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THE SHORT HISTORY OF GASTROENTEROLOGY

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In this paper research on the stomach and bowel physiology is presented in a historical perspective. The author tries to show how digestive processes were interpreted by the ancients and how they tried to adjust them to the dominating humoral theory of disease. It is pointed out that the breakthrough which created a new way of understanding of the function of the digestive system was made by Andreas Vesalius and his modern model of anatomy. The meaning of acceptance of chemical processes in digestion by iatrochemics representatives in XVII century is shown. Physiological research in XIX century, which decided about a rapid development of physiology, especially the physiology of the gastrointestinal tract, is discussed. Experiments were performed by all main representatives of this discipline: Claude Bernard, Jan Ewangelista Purkyně, Rudolph Heidenhain and especially Ivan Pavlov, who, thanks to the discoveries in the secretion physiology, explained basic functions of the central nervous system. The XX century was dominated by the research showing the important role of the endocrine system and biological agents in the regulation of secretion and motility of the digestive system. The following discoveries are discussed: Ernest Sterling (secretin), John Edkins (gastrin) and André Latarjet and Lester Dragstedt (acetylcholine). It is underlined that Polish scientists play an important role in the development of the gastroenterological science - among others; Walery Jaworski, who made a historical suggestion about the role of the spiral bacteria in etiopathogenesis of the peptic ulcer, Leon Popielski, who stated the stimulating influence of histamine on the stomach acid secretion, Julian Walawski, who discovered enterogastrons - hormones decreasing secretion. As a supplement, there is the list of achievements in the field of the physiology and pathology of the gastrointestinal tract awarded with Nobel Prize and the list of most important Polish papers in this field.

Key words: *history of medicine, gastric secretion, gastroenterology, stomach, pancreas, liver and bile, and bowel physiology*

The first medical agent had appeared long before man entered history. There is no doubt that the appearance of the first medicine was connected with food intake. Early man, eating fruits, herbs and roots, felt stunned, relieved, and fell asleep, might have also vomited or suffered diarrhea and acute diseases, some of which could have a fatal outcome. At some stage food agents became medicines.

Since prehistoric times, shamans have thought that particular organs are the seats of specific spiritual forces. These forces control body processes in a mystical way. There are many references to digestive processes, digestive system pathology, condition and meaning of food, and magical procedures contributed to nutrition in the oldest papyruses (esp. Papyruses of Ebers), on the holy pages of the Bible, in ancient Chinese and Indian medical papers and especially in classical manuscripts of Greeks and Roman physicians.

Greeks had a special respect to food digestion. According to their theories, food in the stomach was changed to the chyme and then to four basic systemic fluids - blood, mucous, bile and so-called black bile (actually - blood splenic). That theory became a foundation for the hypothesis based on humoral pathology, which tried to explain the essence of pathological changes in the organism. Hipocrates (460-377 B.C.) named a digestion as "pepsis". Alexandrine researchers from Greek medical school left some precious descriptions of gastrointestinal tract, although they focused mostly on the brain anatomy. Herofilos from Chalkedon (355-280 B.C.) distinguished a short part of the small bowel following the stomach and named it duodenum because its length amounted to 12 Greek measures. Erasistratos from Keos (circa 310-250 B.C.) established a theory that blood is made from food after it is divided into useful and worthless parts. Then food mixed with blood gets to the right chamber of the heart and is used to nourish lungs. Through veins blood is transported further to nourish the rest of the organs. That concept was accepted later by Galen.

Claudius Galen (circa 130-200), who lived at the end of ancient times and who undertook great Hipocrates' concept, is thought of as the first creator of the entire functional human body system theory. Galen assumed that digestion starts in the stomach where food is first minced. Then it goes to bowel where it is decomposed and then is transported to the liver through the vessels, thanks to the sucking ability of veins, and with the help of "*pneuma psychicon*" and animal warmth. In the liver food is changed into blood, which is pumped to the hepatic vein and further through the lower caval vein to the heart. Galen thought that the blood level is directly proportional to the amount of food intake. That theory existed till the Renaissance. However, Galen's concept of body fluids production as processes of brewing and "chemical boiling" of raw or fermented foods ("*apepsis*") survived till the heyday of the iatrochemical school in the 17th century.

Early digestion problems were connected mainly with stomach diseases, influences of "bad" systemic fluids (depending from school - *pneuma* or *archeus*) or even with having one's vital forces possessed by the devil. Because of the lack of precise medical knowledge, inability to recognize and diagnose diseases and to provide a surgical treatment - physicians had only herbs to manage gastrointestinal problems. Herbs were likely to be used especially in acute diseases with symptoms like colic pain, vomiting, diarrhea, melenea, constipation and flatulence. One can read about that in the books of great Arabian doctors of the end of the first *millennium* of our era. Still Razes (about 850-923) and especially Avicenna (980-1037) abided by Galen theories and it is very hard to find their own, original concepts of physiology and pathology of digestion. Paracelsus (1443-1541) first had some reasonable attitude to the pharmacological side of internal diseases, including gastrointestinal problems. He came from Switzerland and he was the greatest doctor at the turn of the Middle Ages and the Renaissance. First of all, he developed the thesis that disease is a natural phenomenon connected with human body. He claimed that it results from several conditions like low life standard, inappropriate lifestyle, and, what is particularly interesting, inadequate nutrition. Thus, he recommended dietary treatment according to the signatures theory, with natural, plant medicines. According to this theory failure organs should be treated with the plants that resemble them physically, e.g. jaundice or liver diseases should be treated with yellowish leaves of saffron.

Scientific foundations of medicine

The breakthrough in the medical world as well in physiology and pathology of the gastrointestinal tract was the appearance of Andreas Vesalius (1514-1564). In his great work *De humani corporis fabrica* (1), published in seven volumes in 1543, this genius Flemish destroyed the obsolete monument of anachronistic Galenic anatomy and gave medicine the scientific foundations. Apart from numerous corrections and factual descriptions of different organs, it also included the correct description of gastrointestinal tract, based on human autopsies. But it must be said, though, that Galen's idea of the construction of the system was the closest to the real pattern. In Vesalius' work there is no four lobules of liver, double bile duct and no totally absurd canal, connecting the stomach with the spleen through which "undigested" part of food goes to the spleen where it is changed into hypothetic black bile. Since the publishing of *De humani corporis fabrica* we have had the whole digestive system described, from the oral cavity to the large bowel.

Further detailed corrections in the respect of natural and topographic anatomy were made by Vesalius' students. In 1605 Caspar Bauhin (1560-1624) described the ileocolic valve and correctly explained its function of preventing the intestinal contents from coming back from the colon to the small intestine (2). In 1642

Johann Georg Wirsung (1600-1643) discovered the pancreatic duct in man, and Francis Glisson (1597-1677) in 1654 carried out the most detailed investigations of the liver anatomy till then (3). Because of this fact the liver fibrous sack has been named after Glisson. 23 years later Johann Conrad Peyer (1653-1712) was able to identify duodenal glands (4), and later, in the middle of the 18th century, Johann Nathanael Lieberkühn (1711-1756) - mucous glands of the small intestine (5), so called later Peyer's patches.

Modern iatrochemistry

The beginnings of modern iatrochemistry are connected with the outstanding Flemish physician and chemist - Jan Baptiste van Helmont (1579-1644) (6), who discovered the carbon dioxide (gas silvestre). According to him, living processes are regulated by specific chemical substances, which he called the ferments, and he reduced all physiological phenomena occurring in the body to fermentation processes. Certainly, reducing living processes only to chemical phenomena was a mistake but it was an important reaction to the extremely morphological concept of medicine presented by Vesalius' school. Vesalius' followers totally ignored chemical processes in the body and all physiological effects explained as a mechanical reaction. Van Helmont was the first who paid attention to chemical reactions occurring in living organisms. In his times his theories were ignored. Van Helmont's work is described in a witty way as introducing some intellectual ferment to medical science.

He was especially interested in the processes of the stomach and intestine digestion. He divided them to five parts. In the stomach food is decomposed into simple agents through acids and ferments. The second stage takes place in the duodenum, where the earlier prepared food is neutralized by alkali and bile ferments. The third stage occurs in the liver where chyme changes into blood and then blood into bile. Further van Helmont described a specific "head phase", in which, under the influence of blood, "archeus", which invigorates all body parts, is developed. The fifth stage applies to the particular body organs, where "meat", the most basic component of all organisms, is produced. A new look on physiological reactions, seen by Van Helmont by the prism of digestion, gave the most important role in the process of digestion to ferments and took it away from warmth. It is fermentation that produces warmth, carried by the pulse and breathing through the entire body (7).

Beginning of digestive physiology and medicine

The theory of disease proposed by Jan Baptiste van Helmont, based on ferments and digestive functions, is also very original. According to him, as the result of the actions of the "influencing spirit" in the stomach harmful acids, producing in fermentation, are gathered. They are responsible for disturbances.

Ideas about the essence of physiological and pathological processes van Helmont included in his published post mortem work, titled "*Ortus medicinae*" (1648). His concepts were definitely rejected by Franciscus de la Boë Sylvius (1614-1672) - professor of medicine in Paris and Leida. He also thought that fermentation is a basic physiological process in the body but much more precisely and specifically described its meaning in the digestion process. He was first to describe the digestive ability of saliva, and in doing so to point to the oral cavity as the first place of the digestion process. When food enters the stomach, it is subjected to the gastric acid juice and then in the intestine to the alkali of bile. Disease, according to Sylvius, is the consequence of disturbances of the fermentation processes. When the balance between acidity and alkali is upset, the so called *acrimonia* are produced, which gather in fluids and tissues. Diseases are divided into resulting form the excess of acids or their strength, or the excess of alkali or their strength. It was a totally new, significantly expanded humoral theory of disease. Apart from blood, mucus, bile and black bile there appear new physiological fluids like saliva, pancreatic juice, lymph and the animal spirit, which was a fluid circulating in peripheral nerves. The theory of the animal spirit he took from Harvey's concept of blood circulation of which he was a fervent supporter.

Sylvius gathered around himself a great number of students who continued his work. One of them - Regnier de Graaf (1641-1673) investigated functions of the pancreas. He applied chronic fistula to the dog model and then he showed the results in his work *De succi pancreatici natura* (1664) (8) describing the mechanism of the secretion of the pancreatic juice (according to him - the pancreatic acid). Regnier de Graaf and his master thought that bile as well the pancreatic juice originate from digested and fermented food (9).

A very important, though little known by us, was the doctoral thesis from 1777 by Edward Stevens (1755-1804), titled *De alimentorum concoctione* (10). Stevens came from the West Indies. He came to New York for medical studies. In 1774 he graduated from Kings College (present Columbia University) and then he took additional medicine classes in Edinburgh University, where soon he became the chairman of the Medical Students Society. In his doctoral dissertation he included all up to date information from the field of digestion and physiology of gastrointestinal tract. He also presented the results of his own original experiments. He described in detail - in comparison with his times - the physiological function of the whole gastrointestinal tract.

In the second half of 18th century there appeared another man of merit in the field of the stomach physiology. It was Lazzaro Spallanzani (1729-1799), professor of natural history in the Padua University. This outstanding scientist entered history mainly because of his bad attitude to the theory of the abiogenesis but, what is less known, he has its place in the gastrology history because of his simple experiment. He obtained the stomach juice from people with a little sponge on a thread, which people swallowed and which was then removed. The

experiment showed that the stomach juice dissolves meat but does not dissolve a flower (11). This great scientist was not a doctor, though he was a biologist, logician, metaphysician, geometrician, Hellenist and a Catholic priest. He was very critical about the ongoing discussion between iatrochemics and iatrophysics about the mechanism of digestion. He complained to doctors that they were losing their energy on fruitless guessing at the mechanism of digestion, instead of trying to investigate this phenomenon. Together with another professor from the Padua University - Giovanni Scopoli, Spallanzani performed cyclic experiments, which allowed him to formulate a thesis that the stomach produces other digestive substances apart from acid, probably hydrochlorids (many of Spallanzani writings contained polemic passages in anonymous letters to G. Scopoli: *Lettere due…al Sig. Dottore Gio. Antonio Scopoli… and Lettere tre…al chiarissimo Signore Gio. Antonio Scopoli, professore di chimica e di botanica…*, Modena 1788).

Start of modern gastroenterology

The clinical investigations started at the beginning of 19th century concerned the stomach functions and its chyme. A pioneer of this movement was the American physician William Beaumont (1785-1853), a student of the prestigious London and Edinburgh Universities. He worked in the Army Hospital in Fort Mackinok on the American-Canadian border. One day a patient was transported to the hospital with an abdominal gunshot wound with the stomach fistula. Beaumont who was thought of as a very good surgeon, healed the wound leaving - with the permission of the patient - the stomach fistula. That fact allowed him to observe for several years the interior of the stomach and examined its contents. In July of 1822 Beaumont started the first modern experiments of the physiology of digestion. They resulted in the isolation of the hydrochloric acid from the stomach juice, the discovery of the connection between the stomach secretion and emotional changes and the first attempt of describing of the stomach motility. His book in short titled *The Physiology of Digestion* (12) was a breakthrough work in the field of experimental gastrology.

Beaumont's hypothesis of the hydrochloric acid as the main ingredient of the stomach juice was definitely confirmed by a doctor from London's Gray's Hospital - William Prout (1785-1850), on the meeting of the Royal Society in London, December 11th 1823. He had found the hydrochloric acid in the stomachs of several species, e.g. dogs, rabbits, horses, cats, hares and of course in humans. He presented the results in his great work titled *On the Nature of the Acid and Saline Matters*, published soon in 1823 (13).

In the 19th century the foundations of the totally new physiological school were created. It happened mainly thanks to the support of French and German scientists which were connected in those times with the greatest schools and institutes. François Magendie (1783-1855), professor of pathology in College de

France and the best student of the great pathologist - Xavier Bichat, was the creator of the new French physiological school. He belonged to the group of men who opposed the concept of vitalism. Physiological functions were for him clearly physical and chemical reactions taking place in the organism. Despite the fact that he was a pathologist, he was not only interested in morphological or static aspects of diseases. He was the first to develop disease and pathological symptoms on the animal models and then described them. Those investigations allowed him to become the author of the modern trend - experimental physiology. As far as the field of the gastrointestinal tract physiology is concerned, he gave in 1813 a detailed description of the swallowing and vomiting mechanism (14) and in 1844 showed (in unpublished data) that food first digested in the bowel is transported through the portal vein to the liver.

Claude Bernard (1813-1878), student of Magendi, known as the creator of modern physiology, at his times was the most outstanding French physiologist. First he became a professor of physiology in Parisian Sorbona and then, after his master, he took over the Department of Physiology on College de France. Bernard was the unquestionable master of experiment. During his life he discovered several physiological phenomena. He determined new directions in physiology, like the study on endocrine secretion, neurophysiology, the methodology of experiments and experimental pharmacology, which became shortly new medical disciplines. Examining physiological function of the liver he discovered its ability to synthesize and store the glycogen. In 1849 he performed the first glucose injection into the fourth chamber of the brain (so called the Claude Bernard injection), causing a rapid and significant increase of the sugar blood level, the result - as he assumed - of a sudden glycogenolysis in the liver. This discovery became the basis of the thesis that all glands besides the external secretion secrete also some special substances directly into blood. These processes he described in the thesis presented in 1853 to the Faculty of Sciences about function of the liver as the endocrine secretion (15). His very impressive achievements include, chronologically, the investigations of the enzymatic functions of the liver and the pancreas, the discovery of the digestive function of the pancreas (1856) (16) and the reflux of the bowel contents to the pancreatic duct, which causes severe changes in the gland as an acute inflammation (in the experiment he injected bile mixed with oil into animal pancreatic ducts).

The greatest the 19th century physiological school was established in Germany. Its creator was the great Czech scientist, doctor and social activist - Jan Evangelista Purkyně (1787-1869). He was professor of physiology and pathology in the Breslau University. He was known as a wide-ranging investigator. Beside his own disciplines he was very concerned with anatomy, histology, embryology, anthropology, biology but also philosophy and philology. He wrote his works in Latin, German, Czech and Polish. He was the creator of the first institute of experimental physiology, in which he performed his greatest discoveries -

pioneering works in physiology and cytophysiology, e. g. conducting fibers of the heart named after him.

All the best physiologists of the first half of the 19th century came from Purkyně school. Among them were Johannes Müller, Karl Ludwig and Herman Helmholtz. In the field of gastrointestinal tract physiology the greatest achievements laid Karl Ludwig (1816-1895) (17). First he was professor of Comparative Anatomy Department in the University in Marburg, then professor of Anatomy and Physiology in the Universities of Zürich, Vienna and Leipzig. His most important achievements concerned e.g. the filtration theory of the urine secretion, diagnosing and explaining the essence of the heart chamber fibrillation, describing (together with Ilia Cyon) the cardiovascular reflux after the aortal branch of the vagal nerve irritation and the application of a kymograph (which serves to measure the arterial blood pressure) in physiological experiments. It is worth remembering that Ludwig was the author of a very detailed prescription of the saliva gland innervation and the theory of the saliva secretion (18).

Other important German physiologists from the end of XIX century include Ernst von Brücke (1819-1892) and professor of physiology of the Breslau University - Rudolph Heidenhain (1834-1897). Von Brücke by the end of his carrier had isolated a pure pepsin (19). This achievement was one of those that started the era of the modern medical diagnostics. Heidenhain who was working at the beginning of his carrier on the function of endocrine glands in 1866 observed that secretion always causes structural changes in the gland. Examining the gastric secretion in 1878 he found and described three types of cells in gastric mucosa: chief or zymogenic cells which release pepsin, parietal cells secreting the hydrochloric acid and epithelial cells (20).

The isolation of the spiral, rod bacterium, which is characteristic of the stomach cancer and ulcer disease, was another very important discovery. It was done in 1889 by a Polish scientist - professor of the Jagiellonian University - Walery Jaworski (1849-1924). He called the newly discovered bacteria as *Vibrio rugula* and found them also in the sediment of specimen from the gastric contents (21). Further investigations confirmed the presence of the bacteria in the stomach. In 1983 two Australian scientists from Royal Perth Hospital - Robin Warren and Barry Marshall proved that the stomach mucosa can be colonized by the spiral bacteria named *Helicobacter pylori* which are capable of developing inflammatory changes and cause disturbances in the gastric juice secretion.

From the scientists living at the turn of the 19th and 20th century first of all Ivan P. Pavlov (1849-1936) - great Russian scientist, professor of pharmacology and then professor of physiology in the Military Medico-Surgical Academy in St. Petersburg needs to be mentioned. He was a student of the greatest German physiologists - Heidenhain and Ludwig. As the main subjects of his investigations he took the physiology of the gastrointestinal secretion and higher neural functions. His achievements in both fields were tightly interconnected. They were possible thanks to Pavlov's combining original ideas with surgical

skills. His first great discovery was describing the neurally stimulated secretion from the pancreas in 1888. Already as a professor in the Experimental Medicine Institute of St. Petersburg Academy he introduced a basic model of the investigation of the stomach secretion modified by the implications the old model. In 1897 Pavlov worked out an original surgery technique allowing the isolation of a part of the stomach, saving not only blood supply but also with innervation (22). Thanks to that it was possible to investigate functional changes in the stomach under different nerve stimuli. That model carries the name of the "small Pavlov stomach". This model with an esophageal fistula (enabling the so called the "sham feeding": swallowed food leaving the esophagus through the fistula) helped him to observe the secretion of the gastric juice under the influence of taste stimuli, which was named the reflex or nervous phase of secretion and differentiated from the secretion under the influence of food in the stomach, which was called the chemical phase of secretion. Following his great achievement in this field was the investigation concerning the intestinal juice and the confirmation of the theory that its enzymes activate proteolitic agents of the pancreatic juice. In 1899 Pavlov introduced the name "enterokinase" for the enzyme of the intestinal juice (23).

The greatest achievement of Pavlov was establishing the influence of the nervous system on the stomach and the pancreas secretion and explaining the mechanisms which regulate those processes. Pavlov's investigations of the physiology of the gastrointestinal secretion laid the foundations of the theory of *nervism* according to which functions of an organism are developed not only during the filogenetic processes but they are also preserved from generation to generation. In his famous experiments on dogs with gastric fistulas he observed and confirmed the fact that some behaviors may be learned by animals and - appropriately increasing stimuli - may be saved for a long time and preserved as a classic reflex. He distinguished the two phenomena and named the first the "unconditioned" and the second one the "conditioned" reflex (24). Pavlov's experiments were not only so precious because of their outstanding discoveries but maybe first and foremost because they opened the organism to further objective investigations. Pavlov was awarded Nobel Price in 1904 for his achievements in experimental gastroenterology and especially for the original invention of the vagally innervated gastric pouch called according his name "Pavlov's pouch" that secretes gastric acid in similar manner as the main stomach from which it was prepared (*Table 1*).

The epoch in which Pavlov led his memorable study was also times of the exploration of new biological agents discharged by particular tissue cells directly into blood. At the beginning of the 20th century they were called hormones, the name coined by English physiologists William Bayliss (1860-1924) and Ernest Starling (1866-1927) from the University College in London. They introduced the conception of the chemical (not only nervous) regulation of the secretion processes in the digestive system. In January 1902 they suggested that there exists

Table 1. Nobel Price Winners in the gastroenterology

1.	1904 - **Iwan Pavlov** (1849-1936). Prof. of the Military Medical Academy in St. Petersburg. Chief of Departament of Physiology in Institute of Experimental Medicine in Petersburg. Nobel Price awarded for researches on the digestive processes and for introducing a new scientist discipline - physiology of superior neurological function;
2.	1926 - **Johanes Andreas Fibiger** (1867-1928). Prof. of pathology in University in Kopenhagen. Nobel Prize awarded for discovering the etiopathogenetic agent causing the stomach cancer. It supposed to be larva of Spiroptera neoplastica (changes found in rats stomach mucosa occuring after feeding them with infected cockroaches, appeared to be not neoplastic but inflamatory and degenerative);
3.	1936 - **Sir Henry Hallet Dale** (1875-1968). Director of National Institute of Medicine Study in Hampstead and prof. of chemistry in Davy and Faraday Laboratoriums in Royal Institute in London. Nobel Prize awarded for isolation of acetylcholine and determining its role in transmission of stimuli between neurons and effectors.
4.	1988 - **Sir James Whyte Black** (born in 1924). Prof. of pharmacology in University in London. Nobel Prize for researche on H_1 receptor blockers and for discovering a specific substance inhibiting hydrochloride acid secretion by parietal cells by antagonism of H_2 receptors in the stomach.

specific chemical transmitter in the duodenal mucosa which can stimulate secretion of the pancreas. Further they suggested the presence of other mechanisms, different from the ones in the nervous system, which can regulate physiological reactions of the organism and are connected biological agents, stimulating or inhibiting the functions of the organism, secreted into the blood (25). Starling named the discovered agent - secretin and this kind of biocatalysts - hormones (from Greek - "hormao" means "to stimulate"). The name of the whole discipline - endocrinology (about "internally discharged substances") - was also created.

As a consequence of that position in 1905 there appeared a hypothesis created by John Edkins, according to which in mucosa of the gastric antrum there is produced a substance that might be responsible for the hydrochloric acid secretion. Following Starling's idea of secretin he named it "gastrin" (26). Shortly afterwards, in 1928 there were discovered further hormones, stimulating the gall bladder motility and the pancreatic exocrine secretion - cholecystokinin (isolated by Andrew Ivy and Erick Olberg) and enterogastrons - substances produced in the large bowel inhibiting the stomach secretion, discovered and named by Julian Walawski (1898-1979) (27) and Jerzy Kaulbersz. In June 26th of 1964 Roderic Gregory, professor of physiology from Liverpool, published for the first time the amino acids structure of gastrin, which was the crowning of the studies of this hormone. That was also the final confirmation that this hormone in pure condition is a very strong stimulant of acid secretion in the stomach.

At times when Starling, Bayliss and Edkins were conducting their studies, their conceptions lagged behind because gastroenterologists' attention was focused on another more and more trendy endogenous chemical agents that strongly influenced secretion - histamine and acetylcholine.

In October 28th of 1916 Leon Popielski (1866-1920), professor of pharmacology in the University in Lvov, discovered the role of histamine as an agent increasing the secretion of the hydrochloric acid. In 1916 he described his research on dogs with the gastric and duodenal fistulas which underwent the injection of beta-imidazolylethylamine, lately named "histamine". After the administration of scopolamine or after vagotomy, secretion also remained on a very high level. As Popielski strongly objected the hormonal theory, he was challenging Edkins' concept according to which the secretion of the stomach juice is stimulated by the "stomach secretin" (gastrin). He thoughts that these effects could be attributed not to hormones but tissue extracts, containing vasodilatine, which besides the influence on secretion, might decrease the blood pressure and the coagulation. Popielski published his work shortly afterwards but only in Polish in dissertations of Academy of Arts and Sciences in Cracow (28). Because of World War I his work in German appeared in 1920. The results of his study pointed that histamine increased secretion of the gastric juice in humans, causing soon after its subcutaneous injection a rapid increase of the rate of acid juice secretion in the stomach with the peak after 30-55 minutes.

Andre Latarjet (1877-1947) gave a detailed description of the vegetative innervation of the stomach. He studied the influence of acetylcholine on the stomach secretion. Latarjet stated that branches of the vagal nerve ending along the lesser curvature of the stomach played a vital role in stomach hydrochloric acid secretion. Latarjet performed a local vagotomy, limited to that region of the stomach and obtained an evident decrease of the juice secretion. Those studies were performed in 1923. What is important, Latarjet, besides all physiological effects described above, made a strong suggestion based on his own original experimental studies that the vagal nerves play a significant role in developing the peptic ulcer (29).

Twenty years later in Merritt Billings Hospital in Chicago L. Dragstedt (1893-1975) showed clinically proved results of his own study on the significance of vagotomy for the hydrochloric acid secretion and etiopathogenesis of the stomach ulcer disease. He demonstrated that the vagal denervation of the stomach significantly decreases (20-30%) secretion of the gastric juice and accelerates the healing of the peptic ulcer or at least stops or arrests its development and relieves pain. Dragstedt confirmed by that earlier Latarjet's suggestion about the surgical treatment (vagotomy) of the peptic ulcer as a method of choice (30).

Such, in a great abbreviation, is the story of the physiology of the gastrointestinal secretion. The history written by a medical historian usually ends half century ago, everything afterwards is a more remote or nearer present. The present that is being dominated by the research on discovered in 1972 H_2-

receptors, for which J. Black was awared Nobel Price in 1988 (Table 1) and their antagonists, which were introduced to the treatment in 1976.

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