Pavlov and integrative physiology

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Smith, Gerard P. Pavlov and integrative physiology. Am J Physiol Regulatory Integrative Comp Physiol 279: R743–R755, 2000.— Ivan Petrovich Pavlov was the first physiologist to win the Nobel Prize. The Prize was given in 1904 for his research on the neural control of salivary, gastric, and pancreatic secretion. A major reason for the success and novelty of his research was the use of unanesthetized dogs surgically prepared with chronic fistulas or gastric pouches that permitted repeated experiments in the same animal for months. Pavlov invented this chronic method because of the limitations he perceived in the use of acute anesthetized animals for investigating physiological systems. By introducing the chronic method and by showing its experimental advantages, Pavlov founded modern integrative physiology. This paper reviews Pavlov’s journey from his birthplace in a provincial village in Russia to Stockholm to receive the Prize. It begins with childhood influences, describes his training and mentors, summarizes the major points of his research by reviewing his book Lectures on the Work of the Digestive Glands, and discusses his views on the relationship between physiology and medicine.

sham feeding; Pavlov pouch; gastric secretion; appetite; vagus nerve

Physiology was first recognized as a discipline capable of distinguished international achievement by the award of a Nobel Prize in 1904. The recipient was Ivan Pavlov, a 55-year-old Russian from Saint Petersburg (Fig. 1). The choice must have raised eyebrows. What had this Russian done that transcended the achievements of other prominent physiologists in Europe or England?

The prize was given “in recognition of his works on the physiology of digestion with which works he transformed and broadened substantially the knowledge in this field” (9, p. 287). The works referred to were the results of experiments performed over 10 years on the neural control of salivary, gastric, and pancreatic secretions that he summarized in 1897 in Lectures on the Work of the Principal Digestive Glands (13). Quickly translated into German by A. A. Walther in 1898, French by Pachov and Sabrazes in 1901, and English by W. H. Thompson in 1902, the book made Pavlov’s international reputation.

This paper reviews how Pavlov made his way from the provinces to the Prize. It has three purposes. First, because Pavlov’s scientific mind was formed during this journey, we can compare Pavlov’s training, organization of a research program, and academic advancement with that of a contemporary physiologist 100 years later. Second, by a detailed review of his book, we can appreciate Pavlov’s strategy and tactics as an experimentalist and understand how physiological experiments on the neural control of gastrointestinal secretions forced him to confront the problems of prior experience, food preferences, and individual differences, problems usually considered within the province of psychology rather than physiology. Third, the review takes up Pavlov’s views about the relationship between physiology and clinical medicine, a topic that is particularly relevant to integrative physiology today.

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In contrast to Pavlov's later work on conditioned reflexes, the research experiences and achievements of his first years have received little attention since Babkin's biography published in 1949 (1). The 1964 English translation of Essays on the History of Physiology in Russia (9) first published by K. S. Koshtoyants in Russian in 1946 included some additional information. Since then only four relevant references have appeared in English (4, 12, 15, 18). Because all of these address only selected aspects of his gastrointestinal research, I thought a more detailed review of the man who was recognized at the XV International Congress of Physiology in 1935 as the world's greatest living physiologist would be useful, particularly for integrative physiologists.

CHILDHOOD

Pavlov was born on 27 September 1849 in Ryazan, a village about 200 miles southeast of Moscow. He was the first son of a priest and his wife, who was the daughter of a naval priest (1, p. 5–6; 10). As a priest, Pavlov's father had respect, but little money. The Pavlovs lived modestly, close to the earth and dependent on it. There was one unusual thing about the home: Pavlov's father read books, buying as many as he could afford. This influenced Pavlov. He became a relentless reader and often quoted his father's dictum that to understand a book, you must read it twice.

In addition to a stable home life and books to read and discuss, the young Pavlov had two other advantages. Both arose from a bad fall Pavlov had when he was 9 years old. This required a long convalescence that interrupted his schooling for more than a year.

The first advantage was that Pavlov got to know his godfather, the Abbot of Saint Trinity's Monastery near Ryazan, because the old monk decided that Pavlov would recover better at the monastery than at home. Once Pavlov was there, the Abbot set up a regimen of exercise, especially gardening, rest, and plenty of food. During his long convalescence, Pavlov discovered that the Abbot was at his desk day and night and that he ate very simply (1, p. 8–9). Pavlov made both of these traits his own.

The second advantage from this fall was that when Pavlov returned to school, he and his brother Dmitri were in the same class. Intimate and inseparable, the brothers reversed the usual relationship, the younger Dmitri looked after Ivan. By the time they were at the University, Dmitri took over all of Ivan's domestic chores, including buying clothes for him. Thus, at this early age, Pavlov could persuade people that it was important to free him of these personal matters so that he could attend to his intellectual work. Dmitri's role, as you might guess, was later filled by Pavlov's wife.

SEMINARY STUDENT

Pavlov was a conscientious, but unremarkable, schoolboy. At 15, he entered the local seminary in Ryazan. Pavlov was lucky. The seminary was progressive by the standards of the 1860s. It encouraged students to concentrate on developing their strengths and pursuing their interests. Pavlov recalled being attracted to natural science by reading George Lewes's book The Physiology of Common Life (11). The effect of the book was still vivid for Pavlov in 1929, when he visited Boris Babkin, his protege and biographer, at McGill University and saw a copy of Lewes's book. Picking it up, he found a diagram of the gastrointestinal tract (Fig. 2) and said, "'When in my very young days I read this book, in a Russian translation, I was greatly intrigued by this picture. I asked myself: How does such a complicated system work? My interest in the digestive system originated at this epoch'" (1, p. 214).

Pavlov was also influenced in a more general way by the writings of D. I. Pisarev (9, p. 163). Pisarev was an enthusiast for science as a liberating social force. He called for "the struggling with reactionary elements and ignorance through scientific understanding of nature and society" (9, p. 104). Pisarev pitted science against the ideas of German Romanticism (3, p. 114–135) then circulating among the intelligentsia in this way: "Words and illustrations perish—facts remain" (9, p. 102). Pavlov repeated both of Pisarev's beliefs on a number of occasions in subsequent years.
Pavlov arrived in Saint Petersburg in 1870. This city, built on a delta by Peter the Great to be Russia's "Window on the West," was the political and intellectual capital of Russia. The salons and newspapers seethed with debates about the social changes underway and the best way to a better future. It was symptomatic of the times that the emancipation of the serfs by Alexander II in 1861 had satisfied no one—serfs or landowners, radicals, liberals, or conservatives. It had, however, encouraged the radicals, who considered themselves to be progressive, but who were seen by their opponents to be nihilists wanting to smash people and to believe only in what the dissection of frogs could reveal (3, p. 261–305; 20).

The University and the Imperial Medical-Chirurgical Academy were a hotbed of reform and agitated political discussion. It was a time when ideology could shape academic policy and faculty appointments. An egregious example of this occurred in the appointment of I. F. Tsion to succeed Sechenov as the Professor of Physiology. This incident is worth reviewing because Tsion made a lasting impression on Pavlov.

Born in 1842 or 1843 in the Lithuanian part of the Jewish pale, Tsion was intellectually precocious (7). At 16, he entered the Medical-Surgical Academy in Warsaw. A year later he was ostracized for being a Russian. He studied in Kiev for a year and then went on to Berlin where he received a doctorate in Medicine and Surgery from the University of Berlin in 1862. From there he went to Saint Petersburg. He earned his second doctorate in medicine from the Imperial Medical-Chirurgical Academy in 1865. Tsion was sent by the Russian ministry of education to Paris for postdoctoral training. It is possible that he worked with Claude Bernard. From Paris he went to Leipzig to work with Karl Ludwig. Here he made a major discovery: he observed in anesthetized rabbits...
that stimulation of the central end of a specific vagal nerve trunk connected to the heart produced hypotension and vasodilatation. This was the depressor reflex.

Tsion returned to Saint Petersburg in 1868 to become the Director of the Physiological Laboratory at the University. This post allowed him to lecture, but it was not an established faculty position.

Tsion quickly made a name for himself. He was a brilliant lecturer, being one of the first in Russia to combine lectures on anatomy with dissections in animals. He was also a very accomplished experimental surgeon. A story went the rounds that, pressed for time before a formal academic meeting, Tsion had operated on a dog without getting a drop of blood on his frock coat. Furthermore, his experimental work was honored in 1868 and in 1870 by the French Academy of Science.

On the basis of these skills, professional recognition, and the rigor of his work on the spinal reflex, Sechenov recommended Tsion to be his successor as the Professor of Physiology at the Medical-Chirurgical Academy when Sechenov resigned in 1872. But the faculty balked. They considered Tsion a reactionary. His religious and socially conservative views were repugnant to the faculty’s spirit of scientific materialism, a spirit Kennan described as a “passionately held philosophy commonly expressed. . .in a contemptuous repudiation of the existing religious, political, and social establishments, which were seen as unscientific, hypocritical, and obscurantist, and in a determination to see those establishments swept away by revolution in the name of scientific socialism” (7, p. 451).

Tsion not only lacked the “right” ideas, he was also considered a difficult person—vain, touchy, and vindictive. The faculty may have felt that it already had a sufficient number of such people.

Faced with the choice between scientific talent and the faculty’s ideology, Milyutin, the Minister of Education, chose talent. At the time of his appointment in 1873 Tsion was 29, the youngest Professor of Physiology in Russia and the first Jewish one.

In his inaugural lecture, Tsion decided to instruct his critics, “Between the knowledge of the mechanical processes that occur in thought and the understanding of the way in which these processes actually form the thought, there lies an entire great chasm that human intelligence will never be able to bridge” (7, p. 457). Faced with an angry reaction by students and faculty, Tsion added oil to the fire by presenting his views in more extended form in a pamphlet. But attempts at rational argument never satisfy ideologues because they want simple answers to complicated problems, even if the answers are illusory.

As time passed, the opposition to Tsion became more intense. Students rioted in his class; armed guards had to be posted during his lectures. When he flunked half of the sophomore class for neglecting their studies in favor of radical politics, the dam of protest broke. Tsion was forced to resign. In October 1874, he left Saint Petersburg for Leipzig, where he stayed with Ludwig before settling in Paris. Tsion never returned to Russia except for two brief visits to Moscow in the late 1880s.

Pavlov’s view of Tsion as a teacher is an insight into the quality of the young Pavlov’s mind and character. Pavlov never discussed Tsion’s religious or conservative views or the angry reactions of the students and faculty. On the other hand, he always credited Tsion with showing him how first-class physiology could be done. From Tsion, Pavlov learned about experimental design, operative technique, and demonstration lectures, skills that he was to master.

This episode also reveals Pavlov’s ability to focus on what serves science despite disturbing distractions produced by a complex social and political situation. He was grateful to Tsion for his excellence as a scientific mentor; Tsion’s personal beliefs and opinions were something else. Pavlov’s belief in science did not lead him into social or political nihilism then or later (17).

Before Tsion moved from the University to the Medical-Chirurgical Academy, he suggested that Pavlov begin experimental work with Professor M. I. Afanassiew. The problem was the existence of secretory nerves to the pancreas. Pavlov and Afanassiew observed an inhibitory effect of atropine on the pancreatic secretory response to a meal and proposed this as evidence for secretory nerves. Although the evidence was inconclusive and the interpretation was wrong, the work resulted in four papers and earned a gold medal for Pavlov at graduation from the University in 1875.

After graduation, Tsion offered Pavlov an assistantship in his laboratory at the Medical-Chirurgical Academy. Pavlov accepted this and also matriculated as a third-year medical student (1, p. 14). It is clear that Pavlov was not interested in the practice of medicine. He took courses in medicine to broaden his knowledge of physiology. His experience in medicine was formative. Not only did it give him an acquaintance with human physiology and current ideas of the pathophysiology of diseases, but it also encouraged him to be on the lookout for ways in which experimental progress in the laboratory could be transferred to the bedside and clinic. Pavlov was one of the new generation who saw physiology as the basic science of medicine. This was a doubly subversive idea: it undermined clinical authority and it went against a popular and crude nationalism because it was a European concept developed by the French and Germans.

When Tsion was driven out of the country, Pavlov joined the laboratory of Professor Ustimovich in the Veterinary Institute in 1876. During the next 2 years, Pavlov did not pursue his work on pancreatic nerves. Instead, he returned to problems of the reflex control of the circulation that he had done as an undergraduate with Veliky and that had resulted in two papers in 1874. In one of these, “On the centripetal accelerators of heart beat,” Pavlov first suggested a reflex pressor action to complement the depressor reflex of Tsion and Ludwig (9, p. 292).

Pavlov now took up the problem of how large changes in blood volume produced unexpectedly small changes in blood pressure. Although he did not solve this problem, Pavlov’s experiments produced novel and interesting results because he devised a new technique
to measure blood pressure repeatedly in dogs that were not anesthetized.

Pavlov's technique consisted of training dogs to lie absolutely quiet on a table. Then Pavlov inserted a fine catheter attached to a manometer into a superficial artery on the inner side of the knee joint through a small skin incision that was made so rapidly the dog showed little or no reaction. Repetition of this procedure permitted measurement at different times over months in the same dog. This is the first example of the famous chronic method of Pavlov. Note that it is fully developed in his predoctoral experiments.

Pavlov's experimental talents are on full display here. Technical mastery is the most obvious. At a time when most experiments in physiology were carried out in anesthetized animals, Pavlov trained dogs to lie still and then operated so quickly that they were not disturbed or distressed. But the dazzling technique served a new view of physiology. Seeing the limitations of acute anesthetized preparations, Pavlov believed that real progress in integrative physiology could be made only by repeated experiments in unanesthetized animals. This is his controlling vision as an investigator, and it is the foundation of all of his research. Thus, despite his scientific inexperience, Pavlov is already asserting his independence as an experimental thinker.

During the 2 years (1876–1878) in Ustimovich's laboratory, Pavlov also developed a new operative procedure for making a permanent pancreatic fistula. In the summer of 1877, he worked with Heidenhain in Breslau on the atrophy of the pancreas after ligation of the pancreatic ducts in rabbits. This is the only time Pavlov used a histological technique.

Pavlov received his medical degree on 19 December 1879 with honors. He was awarded a gold medal for his experimental work on the circulation and competed successfully for a postgraduate fellowship that would support him to do full-time research at the Medical-Chirurgical Academy for 4 years.

Pavlov caught the eye of Professor S. P. Botkin, the leading clinician of Saint Petersburg. Botkin was the doyen of the Russian school of scientific medicine that aimed to replace the authority of anecdotal clinical experience with medical science from controlled experiment. Botkin had converted a shed in the garden behind his clinic into a primitive laboratory for animal experiments. Botkin invited Pavlov to direct the animal laboratory. This is the kind of offer young physiologists dream of, and it worked perfectly for Pavlov. Botkin was supportive, and, because of his extensive teaching and clinical responsibilities, he left Pavlov alone. Botkin also taught Pavlov to search for the experimental facts far more important. Through-out his career, Pavlov described his experimental style in these terms.

And then there was the miniature stomach that Heidenhain had invented to obtain gastric secretion uncontaminated by ingested food. This was a major technical advance beyond the gastric fistula technique reported by Blondlot and Bassow. The miniature stomach was a pouch formed surgically from the fundic region of the main stomach. It had a cannula implanted in it to obtain its secretions. The only drawback of the Heidenhain pouch as a miniature stomach is that it did not have vagal innervation because the vagal fibers were cut during the surgical procedure. Both the advantage of the pouch over the fistula and the lack of vagal innervation of the pouch impressed
Pavlov and affected his subsequent gastrointestinal research.

Pavlov returned to Botkin’s laboratory from his 2 years abroad in 1886. Chistovich, a young physician in the laboratory had been floundering during Pavlov’s absence but had been told that things would go better when Pavlov returned. And so they did: “At last,” Chistovich said, “the passionately awaited Pavlov returned, and at once our poor, pathetic laboratory came to life” (1, p. 22).

Pavlov set to work with Chistovich on developing an isolated heart preparation in a dog. With such a preparation, Chistovich could test the effects of the root extract Hellebori virdis on the heart in absence of its effects on the circulation; this was the problem Botkin assigned him for his thesis. Pavlov succeeded in making a heart-lung preparation as well as a totally isolated heart. Chistovich used both preparations in the series of experiments that fulfilled the requirements for his thesis.

HIS OWN LABORATORY

On the basis of his work in Botkin’s laboratory on the cardiovascular effect of drugs and other medicinal substances, Pavlov was offered the chair of pharmacology at the Military-Medical Academy in April 1890. He accepted and held this position until 1895, when he was appointed to the chair of physiology. In 1891, Pavlov also became director of the Physiological Department of the new Institute of Experimental Medicine. The apprentice years were over. Pavlov now had two laboratories and the opportunity to develop his own research program on the control of gastrointestinal secretions. This program began when he reported that the vagus was a secretory nerve of the pancreas in 1888 and of the gastric glands in 1889. These were the opening shots in his great campaign of research in the late 1880s and 1890s that transformed gastrointestinal physiology.

THE BOOK

Pavlov published the record of that campaign in April 1897 in his book Lectures on the Work of the Digestive Glands (13). The book was a series of lectures Pavlov gave to physicians at the Institute for Experimental Medicine in 1895 and at the Military Medical Academy. The preface is unusually informative. It reveals what Pavlov thought he had done and how it had been accomplished. It begins with a disclaimer: “It was not at all my intention, in these lectures, to treat of everything which has been written concerning the work of the digestive glands. I only wished to make known the results of an experimental investigation which, I am convinced, correctly indicates the present position of the subject, and to communicate the same to my hearers, partly by word of mouth and partly by direct demonstration. The subject of these lectures represents the work of my laboratory for nearly ten years; and since every experiment which deals with the functions of the gastric glands, and of the pancreas, has been many times repeated, elaborated, varied, and extended; [sic] the material has, for us at least, lost its fragmentary character and grown into a complete whole” (p. ix).

Pavlov’s view of how this work had been accomplished reveals his conception of the group dynamics of a laboratory: “When I employ the word ‘we’ in the following text, I wish to indicate the whole laboratory. In the description of the several experiments I always mention the author. But the object of the experiment, its meaning and its position in the whole series [my italics], is spoken of from the point of view of the laboratory, without giving the individual opinions and views of the author. It is of essential advantage to the reader to see how a uniform guiding principle has developed, and taken shape in the form of tenable and harmoniously linked experiments. In its main idea the book embodies the latest views of our laboratory; it embraces all the facts, even the most recent, which have been constantly tested, frequently corrected, and now appear to be securely established. In its production all my fellow workers have individually taken part; but it is a joint work, the result of the principle, which animates the whole laboratory. It owes its existence to the acuity of each individual, but in its totality to the guiding conception which has inspired us all” (p. ix-x).

This is a generous and sophisticated view. But I agree with Todes (18), who recently argued that it underestimates Pavlov’s contribution to the “guiding principle” that placed each experiment in a mosaic of meaning.

RATIONALE AND TECHNIQUES

The first lecture describes the problems investigated, the criteria of adequate experimental conditions, and the new methods devised that made progress possible. The problem was to understand how the secretory responses of the digestive glands were adapted and integrated for the digestion of different food stimuli. The physiologist “must, in order to fully grasp his subject, include also within the sphere of his observations the actual progress of digestion as a whole” (p. 3).

To solve these problems, the experimental methods had to satisfy four criteria (Table 1). These criteria were revolutionary because they excluded acute experiments in anesthetized animals, the usual experimental preparation of the late 19th century. Having seen the limits of this approach while still a predoctoral student, Pavlov now makes his case in the strongest possible terms: the acute experiment is a “great hindrance to the efforts of analytic physiology while, in the

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<th>Table 1. Criteria of adequate experimental conditions</th>
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<td>1. Obtain reagents (secretions) at all times and in absolutely pure condition.</td>
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<td>2. Estimate the quantities of volume and contents accurately.</td>
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<td>3. The digestive canal should function normally.</td>
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<td>4. The experimental animal should be in perfect health.</td>
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Adapted from Ref. 13 (p. 4).
developments of synthetic physiology, where it is of value to determine the real course of this or that phenomenon on the uninjured and normal organism, it continues to be an unavoidable obstacle" (p. 15).

Pavlov proposed his famous "chronic experiment" as the way to transcend the limits of the acute experiment. Chronic experiments required animals surgically prepared with chronic fistulas that provided easy access to pure secretions during experiments, but did not interfere with normal digestion and nutrition over months and, sometimes, years. This required "surgical thinking." All that had been learned about aseptic surgical technique and postoperative care in human surgery had to be adapted to the dog. Pavlov successfully argued for the construction of a full surgical suite that included individual kennels specifically warmed and cleaned for postoperative care (Figure 3). This renovation had been financed by the Swedish philanthropist, Alfred Nobel, an indication of Pavlov's growing reputation (18).

Three operative techniques had been devised for the work on the stomach and pancreas that was described in subsequent lectures. The first was the chronic pancreatic fistula. As early as 1879, Pavlov described a technique for a chronic pancreatic fistula. Heidenhain described a similar procedure in 1880, and, according to Pavlov, Fedora had recently reported a significant improvement in 1896.

The second technique was chronic esophagostomy reported by Madame Schumova-Simanovskaia and Pavlov in 1889. Because swallowed food dropped out of the esophagostomy, Pavlov initially called such ingestion fictional feeding, but it has been referred to subsequently as sham feeding. Because no food entered the stomach during sham feeding, the gastric secretory response to eating could be measured for the first time during ingestion without the confounding effect of food stimuli in the stomach. Sham feeding produced such copious gastric secretion that Pavlov said, "You can procure gastric juice from a dog almost as one obtains milk from a cow" (13, p. 10).

The third technique was the surgical preparation of an innervated pouch of the stomach. Reported by Khizin in 1894, it was the solution to a problem that gnawed at Pavlov ever since he saw Heidenhain's gastric pouch. The problem was to prepare a pouch while retaining its vagal innervation. Babkin describes the initial difficulties that Pavlov encountered in making an innervated pouch and his stubborn refusal to accept defeat (1, p. 98–99). (Sixty years later, I came to appreciate Khizin and Pavlov's ingenuity and skill when I helped the late Frank Brooks prepare Pavlov pouches in monkeys.) To emphasize Heidenhain's early contribution, Pavlov always referred to his pouch as the Heidenhain-Pavlov pouch. The pouch was of tremendous importance to Pavlov, because he found that the pouch performed as a high-fidelity miniature stomach.

**GASTRIC AND PANCREATIC SECRETION**

Having described his experimental rationale and chronic preparations, Pavlov turned in the second lecture to a description of gastric and pancreatic secretions that lasted for 6–8 h after the ingestion of meat (flesh), bread, and milk. The results were the famous curves in which the volume of secretion increased and then decayed at varying rates (Fig. 4). Gastric acid concentration was correlated with rate of secretion, but digestive power (enzymatic activity) measured by the Mett method was dissociated from the rate of secretion. There were variations in the response across days and animals, but Pavlov claimed that in a given animal, a

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Fig. 3. Plan of the surgical department of the Physiological laboratory in the St. Petersburg Institute for Experimental Medicine. The original is Fig. 2a on p. 17 in Ref. 13.
typical pattern could be obtained, and he published results from two tests that were impressively close. Without a statistical method to deal with these patterns of digestive work, Pavlov considered the variations to be the result of inadequate experimental control and relied on extensive replications to convince himself of their reliability. (See Ref. 18 for further discussion of this methodological issue.)

Pavlov emphasized the specificity of gastric and pancreatic secretory responses to different foods: “the astonishing exactitude of the work: that which is demanded of the glands they furnish each time to a hair’s-breadth, no more and no less” (13, p. 29). “Each separate kind of food corresponds to a definite hourly rate of secretion, and calls forth a characteristic alteration of the properties of the juice” (p. 35). This leads to “the conviction that the work of the digestive glands is, if I may say so, elastic to a high degree, while it is at the same time characteristic, precise and purposive” (p. 36).

The pancreatic enzymatic response to a change of diet was slowly adaptive. It became “from day to day more and more adapted to the requirements of the food” (p. 41).

Pavlov thought that all of these results bore testimony to the complexity and beauty of the digestive mechanism, what he earlier referred to as a chemical factory. He concluded that there was much to learn: “Obviously a rich field of work lies here, full of important and, as yet, unsolved problems” (p. 40).

**VAGAL CONTROL AND SHAM FEEDING**

In the third lecture, Pavlov moves from measurement of response to neural control: “On the last occasion we were occupied with wearisome figures and curves, which, however, have taught us an extremely interesting lesson. It was made evident that the gastric and pancreatic glands have what we may call a form of instinct. They pour out their juice in a manner which exactly corresponds, both qualitatively and quantitatively to the amount and kind of food partaken of. . . .On what does this apparent instinct of the glands depend and in what does it consist? A probable answer to the question is easily given, and naturally an explanation of the adaptability of the glands is above all to be sought in their innervation” (p. 45).

In considering current opinion about the importance of innervation for gastric function, Pavlov noted that
physicians supported it, but physiologists were uncertain. This prompted Pavlov to describe his view of the relationship between disease and experiment: “This is a striking, but by no means isolated, instance where the physician gives a more correct verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never make their appearance in the normal course of life. It is a series of physiological experiments which nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at his command. Clinical observation will consequently always remain a rich mine of physiological facts. It is therefore only perfectly natural that the physiologist should endeavor to maintain a close connection between his science and that of medicine” (p. 46).

Pavlov relied on three sources of evidence for the importance of innervation. The first two, stimulation and lesion, were traditional, but the third, clinical observation and personal experience, was not. An example of this was the common experience of salivating at the sight of appetizing food. Pavlov never neglected such impressions. Never convincing evidence by themselves, Pavlov used them as seeds of experiments or as working hypotheses. His creative use of such observations gave his work a sense of flair, of risk consciously run. His audacity as an investigator came from his complete confidence in the power of experiments to reveal the truth.

After these initial remarks, Pavlov reviewed the evidence he and his co-workers had obtained for the role of vagal efferent nerves in the stimulation of gastric and pancreatic secretion. He contrasted his apparently decisive evidence for vagal influence with previous conflicting reports and attributed his success to the chronic method.

The experiments on gastric secretion are a beautiful example of Pavlov’s experimental approach. First, he gained sensory control by eliciting gastric secretion only by the orosensory stimulation of sham feeding. Because all of the ingested food passed out of the esophagostomy, none of it could stimulate gastric secretion by a local effect in the stomach. Second, Pavlov used a sequential lesion technique to determine if the vagus nerve was necessary for the gastric response to sham feeding. The sequential technique consisted of two operations. The first consisted of cutting the right vagus nerve below the inferior laryngeal and cardiac fibers. This eliminated the pulmonary and abdominal fibers of the right vagus. After recovery, Pavlov did a second operation in which he isolated the left cervical vagus and tied a thread around the nerve. Just prior to a sham-feeding test, Pavlov pulled on the thread to draw the nerve out of the cervical incision and cut the nerve. There was apparently no cardiac or respiratory distress. The loss of vagal innervation had no effect on sham feeding, but it abolished gastric secretion. The same result was obtained when both vagus nerves were cut below the diaphragm.

With these impressive results in hand, Pavlov and Madame Schumova-Simanovskaiia turned to the complementary experiment of electrical stimulation of the vagus and obtained a reliable secretory response.

These decisive experiments were interpreted this way, “In the act of eating . . . the gastric glands receive their normal impulses to activity by means of nerve fibers which run in the vagi” (p. 52). This strong conclusion was tempered by the caveat, “It is possible that other forms of stimuli exist, which act on the gastric glands through other nerves, or even in some wholly different way, entirely without nerves” (p. 52). Note how nuanced Pavlov’s thinking is here. Despite his commitment to nervism, he leaves open the possibility of non-neural mechanisms, i.e., hormonal or humoral. Pavlov’s interpretive caution was vindicated in 1906 when Edkins discovered gastrin (5).

Pavlov followed the strategy of vagal stimulation, but without sham feeding, in experiments on the pancreas. The results supported vagal secretory fibers stimulating pancreatic secretion, but there was much more evidence here of vagal and sympathetic vasoconstrictor effects that could obscure the secretory response. The vagal vasoconstriction was neatly eliminated by delaying stimulation until 3–4 days after cervical section of the left vagus (the right vagus had been sectioned previously). Apparently the secretory fibers degenerated more slowly than the vasoconstrictive fibers.

These observations, particularly the demonstration of the role of the vagus in the gastric secretion elicited by sham feeding, were significant contributions to physiological knowledge. In a rare grumble, Pavlov regretted that physiologists continued to neglect them despite their publication in Russian and in the foreign literature. Whatever their influence on the field, these results gave Pavlov the key to the lock that had kept psychological influences out of the physiological control of gastrointestinal secretions. Pavlov lost no time in using that key.

EATING, APPETITE, AND GASTRIC SECRETION

Pavlov began the fourth lecture with a brief review of the development of knowledge about the neural control of salivary secretion emphasizing the contributions of his mentors, Ludwig and Heidenhain. He used this review to make three points. The first was that the neural control of the salivary glands is the prototype of a general scheme of an innervation mechanism. This is the familiar reflex arc, consisting of the peripheral endings of (centripetal) afferent nerves, the afferent nerves themselves, a group of central neurons, efferent (centrifugal) nerves, and their peripheral terminations. Pavlov emphasized two aspects of this arrangement: the specificity of adequate stimuli of the afferent terminals and that nerve centers in the brain were defined by functionally connected neurons in the brain.
that also showed physiological and pharmacological specificity (see Ref. 15 for Pavlov’s conceptual nervous system). Pavlov believed that this peripheral and central specificity was the basis of the apparent purposefulness in neural control of gastrointestinal secretions.

The search for the specificity of adequate stimuli of afferent terminals is the fundamental drive behind Pavlov’s research program. The “purposeness” of glandular response to changing conditions required it. This biological insight accounted for his skepticism of non-specific responding: “I always look upon it as a period of scientific inadequacy so long as the effects of the most diverse external agencies upon any normal physiological process, are admitted to be indistinguishable” (p. 64).

The second point of reviewing the control of salivary secretion was to warn of the danger of deducing the control of gastric or pancreatic secretion from the more extensive knowledge of the control of salivary secretion. This is another argument for specificity: “...one must never push the conclusions drawn from analogy too far, but must constantly bear in mind that the life-functions of all organs are extremely complicated, and that the work of even the most apparently similar organs should be submitted to separate and careful observation” (p. 65–66).

The third point of the review was the most important. Pavlov reminded the reader that “...experiences of daily life teach us...that the activity of the salivary glands begins even before the introduction of food into the mouth. ...Hence a psychic event, the eager longing for food, must be accepted as an undoubted excitant of the nervous centre for the salivary glands” (p. 66).

Did food exert a similar action-at-a-distance on gastric secretion in the dog? Recalling that Bidder and Schmidt reported in 1852 that the sight of food increased gastric juice in the dog and that in 1878 Richet observed gastric secretion increase when sweet or acid stimuli were put into the mouth of a gastrostomized patient with an esophageal stricture, Pavlov thought the gastric glands were influenced by “distant effect” [sic] mediated by nerves. Because positive results were not always obtained in such experiments, Pavlov set to work “to make the experiment constant and simple; in other words to facilitate its reproduction and seek out its proper interpretation” (p. 50). He was completely successful: gastric secretion increased when food was prepared or presented to a food-deprived dog even though the dog was not permitted to eat it. This was “psychic excitation of gastric secretion” (p. 73). The key had turned the lock; the psychological entered into the control of gastric secretion.

Pavlov’s first reaction was concern, because the efficacy of psychic stimulation complicated the interpretation of what he had considered to be purely physiological experiments, “...what a dangerous source of error this psychic excitability may become in the different experiments...If the dog has not eaten for a long time, every movement, the going out of the room, the appearance of the attendant who ordinarily feeds the animal—in a word, every little triviality—may give rise to the excitation of the gastric glands” (p. 73). Controlling such potential sources of error in physiological experiments led Pavlov to build his special experimental rooms in the famous “Tower of Silence” in the Institute of Experimental Medicine and to study gastric secretion in the sleeping dog. Although his initial reaction was to eliminate such psychic excitation during physiological experiments, Pavlov gradually became convinced of the biological importance of psychic control and, within a few years, began his sustained investigation of these phenomena that he called conditional reflexes (see Refs. 6 and 19 for interesting and different discussions of this transition).

The gastric secretory response produced by sham feeding was much larger than the response to psychic stimulation. This suggested that chemical and mechanical stimulation of the mouth, oropharynx, and upper esophagus by food ingested during sham feeding were potent stimuli for gastric secretion. But when food stimuli were placed directly into the mouth of a dog, they produced little or no gastric secretion. Pavlov’s response to these negative results was characteristic—he made a strong inference that could be tested experimentally. The inference was that the act of eating during sham feeding increased the desire for food, i.e., appetite, and this increased appetite stimulated the central nervous center for gastric secretion. The inference was tested by varying the period of food deprivation before sham feeding and by comparing the gastric secretory response to sham feeding of foods that a dog showed differential preference for. Both increased deprivation and increased preference were correlated with increased secretion. Because increased deprivation and increased preference had face validity as procedures that increased appetite, Pavlov concluded that appetite equaled gastric juice. This was and is an extraordinary assertion. It implied that a psychological state could be measured quantitatively by the volume of gastric secretion produced. This was to introduce a psychological state into the action of the functionally connected neurons in the brain that transformed afferent input into efferent output. In contrast to the psychic control exerted by food stimuli acting-at-a-distance, the psychic control by appetite operated within the reflex arcs stimulated by direct contact of food stimuli on the mucosa of the mouth. If the psychic control by distant stimuli opened the door to the psychological, the insertion of appetite into reflex activity driven by stimuli in the mouth was revolutionary because it suggested that under normal conditions, psychic states or factors could determine physiological function in the gastrointestinal tract. The insight was that the psychological and the physiological interconnected in the function of the central gastric secretory neural center, and, therefore, their combined effects were expressed in vagal efferent output and glandular secretion. For Pavlov, appetite had the logical status of an intervening variable of motivation—the desire for food. This intervening variable was detected by a change in the input-output function of gastric secretion, what we now refer to as a change in central...
processing. If one of the major themes of physiology in the 19th century was how to move psychological issues into physiological discourse (16), these results and interpretations of Pavlov were a major and overlooked success.

Having made a novel interpretation, Pavlov moved to test it by looking for its significance in gastric function. This consisted of comparing the digestion of various foods when placed into the stomach with or without sham feeding. In every case, gastric digestion was more complete when sham feeding occurred. Indeed, in the absence of prior sham feeding, starch and egg white were not digested.

But was acid secretion the necessary contribution of sham feeding to gastric digestion? This question was addressed by repeating these experiments after bilateral vagotomy. Vagotomy did not change sham feeding, but it abolished the effect of sham feeding on gastric secretion: after vagotomy, food placed in the stomach during sham feeding was as little digested as when no sham feeding occurred.

Armed with this evidence, Pavlov pushed its implications. The implication for the physiology of gastric secretion was that local stimulation of the gastric mucosa by food stimuli acting in the absence of sham feeding produced inadequate gastric secretion for normal gastric digestion. This contradicted the common assertion that local stimuli were the primary cause of acid secretion produced by food stimuli in the stomach. Pavlov considered that his results obtained under better experimental control demolished this assertion that he dismissed as “a sad misconception degenerated into a stubborn prejudice” (p. 85).

Pavlov also thought that his results illuminated the numerous clinical symptoms associated with poor appetite. He argued that poor appetite would produce less acid and this would decrease gastric digestion. Incomplete gastric digestion could lead to a variety of symptoms, an example of the contemporary clinical concept of autointoxication.

These ideas led to the therapeutic suggestion of improving gastric digestion by prescribing acid solutions prior to each meal. And, in a model of biotechnology transfer from basic science to clinical therapeutics, Pavlov sold the copious gastric juice produced by sham feeding to clinicians, using the proceeds to support his research (18). Although Pavlov’s pathophysiology never amounted to much scientifically, it remained an attractive clinical explanation for some time. I last heard the prescription of hydrochloric acid solution for this purpose defended at a medical meeting in Washington, DC, in the mid 1960s.

PANCREAS, PROGRESS, AND PROSPECTS

After the intellectual and experimental fireworks of this lecture, the next lecture on the control of pancreatic secretion seems anticlimactic. Psychic control is much less evident in the pancreas than it was in the stomach. The dominant stimuli are local; they enter the duodenum from the stomach. About the potency of acid as a stimulant, Pavlov wrote “the sensitiveness of the pancreas is about as great as that of the organs of taste, for a fluid which just tastes acid acts distinctly as an excitant of the gland” (p. 115). This comparison suggested that there were cells in the duodenal mucosa that were as sensitive and specific as taste cells in the mouth for the neural transduction of chemical information. It is interesting that this is our current view.

Pavlov argued that neural reflexes must mediate the effect of the local, preabsorptive stimuli on pancreatic secretion, but the details of this needed to be worked out. Pavlov had no premonition that the details would reveal a prominent role for hormonal mediation by secretin within 5 years after his book was published (2).

In addition to reviewing work on the pancreas, Pavlov used this lecture to summarize his progress and prospects.

First the progress: “Instead of a crude indefinite scheme, we see now the outlines of a skilled mechanism which, as with everything in nature, proves itself to be adapted with the utmost delicacy and in the most suitable manner to the work which it has to perform” (p. 129).

Then the prospects: “We have now many more open questions before us than we had a short time ago, and all these questions mean progress in our investigations because they testify to the existence of a wide field of inquiry which we have studied from a general point of view, but which we now wish to submit to exhaustive research” (p. 127).

PHYSIOLOGY AND CLINICAL MEDICINE

Pavlov’s eighth and concluding lecture was primarily concerned with the relationship between physiology and clinical medicine, a topic that seemed worth exploring for his audience, most of whom were clinicians. Despite Pavlov’s lack of clinical experience, he had great respect for the difficulties of clinical work and saw physiology as a body of knowledge and a way of thinking that would diminish these difficulties.

Medicine needed the mechanisms physiology discovered: “When we know that an effect takes place it does not by any means imply that we know the mechanism by which it occurs, and although medicine is broad enough and comprehensive enough to make free use of empiricism in practice, yet it often thinks in narrow grooves when it turns to the explanation of facts” (p. 145).

Physiology’s role in medicine is important, but limited: “…physiological knowledge is often able to explain the causation of an illness and the meaning of empirical curative methods. To employ a remedy the mode of action of which is not clear, is quite a different thing from knowing precisely what we are doing. … But physiology naturally can make no pretence to guide the field of medicine, since the knowledge at its disposal is incomplete, and is much more restricted than that of the broad world of clinical reality” (p. 133).
If the relationships between physiology and medicine were pursued vigorously, Pavlov's grand vision of the new medicine would be achieved. “It is thus that medicine, being daily enriched by new physiological facts, will at length grow into what it ideally must become, namely, the art of repairing the damaged machinery of the human body, based upon exact knowledge or, in other words, applied physiology” (p. 133).

Pavlov thought that he had seen these relationships in action in the laboratory he directed for S. P. Botkin. In a memorial lecture in honor of Botkin that Pavlov included as the last chapter in the first English translation of his book in 1902, Pavlov reminded his listeners that the celebrated clinician sought the answers to clinical problems in animal experiments. “Before my own eyes he has directed many of his pupils to the laboratory. And this great appreciation of the method of experiment on the part of a clinician, in my opinion, does no less honor to the name of S. P. Botkin than his clinical activity which is known to all Russia” (p. 186).

Nobel Prize

This book of lectures, rapidly translated into German, French, and English, carried Pavlov’s thought and work to the entire physiological community, most of whom did not read Russian. Like most authors, Pavlov was dissatisfied with what he perceived as a lack of an enthusiastic response to the book, but there is no doubt that the book had a lot to do with Pavlov’s nomination for the Nobel Prize in 1901 (21). It is a testimony to the international recognition of his work that one of his four nominators was W. H. Howells of Johns Hopkins.

The nomination prompted a site visit by J. E. Johansson, Professor of Experimental Physiology at the Karolinska, and Robert Tigerstedt, a distinguished Finnish physiologist. Pavlov could expect a sympathetic critique from Tigerstedt because they had corresponded and met prior to this visit and Pavlov had given Tigerstedt samples of gastric juice obtained from sham-feeding dogs. The visit lasted 5 days, and the report was very favorable. But the Nobel committee was concerned about Pavlov’s publication record. Although Pavlov had published 45 papers and one book from 1888 to 1900, only 35 publications were on digestion and 17 of these were lectures published in Russian in the Proceedings of the Society of Russian Physicians in Saint Petersburg. Furthermore, as we have seen, his book was also a collection of lectures. Strictly speaking, such publications did not count. These concerns were sufficient to reject Pavlov. The committee awarded the first Nobel Prize in Physiology or Medicine to E. A. von Behring of Germany for his work on serum therapy, especially its application against diphtheria.

Pavlov was rejected again in 1902 and in 1903. In 1902, the prize was given for work on malaria by Ross of Great Britain and in 1903, for radiation treatment of various diseases by Finsen of Denmark in 1903.

Undeterred, Pavlov’s advocates tried again in 1904. They argued against all the objections, such as the work involved experimental animals rather than patients, it was theoretical rather than applied, and it was physiology not medicine. The committee was finally convinced.

And that is how Pavlov came to be sitting to the right of King Oscar II in the Royal Musical Academy’s Great Hall on Friday, 10 December 1904. K. A. H. Morner, Professor of Physiology at the Karolinska, Chairman of the Nobel Committee, and strong supporter of Pavlov reviewed Pavlov’s achievements and made the presentation. The citation read

The Caroline Medico-Surgical Institute, according to the will executed 15/27 November 1895 by Alfred Nobel,

Having the right to award the Nobel Prize for important discoveries that in recent times have enriched physiology and medicine, has resolved on this date to award a prize, in this year 1904, to Ivan Petrovich Pavlov in recognition of his works on the physiology of digestion with which works he transformed and broadened substantially the knowledge in this field.

Stockholm
7/20 October, 1904
The Professorial Council of the Caroline Medico-Surgical Institute.

Thus ended Pavlov’s arduous trip from the provinces to the Prize. His lecture announcing new work on conditional reflexes, rather than reviewing what he had achieved in the analysis of digestion was characteristic. Pavlov always faced forward: current problems and their future solutions were what absorbed him. An experimentalist to his fingertips, he had a total belief in science that left little room for an exaggerated view of himself or his accomplishments. As he told his wife when notified by Tigerstedt that he had been awarded the Prize, “There is nothing exceptional in my work; it is all based on facts from which logical conclusions were drawn. That’s all.” (1, p. 45).

Perspectives

Pavlov’s basic intuition was that the physiology revealed by acute experiments in anesthetized animals was limited. This limitation was inherent in the method, because the acute experiment did not address the fundamental question of how the organs of the body were integrated for adaptive action in response to the flux of environmental stimuli. This limitation was overcome when Pavlov invented the chronic experiment in which the same animal could be investigated repeatedly for months or years without interference from anesthesia and recent surgery. The chronic experiment was the platform from which integrative physiology was launched.

The results of the chronic experiments on digestion revealed that glandular secretions responded to the environmental stimuli of perceived and ingested foods in specific, precise, and adaptive ways. This was the first experimental vision of integrative gastrointestinal
physiology. What was unexpected, of course, was the discovery that “psychic events” affected physiological function. From this time on it was clear that if integrative physiology was to be comprehensive, it had to deal with aspects of central neural integration that in this century have been claimed by psychology. That problem is still with us and is likely to remain for some time because it is one of the ways in which the tangled relationship between the brain and the control of visceral function presents itself.

Pavlov’s journey from the provinces to the Prize reveals how little the structure of the training and practice of physiology has changed in the last 150 years. His graduate education was equivalent to our MD-PhD programs. Pavlov made his way by winning prizes for outstanding research. This was followed by 2 postdoctoral years in top European laboratories. He worked initially as a director of a laboratory under a senior professor and then became head of his own laboratory, where he showed outstanding scientific, mentoring, and entrepreneurial skills. His achievement of the Prize was a triumph over bureaucratic rigidity as well as scholarly issues of productivity and responsibility that are still inherent in research that is produced by a relatively large laboratory organized around a leader (8, 18).

Pavlov’s view of the necessary reciprocal relationships between physiology and medicine was intelligent and unusually sensitive to the problems of communication between the laboratory and the clinic. It remains a wise guide to integrative physiologists currently working on animal models of human disease, particularly those concerned with genetic mechanisms. The most unusual thing about Pavlov does not appear in this paper. That was his ability to change his research program at the age of 55 and to go on to invent a new field of research, i.e., the investigation of conditional reflexes, that he actively pursued for 30 more years through the social and political upheavals caused by two wars and two revolutions. This work was the basis for his nomination for the Nobel Prize again in 1925 and 1927. The Committee was not convinced either time (21). I have not found a record of his reaction to these rejections. I like to think there was none because he was too busy planning the next experiment.

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