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## **ROLE OF HISTAMINE IN GASTRIC SECRETION: FROM DISCOVERY TO CLINICAL APPLICATION (A TRIBUTE LEON POPIELSKI TO 150-ANNIVERSARY FROM HIS BIRTH)\***

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*Professor of Lviv National Medical University (formerly known as Jan Kazimierz Lemberg University), Ukraine, Leon Popielski was the first to recognize that histamine stimulated gastric acid secretion 100 years ago, at 1916. He produced over one hundred publications and founded Lviv's experimental gastroenterology school (Koskowski, 1931), and strong pharmacology tradition. He is less well known today than he deserves to be. Popielski began his scientific career at the Military Medical Academy in St Petersburg, then dominated by I. Pavlov. In 1901, he published work indicating the existence of a peripheral 'reflex center' controlling gastric secretion (Popielski, 1901). His findings contradicted the prevailing 'nervism' theory of Pavlov, who had supervised Popielski's PhD thesis. Perhaps not surprisingly this caused friction between them. Pavlov then started a process to verify Popielski's results, which was later described in Boris Babkin's memoirs. The results were confirmed thereby establishing the idea that processes other than conditional-reflexes, and in particular peripheral mechanisms, also controlled gastric secretion.*

*Popielski's work on histamine was carried out in Lviv during the World War I period, although published only later. He clearly showed that histamine was a strong stimulant of gastric acid secretion. His PhD student W. Koskowski subsequently introduced the histamine test for gastric secretion in patients, which in a somewhat modified form, was used clinically for many decades in Poland at 1930's. In the 1960's and early 1970's, Professor Sir James Black, at what was then Smith, Kline and French, brilliantly extended Popielski's model of the role of histamine in gastric*

*secretion through the development and use of a new class of antisecretory drug – the H<sub>2</sub> receptor antagonists (Black et al., 1972). These proved the essential role of histamine in stimulating acid secretion. An early example, cimetidine, became the first truly blockbuster drug, and revolutionised the treatment of peptic ulcer disease. At 21<sup>st</sup> century the novel gastric acid blockers – inhibitors of proton pump (PPI) were included in standard protocols for treatment several acid-related diseases. Long-term gastric acid suppression has been associated with different complications in gastric mucosa. Moreover, the roles of gastric acid inhibition in extragastral damage manifestation and several groups have reported abnormal proliferation in gastrointestinal tract during long-term treatment by IPP or H<sub>2</sub> receptor antagonists. In the past 10 years due to these side effects, there is a need to study dual actions of histamine on gastrointestinal mucosa.*

*Progress of scientific thought allowed to identify numerous histamine receptors (H<sub>1</sub>-H<sub>4</sub>) and their multifunctional meaning, and in that way to facilitate appearing of new medicine, which have totally changed treatment tactic of gastroenterological and neurological diseases. Popielski's work provides a clear example of how basic physiological research can be translated into the clinic for patient benefit. Scientific portrait of L. Popielski doesn't limit in his scientific and studying publications, he is an author of numerous publications, dedicated to the healthy way of life. Intellectual courage, belief in the reliability of obtained results and incredible assiduity of L. Popielski, deserve to be respected nowadays.*

Key words: Leon Popielski, histamine, gastric secretion, humoral concept

\* Based on presentation earlier this year at the seminar: "Physiological and clinical significance of histamine for practical medicine" (to 150<sup>th</sup> anniversary of Leon Popielski)

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## **РОЛЬ ГІСТАМІНУ У ШЛУНКОВІЙ СЕКРЕЦІЇ: ВІД ВІДКРИТТЯ ДО КЛІНІЧНОГО ЗНАЧЕННЯ (НА ЧЕШТЬ 150 РІЧЧЯ З ДНЯ НАРОДЖЕННЯ ЛЕОНА ПОПЕЛЬСЬКОГО)\***

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*100 років тому Леон Попельські став першовідкривачем впливу гістаміну як ключового та потужного фактора на шлункову секрецію, а у теперішній час визнається світовою науковою спільнотою співавтором гуморальної концепції у механізмів контролю секреторних процесів у травній системі.*

*Доля проф. Л. Попельські тісно пов'язана із буремними політичними та воєнними подіями в Східній Європі та з її двома провідними університетами, а саме Військово-медичною академією у Санкт-Петербурзі, де він навчався (1889-1894) і розпочав наукову діяльність (1894-1900), а також з Львівським університетом, де він отримав посаду професора і завідував кафедрою фармакології і фармакогнозії (1905-1920). У 1909-1910 рр. був деканом медичного факультету, який став основою Львівського національного медичного університету імені Данила Галицького. Через важкі історичні обставини, спричинені 1-ю Світовою війною, винахід Л. Попельські не був належно оцінений, хоча у 30-х рр. минулого століття його учень В. Косковські розпочав застосувати у клінічній практиці гістаміновий тест для визначення кислотності шлункового соку. Прогрес науковий думки дозволив ідентифікувати численні гістамінові рецептори (H1-H4) та їх поліфункціональне значення, сприяючи появі нових ліків, які кардинально змінили тактику лікування гастроентерологічних та неврологічних хвороб. Науковий портрет Л. Попельські не обмежується переліком його наукових та навчальних публікацій, йому належить численні науково-популярні видання, присвячені здоровому способу життя. Інтелектуальна відвага, переконання у достовірності здобутих результатів і неймовірна працьовитість Л. Попельські варта шани у наш час.*

*Ключові слова: гістамін, шлункова секреція, гуморальна регуляція, Леон Попельські*

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\* Based on presentation earlier this year at the seminar: "Physiological and clinical significance of histamine for practical medicine" (to 150<sup>th</sup> anniversary of Leon Popielski)

*The past is not dead history,  
it is living material  
of which man builds its future*

**Rene Dubois, 1901**

Among several prominent scientists and respected leaders in gastrointestinal (GI) Physiology and 20th century leading scientists in humoral concept in GI secretion is Prof. Leon Popielski (1 III 1866 - 8 X 1920), whose 150th anniversary was celebrated in 2016 (Fig. 1).



Fig. 1. Leon Popielski during his work at Lviv University.

Leon Popielski was the first to recognize that histamine stimulated gastric acid secretion 100 years ago, at 1916. He produced over one hundred publications and founded Lviv's experimental gastroenterology school (Koskowski, 1931) and strong pharmacology tradition. His work and life are tightly connected with St. Petersburg and Lviv.

Dr. Leon Popielski finished medical studies at the Military Medical Academy in St. Petersburg at 1894 and graduated with degree *cum eximia laude* (Fig. 2). For his work on the "role of liver in transformation of blood" he earned the First D. Busz Prize award.



Fig. 2. Leon Popielski (1889-1894) as medical student of at the Military Medical Academy in St. Petersburg (in the center of group)

Combination of his devotion to science and ability for analytic thinking were background that at 1894 L. Popielski, MD, began for research in Institute of Experimental Medicine in St. Petersburg (Fig.3). On the basis of his work on secretary and inhibitory nerves of pancreas he was awarded second PhD under mentorship of Ivan Pavlov. 20 years later, at 23d of July, 1923 Time magazine named Popielski together with Bechterew is the most prominent follower in I. Pavlov scientific team (Poniatowska H., 1983).



Fig.3. A group of experiments in one of the laboratory which conducted by L.Popielski during his work in Pavlov's team.

In subject of gastrointestinal secretion interesting seems Popielski work from Pavlov's period of research. In his work 'about secretions and inhibitory nerves of pancreas' he discovers that duodenum provide secretory function under the influence of acid, even after complete isolation of pancreas from central nervous

system, what he achieved by cutting vagus nerve and sympathetic nerves, by cutting out celiac plexus and by complete removing of spinal cord. Popielski finds "nerve cells" in pancreatic gland. These unusual data was published in 1896 in his article about the secretory activity of pancreas in the *Centralblatt für Physiologie*. Secretion of pancreatic juice under the influence of acid he recognize as a "short reflex" arc between mucosa of duodenum, proximal part of small intestine and nerve cells located in the gland (Popielski, 1896).

In 1901, Popielski published work indicating the existence of a peripheral "reflex center" controlling gastric secretion. In his experiments were confirmed that stomach ability to secrete gastric juice was not interrupted by bilateral vagotomy and sympatectomy as well as by removing of truncus celiacus and cutting of spinal cord. This proved that external innervation is not essential for gastric secretion (Fig.4). "Nerve plexuses" located in gastric wall played important role in formation of secretory reflex (Popielski, 1901).

His findings contradicted the prevailing "nervism" theory of Pavlov, who had supervised Popielski's PhD thesis (Popielski, 1894). Perhaps not surprisingly this caused friction between them. Pavlov then started a process to verify Popielski's results which was later described in Boris Babkin's memoirs in repeated experiments of Popielski concerning the influence of hydrochloric acid on secretion of pancreatic juice, choosing endocrine way of action and establishing by Bayliss and Starling the term 'secretin' in 1903 and in 1906 the term 'hormone'. The results were confirmed thereby establishing the idea that processes other than conditional-reflexes, and in particular peripheral mechanisms, also controlled gastric secretion.

Later experiments of Bayliss and Starling has been repeated by Pavlov in St. Petersburg: 'I think it was in the fall of 1902 that Pavlov asked V. V. Savich to repeat the secretin experiments of Bayliss and Starling. The effect was self-evident. Then, without a word, Pavlov disappeared into his study. He

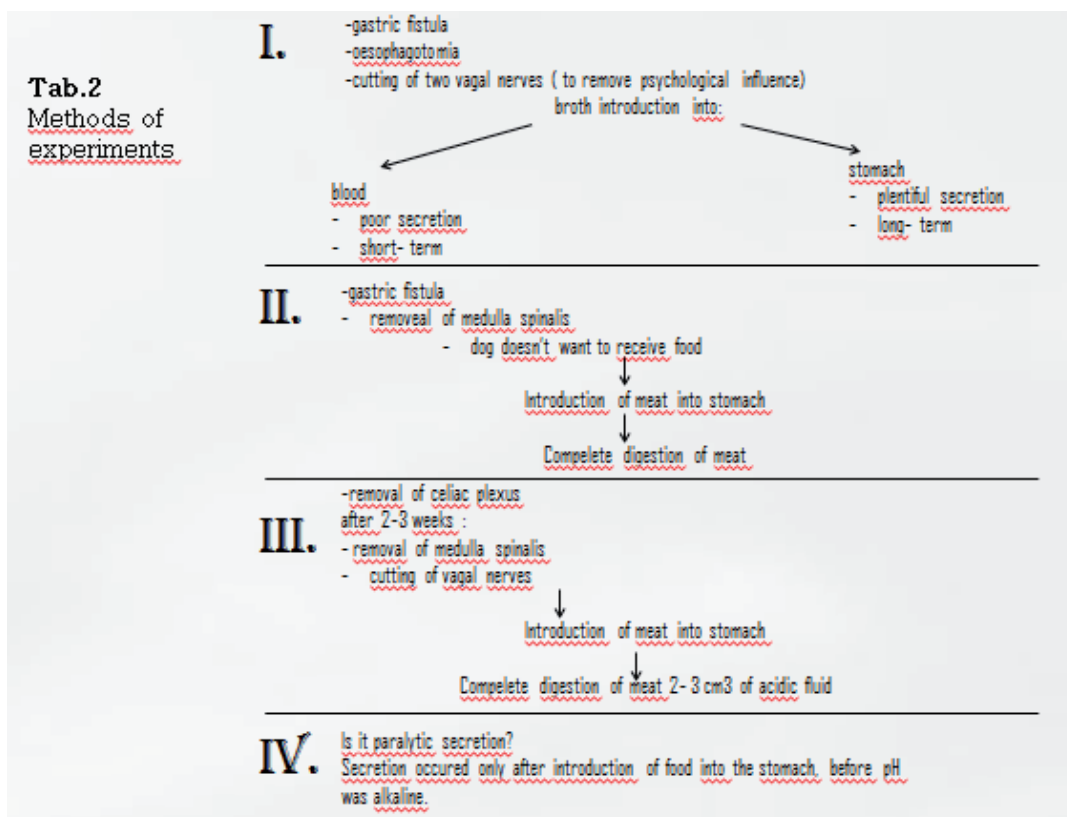


Fig.4. Summary of experimental methods which used L. Popielski for confirmation role of "peripheral, reflective centres" for gastric glands secretion, regarding to L. Popielski publication in "Cosmos", 1901 (Zakrzewska J., 1961)

returned half an hour later and said: "Of course they are right. It is clear that we did not take out an exclusive patent for the discovery of truth".

At 1905 L. Popielski obtained position Professor of University of Lemberg, now namely Lviv National Medical University (Fig.5) where he continued experiments related to Gastrointestinal Physiology with focus on humoral control in the gut, and introduced creative intellectual atmosphere for his medical students and trainers.

*D<sup>r</sup> Leon Popielski,  
ordentlicher öff. Professor an Universität  
Lemberg.*

Fig. 5. Visit card of Prof. Leon Popielski (1907)

The turbulent history of Lviv (formely Lemberg-Lwow) is expressed on the life and work of Prof. L. Popielski and his family (Fig. 6 and 7).



Fig. 6. Leon Popielski, the Dean of Medical Faculty of University (1909-1911) with his daughter and his son Boleslaw later Professor of Forensic Medicine in Wroclaw university

The relative calm atmosphere in Galicia disappeared at the start of First World War (IWW) when his capital was occupied by Russian troops. At that time L. Popielski with children were on summer vacation and

just came back home only at 1916 when Russians leaved the city. In 1916 during IWW he performed many valuable experiments and first in the World discovered the role of histamine as an agent increasing the secretion of the hydrochloric acid. He studied on dogs with the gastric and duodenal fistulas, which were administered compound lately named «histamine».



Fig. 7. Leon Popielski with his wife Helena and sons

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. Popielski had written an important paper about effects of histamine on gastric secretion in Polish but unfortunately, because of the wartime it wasn't published at 1916 but printed only at 1920 after his death (Fig. 8).

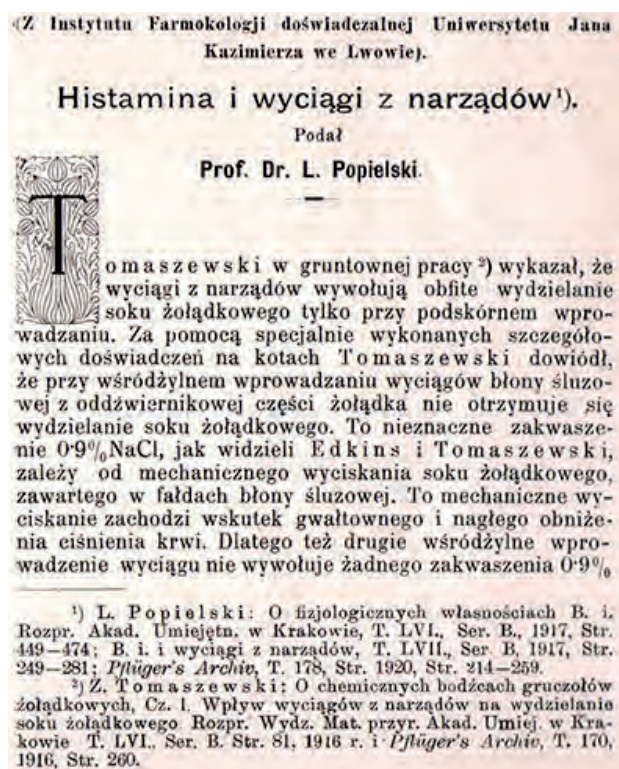


Fig. 8. First page of L. Popielski publication "Histamine and tissue extract" (In original "Histamina i wyciągi z narządów" Księga Pamiątkowa wydana w dwudziestopiątą rocznicę istnienia Wydziału Lekarskiego Uniwersytetu Jana Kazimierza 1894-1919 przez członków Wydziału lekarskiego / pod redakcją W. Nowickiego. Lwów, 1920: 67-74)

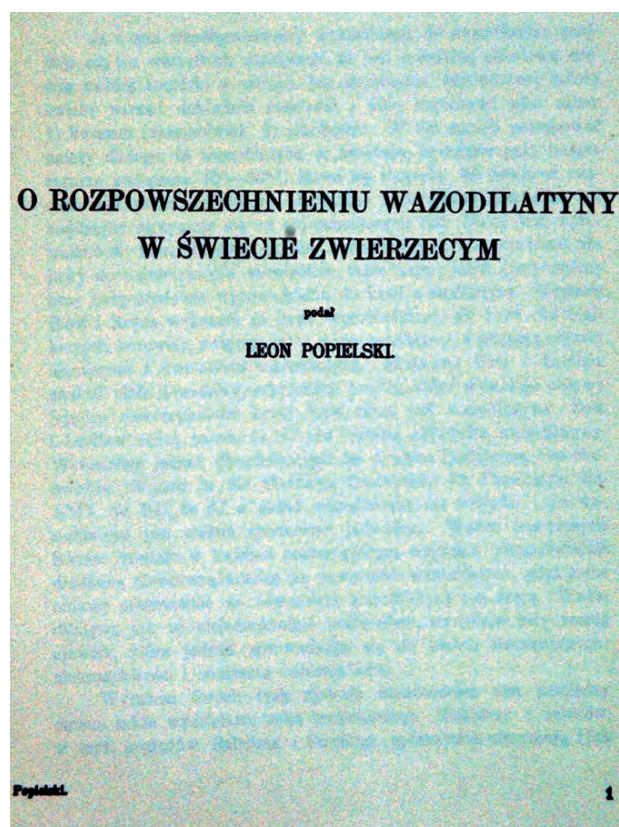


Fig. 9. Publication of L. Popielski about distribution of vasodilatin in animal World (In original: O rozpowszechnieniu wazodilatyny w świecie zwierzęcym // Księga Pamiątkowa Uniwersytetu Lwowskiego. – 1911. – S. 1-5).

Histamine as itself was discovered in 1907 by A. Windaus and W. Vogt (Thurmond, 2014). The name of substance "histamine" because it was extracted from tissue, the word "histo" was used to describe this "amine". Next important discovery was its importance in anaphylactic shock development what was established by Dale and Laidlaw in 1910. Dale instead of histaminę used the chemical name  $\beta$ -iminazolyethylamine. This chemical name was also used by Popielski in his later articles (Popielski, 1920). In this period these two scientists pointed out similarities between histamine and hypothetic vasodilatine, which was believed by Popielski to be responsible for the effects produced by peptone and extracts he prepared of certain organs (Fig.9). Statement that vasodilatine is histamine turned out wrong - Popielski himself with cooperation with his students: Koskowski and Steusing, pointed out important differences between two substances (Tab.1). But before, it pushed Popielski to re-examine action of his extracts and study physiological properties of histaminę.

Tab. 1.  
**Comparison of vasodilatine and histamine according to Prof. L. Popielski**

	vasodilatine	histamine
Blood pressure influence on blood	decrease immunization long term blood clotting disturbances	decrease blood pressure no immunization normal blood clotting

Due to World War I, Popielski's paper describing the results was unfortunately not published until 1917 (in Polish). The research results were published in the prestigious international journal "Pflügers Archive für die gesamte Physiologie des Menschen und der Tiere" only in the year of his death (1920, Tab. 2).

Tab.2.

**Leon Popielski's life and work calendar**

Years	Developments
11 III 1866	Leon Popielski was born in Sośniczany, village now situated in Świętokrzyskie voivodship near Sandomierz, as a son of Bernard and Antonina. In Popielski family there was a strong tradition of armed struggle for independence. His grandfather was fighting in 1830 in Wielki Dąb and Ostrołęka battles. Two of his sons were executed by hanging because of taking part in uprising in 1863.
1866- 1884	Popielski was growing up in Poland, in Sandomierz he finished middle school, and then a high school in Piotrków, however he continued education in Tsarist Russia which ruled Poland at that time.
1884- 1887	Popielski was studying mathematics and physics at the university in St. Petersburg where he was granted his doctor's degree working on a subject of Bessel's functions.
1887- 1888	He was studying at the Institute of Technology in St. Petersburg but he was expelled because of taking part in student walkout. After that, he was working in Finland as a tutor for son of General of St. Petersburg whose patronage helped him in getting into medical university.
1889- 1894	Finished medical studies at Military Medical Academy in St. Petersburg. He graduated as a first Pole cum <i>eximia laude</i> . For his scientific work focusing on role of liver in transformation of blood he was awarded the First D. Busz Prize.
1894- 1897	With I. P. Pawlow and I. R. Tarchanow he majored in physiology and in bacteriology at the Institute of Experimental Medicine in St. Petersburg. He was granted a doctor's degree at the Military Medical Academy in Petersburg on a basis of work about secretory and inhibitory nerves of pancreas (1897).
1899	He was granted the higher doctoral degree in physiology.
1898- 1900	He was a prosector at the Department of Physiology at the Military Medical Academy and also a lecturer at the Female Medical Faculty and on P. Lesgaft's biology course where he met his future wife, Helena Iwanow.
1900- 1903	Popielski was the chief of bacteriological and chemical departments at the Military Laboratory in Moscow. During the years from 1899 to 1901 he visited few institutes of experimental medicine in Lviv, Krakow, Vienna, Budapest, Munich, Berlin, Turin, Genoa, Lyon, Marseille and Paris.
1904	As a scholar of Ministry of War he was working at Russian zoological-marine station in Villefranche sur Mer, a pharmacological O. Schmiedenbergs laboratory in Strasbourg and of R. Boehm's in Leipzig as well as in laboratories of physical chemistry (W. Oswald's) and organic chemistry (C. Hantsch's).
1904- 1905	During the Russian-Japanese war he was fighting with plague and cholera epidemics in Manchuria. In 1905 he was appointed to the head of the Pharmacology and Pharmacognosy Department of the University.
1905- 1914	During that time he was professor of pharmacology and pharmacognosy at the Lviv Medical University because of what he had to change his Russian citizenship to Austrian. Popielski stayed in Lviv and didn't get back to Russia. In 1909/10 he was the Dean of the Medical Faculty. When he was with his little children on holidays in Bieszczady, The Great War started. He lost contact with his wife who stayed in Lviv. Professor escaped with children in the direction of Baligrod. On the way from the city he met the Hungarian soldier-Geze Machno who took him with a horse and carriage to Krynica. There Dr. Ebers and Dr. Kmietowicz took care of him.
1914- 1916	At the end of November Popielski with children went to Tarnów, where he met his student and co-worker Dr. Z. Tomaszewski at the railway station. With his help the Professor and children were taken by train to Kraków. Train stopped on the bridge over Grzegorzeczka street and thanks to that Popielski and children could get into the city without being noticed. However he stayed at his friend Prof. Plic. From Krakov he got to Cieszyn and then to Vienna where, thanks to help of Romanian Prime Minister Ionescu, also his wife managed to get. From there family of Popielski went to Brno, where Professor was working with many Poles like Prof. L. Rydygier, Associate Professor T. Ostrowski, dr L. Węgrzynowski in field hospital.
1916- 1919	Together with his family, the Professor came back to Lviv and inhabited at the Institute. From his co-workers stayed only Dr Warchoł who was working in a hospital as a surgeon, and laboratory technicians. New co-workers became W. Koskowski and K. Tyszka.
1919- 1920	Lectures were held in the form of courses, for doctors who served in the army. In August 1920, the Professor was informed that his son Waclaw was lying in the hospital in Przemyśl suffering from dysentery. Popielski went to see his son. Couple of days after his return he came down with a serious flu.
8 X 1920	Leon Popielski died of pneumonia. He was buried in the Lychakivk's cemetery.

First histamine trial was introduced by Popielski's student Dr. W. Koskowski together with P. Carnot, and E. Libert in 1922 that was confirmed by P. Carnot and E. Libert and B. Babkin. In 1937 Bovet and Staub published first data about synthetic compounds blocking of histamine receptors which now well-know anti-histaminic drugs. Despite of their high effective properties in allergy, gastric acid secretion and the positive chronotropic response in isolated atria were not inhibited by them. In the 1960s, the research of British scientist James Black discovery new isoform of histamine receptors at hat mediated gastric acid secretion and other effects and termed them as H<sub>2</sub> receptor (H<sub>2</sub>R), confirming Popielski's model about the essential role of humoral influence in the secretion of digestive glands. It became the basis for a new class of drugs – H<sub>2</sub> blockers. This work significantly changed the strategy of treating peptic ulcer disease; consequently Black was awarded the Nobel Prize (1988). As such, there is no doubt that Popielski's work represented the deepest intellectual rigor, setting the foundation for future generations to come. Leon Popielski who was the pioneer in discovering the key role of histamine influence on gastric secretion. Long time this scientist was still unknown to a wide audience until at 2004 the first international notification was done by Irvin M. Modlin and George Sachs about impact of Leon Popieski on humoral concept in their famoust book "Acid Related Diseases: Biology and Treatment" (Fig. 10).

It remained for Leon Popielski, a student of Pavlov, to identify the acid-secretory effects of histamine. After leaving Pavlov's laboratory in 1901, Popielski had been placed in charge of the military bacteriologic laboratory in Moscow. His initial work was on the mechanism of the intravenous injection of Witte's peptone (a peptic digest of fibrin) in causing a fall in blood pressure. This research continued after he had become the Professor of Pharmacology at the University of Lemberg, and Popielski believed that he had identified a substance, "*vaso dilatant*," as a component of Witte's peptone distinct from histamine or choline. On October 28, 1916, in the course of experiments on the effect of the injection of an extract of the pituitary gland on gastric secretion, Popielski injected 32 mg of beta-imidazolethylamine hydrochloride subcutaneously into a dog with a gastric fistula. Over the next 5.75 hours, the dog secreted 937.5 mL of gastric juice having a maximum acidity of 0.166 N. Because similarly stimulated secretion was unaffected by section of the vagus or by atropine, Popielski concluded that beta-imidazolethylamine acts directly on the gastric glands.

Fig. 10. First international notification about impact of Leon Popieski on humoral concept in Acid Related Diseases: Biology and Treatment (Authors: Irvin M. Modlin, George Sachs, Lippincott Williams & Wilkins, 2004)

George Sachs, one of prominent living leader experts in gastroenterology who has

developed methods for isolation of viable gastric and intestinal enterochromaffin cells (ECC) and has characterized receptors and intracellular mechanisms responsible for release of histamine from the gastric subtype ECC, during meeting at 2016 emphasized Popielski's work provides a clear example of how basic physiological research can be translated into the clinic for patient benefit (Fig.11). Creativities' work of physiologist from Lviv who began to consider on the elemental level impact of histamine control on gastric secretion and for the first time he saw the possibility of understanding the causative connection of elementary mechanism and novel approach for understanding significance humoral effects was conceptual loop in half of century for crucial therapeutic potential largely developed by J.Black, which was a revolutionary step in peptic ulcer treatment, confirming hypothesis of Popielski.



Fig.11. This picture was taken March, 28, 2016 before 4th Global GI Club meeting "Brain-gut axis", Experimental Biology/FASEB San Diego 2016 (from left to right: George Sachs, Oksana Zayachkivska)

Progress of scientific thought allowed to identify numerous histamine receptors (H<sub>1</sub>-H<sub>4</sub>) and their multifunctional meaning, and in that way to facilitate appearing of new medicine, which have totally changed treatment tactic of gastroenterological and neurological diseases (Fig.12). Popielski's



work provides a clear example of how basic physiological research can be translated into the clinic for patient benefit. Scientific portrait of L. Popielski doesn't limit in his scientific and studying publications, he is an author of numerous publications, dedicated to the healthy way of life. Intellectual courage, belief in the reliability of obtained results and incredible assiduity of L. Popielski, deserve to be respected nowadays. Life and work-story of Leon Popielski confirm nice words of Max Plank: "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."

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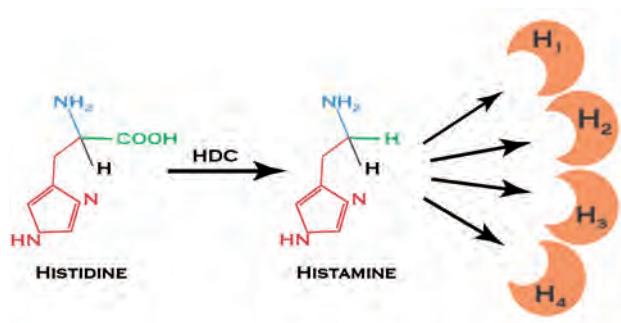


Fig. 12. Modern view on histamine and their receptors (H<sub>1</sub>-H<sub>4</sub>)

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