The centennial of the awarding of the Nobel Prize in Physiology or Medicine to Russian Academician Ivan P. Pavlov (FIGURE 1) is an occasion for assessing the paths opened to modern integrated systems physiology and medicine by discoveries at Pavlov's city laboratory in St. Petersburg and at his country laboratory at Koltushi. Pavlov's Nobel Prize was the first ever awarded for integrated systems physiology and the first for a Russian.

Abbreviated Biography

Pavlov was born the son of a priest in 1849 in Riazan, 200 miles southeast of Moscow, and he studied for the priesthood before matriculating into the Department of Physical and Mathematical Sciences of the University of St. Petersburg in 1873 and later into medical school at the Medical-Surgical Academy of St. Petersburg. He received his medical degree with honors in 1879.

Pavlov was an apostle of Claude Bernard and harbored deep admiration for Bernard's philosophy of modern life. According to G. P. Smith's biographical account (12), Pavlov was never interested in practicing medicine; rather, throughout his lifetime he viewed research in systems physiology as the basic science most likely to contribute to the advancement of the practice of medicine. Therefore, it seems that modern medicine's prevailing mantra of "bench to bedside" is rooted in Pavlov's personal philosophy.

Some years after his postdoctoral stints in famous laboratories of experimental physiology in Germany, Pavlov was appointed chair of pharmacology at the Military-Medical Academy in St. Petersburg in 1890 and to the chair of physiology at the Imperial Medical Academy in 1895. From that time forward, he succeeded in the progressive development of an extensive research "empire" that changed the world's view of brain-gut interactions and digestive physiology.

Nearing the end of his long and distinguished career, at eighty-six years of age, Pavlov presided over the XVth International Congress of Physiological Sciences in St. Petersburg and Moscow in August 1935. The distinguished American physiologist, Walter B. Cannon, attended the Congress and relates that much of Pavlov's characteristic alertness and nervous activity was obvious in his actions during the formalities of the Congress. Cannon states that, "in spite of the demands imposed upon Pavlov by the presidency of the Congress, he fulfilled the duties of his office with admirable grace and skill" (1). Pavlov died in February 1936.

Pavlov's Legacies

Pavlov forever clung to the strong belief that chronic studies in surgically prepared conscious animals were most likely to yield new insights into the integrated physiology of organ systems in general and the digestive system in particular. Leading up to the Pavlovian period, acute preparations in anesthetized animals were the norm for experimental physiology. Pavlov believed, and one might say proved, that sequentially repetitive studies in surgically prepared conscious animals are most likely to advance knowledge basic to humans. That we must understand the normal functioning of an organ in the alert animal, as well as its anatomy, histology, and cellular biology, to know disease has been the standard since Pavlov. Pavlov's legacy in experimental surgery, which could equally well be referred to as "applied surgical physiology," embraces too many subsequent pioneers to mention even a few. An early heir to the legacy was F. C. Mann, followed by L. R. Dragstedt, both of the Mayo Clinic in Rochester, Minnesota, who with a collection of colleagues and trainees in their laboratories built on Pavlov's techniques and demonstrated, for example, that withdrawal of duodenal alkaline secretion and exposure to gastric chyme for abnormally long periods results in formation of an ulcer in a high percentage of dogs (4, 5).

My own introduction to Pavlov's legacy for experimental surgery was at the University of Illinois in 1967–1968 when I was enrolled as a Ph.D. student in F. R. Steggerda's two-semester course in experimental dog surgery, which used the textbook of experimental surgery by Markowitz, Archibald, and Downie (6). The limited number of students admitted to this hands-on course met for most of the day twice each week to learn aseptic methods, suturing techniques, and post-surgical care in the preparation of study models, such as Pavlov and Heidenhain gastric pouches, Thirty-Vella intestinal fistulas, and BielI exteriorized intestinal

[FIGURE 1: Academian Ivan P. Pavlov
A: photograph of I. P. Pavlov from the collection of photos at his country laboratory at Koltushi. B: portrait of Pavlov located in his study at Koltushi.]
loops. J. H. Szurszewski's experience as a student in this course led to his development of methods for recording the electrical and mechanical activity of the intestine in awake dogs over extended periods of weeks and to the data for his doctoral dissertation (14, 15). Szurszewski continued the work as a fellow with C. F. Code at the Mayo Clinic and made the seminal observations on the now-classic intestinal migrating motor complex (MMC) that was named by Code as the "housekeeper" of the small intestine (13). Hundreds of studies on the MMC now appear in the literature! My own experience and insight gained from Steggerda's surgery course translated forward to the year 2000 in a project in which my colleagues and I studied effects of stress on inflammation in Thiry-Vella colonic loops surgically prepared in a chronic primate model for idiopathic ulcerative colitis (20).

**Gastric and pancreatic secretion**

The traditional teaching of the "cephalic phase" of gastric and pancreatic secretion originated with Pavlov. Students learn that stimulation of gastric secretion of acid and pepsin and stimulation of pancreatic secretion of digestive enzymes starts with the anticipation of the ingestion of a desirable meal and is mediated by input to the stomach and pancreas from efferent nerves of the vagus. Pavlov's cephalic phase was a brilliant demonstration of a brain-gut interaction. The stimulation of secretion evoked by linking environmental stimuli (e.g., lights and sounds) with presentation of appetizing food was discovered by Pavlov in his dogs and was called by what is now a classic term: a "conditioned reflex." The descriptions by the American army surgeon, William Beaumont (1785–1853), of how the appearance of the gastric mucosa mirrored the emotional state of his patient Alexis St. Martin preceded Pavlov's work on brain-gut interactions in dogs. Beaumont's studies laid the groundwork for Pavlov's work and are the beginning of the arrow of time that points to what modern physiologists now understand about the digestive tract as an integrated system.

Pavlov was a master experimental surgeon. His development of the "Pavlov pouch" enabled the discovery of the cephalic phase of secretion and its role in the anticipatory preparation of the upper digestive tract for the ingestion of a meal. The Pavlov gastric pouch is essentially the same as the pouch developed by Rudolph Heidenhain in Germany, with the exception that the vagal innervation remains intact (FIGURE 2). Pavlov's discovery that severing the vagal innervation eliminated the cephalic phase for both gastric and pancreatic secretion underlies the discovery of acetylcholine as the neurotransmitter and the muscarinic subtype as the involved receptor.

Needless to say, the invention of the now-obsolete selective vagotomy for treatment of peptic and duodenal ulcer disease in humans in the 1930s and the successful pharmacological development of selective muscarinic receptor antagonists as therapy for gastric acid-related disorders emanate from Pavlov's discovery and those of Latarjet in France (19). Likewise, modern knowledge of the action of histamine as a powerful gastric acid secretagogue evolved directly from Pavlov's physiology factory. Nobel Laureate Adolf Windaus synthesized histamine in 1906, and the extensive investigation of its actions in the body were published by Sir Henry Dale and P. P. Laidlaw in 1910–1911. Dale and Laidlaw did not report on the action of histamine on gastric secretion, perhaps due to lack of experience in surgical preparation of Pavlov-type gastric fistulas in dogs. This was left to L. Popielski, who was one of Pavlov's Polish trainees. Upon completion of his studies with Pavlov and upon his return to work in Poland, Popielski reported in 1916 that injection of histamine stimulated copious secretion of gastric acid in dogs with surgically prepared gastric fistulas.

Now, in the 21st century, we can speculate on the extent to which Pavlov's legacy applies to what we teach as the "gastric" and "intestinal" phases of mucosal secretion in the stomach. The presence of food in the stomach stimulates the Pavlov or Heidenhain pouch to secrete, and this we teach as the "gastric phase." The significant difference between the cephalic and gastric phases of secretion is that the former is only effective in a vagally innervated Pavlov pouch, whereas the gastric phase is also observed in a Heidenhain pouch, which is denervated. This showed that the gastric phase must be due to a hormonal mechanism, which we now know reflects the
food-stimulated release of the hormone gastrin from enteroendocrine cells in the gastric mucosa. The physiology of the "intestinal phase" is similar to the gastric phase, except that gastrin is released from enteroendocrine cells in the small intestinal mucosa and the volume of gastric juice secreted is relatively small.

The eventual understanding of the physiology of acid secretion and the role of gastrin in the functioning animal turned out to be basic to insight into the pathophysiology of the Zollinger-Ellison syndrome in humans. This syndrome, which was described by R. M. Zollinger and E. H. Ellison of the Ohio State University Department of Surgery in the early 1950s, is characterized by hyperplasia of acid-secreting cells in the stomach, hypersecretion of acid, and multiple persistent ulcers of the stomach and small intestine together with the attendant symptoms (21). Elucidation of the syndrome, which is due most often to a pancreatic islet cell tumor that hypersecretes gastrin, might not have been possible in the absence of the chain of advances started by Pavlov.

**Pavlov's physiology factory**

"Pavlov's physiology factory" is a designation used by D. P. Todes in his scholarly biographical analysis of Pavlov's scientific career (17, 18). Todes aptly used the analogy of an assembly line in a highly organized factory to describe Pavlov's laboratory, because large numbers of research fellows and assistants, working simultaneously at any one time in a large laboratory space, efficiently produced large quantities of data and publications that advanced science, gained doctoral degrees for trainees, and advanced Pavlov's prestige. Neither the Russian Revolution nor World War I interrupted Pavlov's physiology factory. In the laboratory, Pavlov was the Professor-In-Chief, moving about to oversee the ongoing work of 15–20 personnel, dictating the studies to be done, fine-tuning each project as it progressed, and evaluating the results for publication. His factory approach to research was vastly different from the norm in the 19th century, when senior investigators ran a small laboratory with only one or a few colleagues and did hands-on research at the bench. The factory approach might be construed as a Pavlovian legacy, especially in the United States, because it is not uncommon in the 21st century for senior investigators to embellish prestige by supervising large laboratory groups supported by funding from the National Institutes of Health and not to spend time at the bench themselves. Senior-in-Chief status is identified by the appearance of his or her name at the end of a string of junior authors on published manuscripts.

Pavlov's offering of research opportunities to young physicians was a forerunner of modern-day fellowship programs in clinical subspecialties. The young Russian physicians in their first decade of practice were accepted into a two-year research fellowship, in which they became a cog in Pavlov's unified productive research machine. Pavlov personally assigned specific research projects, saw to it that the fellows received the necessary training and materials for pursuit of the project, and supervised the preparation of the fellow's doctoral dissertation. Upon completion of the dissertation and awarding of the dissertation and awarding of the doctoral degree in medicine, the research fellow usually returned to clinical practice. Pavlov's opportunity for acquisition of a large workforce of clinical fellows grew from an emerging philosophy in Western European countries and Russia that medicine was more than an art and that physicians should be grounded in the scientific basis of medicine.

**Pavlov's gastric juice factory**

Among Pavlov's many experimental surgical innovations was the esophagogastomy (FIGURE 3). The operation involves dividing the esophagus and bringing the superior and inferior ends out as stomas sutured to the surface of the skin in the neck. It was designed for "sham feeding" and appetite studies in which the swallowed food is diverted to the outside via the superior stoma before reaching the stomach. The inferior stoma provides access for introducing food and liquids directly into the stomach and thereby maintaining the health of the dog. A fistula placed in the stomach drains the gastric secretions for collection and analysis. The dogs are placed on a stand (i.e., a Pavlov stand) facing an elevated platform with a bowl of food (FIGURE 3). As they eat, the food falls into a container on the outside and gastric juice drips continuously from the gastric fistula. Published accounts from Pavlov's laboratory describe how the dogs immensely enjoyed participating in the sham-feeding studies. They would enthusiastically jump up onto the stand and remain compliant for hours as they continued to eat voraciously while their stomachs secreted copious amounts of gastric juice. These were early indications of the importance of the palatability of food in the interactions of appetite and digestive functions.

The breakthrough provided by the esophagogastomized dog model was the ability, for the first time, to collect copious volumes of pure gastric juice uncontaminated by ingested food and saliva. Approximately 150–300 ml of gastric juice per day could be obtained from a single dog without ill effects. One dog was reported to produce 10,606 ml of gastric juice in 45 sessions (18). The juice was described as being an "entirely transparent, colorless liquid without any scent, or sometimes with the same light scent of a fresh solution of hydrochloric acid." Laboratory workers who tasted it described the taste as acidic and not at all unpleasant. For the biochemist, the pure samples were ideal for the analysis of uncontaminated pepsin, which at the time was already identified as a proteolytic enzyme present in gastric juice.

It so happened in Europe in the late 19th century that concoctions of pepsin and hydrochloric acid were widely touted as therapy for dyspepsia. The symptoms described as dyspepsia then were not so different from what is described as dyspepsia in modern gastroenterology. In the Rome II approach to symptom-based diagnosis of functional gastrointestinal disorders, the spectrum of symptoms in dyspepsia includes 1) pain centered in the upper abdomen, 2) discomfort centered..."
in the upper abdomen, 3) early satiety, 4) unpleasant sensation of fullness, 5) bloating in the upper abdomen, 6) nausea, and 7) retching (16). Patients diagnosed with dyspepsia are divided into those in which a cause can be identified (e.g., peptic ulcer, acid reflux disease, or biliary tract disease) and those in which laboratory tests and clinical examination find no identifiable explanation for the symptoms. The latter satisfy symptom-based criteria for functional dyspepsia (16). The prevalence of dyspepsia in the year 2000 was estimated to be ~25% in populations around the world (16). Obviously, dyspeptic symptoms have been present in human populations for a long time. The prevalence was probably similar in the 19th century Pavlovian era and explains the strong interest of the pharmaceutical industry in finding and marketing therapies then, as is the case today.

Before Pavlov developed his gastric juice preparation, none of the multiple pharmaceutical concoctions with pepsin extracted from animal stomachs were consumed enthusiastically by dyspeptic patients, because they were putrid with a foul odor and taste. Acceptance of Pavlov's product as an effective natural medicinal product was slow because of Pavlov's reluctance to divert resources from basic studies to produce commercial quantities of the juice and because of patients' aversion to using gastric juice from dogs as medication. Nevertheless, daily consumption of multiple doses of the juice proved to be efficacious in treating dyspeptic symptoms. Anecdotal praise from the many clinical fellows in the laboratory who tried it included statements such as "when taken after a meal, I always received a sensation of special lightness in the stomach area, an absence of that sensation of unpleasant heaviness during digestion that is characteristic of the chronic, low degree of dyspepsia that I have...[In just the same way, my comrade physicians in the laboratory and those who visited the Institute drank the juice, in part from curiosity, in part with the medicinal goal of easing a sense of heaviness during digestion, which was quickly attained" (18). Daily doses of St. Petersburg gastric juice were reported to be efficacious (in some cases with placebo controls) in treatment of poor appetite, neurosis of the stomach, postprandial epigastric pain, heartburn, gastritis, diarrhea, constipation in patients with typhus infections, globus hystericus, and anemia.

Ultimately, the dispensing of gastric juice by prescription through pharmacies, a growing demand for the juice, and financial exigencies in the Institute led to expansion into a commercial enterprise that generated significant monetary income. Additional assistants were hired, and five large dogs were carefully maintained for the specific purpose of the production of gastric juice. Thus was the beginning of what Todes called "Pavlov's gastric juice factory" (17, 18).

Therapeutic action of Pavlov's gastric juice

The mechanism of therapeutic action of Pavlov's "pure" gastric juice remains open to speculation. It is possible that enhanced digestive action with the acid-pepsin mix facilitates the trituration of solids to reduced particle sizes and thereby facilitates gastric emptying. On the one hand, additional acid might suppress gastric release and its stimulatory action on gastric parietal cells and enteric neurons. On the other hand, the lowered pH of the gastric contents is expected to slow gastric emptying through duodenal feedback.

Reports that treatment with Pavlov's gastric juice stimulated production of red blood cells in patients with anemia might now be explained by what is now known about the necessity of gastric secretion of intrinsic factor for the absorption of cobalamin (vitamin B12). Cobalamin was not isolated until 12 years after Pavlov's death and was therefore unknown as a possible explanation for the efficacy of gastric juice in the treatment of pernicious anemia. Nevertheless, it was suggested by W. B. Castle shortly before Pavlov died that a factor (i.e., intrinsic factor) necessary for the production of red blood cells was secreted by the stomach in association with acid secretion (2). Castle's hypothesis was based on his finding that 200 g of beef fed daily in combination with 150 ml of normal human gastric juice stimulated erythropoiesis and maintained anemic patients in remission. However, not until the mid-20th century was it firmly established that binding of cobalamin to intrinsic factor was necessary for absorption of vitamin B12 by the terminal ileum (3).

Finally, on the subject of therapeutic actions of gastric juice, I mention the more recent reports from the Pharmacology Institute in Zagreb, Croatia that propose that a peptide isolated from human gastric juice has broad protective and healing powers. Immunoreactivity for the 40,000-mol wt peptide is present in stomach and brain, and therapeutic activity is reported to be achieved with a 15-amino acid fragment that has no homology with known messenger peptides in the gut (9, 11). The Croatian proponents called the pentadecapeptide "body protection peptide 157" (BPC-157). Testing with BPC-157 in animals reportedly found protection of the gastric and duodenal mucosa against lesion formation in several ulcer models, including restraint stress and ethanol or cysteamine administration and against pancreatitis in a bile duct-ligation model (10, 11). Moreover, BPC-157...
was reported to have anxiolytic actions (8) and to promote burn-wound healing when applied topically (7).

Pavlov and the antivivisection movement

Pavlov graduated from the university in 1875; restrictive legislation against the use of animals for medical research was passed in England in 1876. The antivivisection movement, which reared its head throughout Pavlov’s lifetime, has progressed unabated into the 21st century as a smothering damper on physiological systems research. As Pavlov’s career progressed, the significance of his discoveries, the successful development of a research-based therapy for dyspepsia, and candidacy for a Nobel Prize elevated him to star status on the world’s scientific stage. As one of the most visible experimenters on animals, he was not deterred by the attention of the antivivisectionists and served effectively as the physiologists’ spokesperson against their perverse and absurd accusations.

Explanations for Pavlov’s success include his concern for his dogs and, in particular, their comfortable recovery from the surgical procedures. He understood that valid results would come only from studies in which the surgical technique was impeccable and the postoperative care of the animal the best possible. One particular event supports the impression that he genuinely cared for his dogs. Early on, Pavlov’s work progressed in the facilities located in St. Petersburg. As time passed and his respect from the Russian leadership grew, an expansive, modern facility was constructed for his work outside the city in a village called Koltushi. Legend has it that a lady caretaker in his St. Petersburg laboratory one day commented that she felt the dogs would be happier if they were free to exercise in the open air in the countryside. As the story goes, this was the motivation for Pavlov to move his research operation to Koltushi. Still standing on the grounds outside his laboratory and apart from the Koltushi, a statue of Pavlov with one of his beloved dogs on it that a lady caretaker in his St. Petersburg laboratory had the antivivisectionists in Pavlov’s pages had the antivivisectionists of his research with animals. Availability of pan-creatic enzyme formulations for the child with cystic fibrosis and our choices of treatments for our acid-related disorders and discomfort might not be available had the antivivisectionists in Pavlov’s time, and through the years to the present, achieved their persistent objective of stopping all animal research.

References


