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Physiology in Natural Sciences and in the History of the Russian Academy of Sciences

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Abstract—The beginning of physiology studies at the Academy of Sciences and Arts in St. Petersburg dates back to 1725. The first studies were carried out at the Chair of Anatomy and Physiology; and in the 19th century, at the Physiological Laboratory. The 20th century saw the establishment of the first Institute of Physiology within the USSR Academy of Sciences. Natural sciences had been developing with the emergence of new research methods and new scientific fields, but the interest in understanding the mechanisms underlying functions of the human body and their regulation has remained unchanged. Adequate approaches to the nature of dysfunctions on the foundation of physiological functions lie at the core of every clinical discipline. Stemming from the methods of molecular biology, genetics, and bioinformatics, the outstanding achievements of the last decades of the 20th century and the first decades of the 21st century necessitate a transition to a new level through the interaction between different sciences in order to elucidate regulation mechanisms for creating a vision of the physiological activity of the body as an integral whole.

Keywords: physiology, history of the Russian Academy of Sciences, homeostasis, kidney, water–salt metabolism

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There is a stage in the development of any science when a need arises for self-reflection, generalization, and evaluation of the accumulated experience. This way one can more consciously set goals for the future. The structure of science, as well as its transformations, can be traced from textbooks and manuals, which store the most important knowledge about the state of research in a given field. Understanding trends in the development of a given science and making an adequate forecast, at least for the near future, requires intuition. The development of science is often uneven; major achievements in related fields exert a serious influence on any field. The same is true for physiology as well. When analyzing the trends in its development, one needs to answer the question about its place in modern natural sciences, its role in the applied areas of science, and its influence on the progress of medicine and education.

This article focuses on the history of physiology studies at the Russian Academy of Sciences. From the first days of the existence of the Academy of Sciences and Arts in St. Petersburg, physiology has held a rightful place within its scientific institutions and has been closely connected with medicine, outstanding representatives of which became members of the academy.

DEVELOPMENT OF PHYSIOLOGY AT THE ACADEMY OF SCIENCES

Physiology as a science has virtually always been one of the key disciplines at the Academy of Sciences in Russia: St. Petersburg Academy of Sciences and Arts, the USSR Academy of Sciences, and the Russian Academy of Sciences [1]. As is known, the decree on the establishment of the Academy of Sciences was signed by Peter the Great in 1724. At that time, there were only a few people in Russia who had received education in Europe and had defended dissertations. Therefore, the Emperor's *Leib-medik* (Physician-in-Ordinary) Laurentius Blumentrost (1692–1755), who became the first president of the academy, and a group of like-minded people looked for foreign scientists from various fields of knowledge and invited them to move to Russia.

It was necessary to set the stage for the development of science and the education system and for training people for the academy itself. The deliberations of Peter I and his advisers resulted in creating

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Fig. 1. Academician of St. Petersburg Academy of Sciences Leonhard Euler. The marble bust stands in the hall of the Presidium of the Russian Academy of Sciences in Moscow (Leninskii prospekt, 14). Sculptor J.-D. Rachette. 1788. *Photo by Yu.V. Natochin*.

Fig. 2. Signature on the copper base placed under the bust of Leonhard Euler. *Photo by Yu.V. Natochin*.

a productive state system of science and education with stable funding from the treasury and a well-thought-out structure of the Academy of Sciences, which was integrated into the empire's system of state institutions. Three centuries later, one can confidently speak about the outstanding role played not only by the Emperor but also by Blumentrost in resolving these issues [2]. It is also worth noting that, as early as in the first years of existence of the academy, the roles of its administration, the president, and the scientists themselves became demarcated. The president of the academy was not a full member of the academy, the number of full members was kept constant, and they were appointed (subsequently, elected) for vacant positions only.

At that time, of course, there were no research institutes as such (they appeared two centuries later), so the development of science depended on ideas put forth by individual bright scientists. These ideas were gradually implemented by their followers; scientific schools arose within the academy's chairs or at universities [3, 4]. In the second half of the 19th century, the Physiological Laboratory was established with the Academy of Sciences, but the first physiological research institute appeared only in 1925.

The Chair for Anatomy and Physiology became one of the first to be established with the Academy of Sciences. The first head of the chair was Daniel Bernoulli (1700–1782), who had come from Basel (Switzerland). He was appointed professor of physiology on July 5, 1725, and then, in 1727, he changed his major field of studies to become professor of mathematics. On December 17, 1726, Bernoulli's friend Leonhard Euler (1707–1783) was invited to this chair as an adjunct. He worked at the Chair for Physiology until January 1, 1731, after which he moved to the Department of Higher Mathematics. In the photo (Fig. 1), the inscriptions engraved under the marble bust of Euler show the names of the sciences to which this scholar made a particularly noticeable contribution, the first one on the list being physiology.

Over the next two and a half centuries, outstanding physiologists and physicians were elected to the various divisions of the Academy of Sciences, and the Chair for Anatomy and Physiology worked for many decades. An independent Department of Physiology, USSR Academy of Sciences, was established only in the second half of the 20th century, a decade after the evisceration of this science, which was committed in 1950 during the infamous Joint Session of the USSR Academy of Sciences and the USSR Academy of Medical Sciences, dedicated to the physiological teachings of Academician Ivan Pavlov [5]. This session took place two years after the even more notorious session of the Lenin All-Union Academy of Agricultural Sciences (VASKhNIL), at which Russian genetics was actually destroyed and Trofim Lysenko was put on a pedestal.

In those years, the Academic Secretary for the Biology Department of the USSR Academy of Sciences was Academician Levon Orbeli, a student and successor of Academician Pavlov. In his post of the Academic Secretary, he tried—in accordance with academic traditions—to ensure the possibility of development of different scientific schools. But this approach ran counter to Lysenko's ideas, and harsh

Fig. 3. Academician Levon Orbeli and Aleksandr Ginetsinskii, Corresponding Member of the USSR Academy of Medical Sciences. 1956. *Photo by Yu.V. Natochin*.

retribution followed. After the VASKhNIL session of 1948, and then the Pavlov session of 1950, Orbeli was persecuted [6], as was his scientific school. He was removed from the post of director of the Pavlov Institute of Physiology (organized in 1925 on the basis of the Physiological Laboratory); the same fate befell Aleksandr Ginetsinskii, Corresponding Member of the USSR Academy of Medical Sciences, who was both a deputy and student of Academician Orbeli.

However, Orbeli continued to work. By order of the President of the USSR Academy of Sciences, he was allowed to organize a research group of eight people. As for Ginetsinskii, he was dismissed from the Institute of Physiology, but he was allowed to continue working at the Chair of Normal Physiology (Pediatric Medical Institute), which he created in 1932 and headed for many years. But in 1951, a commission from Moscow demanded that he be dismissed, and he was sent to work in Siberia, where he headed the Chair of Normal Physiology at Novosibirsk State Medical Institute. The difficult times for the participants in the destroyed physiology schools continued until Stalin's death in 1953.

In 1951, with the participation of well-known physiologists Ezras Asratyan, Vladimir Rusinov, and Mikhail Livanov, the Institute of Higher Nervous Activity and Neurophysiology, USSR Academy of Sciences, was founded in Moscow. In 1954, the Presidium of the USSR Academy of Sciences made a decision to create the Laboratory of Evolutionary Physiology, USSR Academy of Sciences, and appointed Orbeli as its head. In 1954, Ginetsinskii to returned from Novosibirsk to Leningrad, at the invitation of Orbeli, for the position of senior researcher with this laboratory. In January 1956, the Presidium of the USSR Academy of Sciences transformed the Laboratory of Evolutionary Physiology into the Sechenov Institute of Evolutionary Physiology, USSR Academy of Sciences. Academician Orbeli became its director, and soon Ginetsinskii became his deputy director for scientific work. This marked the end of one of the difficult stages (concisely depicted here) in the development of Russian physiology at the Academy of Sciences, which was followed by the healing of intellectual wounds and the rapid restoration of physiology as a science.

THE PHYSIOLOGY DEPARTMENT OF THE USSR ACADEMY OF SCIENCES

On May 19, 1961, the General Meeting of the USSR Academy of Sciences elected Academician Mstislav Keldysh as its president. Later, he would carry out a reform of the academy. By the decision of the General Meeting on July 1, 1963, a new Statute of the USSR Academy of Sciences was adopted, and by the decree of the Presidium of the USSR Council of Ministers, dated June 28, 1963, the Physiology Department was established as part of the Academy of Sciences. The department's first Academic Secretary was Vladimir Chernigovskii (1907–1981). In 1959, he headed the Pavlov Institute of Physiology (after the death of Academician Konstantin Bykov). In June 1960, he was elected Academician of the USSR Academy of Sciences. In 1963, a decision was made to hold a joint first session of the Physiology Department and the Scientific Council on Physiology as an Integrated Problem, which had yet to be created. The work on organizing this council within the Physiology Department was assigned by Chernigovskii to Kirill Lange, who was appointed scientific secretary of the council. The Pavlov Institute of Physiology set up a group that

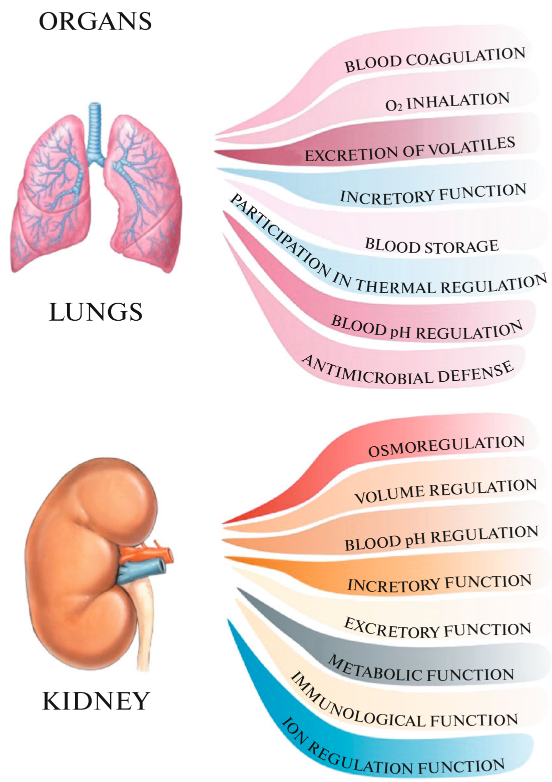

Fig. 4. Physiological functions of the lungs and kidneys. *Drawing by Yu.V. Natochin and E.V. Balbotkina*.

Fig. 5. Monument to Claude Bernard, a foreign member of the Imperial St. Petersburg Academy of Sciences, in Paris. *Photo by Yu.V. Natochin*.

was actively involved in preparing the session of the council. The group included Aleksandra Borgest and Nonna Rosina. The first session of the Scientific Council on Physiology as an Integrated Problem, together with the meeting of the department, was held on January 7–9, 1964.

On Tuesday, January 7, 1964, at 11 a.m., in the conference hall of the Pavlov Institute of Physiology, Academician Chernigovskii opened the General Meeting of the Department of Physiology, USSR Academy of Sciences. At 3 p.m., the first joint session began of the General Meeting of the Physiology Department and the Plenum of the Scientific Council on Physiology as an Integrated Problem. Chernigovskii became the chairman of the council; his deputy was Evgenii Kreps, Corresponding Member of the USSR Academy of Sciences. The speakers were V.N. Chernigovskii, E.M. Kreps, P.G. Kostyuk, P.V. Simonov, and Yu.V. Natochin (at that time a candidate of biological sciences). All of them, precisely in this sequence, would be the heads of the Physiology Department, USSR Academy of Sciences, then Russian Academy of Sciences (RAS), over the next four decades, from 1963 to 2002, until in 2002, within one of the RAS reforms, the Physiology Department and the Biological Sciences Department would be merged. Stunning is the visionary gift of Chernigovskii, who put on the list of the speakers precisely these scientists, who would later become full members of the Academy of Sciences.

For decades, the Scientific Council on Physiology as an Integrated Problem remained very active and its problem-based commissions turned out to be effective. The latter included commissions on the physiology of digestion, the physiology of nutrition, the physiology of the kidney and water–salt balance, etc. Every year since the mid-1960s, conferences and scientific schools were held on these problems, lasting seven to ten days. Their venues were located in different republics of the Soviet Union. About 300 to 400 participants came to each session. During the reorganization of the USSR Academy of Sciences into the Russian Academy of Sciences, the RAS Scientific Council for the Physiological Sciences was established on the recommendation of the General Meeting of the Physiology Department dated March 22, 1993. The new scientific council held its first session in St. Petersburg in December 1993; the focus of its second session, held in July 1994, was on molecular physiology. The session was held at Petrozavodsk State University in Karelia. Among the participants there were well-known Russian physiologists Academicians Oleg Gazenko, Platon Kostyuk, and Pavel Simonov; foreign members of the RAS, including Prof. Masao Ito, President of the International Union of Physiological Sciences; and scientists from the United States, Germany, and Finland.

PHYSIOLOGY: ITS PLACE IN LIFE SCIENCES AND ITS PROBLEMS

The end of the 20th century and the beginning of the 21st have seen great progress in the various fields of life sciences [7, 8]. It is obvious that new areas—bioinformatics, molecular genetics, and molecular biology—are of paramount importance for understanding the intrinsic mechanisms of life phenomena. Physiology represents another level of research into the world of living beings. This level comprises an in-depth look into the molecular foundations of their functions and their regulation within an integral organism; an explanation of how molecular elements become building blocks of systems, or multicellular organisms; and a study of the regulation of functions and the synchronization of physiological processes [9]. This construction of living systems allows one to understand how physiological systems originate within a single organism; how adaptation processes improve; what ensures the organization of living systems; and how conditions form for the birth of thought and art, i.e., of anything associated with creativity given all the ambiguity and grandeur of this word [10]. The study of physiological mechanisms underlying these phenomena is one of the tasks of physiology.

Physiology is one of the branches of fundamental science, and to do science—for those who live and breathe it—is to make a miracle of knowing. Science is a synonym for creativity; a researcher dissolves in it, preserving him/herself. Each generation of researchers creates science by building new tiers on the shoulders of the titans of the previous eras. Physiology is an integral whole; its components are the functions of every system (nervous, cardiovascular, etc.) of a living being. A troubled state of any of the systems is fraught with the weakening of the whole and of its components. Advances in every branch of physiology nourish the whole. Individual sections of physiology are often described by a combination of two terms, i.e., the term physiology plus an "epithet," which indicates a specific field of this science; e.g., medical physiology, physiology of microorganisms, plant physiology, etc. (Table 1).

Table 1. Physiological sciences

Branches of physiology	Physiological sciences
Physiology of groups of organisms	Human physiology
	Animal physiology
	Physiology of protozoa
	Physiology of microorganisms
	Plant physiology
	Fish physiology
Physiology of systems	Physiology of respiration
	Physiology of sensory systems
	Physiology of digestion
	Physiology of the immune system
	Physiology of blood circulation
	Physiology of blood (hematology)
	Physiology of the endocrine system
	Physiology of reproduction
	Physiology of the kidney
	Physiology of the nervous system
Physiology of states; adaptation	Ecological physiology
	Physiology of aging
	Evolutionary physiology
	Gravitational physiology
	Physiology of sports
	Physiology of labor

Living organisms have a form as well as a notable distinctness of functions and chemistry. They are studied by *life sciences*, such as anatomy, histology, microanatomy, etc., each of which applies a wide range of methods. The organs of the body have a set of functions that underlie the manifestations of life—from vegetative functions (digestion, respiration) to higher brain functions (consciousness, intellectual activity in the broadest sense). A crucial theoretical task is to determine the level of *morphofunctional organization of an individual organism,* and this is what physiology does. I believe that the first level in the performance of functions in an organism capable of independent existence is a cell with all subcellular components, and the highest level is an individual organism as such, if we are talking about a multicellular being [11]. Other points of view are expressed too, which consider subcellular organelles (mitochondria, ribosomes, etc.) as the lowest physiological level and a community, ecosystem, etc., as the highest one [12]. However, in physiological terms, a primal individual capable of independent life is a cell, a microorganism, or a protozoan (e.g., ciliates) and the highest form of life is a multicellular organism, be it a human, a mollusk, or an insect, but not an ecological community, although a multicellular being lives in an environment and is closely connected with it.

Physiology studies the *functions of living organisms*; this is the role it plays in the system of sciences [13, 14]. Its purpose is to elucidate the organization, the forms of manifestation, and the intrinsic mechanisms of regulation for every function. The functional activities of the body include nutrition, digestion, respiration, reproduction, circulation, excretion, etc. (naturally, the list can be continued); it is necessary to investigate comprehensively the intrinsic mechanisms of realization of every function, including the ways of their regulation. To this end, physiologists apply a wide range of research methods, including molecular biology and molecular genetics, bioinformatics, and behavioral studies. It is important not only to delve into the nature of life phenomena at every level but also to find out how the regulation system works in such an extremely sophisticated entity as an organism, which is incredibly extensive in the variety and quantity of components, i.e., regulatory molecules, and to try to understand what mechanisms ensure the integrity of an organism and the interaction of its parts [15]. Building upon this principle, at least in relation to man, physiology cooperates with psychology in an attempt to find out how consciousness and awareness arise and how thought emerges, i.e., what gives birth to it. All these problems acquire new contours and new meanings in the context of the study of artificial intelligence.

The use of methods of natural sciences enabled progress in understanding the nature of bodily functions. Physiology has been developing through the application of methods of biochemistry and biophysics as well as molecular biology and genetics to lay the foundation for our understanding of the intrinsic mechanisms of physiological functions. In this case, one can speak of *the transitory in the permanent*. New methods of research, or, in other words, transitory ways of cognizing life phenomena, yield the fruits of new knowledge, which, in turn, allow the building of the permanent, i.e., fundamental science, an understanding of the fundamentals of functions in living beings. The humanities, too, develop along with natural sciences. Language is grand. Thanks to the many generations of speakers, terms become so polished that they can strictly and accurately characterize phenomena of the inner and outer world. At the core of natural sciences lies physics, the science of the physical foundations of the Universe, and physiology is central to understanding the nature of the functions of living beings. In both cases, the language uses the same word root—*physis*, or nature. It turned out that the evolution of language is based on the same principles as the evolution of physiological systems [16].

The tree of science branches out, new stems sprouting, one-by-one, from the common trunk. The same branching is also observed in the history of physiology. In the 19th century, two hundred years after William Harvey published his well-known treatise, which became a milestone in the development of physiology as an independent science (1628), scientific studies appeared—in connection with the development of chemistry and physics—into the physical and chemical mechanisms of physiological functions. At the turn of the 19th and 20th centuries, physiological chemistry sprouted out from physiology to form biochemistry; simultaneously, scientists began to penetrate into the physical foundations of functions, which led to the development of biophysics. In the mid-20th century, especially in its second half, the development of molecular biology and genetics enabled a breakthrough in our understanding of the molecular foundations of physiological functions, thus making it possible to penetrate deeper into *the mechanisms of the functions*, which means a huge contribution to the development of medicine. Understanding the nature of changes in the genome, which lead to deviations in the structure of proteins and the realization of the functions, has become an impetus for the development of clinical methods for diagnosing hereditary diseases caused by disorders in a particular gene and has opened a new chapter in medicine concerning the nature of orphan diseases.

Interesting ideas about the relationship between molecular biology and modern physiology were recently put forth by Academician Evgenii Sverdlov [17]. In his opinion, the problem of a human individual should be looked at not only through the prism of the genome but also from afar, so to speak. Such a standpoint allows one to see a combination of genes rather than one single gene and thus reconstruct the organism as a whole; this way it becomes possible to carry out the study of man and characterize the factors underlying his formation. The genome is treated as the foundation for the realization of the potentialities of an individual; at the same time, one can see the instantaneous reactions associated with the interaction of the body's regulatory systems, which arise on the basis of its structures but function independently of one another. Different reactions of an individual to the same stimulus depend on the integration of a complex of regulatory factors acting at a given moment; therefore, even identical twins demonstrate different behaviors.

Let us consider a simple but, unfortunately, real situation. Some children suffer from nocturnal enuresis, i.e., involuntary urination at night. When looking into the causes and physiological mechanisms of this condition, it turns out that during an enuresis episode in the kidney in the initial phase of urine formation, the rate of this first phase (i.e., glomerular filtration) remains the same but the volume of osmotically free water reabsorbed in the tubules increases and so does the diuresis, which increases simultaneously. The first reaction of a specialist to such a pattern would be to deny such a possibility since according to the conventional ideas, diuresis (the volume of urine released) is equal to the difference between the volume of glomerular filtration of the fluid and that of its tubular reabsorption. However, our studies have shown that, in this case, we have another, previously unknown mechanism. The glomerular filtration does not change;

however, the reabsorption inside the renal tubule undergoes redistribution—it decreases in one section of the nephron and grows in another one. This process is influenced by a regulatory factor that arises at that very moment in the kidney itself and causes one of the forms of the pathology by changing the function of individual parts of the kidney, leading to the development of nocturnal enuresis. The data obtained allowed us to develop an effective method for the treatment of this condition.

Physiology allows one to understand the nature of many phenomena on the basis of ideas about the organization of functions in an integral organism. The structure of each clinical discipline includes a section devoted to the physiology of a given system (Table 2); here the Rosenberg rule applies: "The whole is greater than the sum of its parts." The realization of the integrity principle [15] makes it possible to search for missing elements when building the image of each function. This has implications for solving fundamental problems in medicine because this way one can search for missing parts in the system and find a specific locus of the functional impairment. In addition, physiological methods revealed new regulatory systems. I am now talking about the early 20th century, which marked the discovery of the endocrine system, along with the nervous system, and then of the existence of cells in various organs, the function of which is associated with the formation of physiologically active substances (incretins, autacoids, etc.) [14].

Amazing is the accuracy of physiological regulations, which simultaneously involve multitudes of elements, with huge quantities of cells performing their functions synchronously. One such example is the total amount of Na^+ in the body of a man weighing 70 kg: about 5000 mmol, including 2835 mmol of exchangeable Na^+. The corresponding figures for K^+ are 3350 and 3367 mmol, respectively [18]. The volume of extracellular fluid in young men 16–30 years old reaches 15.6%, i.e., 10.6 L for a body weight of 70 kg. Given an average Na^+ concentration in the extracellular fluid of 139 mmol/L, the total Na^+ content of the entire extracellular fluid is ~1517 mmol. For K^+ ions, it is 42.4 mmol. Consequently, the body's entire exchangeable Na^+ is filtered in the glomeruli of the kidneys 8.5 times during the day. Meanwhile, the Na^+ excreted by the kidney over 24 hours is only 0.56% of the huge amount of sodium filtered in the glomeruli. A simple calculation shows that the main purpose of the kidneys in humans is not to excrete but to *return* to the bloodstream fluid with an ideal composition and concentration of each component. Like sodium and potassium ions, most of the elements of the periodic table are filtered in the glomeruli of the kidneys to be immediately returned to the blood in the right amounts. This ensures the constancy of the composition of the fluids in the body's internal medium. This process expends enormous amounts of energy in order to achieve the main goal, i.e., the *constancy of the blood composition,* which ensures the stability of conditions for the effective operation of all cells in the body. The blood flow of the kidneys in humans is higher than that of the brain, and these colossal energy costs are needed to create an ideal medium in terms of composition, primarily for intellectual activity. This necessitates solving the fundamental problems of science in order to elucidate the mechanisms and regulation of transmembrane transport systems and the reception of each substance so that the receptors could measure accurately its amount in the blood. All the chemical elements that the body needs must be returned to the blood from the nephron lumen, and the excess ones must be eliminated and will not be absorbed. This description shows how important the work of the kidneys is when one consumes any substance in excess amounts with food or drinks. In pathology we see symptoms of impaired renal function: edema, muscle contractility changes, etc.

Table 2. Connections between physiology and medicine

Branches of physiology	Medical sciences
Physiology of the nervous system	Neurology
	Psychiatry
	Neurosurgery
Physiology of the sensory systems	Ophthalmology
	Otorhinolaryngology
Physiology of blood circulation	Cardiology
	Heart surgery
Physiology of digestion	Gastroenterology
Physiology of excretion	Nephrology
	Urology
Physiology of the endocrine system	Endocrinology
Physiology of reproduction	Andrology
	Obstetrics
	Gynecology
Physiology of the immune system	Infectious diseases
	Allergology
Physiology of the skin	Dermatology
Physiology of the lungs	Pulmonology
Physiology of the blood	Hematology
Physiology of the oral cavity	Stomatology

THE CASCADE REGULATION SYSTEM

Our new studies have revealed yet another system of bodily defense against the effects of rapid entry into the blood of excess water as well as organic and inorganic substances in the case of drinking excess liquid or eating excess food, including the role of incretin (glucagon-like peptide 1, GLP-1) in this defense system [19]. It turned out that incretin participates in the regulation of not only carbohydrate but also water–salt balance. When examining healthy people, we have shown that, after drinking water, GLP-1 is secreted into the blood in the same large amount as when consuming sugar. The kidney is sensitive to GLP-1; this hormone causes a redistribution of fluid reabsorption in the tubule and accelerates the excretion of water; this way the osmolality of the blood is normalized. The physiological meaning of this phenomenon is that the kidney supports both carbohydrate and osmotic homeostasis. After drinking water and absorbing it into the blood, the blood serum osmolality decreases; at this very moment, the body cells have an initially higher concentration of osmotically active substances, and the water moves through the plasma membrane into the cell. The cell increases in volume; i.e., it swells. This happens to all cells, including those of the nervous and sensory systems. Osmoreceptors respond to such a situation; the signal reaches the hypothalamic region of the brain; the secretion of vasopressin decreases, and so does the osmotic permeability of the kidney tubule epithelium; the excretion of solute free water increases; and the osmolality of the blood normalizes. When measuring the GLP-1 concentrations, one usually takes into consideration its role in the regulation of carbohydrate metabolism but, in fact, this role is much wider, which is of great clinical importance. Such situations occur frequently; therefore, a clinician needs to look into physiology problems when carrying out a differential diagnosis of diseases.

The data obtained are a testimony to the need to integrate molecular research of life phenomena with a systematic approach in physiology. It is important to understand the interaction of parts within a single whole and ensure deep insight into the real role of the regulatory systems for the performance of each function. Every day, a human or animal should consume only the necessary amount of liquid and food for metabolism. When an excess amount of food or water enters the body, it is necessary to remove it quickly from the blood. When getting from the intestine into the blood, excess water leads to swelling and, hence, dysfunction of the cells. It is well known that in many cases a human or animal develops a conditioned reflex that protects against repeated exposure to a harmful factor. The results of our experiments on animals as well as human studies have shown that the system involving GLP-1 acts like a protective unconditioned reflex. When the stomach is distended by inflating a rubber balloon as an imitation of drinking water, the stimulus is transmitted to the L-cells of the intestine, and they begin to secrete GLP-1. The hormone enters the bloodstream, reaches the kidneys, and promotes the accelerated release of water from the body. Thus, we were able to establish yet another cascade of physiological reactions that help neutralize the harmful effect of excess water on humans.

It is difficult to comprehend fully the complexity of physiology as a science. In wildlife, an individual, the body of which consists of many billions of cells, adapts to the environment and finds a solution to the countless issues it is faced with. How could we gauge the real complexity of the organization of a living being if, e.g., one compares ciliates, whose entire body is a single cell containing a full set of vital functions, with a large individual—a human, an elephant, or a whale—whose body unites a multitude of cells? Such an organism is a "many-voiced orchestra" that, being directed from a single center, ensures the coordinated work of a hard-to-measure number of cells.

The discussion of this truly multifaceted problem touches upon the fundamental questions of physiology as a science as well as the contribution each new era makes to its architecture. (The term *architecture* in relation to physiology was used by Joseph Barcroft about a century ago [20].) The principles of physiology converge with the general provisions of philosophy that concern the problems of development and evolution. These principles are built into the foundation of *evolutionary physiology* (this term was proposed by Aleksei Severtsov in 1914). The Soviet physiologists Khachatur Koshtoyants, Levon Orbeli, and Evgenii Kreps made a great contribution to the development of this problem. It was they who developed the general principles of evolutionary physiology and obtained new facts, which were reflected in the understanding of the evolution of kidney functions and the physiology of water–salt metabolism. These principles turned out to be applicable in sciences that appear to be far from physiology: philology, computer science, engineering, etc.

THE TRUE MEANING OF THE KIDNEY

In school textbooks, as well as in a mundane sense, the kidney is seen only as an organ of excretion. In fact, both the kidneys and other organs perform several different functions.

Ensuring the high effectiveness of each cell in the body requires an extracellular fluid that is ideal in terms of its physicochemical characteristics. This fluid bathes all the cells; i.e., it serves as the internal medium of the body. The idea of the physiological significance of such a medium was put forth by the French physiologist Claude Bernard (1813–1878), who was elected a foreign member of St. Petersburg Academy of Sciences in 1860.

The key role in maintaining homeostasis, i.e., the physicochemical constancy of the fluids in the internal medium, belongs to the kidneys. The figures strike the imagination: in humans, more than one ton of blood flows into the kidney vessels in one day; the kidney tubules filter about 180 liters of protein-free liquid (filtrate) and almost 178 liters are immediately absorbed into the blood, and only a little more than one liter is excreted [13, 14]. At the beginning of the 20th century, the physiological mechanism of urine formation in the kidneys was explained as follows: protein-free fluid is filtered in the kidney glomeruli (there are about two million of them in a human); the substances needed by the body are absorbed in the tubules, and the unnecessary substances are eliminated. Young English physiologists of that time often spent time in bars, discussing their ideas over drinks, as the eminent physiologist Barcroft wrote later [20]. In their opinion, nature could not have created a "meaningless" system in the kidney, i.e., to filter the blood and immediately suck back the filtered substances. Why is this? To one of the leading English physiologists of that time, John Langley, the idea of parallel filtration/reabsorption seemed too cumbersome. He argued that it was too complicated, to which Barcroft replied that "after all it seemed no more complicated than the kidney itself" [20, p. 270]. Today it is obvious that the work of the kidneys includes both filtration and reabsorption and that the kidney is an organ for preserving *the ideal internal medium of the body*.

A century later, we have come to understand the molecular mechanisms of filtration and reabsorption of substances in the kidney. The physiological meaning of these processes is to return to the blood an internal medium of an ideal composition. No one knows what will prove to be redundant; the kidney filters everything but returns only what is needed, eliminating all that is unnecessary.

PHYSIOLOGY IS THE FOUNDATION OF MEDICINE

Like kidney function, the science of physiology has described the activity of other physiological systems: nervous activity, blood circulation, respiration, digestion, etc., as well as the problems of regenerative medicine. Physiology is developing along with such classical sciences as physics, chemistry, genetics, and zoology through the use of new methods and achievements of other sciences to form an idea of how functions are organized in the body as a whole. Physiology serves as the foundation for the development of medicine and the entire complex of related sciences (see Table 2). The increasingly deeper knowledge integrated by physiology allows one to understand the nature and mechanisms of physiological functions and to diagnose more precisely the causes of deviations. This is not about physiology absorbing other sciences but about the logic of cognition. The purpose of physiology is to elucidate the structures of the organ under study and the regulation of its functions and to understand what happens in the body under extreme conditions or pathology.

Medicine is one of the sciences that use the fundamental laws deciphered by physiology. Today, we see a new surge in interest towards the problems of personalized medicine. (It had long been forgotten that the individual approach was the calling card of classical medicine in Russia in the 19th century. After all, it was Sergei Botkin who urged treating the patient—not just the disease.). Naturally, the methods of molecular genetics have opened up new prospects for personalized medicine. Nowadays, the new developments in physiology are due to the fantastic possibilities that have opened up by the methods of molecular biology and molecular genetics. Today it is obvious how important it is to consider not only the genotype but also the regulatory capabilities of the phenotype, which determine its momentary state. Undoubtedly, there is a need for laboratory diagnostics, which makes it possible to determine the value of a given parameter and the lower and higher boundaries of the norm. But the next step, too, ought to be taken, and that is to understand the *state of regulatory systems*, including their influence on the realization of a given function.

Physiology studies the mechanisms underlying the activity of the various organs and systems and plays the key role in clarifying the nature of each of the functions under normal conditions, i.e., in a healthy living being. Physiology can help formulate the foundations of a healthy lifestyle, understand the nature of deviations, and set the groundwork for answering the question about the nature of pathology. Within this approach to the essence of science, modern physical and chemical methods of natural sciences become, *inter alia*, the methods of physiology. This statement may be regarded as *physiologocentrism*, but it accurately reflects the role of this science in natural sciences and its significance for medicine, along with ecology and evolutionary biology. Looking into the connection of these sciences with physiology, one can understand and formulate the conditions for the emergence of functions in the first living beings, the very phenomenon of the origin of life, and the stages in the evolution of functions [11].

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It is known that adaptation to different living conditions plays a key role in the life of organisms. But how do they adapt to changing conditions? What changes occur in them under the influence of external factors? What mechanisms support adaptability? In response to the need to understand the principles of adaptation of a living organism to the external environment, i.e., an ecosystem, humankind developed the science of ecological physiology. Physiology acquired new facets in the context of exploration of outer space (space and gravitational physiology, physiology of extreme conditions) and the world ocean; development of the physiology of aquatic organisms and diving (hyperbaric physiology). Physiologists have made a great contribution to solving the problems of manned cosmonautics, unraveling the mysteries of the sea depths, and exploring the possibilities of adaptation to extreme living conditions.

It makes sense to consider as a separate group those branches of physiology that are relevant for medical practice and the various types of human activity. These are the physiology of sports, psychophysiology, or the physiology of various human organs, which precedes the understanding of the processes underlying the various forms of pathology.

One of the branches of physiology, especially human physiology, is associated with deciphering the nature of speech and consciousness. This requires a close relationship with the humanities (philology, linguistics) and psychology as well as the physics of sound (acoustics) and involves a comparison of natural and artificial information systems. Human physiology seeks to delve into the mechanism of the birth of thought, and in the field of art, it seeks to uncover the relationship between the mind and feelings. We are talking about a broad understanding of the problem, about the emergence and formulation of a thought or an artistic image rather than about remembering things. A thought dawns suddenly, in a dream or in reality, but it is not yet formalized, it is loose, it is only a skeleton, only the idea itself. This is followed by an attempt to build the idea into the existing images, to ground it in evidence and test its truth in an experiment. This is true not only for various sciences but also for art. First comes an idea, then a sketch, and only then begins the long journey to a painting or a literary work, like in science—first to a hypothesis, then to a coherent concept, and, finally, to a theory. Thinking about the evolution of painting, one can find it to be amazingly similar to the development of classical sciences: primitive art, incessant complication of primitive art, realism, impressionism, image enhancement (expressionism), and so on. Speaking about science and art, it is necessary to renounce the conventional wisdom about their fundamental differences and try to follow a synthetic approach, looking for elements of similarity. The primitive visual art of primitive society gives way to the great creations of the sculptors of Greece and Rome. The end of the 19th century sees the emergence of impressionism with its desire to capture an elusive impression and to revive an image with light, which, at first, was not taken seriously by the academic community but soon conquered all of Europe and stimulated a wave of new trends in art.

Returning to science, one cannot but notice that the successes of biology in recent decades have far exceeded the imagination of science fiction writers of the mid-20th century, when molecular biology was born. For instance, we now can create proteins with a given structure and function, and the task of physiology in the new world is to understand the meaning and possibilities of applying the new proteins and using genetically modified organisms, new drugs, and new foods.

The questions that arise require an answer both in general, i.e., by solving problems of fundamental science, and in particular, i.e., within the framework of the applications of fundamental science. The physiological approach to understanding the role of each element of the body as an integral whole remains relevant, and, I think, it will continue to do so in the future. In this regard, of particular importance is the insight into the nature of physiological regulations. The question is the following: What ensures the performance of the accurate, strictly verified reactions of an organism consisting of billions of cells?

Let me conclude this review with the words of Academician Sverdlov, who said that we should strive to understand how our consciousness had reached such a high level of organization that it began to explore our own existence.

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