Jerzy Kaulbersz was undoubtedly the father of experimental gastroenterological physiology in Poland. He pioneered the neural and endocrine aspects of the mechanisms controlling gastric and pancreatic secretion by assessing the influence on this secretion of vagal nerves and endocrine factors such as gastrin, enterogastrone, urogastrone, pituitary, adrenal, thyroid and sex hormones as well as bile, hypoxia and X-ray irradiation. He introduced various models of peptic ulcerations such as induced by pylorus-ligation (Shay ulcers) or Mann-Williamson ulcers to test the influence of neuro-endocrine factors on the formation and healing of these ulcerations. This review is designed to commemorate the outstanding contribution to experimental gastroenterology of Professor Kaulbersz, who first studied biology in German universities to obtain the title of Doctor of Natural Philosophy (Ph.D.) in Freiburg in 1913 and then completed medical studies at the Medical Faculty of the Jagiellonian University in Cracow receiving the title of Doctor of Universal Medicine (MD) in 1920. He then joined Department of Physiology of Jagiellonian University in Krakow as its assistant and gradually was appointed docent and finally promoted to professor in this Department, working here as chairman from 1934 to 1964 with only 7 years interruption when he spent the time of world war II in USA, working at various departments of experimental gastroenterology and publishing his outstanding papers in most prestigious physiology journals such as American Journal of Physiology. He possessed comprehensive knowledge of physiology and was gifted to create and organize Cracow Department of Physiology. Moreover he became co-founder of the of Polish Physiological Society, the honorary member of American Physiological Association, honorary member of Polish Society of Gastroenterology and Physiology and received the diploma of Doctor Honoris Causa of Medical Academy in Cracow. This ad memoriam note commemorates his achievements at one hundred twenty anniversary of Prof. Kaulbersz birth with intention to bring his fundamental discoveries to younger physiologists and pharmacologists.

**Key words:** enterogastrone, gastrin, histamine, hypoxia, peptic ulcer, physiologist, urogastrone
In the second period of work at the Cracow Department of Physiology, Dr Kaulbersz, besides teaching medical physiology, was scientifically interested in the assessment of the role of nervous system in the regulation of gastric and pancreatic secretion as outlined in his habilitation thesis (3), confirming major I.P. Pavlov’s results (4) that vagal nerves activated in dogs by sham-feeding or by direct electrical excitation are important for the stimulation of both gastric and pancreatic secretion. His original finding was that the secretory response to central (sham-feeding) and peripheral electrical vagal excitation starts after the 4-7 min of latency period being followed by an increase in gastric acid and pancreatic protein secretion. This latency period was attributed by Jerzy Kaulbersz to the existence in vagal nerves of both inhibitory fibers (more sensitive) and excitatory fibers activated after longer excitation. Similar secretory reactions of the stomach and the pancreas to sham-feeding, were attributed by Kaulbersz to the excitation of stimulatory vagal fibers in these experiments on conscious dogs.

Major scientific achievements of Prof. J. Kaulbersz after his habilitation thesis included: A) Involvement of endocrine factors (pituitary, thyroid and gonads) in the control of gastric secretion in dogs (5-7); B) Effect of endocrine glands (pituitary, thyroid and gonads on the formation of Shay ulcerations and gastric secretion in rats (8, 9); C) Influence of inhibitory factors released from the intestines by fat, glucose and peptone on gastric secretion and healing of various types of experimental peptic ulcerations (10); D) Influence of gastric luminal environment on gastrin release (11); E) Gastric acid secretion.
after introduction of gastrin into the portal vein (12); F) Implication of bile in gastric secretion (13); G) Effects of various pharmacological agents (reserpine, neurotropic agents) and vagotomy on gastric secretion and peptic ulcerations (14); H) He combined action of cobalt and low atmospheric pressure on hematopoiesis (15); I) Gastric secretion following hypoxia and X-ray irradiation in cats (16); J) Isolation and purification of enterogastrone and urogastrone and their gastric inhibitory effects (17-20).

It should be emphasized that despite very difficult economic and political conditions after WWII in Poland, Jerzy Kaulbersz was able to attend most of major international physiological and gastroenterological congresses and to collaborate with his former American colleagues in completion and publication of his papers in the most prestigious journals such as *American Journal of Physiology* (5-7) and *Gastroenterology* (19, 20) without asking local authorities for permission as it was requested by official regulations. This probably explains why Kaulbersz despite of outstanding achievements in modern physiology was considered “unsuitable” scientist for the election as member to Polish Academy of Sciences.

As mentioned before, the major studies of Prof. Kaulbersz and his co-workers were focused on the neuro-hormonal mechanisms of gastric and pancreatic secretion and the induction or healing of peptic ulcerations in animals.

The most elegant and comprehensive studies were carried out by Prof. Kaulbersz with American co-workers (5-7) in surgical and physiological departments at Wayne University College in Detroit, and prepared for the publication in *American Physiological Journal* in early 50th already after his return to Poland from USA. He was the only Polish physiologist awarded honorary membership of American Physiological Society and received regularly subscribed charge-free journals from this Society. As he was employed during the WWII at the University of Wayne, he received regular income in dollars even after return to Poland and this small amounts of “hard currency” allowed him to attend scientific meetings abroad and pay for the reprints of the papers published in foreign journals.

Using highly purified extracts of urine (urogastrone) and mucosa of the small intestine (enterogastrone) prepared according to Gray’s techniques (17, 18), Kaulbersz et al. showed that the removal of the pituitary and adrenal glands affected the inhibitory activities of these substances in dogs, suggesting that the release and action of these potent natural gastric inhibitors may be modified by major endocrine glands (Fig. 3). The studies on enterogastrone and urogastrone raised substantial international interest as following their publication (19, 20) in prestigious journal such as *Gastroenterology*, numerous US pharmaceutical companies turned to us with the proposition of a close collaboration regarding clinical application of these natural gastric inhibitors in the treatment of peptic ulcer disease in humans but Polish regulations at that time did not allowed for such collaborative studies. It is of interest to mention that following our report of urogastrone as anti-secretory and antiulcer agent, we received from Japan (Hitachi Chemical Company, Ibaraki, Japan) the synthetic urogastrone that exhibited similar peptide structure and activity similar to natural urine extract, being called urogastrone-epidermal growth factor (URO/EGF). It was found in our hands to be highly effective gastric inhibitor and ulcer healing promoting substance at least in rats with various ulcerations such induced by stress, cold water immersion and immobilization, taurocholate or ethanol application (21). These effects of URO/EGF were observed also after oral application of this substance and found by our group to be mediated by the stimulation of ornithine decarboxylase (ODC) activity and release of polyamines such as spermine and putrescine as well as by increased generation of prostaglandin E2. The antiulcer effects of URO/EGF could be reversed by the suppression of the prostaglandin-cyclooxygenase activity with aspirin or ODC activity with difluoro-methyl-ornithine (DFMO). Our further studies showed that urogastrone is actually epidermal growth factor (EGF) secreted with urine (21).

Another topic that was extensively studied under Jerzy Kaulbersz’s supervision in collaboration with Janina Tasler and Andrzej Oginski (11), both active members of the Department of Physiology. These studies concerned the mechanisms involved
in the release of gastrin, particularly the inhibitory effect of the acidification of pyloric area on this release and gastric acid secretion. These studies were carried out on conscious dogs equipped with double antral pouches, one perfused with acid solution and another with meat extract and additionally with pouch fashioned of fundic gland area (Heidenhain pouch) to monitor gastric acid secretion (Fig. 4). It was found that meat extract perfusing one antral pouch resulted in the copious gastric acid secretion from the Heidenhain pouch due to the release of gastrin and this effect was suppressed by acid perfusion of another pouch, in the same dog, indicating that the same pyloric mucosa that is capable to excite gastric acid secretion (via gastrin release) when perfused with meat extract and may at the same time inhibit this secretion when perfused with HCl solution possibly by direct acid suppressing effect on gastrin release from the antral mucosa or indirectly by the release by acid of local inhibitor of the gastrin release (Fig. 5). Since acidification of the antral mucosa in one antral pouch also inhibited acid secretion from the Heidenhain pouch stimulated by the ethanol placed in the main stomach or by injection of exogenous gastrin, it has been proposed that the antral mucosa may release both excitatory (gastrin) and inhibitory (gastrone or antrogastrone) acting via endocrine pathway to control acid secretion from the fundic mucosa (Fig. 6). The results of these experimental studies

Fig. 4. Gastric inhibitory effects of enterogastrone originating from proximal and distal intestine of hogs (left panel) and dogs (right panel) (19).

Fig. 5. Inhibitory effect of urogastrone originating from dogs with intact or removed adrenal glands (20).
have been later confirmed by numerous investigators, showing that, indeed, antral acidification causes local inhibition of gastrin release but other substances such as antrogastrone, gastrin-inhibitory peptide (GIP), vasoactive intestinal peptide (VIP) or somatostatin (SST) released by D-cells placed neighbouring antral G-cells have been also considered to play some role in „gastric acid autoregulation” (Fig. 7).

Some controversies regarding the mechanisms of gastrin release with the changes in antral environment were finally elucidated when Gregory and Tracy (22, 23) isolated and purified antral hormone (gastrin), showing that it exists in several molecular forms such as “minigastrin” heptapeptide (G-7), “small gastrin” heptadecapeptide (G-17), both sulphated gastrin I and unsulfated II and larger or ‘big” gastrin (G-34). Further progress in this story was made by Yalow and Berson (24) and McGuigan and Trudeau (25), who accomplished radioimmunological determination technique of plasma gastrin permitting the studies with various factors affecting the release of this hormone from antral mucosa as well as from gastrinoma tumours. Based on the studies of Debas et al. (26), release of gastrin under physiological conditions depends mainly upon the vagal activity and the luminal acidity as it can be enhanced following antral distension e.g. by food and blocked almost completely by pretreatment with atropine and the low pH of antral. In contrast, Thompson’s group (27, 28) proposed that the suppression of postprandial gastrin release depends upon the action on G-cells of various hormones such as gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP) and secretin originating from the intestinal mucosa. According to our study gastric acid secretion and mucosal blood flow can be suppressed by certain hormones such as secretin and VIP (29). With the detailed characterization of the D-cells, situated in close vicinity of the G-cells and releasing the most effective paracrine inhibitor of gastrin release by antral acidification (Fig. 7). At the beginning of this century, the enhanced gastrin release and hypergastrinemia are believed to accompany the gastric infection with Helicobacter pylori, which is now considered as the major pathogen of human stomach (30). Studies in vitro confirmed that epithelial AGS cells infected with H. pylori exhibit the oxidant-mediated activation of inflammatory signaling and beta-carotene suppressed the expression of proinflammatory enzymes iNOS and COX-2 (31).

These studies required not only a variety of animal models, but also the supply of pure synthetic gut hormones and their measurements in plasma using specific radioimmunoassay’s and suitable equipments. They were purchased by funds obtained from the National Institute of Health, Bethesda, USA to support my research activity following my Postdoctoral Fellowship at UCLA, Los Angeles in 1964-66 under supervision of Dr M.I. Grossman, good friend of Prof. Jerzy Kaulbersz. By contacting me with Dr Grossman, Prof. Kaulbersz, already retired in Department of Physiology at Medical Academy on Cracow, could see with satisfaction that our Institute of Physiology could continue and progress in modern research in gastroenterological physiology, competing with other groups from technically more advanced countries than Poland.

The fact that gastrin and most of enterohormones and mediators expressed in the gastrointestinal mucosa are delivered into the portal circulation and then pass the liver, raised the question that hepatic modulation of these substances may affect their activity at the target organ such as the stomach. The interest in the liver modifying influence on gastric secretagogue resulted in numerous studies such as that of Gregory in 1906 (32) showing that the ligation of portal vein or transferring of portal blood into the large veins augmented gastric secretory response to food ingestion, suggesting that the liver plays important role in the modification of antral hormone released postprandially into the portal circulation and its subsequent action on gastric secretion. Kaulbersz and Bilski (12) were the first in Poland who showed that gastrin extract applied in dogs into the femoral vein resulted in significantly higher acid output with shorter latent period and longer duration of gastric secretion than those observed after the administration of this gastrin preparation into the portal vein (Fig. 8). The same authors (13) showed that bile injected intravenously inhibited gastric acid secretion, whereas that applied intragastrically...
stimulated this secretion revealing an important effect of hepatic secretion ( bile) on gastric secretory activity. The mechanism of this interaction between biliary and gastric secretion has not been disclosed at that time.

Kaulbersz and Bugajski (14) carried out the pharmacological type of studies using reserpine, serotonin, atropine, adrenaline in dogs with innervated and vagally denervated stomach. They confirmed that reserpine exerts a marked stimulatory influence on gastric secretion that can be abolished by the application of atropine or adrenaline and reduced by serotonin, suggesting the crucial role of autonomic nerves in the control of gastric acid secretion. Radecki and Kaulbersz (33) documented the influence of psychotropic substances such as barbiturates (luminal), psychedrine, caffeine and strychnine on gastric secretion and the formation of gastric lesions in pylorus ligated rats. They observed an inhibitory influence of barbiturate on gastric ulcerogenesis and gastric acid secretion but no change in gastric secretion and gastric ulcers following the application of psychedrine, caffeine or strychnine. These studies had simply “practical” character as these substances were widely used in various clinical conditions, but it was not clear whether they affect gastric acid secretion and gastric ulcerogenesis. The results of this study were the first to clarify that the agents with inhibitory influence on the CNS such as barbiturate also suppress gastric secretion and prevent gastric lesion formation. Most interesting was the finding that the CNS excitatory agents such as caffeine, psychedrine or strychnine, unexpectedly, reduced rather than stimulated gastric secretion and gastric ulcerogenesis in rats.

Prof. Kaulbersz was highly interested in the effects of other environmental conditions such as X-ray irradiation and alteration in oxygen pressure on gastric secretion and ulcerogenesis. Together with A. Barylak and T. Radecki (16) they studied on cats maintained in low pressure chamber, the
influence of strong X-irradiation in combination with hypoxia on the gastric secretion. It was found that hypoxia which by itself somewhat attenuated the gastric acid secretion induced by histamine in cats, while preventing the strong inhibitory action of X-irradiation on this secretion.

Prof. Jerzy Kaulbersz was very interested in the physiological phenomena (physical activity, respiratory system and hematopoiesis) of adaptation of humans and animals to the climate of high mountains and hypoxia environments (34-37). He travelled to high mountains such as Mount Blanc in Alps or Cerro de Pasco in Peruvian Andes to investigate also on himself, the effects of hypoxia on hematopoiesis and to examine the limits of respiratory, circulatory and metabolic adaptation to lower atmospheric pressure. This particular aspect of Prof. Kaulbersz research activity was closely connected with the Department of Physiology in Physical Education Academy and will be the subject of separate discussion.

This short and incomplete overview of achievements of Kaulbersz and his associates in experimental gastroenterological research placed him in the highest level and top rank scientists comparable to those in developed countries such as USA. With its over 200 papers, predominantly written in English and published in prestigious American and European journals and presented in numerous congresses in Europe and America, Prof. Kaulbersz should be undoubtedly considered as leader in experimental gastrointestinal physiology in Poland. He was the only honorary Member of American Physiological Association in Poland and at the same time he kept friendly personal relation with I.P. Pavlov in St. Petersburg. I had a chance to follow some of Prof. Kaulbersz routes in USA and Europe, where he was considered and well-respected by the top world gastroenterologists and physiologists such as Dr A. C. Ivy (Chicago Ill), Dr M.I. Grossman (Los Angeles, LA), Dr L. Dragstedt (Gainesville, FL), Dr C.F. Code (Rochester MN), Dr R.A. Glass GB (New York), Dr R.A. Gregory

Fig. 9. Physiological and pharmacological profile & regulation of gastric acid secretion.

Fig. 10. The volume and gastric acid secretion in response to application of gastrin extract either to femoral vein or to portal vein (Adapted from Kaulbersz and Bilski (12)).
(Liverpool, UK), Dr A. Robert (Kalamazoo MI), and many others to be a leading world physiological gastroenterologist. An outstanding research activity of Prof. Kaulbersz was partly due to the fact that he actually lived in the small room in the Department Physiology so he could spend most of the time and attention to control the ongoing experimental studies on various species being undisturbed by family. He used to make rounds twice daily in the morning to lecture on physiology to medical students and then afternoon to discuss with students their laboratory work and with his co-workers the ongoing experimental research and preparation of papers for the next national or international meetings of physiology or gastroenterology. Despite enormous capacity to work, Prof. Kaulbersz had a time to spend with his co-workers relaxing time and always invited them for his birthday party, which he prepared by himself and considered as "holy" tradition (Fig. 9).

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