of gastric acid stimulation, Popielski persistently rejected the "Edkin's hypothesis" or "gastrin concept" according to which gastric secretion is stimulated mainly by a hormone released from the antral gland area, and initially called "gastric secretin", then gastrin (22). Popielski studied the effects of extracts of various tissues on gastric secretion and found that after subcutaneous injection they stimulate gastric acid secretion attributing this effect for the first time to the non-nervous mechanism. This stimulatory effect Popielski ascribed to the above-mentioned vasodilatin. It is of interest that in one of his studies, the tissue extract applied to antral mucosa also stimulated gastric acid secretion, thus supporting unconsciously the Edkins hypothesis. Eventually this was explained by hypothesis implicating local vagal nerves excitation (30). It is of interest that Tomaszewski (31) of Popielski's team, also tested the extracts from various portions of the GI tract and found that the extract of gastric *corpus* and *antrum*, when applied subcutaneously, caused vigorous stimulation of gastric acid secretion even after vagotomy and atropinization, but following intravenous injection only hypotensive response was observed. This was interpreted that gastric mucosal extract given subcutaneously is transformed into an active substance, presumably histamine, responsible for gastric stimulatory properties, nonetheless, the implication of histamine was neither accepted by Tomaszewski nor by Popielski.

By 1917 (during turmoil caused by WWI which flared up in the eastern part of Galicia), Popielski finally obtained pure synthetic histamine and found that this compound administered subcutaneously to dogs with a gastric fistula induced a potent and dose-dependent gastric acid stimulation (32). This secretion was not affected by vagotomy or scopolamine, indicating that it acts directly on parietal cells independently of vagal nerves and cholinergic innervation. Popielski injected 32 mg of histamine subcutaneously into gastric fistulas of dogs, which responded with copious secretion (about 937.5 ml within 6 h) and extremely high

acidity (166 mM). When given intravenously, the agent produced negligible acid secretion possibly due to the fall in blood pressure in tested dogs.

The results of Popielski's studies on histamine, which he initially presented as small dissertations at the Cracow Academy of Arts and Sciences in 1916 and 1917, during WWI, were finally published in 1920 in prestigious *Pflüg. Arch. ges. Physiol.*(32) (Fig. 5) Popielski showed for the first time that **histamine is the most powerful gastric secretagogue acting directly on parietal cells without participation of secretory vagal or cholinergic nerves**, because its effect persisted after vagotomy and scopolamine and could be demonstrated in a vagally denervated gastric pouch, as well as in a transplanted gastric pouch deprived of autonomic plexuses. As stated by B.P. Babkin in his famous book "*Secretory Mechanisms of the Digestive Glands*" (23), **it is a historical paradox that the secretagogue action of histamine was discovered by a man who spent practically his entire research career under the strong influence of Pavlov nervism in contesting the theory that the gastric digestive glands could be regulated by hormonal or humoral influences**, such as gastrin which is released from the antral mucosa or histamine which is produced locally in the oxyntic mucosa.

Popielski's discovery had enormous impact on thinking of leaders of gastroenterology such as A.C. Ivy, the most renowned US gastroenterologist in

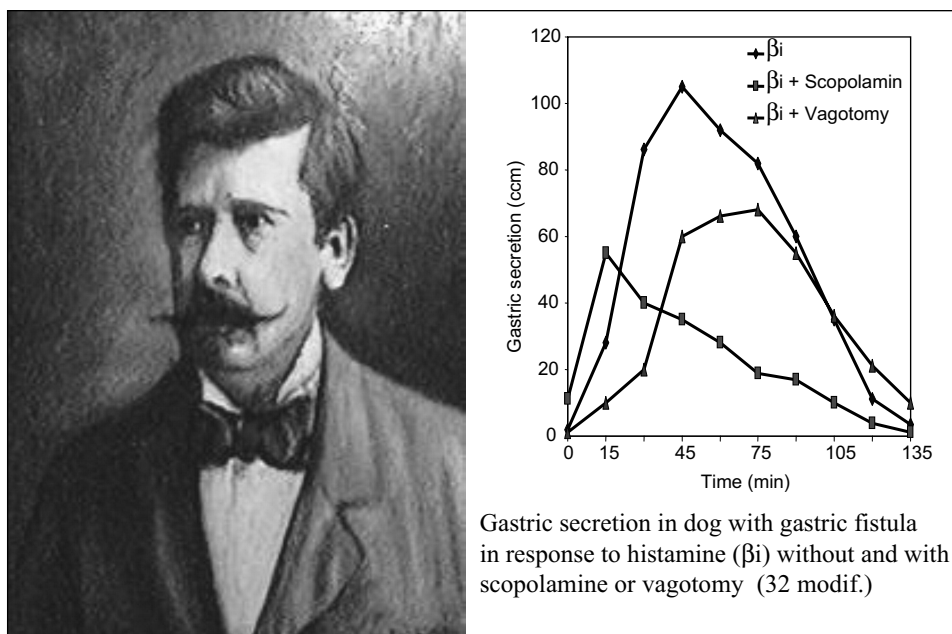


Fig. 5. L. Popielski discoverer of histamine as stimulant of gastric glands, acting directly without involvement of vagal nerves.

the first half of the XX century. Ivy strongly rejected, based on Popielski's work, the hormonal regulation of gastric acid secretion (Edkin's hypothesis) until 1964, when R. Gregory (former pupil of Ivy) of Liverpool isolated, purified, and finally synthesized gastrin, showing that it is a peptide (33, 34). While histamine is a basic amine [2-(4-imidazolyl)-ethyl-amine] formed *via* decarboxylation of histidine, by enzymes present in ECL-cells in the neighborhood of parietal cells. But even at that time when I had an opportunity to meet Ivy in Chicago in 1965, he accepted the fact that gastrin purified by Gregory stimulates gastric acid secretion but expressed his strong belief that histamine, not gastrin, is the major gastric physiological stimulant.

Popielski's discovery should be considered as the greatest achievement of Polish gastroenterological physiology and gastrological history, and also provided a major step in understanding the complex mechanism of gastric acid secretion. His pupils, Carnot, Koskowski and Libert (35) were the first to employ subcutaneous injection of histamine for the stimulation of gastric secretion in humans. Like in Popielski study, the intravenously applied histamine failed to stimulate gastric secretion, probably due to the severe fall in the blood pressure. However, B. Gutowski (36), professor of physiology, at the Warsaw University, was able to show that histamine when given in small doses, not only subcutaneously, but also intravenously, can effectively stimulate gastric acid secretion. Previously, it was thought that only subcutaneous injection was considered to be effective. Hence, this agent became widely used in practical gastroenterology to test gastric acid secretory activity used initially in a small dose of 0.1 mg/10 kg. Thus, Polish discoveries paved the route for practical usefulness of histamine in gastric secretory testing.

Histamine test in examination of gastric secretion in humans

The relationship between the dose of histamine and gastric acid response was widely investigated and again Polish traces can be found in this area, namely the establishment of the so-called "maximal histamine test" in humans. This maximal histamine test was first described in details by K. Kowalewski, a Polish immigrant after WWII, working at the Free University of Bruxelles who published several papers from 1948 to 1958. For this test, he used in humans larger doses of 0.03-0.04 mg of histamine per kg b.w. to achieve gastric acid secretion to reach a maximal secretory capacity in the stomach (37). Four years later, A. Kay of Glasgow repeated and confirmed Kowalewski's test, and published it in 1953 in the *Br. Med. J.* as an augmented histamine test (38). His maximal dose of histamine was also 0.04 mg/kg, which is exactly as in the test studies of Kowalewski. For these reasons, Professor Sródka, the renown Polish medical historian at the Medical College of Jagiellonian University in Cracow, suggests that this test should be called **Kowalewski's maximal histamine test** rather than Kay's augmented histamine test as it is now generally used (39).

Because of the undesirable effects of histamine, it is now usually used in combination with H₁-receptor antagonists such as mepyramide to avoid side-effects. Oleksy and Slowiaczek, (40) proved that the treatment with H₁-antagonists does not affect basal or stimulated gastric acid secretion.

K. Kowalewski resettled to Edmonton, Canada, and his home was always very hospitable for Polish visitors. In difficult times of the communistic regime in Poland, he invited many young, promising researchers from Poland, (including our Institute of Physiology: Prof. J. Bilski, Dr J. Mroczka, Dr J.W. Konturek, Dr Scharf) to the Medico-Surgical Institute of his foundation in Edmonton, which resembled that of Pavlov's in St. Petersburg. His major achievement was to open his physiological department to scientists of other disciplines, especially gastroenterologists and surgeons which resulted in several interesting publications. Some of these included, experimental ulcerogenesis related to experimental ulcerations of Shay's or pyloro-ligated rats, vasopresin-induced ulcers in guinea pigs that were inhibited by H₁-receptor antagonists (e.g. phenergan), and histamine-induced gastric ulcers in guinea pigs perfused for 24 h with histamine. An important aspect of Kowalewski's outstanding research were excellent studies on his original preparation of a stomach that was fully isolated, but perfused by blood from a donor dog, allowing simultaneously measurement of gastric secretory and motor activity for several hours (41-43). The results obtained from such an isolated stomach with fully controlled blood flow, perfusion pressure, oxygen pressure, and intraluminal pressure were published in numerous international journals providing evidence for: 1) the role of gastric *antrum* as inhibitor of gastric secretory function attributed to antrogastrone, which became revealed later to be somatostatin (44); 2) the inhibition of gastric secretion by duodenum ascribed to bulbogastrone, that was revealed later on to be somatostatin, PYY and secretin (45); 3) the role of histamine applied directly to the gastric artery supplying this isolated stomach, and 4) the influence of various drugs and physical factors such as temperature on gastric secretion, etc. The setting of the original Polish preparation of the isolated stomach is shown on *Fig. 6*.

GASTRIN VS HISTAMINE IN GASTRIC STIMULATION

During the second part of the XX century gastroenterology remained under the strong influence of the discovery, isolation, purification, and synthesis of major GI hormones that may affect various aspects of gastric secretions, but the most exciting story concerns gastrin, cholecystokinin (CCK), and secretin, particularly with respect to gastrin-histamine relationship.

After the discovery by Popielski that histamine is the potent direct stimulant of gastric secretion, attempts were made to "revitalize" the "Edkin's hypothesis" of gastrin. Komarov, who joined Babkin (23), in the Department of Physiology at the University of McGill in Toronto, isolated a gastrin preparation, which unlike

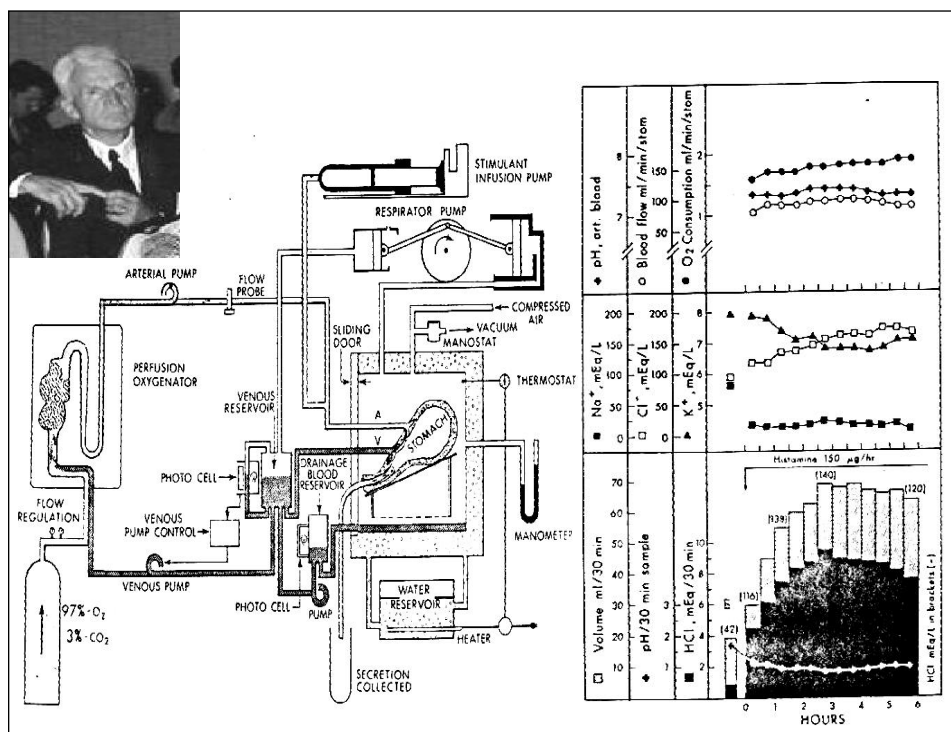


Fig. 6. K. Kowalewski, proponent of maximal histamine test, with his "machine" for studies on isolated stomach (on left) and gastric secretion, blood flow and oxygen consumption (on the right) (Dirtsas K.G., Kowalewski K., et. al. 1966)

previous tissue extracts did not contain histamine yet still potently stimulated gastric acid secretion that could not be inhibited by administration of atropine. Uvnas and his group (46, 47) demonstrated in a series of experiments on dogs with Pavlov and antral pouches as well as esophagostomy, that gastrin release remains under vagal control, as sham-feeding effectively stimulated gastric secretion only in dogs with a preserved and innervated antral pouch. Following antrectomy, when background gastrin stimulation with minute doses of exogenous gastrin or histamine was used to mimic the amounts of these secretagogues released physiologically, sham-feeding was again highly effective, indicating a potentiation of gastrin, histamine and vagus in the stimulation of gastric acid secretion (47).

In the meantime, C.F. Code (49) collected mass evidence for establishing that histamine, rather than gastrin, was the final common chemostimulator of oxyntic cells including that: 1. histamine, as shown by Popielski, acts directly on oxyntic cells; 2. histamine was detected by his assay to be present in large amounts in oxyntic mucosa, released locally by ECL-cells, having histamine decarboxylase to transform histidine by this enzyme into histamine; 3. histaminase, that could

destroy histamine effectiveness, could not be detected in oxyntic mucosa; 4. histamine is released into the blood draining the stomach and into urine following acid secretion and; 5. histamine is released by stimulants of gastric secretion such as food or gastrin. Then, Code described the pathway of histamine metabolism by showing that it is first methylated at its side chain to yield methyl derivatives which are even more powerful gastric stimulants, but when converted to a 1-4-methyl derivatives with methylation at the imidazole ring, they lose stimulatory effectiveness. Code collaborated in this area with C. Maslinski from Warsaw (50), rightly proposed this, and now it is well established, that gastrin and acetylcholine act on histaminocytes (now known as ECL-cells) to release histamine which in turn stimulate oxyntic glands. Gastrin was proposed to stimulate the production, storage, and release of histamine from ECL cells and to aid in the proliferation of these cells (*Fig. 7*).

The promoters of old "Edkin's hypothesis" celebrated their victory with the isolation of 17-aminoacid gastrin both sulphated (gastrin-I) and unsulfated (gastrin-II) and 34 amino acid gastrin (big gastrin), all amidated with phenylalanine at the C-terminus and the G-cells by Solcia in the antral mucosa. Gregory, in collaboration with the ICI Company, produced several shorter peptides, tetra- and pentapeptides, (the last amidated by mistake with β -alanine

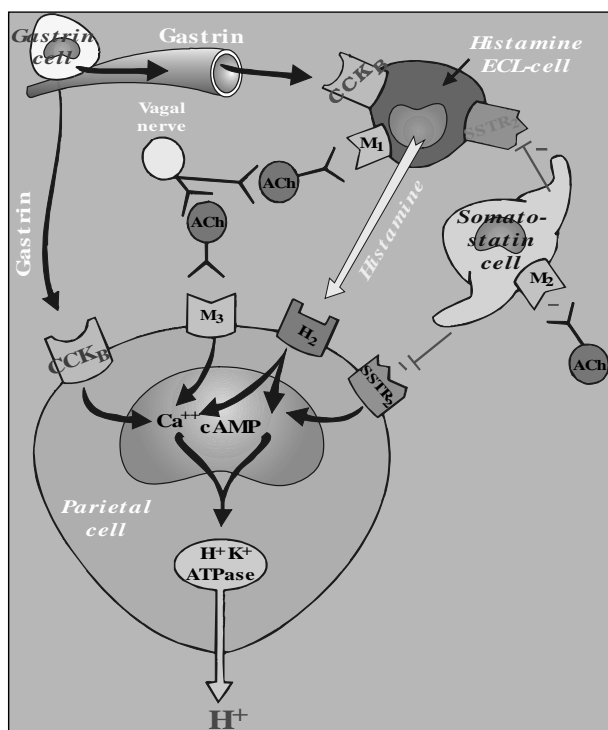


Fig. 7. Histamine released from the ECL cells mediates the action of gastrin on parietal cells. Similarly acetylcholine (ACh) acts via stimulation of histamine release from ECL cells. Both gastrin and ACh exert also direct stimulatory effect on parietal cells via CCK₂ and muscarinic (M₃) receptors on these cells. (Modlin I. et. al., 1998)

and called pentagastrin) have been tested in animals and in man. We were the first to determine the secretory efficacy of these C-terminal gastrin-like active peptides in dogs, and then for the first time on humans to replace the maximal histamine test, that was often accompanied with undesired effects (52-53).

The secretory activity on a molar basis of gastrin and its C-terminal peptides greatly exceeded that of histamine, so that some physiologists, like R. Johnson (a pupil of Grossman) declared that, "there is no room for histamine in gastric acid stimulation" (54). Paradoxically, despite all evidences that histamine is rather a bystander not a real actor in the stimulation of gastric secretion, the histamine concept was revitalized in full strength with a real break-through in the physiology of gastric secretion, which came from pharmacological research on histamine H₂-receptors (55). The discovery by J.W. Black, a Nobel Prize laureate, of the extremely potent and highly specific antagonists of H₂-receptors such as burimamide, then metiamide, and finally cimetidine and ranitidine, opened a new area in the physiology of gastric secretion and in the role of histamine, in particular.

While testing metiamide for the first time in Grossman's lab, I found that this agent caused as strong an inhibition of gastric acid secretion stimulated by exogenous histamine as by vagus (sham-feeding) or a regular meal (56). Code, who at that time visited Grossman's lab, exclaimed, "This is excellent evidence for most important role of histamine in all modes of gastric secretory stimulation". I pressed Grossman to incorporate Code's opinion in the paper describing the effects of H₂-blockade on various modes of stimulation, however, my mentor decided to use a hypothesis that oxyntic cells possess three types of receptors: one for gastrin, one for histamine, and one for acetylcholine; and these receptors interact and potentiate one another to provide the highest rate of stimulation (*Fig. 8*). Inhibition of one receptor reduced the responses of the two others to their proper agonists so that gastric inhibition occurred. The same phenomenon was studied in humans stimulated by a meal (using intragastric titration). We observed in man a similar high inhibitory efficacy of H₂-blockers using a meal, pentagastrin or sham-feeding, but this time we explained that histamine is the most important mediator of gastric acid secretion, while the other secretagogues act *via* the stimulating release of histamine from ECL cells (57). Thus, the struggle that paved the way for the physiological role of histamine as the final common chemostimulators initiated by Popielski and championed for decades by Code finished with a victory for the histamine concept. This was further supported by Waldum et al. (58) finding that gastrin and meal released histamine into the gastric mucosa and drained in blood from the stomach. Thus, Polish contributions are quite significant in the discovery of a major pathway in gastric acid secretion. It should be added to our recent finding (59) that infection with *H. pylori* increases the histamine content in the gastric lumen. This dimethylated derivative of histamine, with a methyl group at side chain rather than at the imidazole ring, is an unusual analog for being highly effective, not

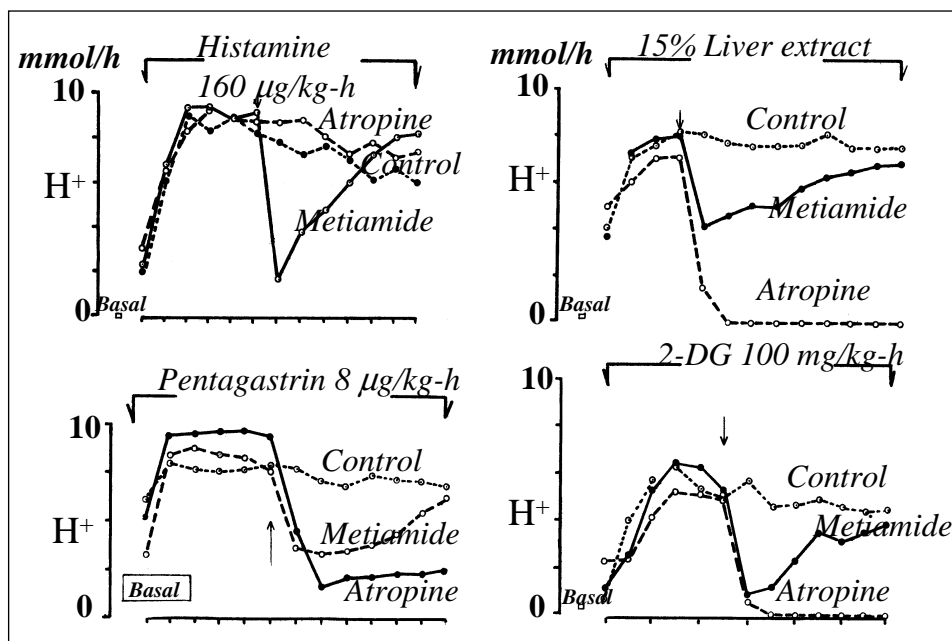


Fig. 8. Effect of H₂-blocker (Metiamide) or cholinergic blockade (atropine) on gastric H⁺ secretion from the gastric fistula in dogs following stimulation with histamine, pentagastrin, peptone meal and 2-deoxy-D-glucose (57). Arrow indicates the administration of Metiamide or Atropine. (Konturek S.J. et. al., 1974)

only in the stimulation of gastric acid secretion, but also in the release of gastrin in the gastric lumen, which stimulates the growth of *H. pylori* and adds to the stimulation of acid secretion (60).

CRACOW CENTER OF GASTRIC RESEARCH ON GASTRIC SECRETION

The continuation of studies started by Popielski in Lvov related to histamine was performed in the Cracow Department of Physiology of the Jagiellonian University, and then at the Academy of Medicine directed by J. Kaulbersz during the period of 1948-68, and then by S. J. Konturek from 1969 to 2002. It was found that vagal stimulation by sham-feeding increases the intragastric release of histamine supporting the earlier concept that vagal nerves enhance gastric acid secretion, at least in part, by the release of histamine. This was amply confirmed by Waldum and Petersen (58) showing that all forms of gastric secretory stimulation increase histamine level in the blood leaving the stomach. Paradoxically, *H. pylori* infected stomach produces large quantities of N α -methyl histamine, which is a potent stimulant of gastric acid secretion and

also potent releaser of gastrin that in turn has trophic action on the germ in the stomach.(59) (Fig. 9).

Here, in Department of Physiology the technique of Shay's rat gastric ulcerations was developed (60) and evidence was provided for the influence of vagal nerves and various hormones, especially pituitary, thyroids, and adrenals on gastric ulcerations. We also developed a technique to produce gastro-duodenal ulcers by continuous 24 h infusion of either histamine or pentagastrin in cats, which mimicked the ulcerations that develop in human gastrinoma conditions, and also for investigating the pathogenesis of ulcerations, particularly the role of the duodenum in ulcerogenesis (61).

Our Institute was first in Poland to apply test with maximal histamine stimulation (62) and then pentagastrin tests for examining the maximal secretory capacity was developed in humans for clinical purposes, establishing the range of secretory rates, age and gender factors, and vagal innervation etc. (53). Following surgical or medical vagotomy (through the use of large doses of atropine), the gastric response to histamine and pentagastrin used in gradually increasing doses in humans tended to decline at lower physiological levels of stimulants, but failed

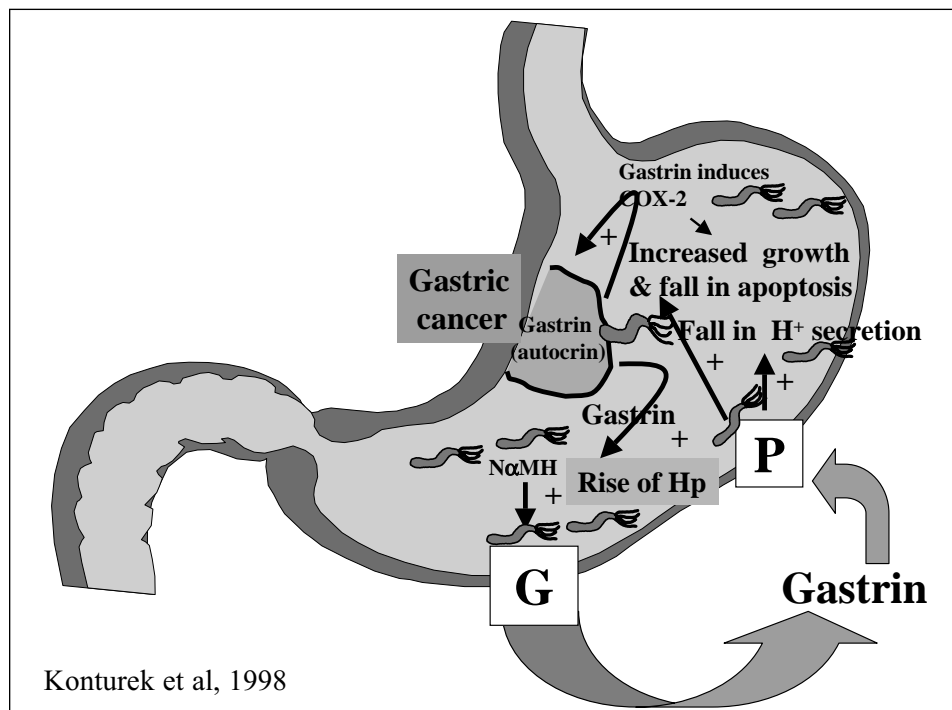


Fig. 9. Role of gastrin released from the G-cells and gastric cancer in *H. pylori* infected stomach releasing N α methyl histamine (N α MH) and COX-2 expression in gastric cancer and in *H. pylori*-induced gastric corpus atrophy.

to alter in response to maximal stimulation of gastric secretion (63, 64). The results originating from our team were used as "norms" in testing gastric secretory activity for the evaluation of hyperchlorhydria or achlorhydria and atrophic gastritis in deciding what type, if any, gastric surgery (vagotomy, antrectomy or gastrectomy) should be performed. Thus, the secretory studies had an important practical value and, what is noteworthy, they were published either in Polish medical journals or in the most renowned international gastroenterological and physiological journals, such as *Gastroenterology*, *Am. J. Dig. Dis.*, *Am. J. Physiology*, *J. Physiol.*, *Gut*, *Digestion*, *Scand. J. Gastroenterol.* and others.

Due to numerous collaborative contacts, a close collaboration was established with numerous GI centers in the USA such as: the Gastroenterology Unit at the Veterans Administration Center in Los Angeles, formerly directed by M.I. Grossman, which exists now as CURE (Center for Ulcer Research and Education), and directed by G. Sachs; the Department of Surgical Physiology, University of Texas led by J.C. Thompson in Galveston; the Department of Physiology of Oklahoma Medical Center, directed by J.E. Jacobson; the Department of Physiology in Houston, Texas, co-chaired by Johnson; the Department of Experimental Medicine of Rochester University in Rochester, New York, directed by W. Chey; the Department of Bioscience of the Upjohn Company in Kalamazoo, Michigan, led by A. Robert; the Department of Biology of Neoplasms of Tulane University in New Orleans, Louisiana, directed by A.V. Schally, a Nobel prize winner; the Department of Biochemistry of Shizuoka University, led by N. Yanaihara; the Department of Biochemistry of Copenhagen University, chaired by J.F. Rehfeld; the Department of Medicine of Erlangen-Nuremberg University at Erlangen led by E.G. Hahn; the Department of Medicine of Munster University chaired by W. Domschke; the Department of Chemistry at Karolinska Institute, chaired by V. Mutt and others.

The Institute of Physiology in Cracow, due to the above collaborative contacts, could carry on numerous projects related to gastric secretion and pathogenesis, the treatment of peptic ulcers, and acute gastric damage induced by a variety of topical irritants including ethanol, non-steroidal anti-inflammatory agents, infection by *H. pylori*, and carcinogenesis. About 540 papers related to gastroenterology have been published in internationally recognized journals, and several editions of the *Gastrointestinal Physiology* and of *Clinical Gastroenterology* handbooks appeared in Polish, English, German and Japanese; giving over 10000 citations of these papers during the previous decades. This created favorable conditions for students and researchers for the exchange between Poland and foreign research centers which generously supplied the Cracow Institute of Physiology with necessary equipment, chemicals, journals, and books allowing the institute to perform research on a large scale, with only small government support (*Fig. 10*).

In addition to its work on gastric secretory stimulators, the research at the Institute of Physiology investigated gastric inhibitors. As mentioned in the



***From left; Dr W. Bielanski, Prof. T. Brzozowski, Prof. P. Thor,
Prof. S.J. Konturek, Prof. W.W. Pawlik, Prof. A. Dembinski and Doc. J. Bilski***

Fig. 10. Team of researchers working at the Institute of Physiology of Academy of Medicine and then Jagiellonian University College, Cracow

introduction of gastric secretion, the gastric mucosal integrity results from the balance of respective stimulatory or protective and inhibitory or irritating factors. In the early 1950s, the work under supervision of J. Kaulbersz was continued on urogastrone, whose research started during WWII in the USA. In studies with urogastrone, we found that its release into the urine is gender-dependent which increases in female particularly during pregnancy. In contrast, it falls after disorder of the pituitary-adrenal axis, as both hypophysectomy and adrenalectomy result in a marked decrease in production of urogastrone (65). Originally, it was believed that urogastrone was just an enterogastrone that was released in urine and was shown to have potent gastric inhibitory qualities, however, it exhibited even stronger ulcer healing properties. In fact, together with T. Radecki, we noticed that the anti-ulcer activity of urogastrone in Shay's rats and dogs with Mann-Williamson ulcerations, exceed that which was obtained with simple gastric acid inhibition, which contrasted with the rigid conclusion of Shay that the anti-gastric efficacy of urogastrone can be attributed solely to its gastric inhibitory effectiveness. After a few decades when urogastrone was purified and found to be a 53 amino-acid peptide named epidermal growth factor (EGF), and produced predominantly by salivary glands, we found, in

collaboration of H. Gregory of ICI, UK that in addition to potent gastric inhibitory action on gastric secretion, EGF-urogastrone displays a prodigious capacity to enhance the proliferation of gastric surface epithelial cells, especially when the mucosa is damaged, and the specific receptor for EGF, located on the baso-cellular membrane, is uncovered. In addition, we found that EGF is highly effective in protecting the gastric mucosa from acute damage exerted by ethanol or acidified aspirin (66). Thus, our earlier observations that urogastrone was more effective in its anti-ulcer than in its anti-secretory activity could originate from its gastro-protective and mucosal recovery effects of EGF.

In another study (67) enterogastrone was extracted in accordance to the Gray & Wiczorkowski technique, which revealed that its highest amounts are found in the upper portion of small bowel, particularly in the upper duodenum and some amount was detected in the distal ileum and proximal colon. The extracted substance was named enterogastrone, which was derived from entero/n, gastr/on and chal/one proposed by Kosaka and Lim in 1930 (68). Enterogastrone was found to be released by fat ingestion and inhibited secretion in an autotransplanted pouch, however, the effect could not be mimicked by fat itself or lymph collected from a thoracic-duct fistula. Therefore, enterogastrone was believed to be responsible for this gastric acid inhibition by fat. At the same time, and independently of Kosaka and Lim, Walawski (1928) from the Warsaw Department of Pathophysiology, found that biodialysates, obtained first by extracting the active principle from the proximal intestine and colon, caused a potent inhibition of histamine-stimulated secretion (69). Thus, another finding provided by a Polish researcher, provided evidence for the presence of potent gastric inhibition induced by extract of duodenal or proximal colon. It should be emphasized that both the enterogastrone-like substance and biodialysate could affect gastric secretion after parenteral administration, at least in part, due to pyrogenic impurities so the results should be assessed with caution. After 5 decades of the enterogastrone or biodialysate discovery, it was found that numerous hormonal peptides are capable of inhibiting gastric acid secretion, and the term "enterogastrone" was coined to identify undefined intestinal factors which inhibited gastric acid secretion that could be ascribed to such peptides as: peptide YY (PYY), neurotensin, secretin, somatostatin, cholecystokinin (CCK), glucagon-like peptide (GLP)-1 and (GLP-2) and leptin. The most likely candidates of enterogastrone include CCK and PYY. CCK is released in the duodenum and the upper portion of the jejunum by fat and protein digestion products to mainly excite CCK₁-receptors (with a high affinity to CCK than to gastrin) and partly CCK₂-receptors (with a high affinity to gastrin than CCK) on sensory nerve terminals to activate-brain-stomach-gut axis resulting in inhibiting gastric acid secretion and slowing gastric emptying. CCK binds to the CCK receptor of somatostatin-producing (D) cells to inhibit gastric secretion and this is predominant effect in relation to the weak stimulation of CCK₂-receptors on ECL-cells to release histamine and stimulate oxyntic cells (46, 70,71). Obviously,

the first effect predominates as the final outcome of action of CCK on the stomach rather small gastric acid stimulation due to simultaneous release of somatostatin, which is a potent inhibitor of gastric acid secretion. In contrast to CCK, PYY was shown by us to be released by distal ileum and colon, and has only inhibitory action on gastric secretion, perhaps by fat digestion products moving to distal portion of gut and releasing PYY (45).

CONCLUSIONS

1. Gastric acid secretion results from the interaction of gastric secretory stimulants and inhibitors and while the later predominate under basal conditions, the former prevail postprandially.
2. The most potent stimulant of oxyntic cells is histamine as indicated approximately 80 years ago by Popielski, who, despite being the most vigorous opponent of hormonal stimulation of gastric oxyntic gland, discovered that histamine is the major gastric acid secretagogue.
3. Histamine is released by food and other gastric secretagogue from the ECL-cells, whose activity is modulated by non-histamine-gastric secretagogue (gastrin, acetylcholine) and by inhibitors of gastric secretion, namely somatostatin.
4. Peptic ulcer, which is most often results from *H. pylori* infection, may be accompanied by hyperchlorhydria, that can be detected by the maximal histamine test, originally introduced by K. Kowalewski; and this is associated with hyperhistaminemia, originating from excessive stimulation of ECL-cells by increased amounts of gastrin, as well as N α -methyl histamine elaborated in excessive amounts from *H. pylori* infected stomachs.

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Received: November 15, 2003

Accepted: December 15, 2003

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