



Pharmacological vector of Rudolf Buchheim

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*Celebrating the 100th anniversary of
Voronezh State Medical University*

Biography

The originator of the experimental pharmacology is considered to have been a professor of University of Dorpat Rudolf Buchheim (Fig. 1), who was born on March 1, 1820 in Bautzen in the kingdom of Saxony, where his father was a practicing district physician. After leaving the high school (Gymnasium) in his hometown, he began studying medicine at the Surgical-Medical Academy (Chirurgisch Medizinische Akademie) headed by J.L. Choulant in Dresden in 1838. In autumn 1841, he resigned from the academy to complete his education in Leipzig. There, while being a student, he had worked as an assistant at the Institute of Anatomy and Physiology under E.H. Weber, where the chemist-physiologist was C.G. Lehmann, who sparked and then supported Buchheim's interest in the chemical aspects of medical science. This way, even before the official completion of his study, Buchheim took up scientific career and received a degree of doctor of medicine on January 7, 1845 (Barkan 1932, Hirsch 1880, Schmiedeberg 1911).

In 1846-1848, he published *The Textbook on Pharmacology (Lehrbuch der Arzneimittellehre)* in 2 volumes of 844 and 929 pages, respectively. The basis of this tractate was a translation of Jonathan Pereira, but Buchheim added to it a large number of medicines that had been hardly known earlier, but left out others which he considered ineffective. The description of individual pharmacologic agents contained a section "Physiological effect", which,



R. Buchheim

Figure 1. Professor Rudolf Buchheim

according to the old tradition, describes only the symptoms caused by the drugs in the body. Buchheim added a new section "Mode of Action". In it, he made a list of changes that, on the one hand, the organs underwent under the influence of drugs, and, on the other hand, the drugs underwent themselves under the influence of the body. It had taken Buchheim four years to process the material. This time can be considered as a period of his apprenticeship in the field of pharmacology and other related fields. He had no teacher other than himself in these areas of knowledge (Loewe 1924).

In 1845-1847, he headed the editorial office of pharmaceutical abstract journal and at the same time published his reports in physiological chemistry in Schmidt's Medical almanacs (Schmidt's Jahrbuecher der Medicine). Such an activity contributed to the introduction of his extensive knowledge and versatile interests in various experimental medical disciplines (Lesch 2002, Scheindlin 2010).

He was appointed to the first-ever university Chair of Pharmacology at Dorpat when he was only 27 years old. His candidacy, despite such a young age, seemed the most suitable for heading the department after its previous head, Fridrich Oesterlen, had left Russia. So he moved from the Department of Drugs ("Materia medica") (Brupacher-Cellier 1971) to the Department of Therapeutic Medicine, and through his decisive refusal from the existing science of drugs in his *Textbook on Pharmacology* he prepared the ground for radical changes and development of pharmacology (Jack 1983, Kabin 1986, Kabin and Lechat 1997).

When F.H. Bidder, then the Dean of one of the faculties of the University of Dorpat, introduced to the University Senate "a private scholar from Leipzig, Mr. Dr. R. Buchheim", applying for the post to head the Department of Materia Medica, Dietetics, and History and Encyclopedia of Medicine, he went into such detail describing his scientific achievements (16.XII.1846) that all those present could hardly imagine that the person who had all those high qualifications, supported with the facts, was a young assistant. He had been a full member of the medical faculty and the Academic Council from the very beginning.

It was in Dorpat where Buchheim began his successful career. There he found a fertile ground and a large field for his work as a scientist and teacher. After his arrival in Dorpat, Buchheim established a laboratory for pharmacological research in his apartment and at private expense, which later became a University structural unit. Then the construction of a new pharmacological institute was started (Kuschinsky 1968, Trendelenburg 1998), which turned out to be much more impressive than it had been envisaged in a draft project, because, in addition to the spacious private offices, several more utility rooms were added, including a large basement, the construction of which was approved already during the construction. Later, this Institute without much extension for a long time served as a workplace for all Buchheim's successors – from O. Schmiedeberg, R. Boehm, H.H. Meyer, R.E. Ko-

bert to the Russian period (S.I. Czyrwiński, D.M. Lavrov) and the period of the German occupation (P. Trendelenburg). Later R. Buchheim, with good reason, considered his Institute superior even to C.D. Schroff's Vienna Institute of Pharmacognosy and Pharmacology (Parascandola 1982, Stille 1994).

Thus, R. Buchheim is the founder of the first pharmacological institute, which for nearly two decades remained the only one of its kind, as in other universities there were mostly only "pharmacognostic collections", but not institutions for experimental pharmacology.

In his laboratory, Buchheim primarily gathered a few staff members, recommended Doctor of medicine applicants what topics to select for their doctoral theses, supervised their research and participated in it personally. The conditions in Dorpat were extremely favorable for this type of research. Since preparation of a thesis only by means of experimental studies required at least a year, it contributed to the fact that young doctors of medicine left the University with a high level of scientific maturity. Along with Buchheim, there worked Friedrich Bidder and Carl Schmitt, the latter – at the Faculty of Natural Science. They formed a triumvirate of researchers, thanks to which all the sections of descriptive and experimental biology were presented equally well (Hoerschelmann 1926, Reverte and Baños 2002). Fine anatomical studies, characterized by close links between morphology and physiology, experimental physiology and pharmacology, as well as physiological chemistry, which was not only the chemistry of substances of animal origin, but actually part of physiology, were studied there with such attention, which was necessary for these medical disciplines as fundamental elements (Habermann 1974, Sourkes 1994).

At this time, William Prout discovered free hydrochloric acid in the gastric juice, C. Schmitt discovered he distribution of potassium and sodium between blood cells and plasma, the blood thickening in cholera as a consequence of transudation in the intestine, as well as the presence of fiber in animals. Then F. Bidder discovered ganglia in the frog heart, and the two scientists did an excellent job when preparing the book *Digestive Juices and Metabolism (Die Verdauungssaefte und der Stoffwechsel)* (Bing 1973, Jones 1850).

On this fertile ground, Buchheim developed his activity that experimentally-based led to the study of drugs. The doctrine of drugs that existed at that time as a medical discipline could be hardly considered as a science. It was mainly a few views based on experience, and some detailed recommendations and prescriptions for the administration of a huge number of pharmaceutical substances and drugs, the effect and efficacy of which were based on ideas and assumptions that were, in turn, based on the natural philosophic dogma. In textbooks, the doctrine of drugs was accompanied by endless prescription formulas and descriptions of plants, crude drugs and minerals (Heymans 1967).

Scientifically educated doctors, when prescribing drugs, followed the traditional views and rules and found

themselves totally confused if, as in the case of a sudden epidemic of cholera, suddenly there was no pattern for treatment. Then they resorted to applying all the available drugs from the beginning to the end of the list.

Seeing this state of the doctrine of drugs, R. Buchheim found it important, along with his experimental work, to subject to sound criticism the existing state of affairs. Back in 1849, in his *Essays on the Doctrine of Drugs* he published a treatise “On the Problems of the Doctrine of Drugs”, in which he characterized the state of affairs in this field of knowledge in a tart manner. The last sentence of that treatise read: “but we may need more than one call for a “*ceterum censeo*” action to wake up the pharmacology from sleep. However, this sleep is not natural, since pharmacology, considering the work it’s done in the past, has no reason for fatigue” (Buchheim 1870).

One of his most important tasks in life Buchheim considered not only the description of the action of drugs, but primarily the explanation for these actions, based on the chemical properties of substances. The most significant things that Buchheim created were the substantiation of the natural system of drugs and pharmacology in general. The need for such a system had never been challenged before, since due to an infinite number of pharmacological agents, only a strictly systematic classification of the latter could ensure their reliable coverage and make it possible to systematically study their effects. The need for using such a systematics was exactly what distinguished the pharmacologist from the physiologist.

When building his system, Buchheim took into account all features of substances, their chemical properties and actions which were worth recording from the pharmacological point of view and combined all the drugs that demonstrated a large number of common features into pharmacological groups, which he called by the name of the most important and well-known representative of a particular group. These pharmacological groups, recognized today by all specially trained pharmacologists and underlying their experiments and research, form a natural system, which, above all, meets the key requirement for each systematics, namely, it is open to revision and allows further improvement. Without this Buchheim’s taxonomy, it is impossible to imagine today’s scientific pharmacology and the doctrine of drugs, and, therefore, the main achievement of Buchheim’s professional career was an elaboration and justification of his taxonomy. One of the significant works by R. Buchheim is *The Guide to Pharmacology* (Fig. 2).

It took a long time before the understanding of this system began to take root. At that time, the Dorpat scientists stayed in a close contact with all the intellectual achievements of the world culture through literature and trips to Germany and other countries during summer holidays. Thus, R. Buchheim was not out of touch as were some scientists at that time.

Under his guidance, in Dorpat within 20 years (1847–1867) about 100 works, including 80 doctoral theses appeared. His laboratory was engaged in study in the

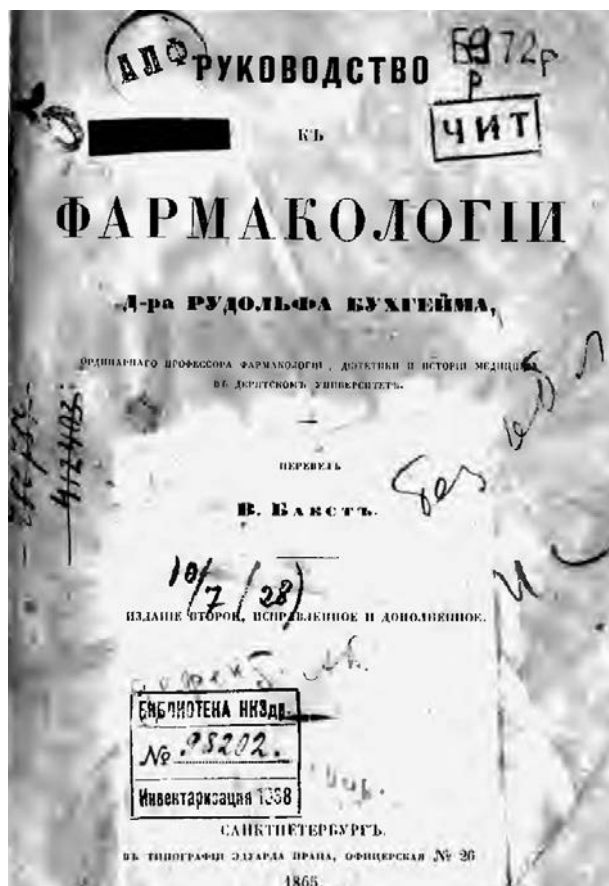


Figure 2. Guide to Pharmacology by Dr. R. Buchheim

absorption and excretion of salts of heavy metals, arsenic, phosphorus, iodine and other substances (Buchheim 1872). The kinetics of ethanol, chloroform, alkali metals, alkalis and acids, as well as various salt formation processes, were studied in details (Leake 1962, Buchheim 1849). The dependence of the action of a substance on its kinetic parameters was demonstrated. Many studies of the Department concerned the issues of pharmacological effects of alkaloids, laxatives and anthelmintic substances on the gastrointestinal motility. R. Buchheim managed to attract students to experimental work, and some of them remained at the Department after graduation.

R. Buchheim appreciated the local favorable conditions for scientific work, which resulted in his decision to turn down the offer to accept a professorship at the University of Breslau received in 1863. At that time, setting up a laboratory for pharmacological studies there was out of the question. But, when at the end of 1866, he received simultaneous invitations from Giessen and Bonn to fill up the vacant positions of Professor at those universities, he decided to leave Dorpat (Leake and Pelikan 1976).

Along with that, there were plans and projects for further research worked out, which basically were aimed at expanding the classification of drugs according to the system he had developed and its further detailed justification.

The abstracts of works by R. Buchheim and his disciples can only give some insight into the scope of their research, but can hardly provide an exhaustive understand-

ding of his ideas. For him, the most important task was to study the interactions and processes between drugs and the body. This core idea was further developed by the followers of R. Buchheim in the Central Black Soil Region (Baños et al. 2002).

Russian period

Buchheim's apprentice Oswald Schmiedeberg is the originator of experimental pharmacology in Germany and the founder of the world's first scientific journal of pharmacology *Archives of Experimental Pathology and Pharmacology* (1873) (Muscholl 1995, Schmiedeberg 1895, Meyer 1921).

From 1897 to 1902, Professor Stanislav Chirvinsky (Stanisław Czyrwiński), who came from Moscow, was the head of the Buchheim's Department. Over that time, three volumes of The Collection of Research Papers of the Pharmacological Institute were published (Chirvinsky 1913, Fisenko and Bondarchuk 2009, Golovinsky 1911, Levickij 1903).

After S. Chirvinsky, in 1902-1908, the Department was headed by another graduate of Moscow University Professor David M. Lavrov (1867-1929) (Fig. 3). He was an apprentice of famous biochemists A.Yu. Danilevskiy and M.V. Nentskii, which had a great influence on his further research activities in Yuryev (Dorpat in 1893-1918). Among his papers, special attention should be paid to the study of the pharmacological effects of lecithin on the volumetric blood flow rate (during catheterization of the coronary sinus), together with the registration of the arterial pressure in the femoral artery and the oxyhemoglobin saturation of arterial and venous blood in acute occlusion of the left anterior descending coronary artery in the middle third in an anesthetized cat.

Soviet period

On February 23, 1918, German troops, breaking the truce between Soviet Russia and Germany, occupied Yuryev (Dorpat). On June 11, 1918, the Council of People's Commissars of the RSFSR (Russian Soviet Federative Socialist Republic) decided to move the University from Yuryev to Voronezh (Fig. 4).

By early September of the same year, 39 professors, 45 teachers, 43 staff and 800 students arrived in Voronezh. Among the arrivals was Professor of the Department of Pharmacology David M. Lavrov and Prosector (Associate Professor) (later Professor) Vasilij Vorontsov. On November 12, 1918, the first lecture was given at the newly opened University of Voronezh (Fig. 5).

To interest young people from the working population in studying and to give them an opportunity to get a good education, the government took a risky step for the moment and issued a Decree on the Admission Rules for Universities of the RSFSR, signed by the Chair of the

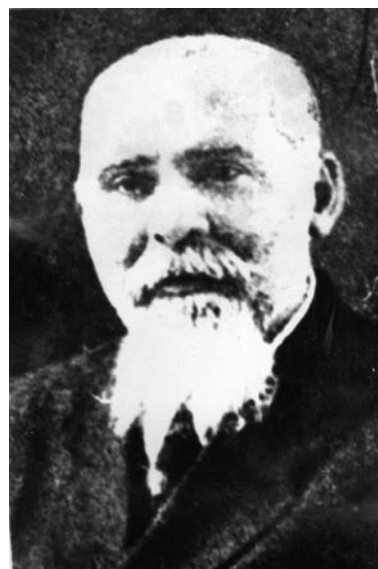


Figure 3. Professor D.M. Lavrov

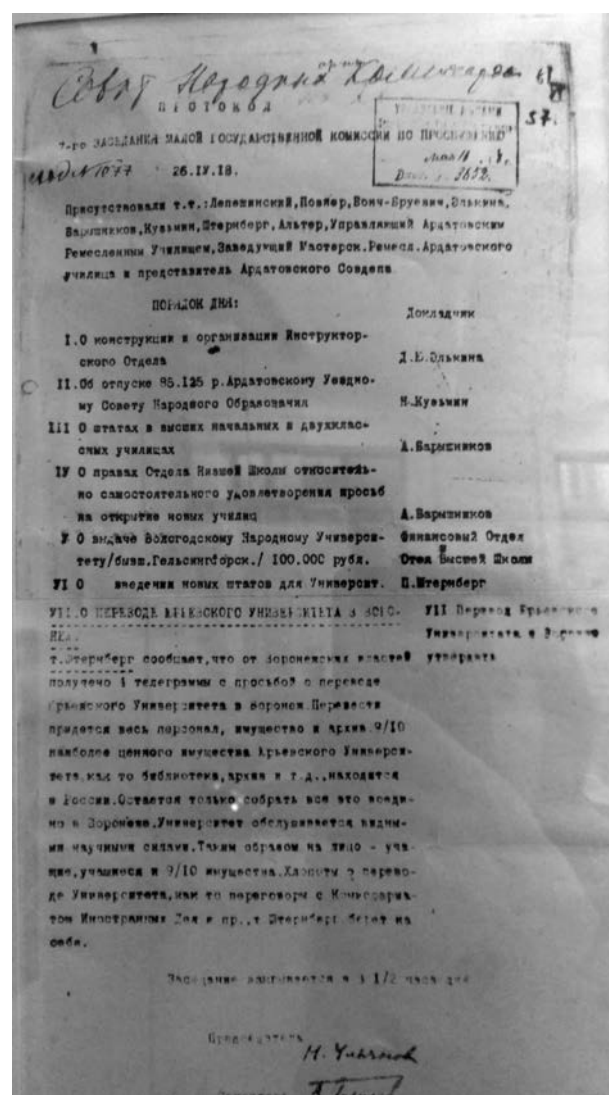


Figure 4. Protocol of the 7th meeting of the Small State Commission on Education, confirming the transfer of the University of Yuryev to Voronezh



Figure 5. Department of Pharmacology of Voronezh State Medical Institute, Voronezh, Revolution Avenue.

Council of People's Commissars V. Ulyanov (Lenin) on May 27, 1918. According to the Decree, "Every person, regardless of nationality and sex, who has reached the age of sixteen, may join any higher education institution without presenting a diploma, high school diploma or General Certificate of Secondary or any Education. Tuition fees in higher education institutions of the RSFSR are canceled. The fee paid for the first half of the academic year 1918/19 is to be refunded."

The first head of the Department of Pharmacology in Voronezh was David M. Lavrov, who was succeeded by Vasilii Vorontsov (1877-1953) in 1923, who in December 1910 in Dorpat had defended his doctoral thesis *Materials on the Neutralizing Role of the Liver in the Animal Body* on 1068 pages (Fig. 6) (Vorontsov 1910a).

Lavrov, continuing the traditions of R. Buchheim, supervised research, integrating pharmacology, physiology and chemistry. His doctoral thesis *On Chemism of Peptic and Tripeptic Digestion of Protein Substances* (Lavrov 1887) started a new scientific direction of the Department of Biopharmacology, with the study of the effect of mineral waters on proteins (Lavrov 1911), and the effect of lecithin on the animal body. D. M. Lavrov published more than 40 scientific papers (Lavrov 1913, Lavrov 1914, Lavrov 1917), most of which were experimental and wrote a textbook *The Fundamentals of Pharmacology and Toxicology* (1923) (Lavrov 1923).

Scientific activity of V.N. Vorontsov (Fig. 7) began in 1904 and continued until the last days of his life (1953). As early as in his doctoral thesis, he opened, as such, a new page in pharmacology: issues of pharmacokinetics and metabolism of drugs (Vorontsov 1910b). One can get an idea about a wide range of V.N. Vorontsov's research interests from his works: "Treatment of Diarrhea with Tincture of Unripe Nuts of the Orange Tree" (1904); "Issues of Obtaining Ricin from Castor Seeds" (1907); "On the Chemical Nature of Ricin" (1908); "Neutralization of Poisons by Isolated Limb Muscles" (1911); "The Influence of Lecithins on the Heart in Poisonings" (1912); "On



Figure 6. Title page of the doctoral thesis by Professor V.N. Vorontsov

the Sensitizing Properties of the Fluorescent Substances" (1913); "On the Role of Calcium in Poisonings" (1914), classified papers on the toxic properties of chemical weapons (1916), the neutralization of poisons by isolated kidney and spleen (1916), the content of phosphorus in a rabbit's brain (1916), etc. (Reznikov and Kitaeva 2018).

G.N. Pokrovskiy (Fig. 8), PhD in Medical Sciences, was appointed an Assistant Professor of the Department

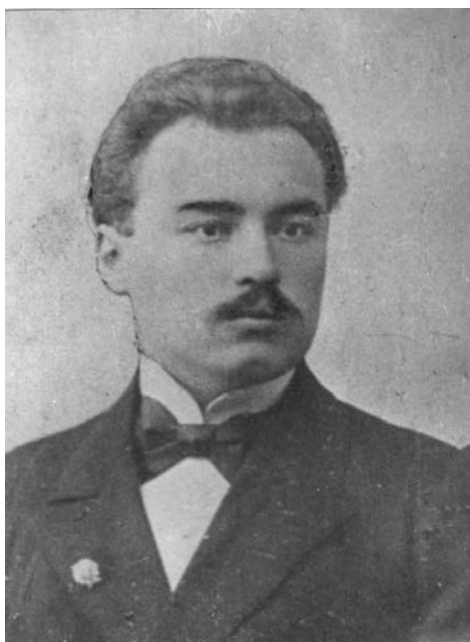


Figure 7. Professor V.N. Vorontsov

of Pharmacology in 1933 and worked until the evacuation of 1942. In 1938, he was elected and approved as an Associate Professor of the Department of Pharmacology. During his work, G.N. Pokrovskiy published several papers on experimental studies of the effect of drugs on the digestive system. Before The World War II he worked hard on his doctoral thesis. Unfortunately, this well-established scientist died during the occupation of Voronezh (Reznikov and Kitaeva 2018).

V.I. Zavrazhnov graduated from the Medical Faculty of Voronezh State Medical Institute in 1932, and after that, he started his post-graduate studies at the Department of Pharmacology because he had been working there as a promoted worker since 1930. He finished his postgraduate studies in 1936, and in 1940 he defended his thesis *The Action of Belogorsk Mineral Water* (Landa and Zavrazhnov 1939). During the post-graduate course, he published 13 scientific papers. From 1941 to 1945, he served in the army. He was decorated with 2 orders and awarded with 3 medals. After the end of the war, in 1946 he was elected as Associate Professor of the Department of Pharmacology.

The development of the educational process depended on the growth and condition of the material equipment of the Department. During the early years (1918-1925), the educational process consisted in systematic course of lecturing. Gradually, the lectures were updated with visual aids, as they had been made and purchased (tables, figures, diagrams, samples of drugs, etc.), and then experiments on animals and isolated organs. Practical training sessions became possible for the entire course in 1926, but only in the form of preparing drugs (prescription workshop).

In 1936, to help the students prepare for classes and exams, the Department set a special room, with the showcases with a systematic collection of drugs, arranged by pharmacological groups, indicating the nomenclature,



Figure 8. Assistant Professor G.N. Pokrovskiy

chemical structure, forms of administration and doses of each substance. There were the tables of the highest single and daily doses of toxic and potent substances for humans, colored medicinal plants drawings, and various schemes of action there. The Museum of medicinal plant raw materials, essential oils, minerals, like the one which existed at the University of Dorpat, was reestablished.

From 1922, a student's pharmacological society began its work. The number of actually active members of the society was usually 10-15 people. The scientific work of the Department was performed mainly in the following areas: anesthetics; pharmacokinetic of drugs (absorption and excretion); the study of herbal medicines and area study materials (Reznikov and Kitaeva 2018).

This way, the use of rectal ether narcosis in rabbits and a suitability of this method in laboratory practice were studied. Magnesia anesthesia was investigated, and it was found that the list of the already known deficiencies of this substance needed to be expanded with its peripheral curare-like effect on the skeletal muscles, including, the heart (Vorontsov 1910a). A number of studies examined changes of such a sensitive indicator as pupillary muscle during anesthesia (V.N. Vorontsov, V.A. Romanenko, V.Yu. Leshchinskiy, I.V. Troitskiy, 1929-1940). New data important for anesthesiology were obtained: on some issues of pharmacodynamics and reactivity of animals in the study of different anesthetics and their combinations. Experiments with chloroform, ether and their combinations with each other and morphine performed in a number of animals showed a possibility of summation and potentiation of anesthetic action (Z.T. Kolosvetova).

Serious pharmacokinetic problems were solved by studying the excretion of picric acid. The initial reason for this study was a case of stimulating jaundice by intake of picric acid. The studies performed by V.N. Vorontsov showed that picric acid could be excreted with urine for

a very long time (for over a month), which was later confirmed in laboratory animals by V.Yu. Leshchinskiy. In addition, the rate of phenolphthalein excretion in different animal species was studied. The experiments performed by V.N. Vorontsov in 1940 showed that depending on the species of animals, phenolphthalein could be excreted in the stool from 15 days (white mice) to 62 days (rabbits). Greater sensitivity to phenolphthalein was noted in cold-blooded (frog) in comparison with warm-blooded animals (Reznikov and Kitaeva 2018).

There was a study of phytoncidal plants, in particular, the pharmacological properties of onion juice (Zavrazhnov 1940-1941) and garlic juice (Leshchinskiy 1940-1941 (Fig. 9)). The results of these experiments were processed and published later in 1946. These juices were considered as containing nonvolatile fractions of phytoncides. Such studies are noteworthy, because the pharmacology of the phytoncides was not developed at that time, and yet these interesting substances are very close to the widely studied antibiotics (Zavrazhnov et al. 1993).

In terms of studying local resources, a pharmacological examination of mineral water discovered in the south of Voronezh region, in the Radcheskiy district, near the village of Belaya Gorka (Belogorsk mineral spring) was conducted through the. The pharmacological studies (V.I. Zavrazhnov, thesis of 1940) showed that the Belogorsk water was well tolerated by animals even in very large doses, significantly stimulated heart activity and increased tone of isolated vessels.

V.N. Vorontsov determined a decreased sensitivity of the vomiting center in dogs after repeated administration of apomorphine (1929). S.D. Sokolov conducted a comparative study of anticonvulsant action of cardiac glycosides (1929). G.N. Pokrovskiy (1938) proved that in milk there was a substance influencing n. vagus. V.I. Zavrazhnov (1938) studied the effect of camphor on isolated vessels, and V.Yu. Leshchinskiy and V.N. Vorontsov (1939) studied the effect of topical anesthetics.

V.Yu. Leshchinskiy (1941) studied the pharmacological properties of so-called "contact gases" of the furnace shop of the local synthetic rubber works. This work by V.Yu. Leshchinskiy was further research of the toxicology of contact gases of the synthetic rubber works, initiated by Professor G.N. Pokrovskiy and consolidated in his thesis *On the Toxicology of Contact Gases of the Synthetic Rubber Works* under guidance of Professor V.N. Vorontsov (1939). The Department also conducted some research on classified topics (Vorontsov and Zavrazhnov 1931-1941).

The treacherous attack of Hitler's Germany on the Soviet Union disrupted the Department's well-established activities. Assistant Professors V.I. Zavrazhnov and V.Yu. Leshchinskiy were enlisted in the field, followed by two PhD students soon afterwards. The teaching was to be done only by Associate Professor G.N. Pokrovskiy. Soon, a PhD student of the Department of Biochemistry P.G. Martynova and a former employee of the Reserve-officer Training Department A.P. Lebedev started working as teaching assistants.

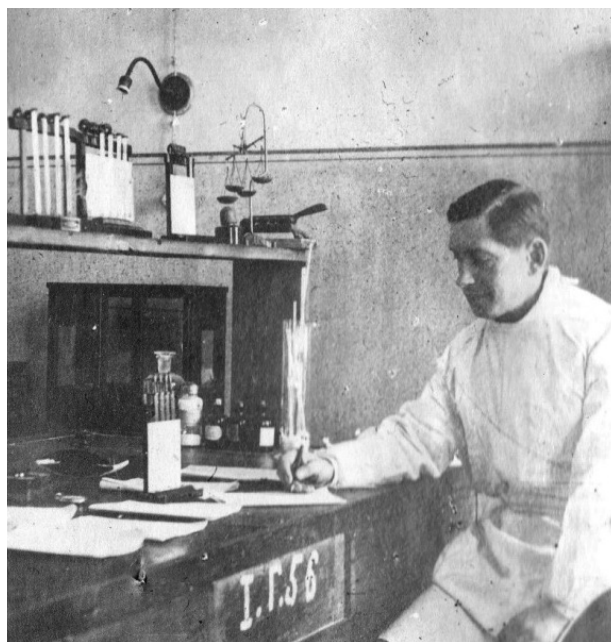


Figure 9. Assistant V.Yu. Leshchinskiy

Under fire and endless air raids, the train with the students and employees arrived in Ulyanovsk. The working conditions in Ulyanovsk were extremely difficult.

In 1948-1949, the Department finally managed to settle on the third floor of the main building of the Institute, receiving 8 rooms, 4 of which were classes (Reznikov and Kitaeva 2018).

Only after resuming classes, further research could be resumed, too. In 1946-1947, there were finally published the articles on the results obtained in the pre-war years of the phytoncidal properties of fresh onion (Leshchinskiy) and garlic (Zavrazhnov) and after storing them for a month (Zavrazhnov 1954). A topic for further research of the Department within the National Program of Research was determined – "Search for and study of new cardiovascular agents".

On February 2, 1953 Professor V.N. Vorontsov died at the age of 76. He was a true patriot of his homeland, who had received an excellent education at the University of Dorpat, who had worked there at the Institute of Pharmacology for 14 years (for the last three years as the acting head of the Institute) and withstood all the hardships of 1918-1922. In 1923, after heading the Department of Pharmacology of Voronezh University, he survived and created the Department preserving the best traditions of the University of Dorpat.

After Professor V.N. Vorontsov, the Department of Pharmacology was headed by his apprentice Associate Professor V.I. Zavrazhnov, who was appointed to this post by order of the Ministry of Healthcare of the RSFSR №1165-L of 08.08.1953.

Victor I. Zavrazhnov was born on October 1, 1909 into a family of peasant farmers who, before the birth of their son, had moved to Kozlov (Michurinsk) of Tambov province and worked as public servants in different organizations of the town. In 1927, after finishing Kozlov high

school №2, he entered the Medical Faculty of Voronezh University and in 1932, after graduating from the Medical Faculty of the already independent Medical Institute, he became a postgraduate student of the Department of Pharmacology of that institute. After finishing his post-graduate studies, he started working as an Assistant Professor at the same Department. The sphere of his research interests was studying the curative properties of the flora of Voronezh (devil-in-the-bush, Far Eastern Lily-of-the-valley, etc.), the toxicology of a number of industrial waste and local mineral water “Belaya Gorka”.

From July 1941 to July 1945, V.I. Zavrazhnov (Fig. 10) served in the Soviet army. He started his army service as a commander of a hospital company of the motorized rifle battalion of the 254th rifle division of the 11th army. From 1943, he was a military toxicologist of the 48th army, and in the last year of the war he was an acting commanding officer of the Ambulance department of Kazan military district. After demobilization in November 1945, V.I. Zavrazhnov was reinstated as an Assistant Professor of the Department of Pharmacology. In August 1953, by Order of the Ministry of Healthcare of the RSFSR he was appointed to the position of acting head of the Department of Pharmacology (Reznikov and Kitaeva 2018).

In 1960, he defended his doctoral thesis *Materials for the Experimental Pharmacology of Myocarditis and Myocardiosclerosis* at Sverdlovsk Medical Institute (Zavrazhnov 1960) (Fig. 11), in which he studied the effect of cardiac glycosides of Hemp dogbane (Cymarín and Strophanthín), pyrimidine derivatives (Metacilum and Pentoxylum), adaptogens of plant origin on these heart diseases. In April 1962, he was awarded a degree of doctor of medicine and an academic title of Professor. He remained the head of the Department until July 1982.

When the Department of pharmacology under guidance of V.I. Zavrazhnov was doing research within the state programme “Looking for and Studying new Cardiovascular Agents”. Eight new cardiac glycosides extracted from plants – Gomphocarpus (Gomphotinum, Gofrusid), Hemp dogbane (Cymarín), Erysimum diffusum (Erysiminum, Erysimosidum), Corchorus olitorius (Corchorosidum and Olitorisidum), and Covallaria majalis (Corglycon) with regard to their cardiotoxic and anti-arrhythmic properties in the treatment of animals with toxic myocarditis and myocardial infarction were studied. In these models of cardiac pathology, both individually and in the combination with cardiac glycosides, Apisarthron and Apilacum, as well as hyperbaric oxygenation were studied, which reflected the traditions of the University of Dorpat (Yuryev).

Not all of the faculty members of the Department worked long at Voronezh State Medical Institute for various reasons, some of them choosing the career ladder with higher academic ranks and becoming heads of departments in young universities of the Soviet Union.

Vasily I. Nikolaev (worked at the Department from 21.09.1953 to 25.08.1955) resigned to move to Irkutsk Medical Institute.



Figure 10. Professor V.I. Zavrazhnov

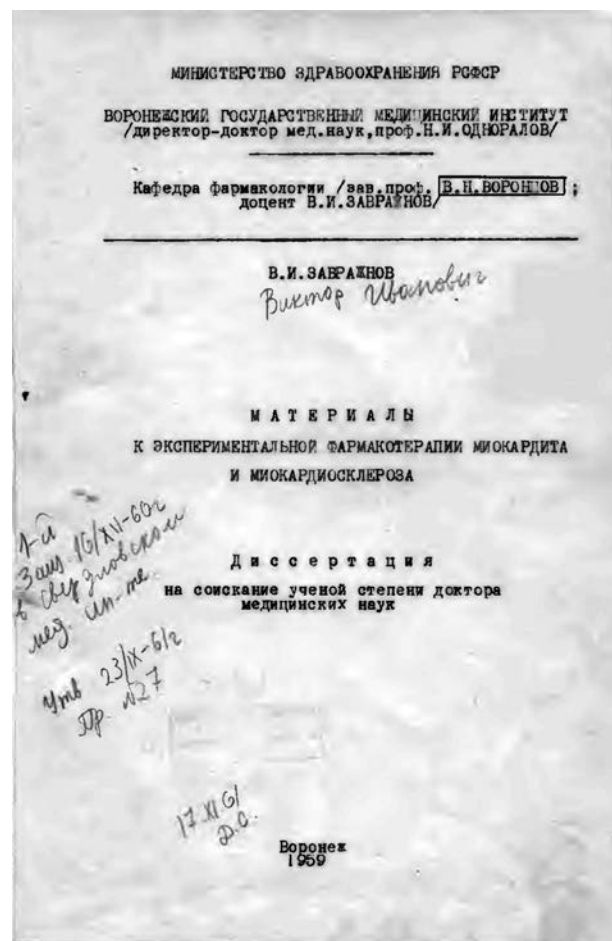


Figure 11. Title page of the doctoral thesis by Professor V.I. Zavrazhnov

Vladimir V. Gatsura (worked at the Department from 23.06.1953 to 01.08.1958) was born in 1927 in Omsk. After finishing high school in 1945, he entered Omsk Medical Institute, the Faculty of Sanitation and Hygiene, which he graduated from in 1950 cum laude and continued his

postgraduate studies at the Department of Pharmacology. In March 1953, he defended his thesis and, on a competitive basis, was accepted as an assistant professor of this department. From his first days of work, he was actively engaged in intensive scientific work on the issue of experimental pathology and therapy of cardiovascular insufficiency in experimental myocardial infarction in dogs. Over the years of work at the Department, he published 9 scientific papers and 3 rationalization proposals. On August 1, 1958 he was transferred to Kemerovo Medical Institute, the Department of Pharmacology as an acting head of the Department, and then, after defending his doctoral thesis on the evaluation of the efficacy of the new glycosides – Gomphotinum, Erysidum, Erysiminum, Cymarín – compared with Strophanthin in acute myocardial infarction, he worked as the head of the Department of Pharmacology of Kursk Medical Institute (Reznikov and Kitaeva 2018).

At Kursk Medical Institute, he organized a complex of scientific studies on the rationale for using intermediates of Krebs cycle in cardiological practice. Under his supervision, there were defended a number of PhD theses and doctoral thesis by Vladimir V. Pichugin (Fig. 13), who became the head of the Department after Vladimir V. Gatsura had left for Moscow.

Professor V.V. Pichugin properly equipped the Department with equipment for research and organized a laboratory for studying new cardiotropic drugs (Fig. 14).

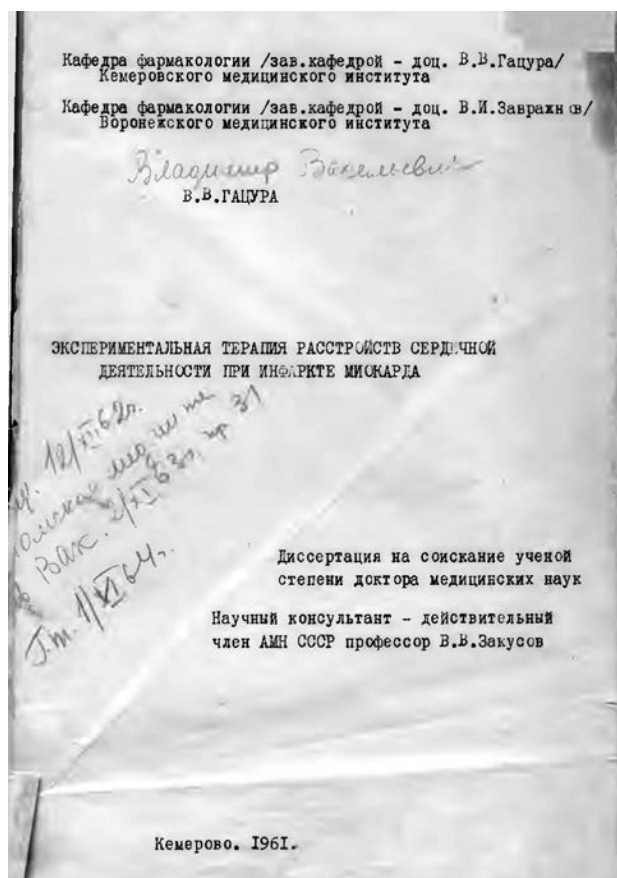


Figure 12. Title page of the doctoral thesis by Professor V.V. Gatsura

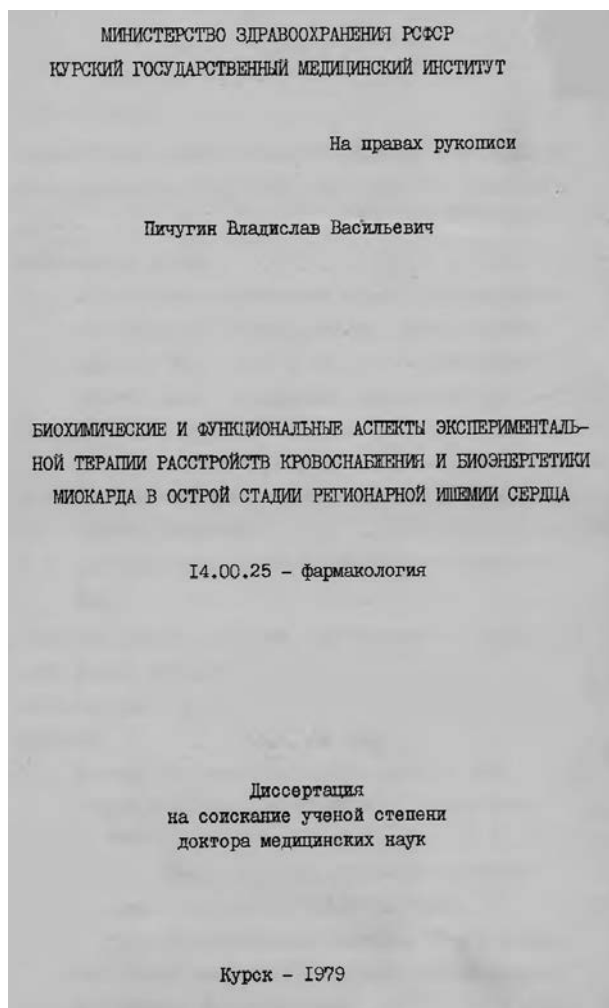


Figure 13. Title page of the doctoral dissertation by MD, Prof. V.V. Pichugin

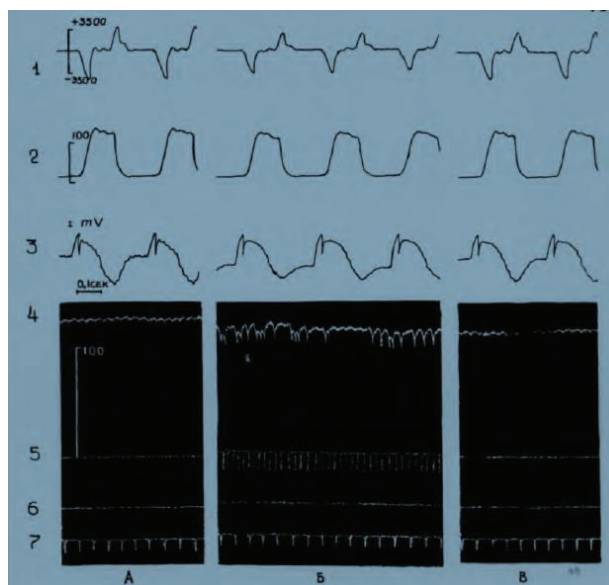


Figure 14. Contractility and electrogram of the heart in a border zone of ischemia during blood drainage from the distal segment of the ligated coronary artery. A – before drainage; Б – during drainage; В – after drainage

One of his most promising apprentices turned out to be Mikhail Pokrovskiy who defended his doctoral thesis in 1995 and who, after the untimely death of V.V. Pichugin, became the head of this Department.

M.V. Pokrovskiy set up a large research laboratory and, using his experience as a Deputy Director for Research at Kursk Plant of Chemicals and Pharmaceuticals, with his team thoroughly explored the problem of correction of the nitric oxide system in the body by pharmacological agents. Over a number of years, he was the Chairman of Dissertation Board in Pharmacology at Kursk State Medical University. An even greater contribution to pharmacological science he made after moving to the Department of Pharmacology of Belgorod State University in 2012. He set up one of the best pharmacological laboratories in Russia, which successfully operates at the moment, established a Research Institute of Pharmacology of Living Systems, continuing the traditions of experimental pharmacology of the University of Dorpat. He is the organizer and editor of the network pharmacological journal, Chairman of the Dissertation Board in medical, biological and pharmaceutical sciences.

In 60-80 years of the last century, the educational process at the Department of Pharmacology of Voronezh Medical Institute was similar in its structure to that in the previous years and included lectures and laboratory classes throughout the academic year (5 and 6 semesters), with one lecture and one practical lesson every week. Lectures and "pharmacological workshops" were still held with experiments, which considerably facilitated the perception of the material and increased the students' interest in learning. Students were still actively involved in the scientific society of the Department (Reznikov and Kitaeva 2018).

Experimental studies were performed in dogs, rabbits, white rats and cats in several directions. The therapeutic

effects of new cardiac glycosides in the comparative aspect with Strophanthin in experimental myocarditis and myocardial infarction were studied in detail, along with studying electrophysiological, biochemical, and rheological parameters. The new cardiac glycosides: drugs of *Covallaria majalis* (Corglycon), Convallatoxin and Cymarine; Erysiminum, Erysimosidum, Gomphotinum, Corchorosidum and Olitorisidum were studied. Based on the study of these glycosides, 2 doctoral theses – by Associate Professor V.I. Zavrazhnov (1960) (Zavrazhnov 1960) and by Associate Professor V.V. Gatsura (1962) (Gatsura 1961), at that time already the head of the Department of Pharmacology of Kemerovo Medical Institute – were defended. During these years, some PhD theses were prepared and defended on studying the action of Corchorosidum-A in experimental myocarditis and myocardiosclerosis (R.I. Kitaeva) and Olitorisidum in experimental myocardial infarction (P.P. Provotorova).

When the Department of Pharmacology was headed by V.I. Zavrazhnov, the book *Medicinal Plants of the Central Black Soil Region* was published (Zavrazhnov et al. 1977), which later went through 3 editions, and also a guide on compatibility of drugs and some guides on all the aspects of pharmacology for students and faculty, etc. At that time, the Department included Professor V.I. Zavrazhnov, Associate Professor R.I. Kitaeva, Associate Professor V.Ya. Kudryavtseva, senior lecturer Yu.N. Chernov, Assistant Professor K.M. Reznikov, Assistant Professor V.A. Nikolaevskiy, Assistant Professor P.P. Provotorova, two senior laboratory assistants and laboratory assistants.

Since 1982, the Department of Pharmacology of Voronezh State Medical Academy has been headed by the apprentice of Professor V.I. Zavrazhnov, Konstantin M. Reznikov (Figs 15, 16) (Reznikov and Kitaeva 2018).

He performed fundamental research of such an important problem as the conditions determining the action of



Figure 15. Honored Scientist of the Russian Federation, Doctor of Medical Sciences, Professor Konstantin M. Reznikov



Figure 16. Professor K.M. Reznikov is operating on a rabbit

drugs in the body. The development of hyperbaric medicine in the Soviet Union and abroad, on the one hand, showed the possibility to saturate the body with oxygen (hyperbaric therapy), and on the other hand, to create the condition of hyperoxia, which can influence the effects of drugs (Reznikov 1980, Reznikov et al. 1982). This problem was successfully solved by K.M. Reznikov in his doctoral thesis *Hyperbaric Pharmacology of Some Cardiovascular Agents* (Reznikov 1981) (Fig. 17), and then elaborated in the works of his apprentices A.V. Filatov (1986), V.V. Ekimov (1987), and S.I. Kedrov (1988). The obtained materials served as the basis for writing the section of the book *Hyperbaric Pharmacology*, published jointly with Moldovan pharmacologists (Mukhin et al. 1985). The significance of the research was confirmed by obtaining a patent of invention (AC 1107359). It is important for pharmacology that oxygen under high pressure (hyperbaric oxygenation) has a beta-adrenolytic effect, alpha-adrenomimetic properties, can change the conformation of protein molecules and modify enzyme activity and membrane permeability (Mukhin et al. 1985).

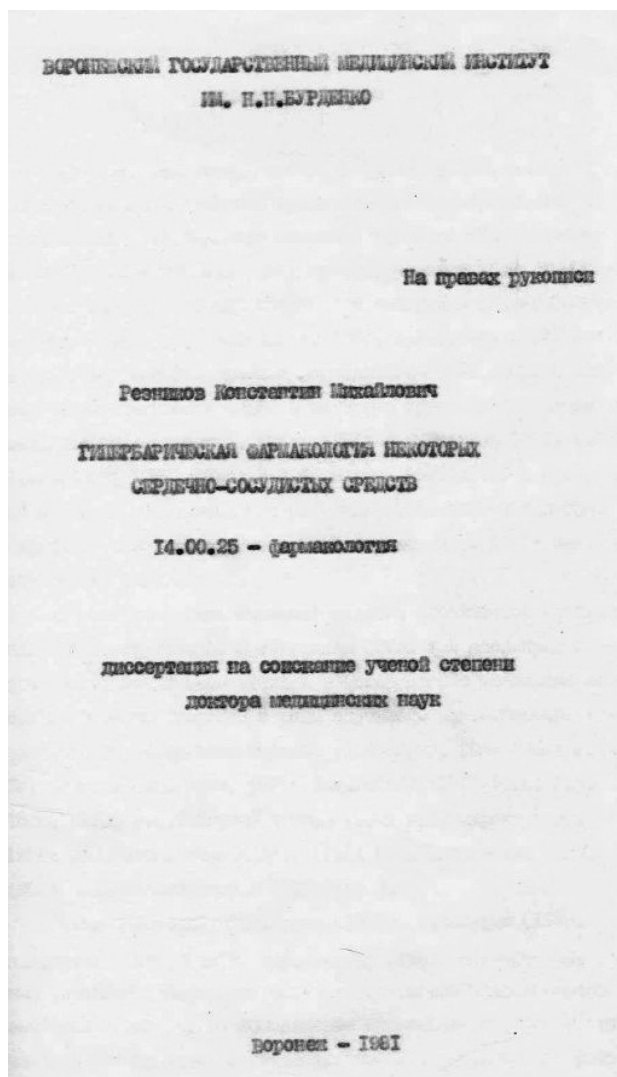


Figure 17. Title page of the doctoral dissertation by Professor KM Reznikova

Post-soviet period

All the studies of new and unknown medicinal substances have been performed using models of experimental pathology, which corresponds to the school of R. Buchheim, and required the development of more optimal models of heart lesions. K.M. Reznikov together with R.I. Kitaeva and others obtained 5 models of heart lesions in the experimental animals by means of using pituitrin, thyroxine, izadrin, which resulted in is recorded in obtaining two inventor's certificates.

Much attention was paid to the search for new cardiotropic drugs. For this purpose, under the supervision of Prof. K.M. Reznikov, an automated complex for studying the functional state of the heart and assessing cardiopathy of biologically active substances was developed, and E.I. Peleshenko (1994), O.V. Trofimova (1994), A.I. Glotov (1996), N.E. Minakova (1997) defended their PhD theses, with obtaining a patent for the invention. There were other successfully defended PhD theses: by N.M. Parfenova (1993) – on the study of derivatives of 1,3-indandione and 1,4-naphthoquinones, by N.A. Shchetinkina (1995) – on the study of phenylpropiophenone, by O.V. Philippova (1995) – on the study of biologically active peptides, by N.S. Nikitskaya (2003) – on the study of derivatives of pyrrole condensed systems, etc. (Reznikov and Kitaeva 2018).

The new equipment, a cold room, a shielding chamber, a number of new biochemical techniques applied, a wide computerization of research have made it possible to move to a new, more detailed level of pharmacological research, and the generalization of the obtained data resulted in formulating the concept of the structural and functional heterogeneity of intracellular components, cells, tissues and organs over time, described by K.M. Reznikov in 1981. This phenomenon serves as a methodological basis for the creation of continuity of discrete processes in the body and was the basis for the creation of the device and the method of controlling drug effects (2 patents have been obtained), which have been awarded a silver medal at an international exhibition. The use of this method has made it possible to obtain new scientific materials on the action of drugs, which were the basis of the monograph by K.M. Reznikov and his co-authors *Monitoring the Action of Drugs* (Reznikov et al. 2014).

For many years, the Department of Pharmacology has been cooperating with clinical departments, especially with departments of psychiatry and dermatology and venereology. The Department of Psychiatry has worked on the problem of drug resistance in mental diseases, which required modern pharmacological approaches and methods for assessing the therapeutic effect (for this purpose, the technique of thermopunctural monitoring, created at the Department of Pharmacology has been used). The first study under the supervision of professor K.M. Reznikov was performed by V.Yu. Zhosanov (PhD thesis, 1994). A fundamental, multi-phase study on this issue was conducted by O.Yu. Shiryaev, head of the Department of Psychi-

atry when he was working on his doctorate thesis, which was successfully defended in 1998. This issue was also studied in the PhD theses by N.A. Petrov (schizophrenia, 2002), N.V. Khorvat (schizophrenia, 2002), E.S. Lyapina (anxiety-depressive disorders, 2002), B.A. Fedorov (depressive disorders, 2002), T.E. Lopatina (anxious-phobic disorders, 2007), A.V. Avilova (schizophrenia complicated by alcoholism, 2008), etc.

Extremely important scientific results were described in a remarkable doctoral thesis by Yu.A. Kulikov (1997) on the evaluation of pharmacodynamics of a number of drugs that affect cerebral circulation, as well as relating dissertation projects by S.M. Fedotkin (2000) and E.A. Borisova (2005). Official recognition of homeopathy as a medical specialty coincided with the defense of the PhD theses by N.M. Plakhova (1998) and E.A. Borisova, which investigated the therapeutic effects of homeopathic preparations. But the recognition of acupuncture, bioresonance method, Reinhold Voll's diagnostic method, homeopathy did not lead to at least the introduction of these topics to students within the education process from the position of informatiology. Even fundamental studies by I.I. Yuzvishin (1993-1996) and a wonderful tractate by V.G. Zilov, K.V. Sudakov, O.I. Epstein *Elements of Information Biology and Medicine* (2000), fully justifying the importance of such knowledge for biologists and doctors and indicating a new way of development of medicine, failed to result in setting a problem and defining a new trend in medicine.

One of the ways to increase the efficacy of pharmacotherapy is to use wave impacts along with drugs. The Department of Pharmacology has conducted a series of studies on the effect of low-intensity laser radiation on the formation of the drug effects. In 2004, S.V. Revenko in his thesis proved that there were changes of the pharmacological properties of drugs after exposing them to radiation and their co-administration with the low-intensity laser. In further studies by A.A. Bakhmetev (PhD thesis, 2007), E.V. Dontsova (PhD thesis, 2011), A.S. Zheltyshcheva (PhD thesis, 2011), E.A. Gamburg (PhD thesis, 2013), these experimental data were confirmed in clinical studies. In 2016, K.M. Reznikov and his co-authors published the monograph *The Effect of the Low-intensity Laser Radiation on the Action of Drugs*, which revealed some of the mechanisms of action of the low-intensity laser radiation on the human body. Some details of these mechanisms were explained on the basis of data obtained earlier in the study of the dependence of pharmacological effects on the value of redox potential of the body fluids.

The value of the redox potential of the body fluids for experiments can be changed by introducing fluids with different redox potential to animals. In the experiments, fluid with negative redox potential (-125-500 mV) – catholyte – and fluid with positive redox potential (+500-1100 mV) – anolyte – were used. It turned out that they were absolutely safe, and the administration of these fluids could cause effects similar to those from drugs, as well as modify the effect of drugs. So, A.D. Brezdynyuk (PhD thesis, 2007) established low toxicity and no negative effect of these solutions on the reproductive function of rats; Yu.A.

Levchenko (PhD thesis, 2008) revealed their minor effects on water-salt metabolism of the body; E.B. Sabitova (PhD thesis, 2009) showed changes in the activity of the central nervous system and the action of neurotropic drugs with the administration of the catholyte and anolyte; M.N. Fuflygina (PhD thesis, 2009) showed the state of the regulation system of the blood aggregate state and action of agents affecting hemostasis under the same conditions; P.D. Kolesnichenko (PhD thesis, 2012) revealed the peculiarities of the functioning of the digestive system with the administration of these fluids to experimental animals. The generalization of these studies is presented in 3 monographs: by K.M. Reznikov et al. *Safety of Administration of Electroactivated Aqueous Solutions of Sodium Chloride for Therapeutic Purposes* (2010, 144 p.), by K.M. Reznikov et al. *Water-salt Metabolism of the Body and the Function of Kidneys under the Effect of Electroactivated Aqueous Solutions of Sodium Chloride* (2011, 137 p.), by K.M. Reznikov et al. *Effect of the Fluids with Different Redox Potential on the Central Nervous System* (2012, 279 p.).

Along with research, the educational process has been also improved; 2 more faculties have been created: the Faculty and Sanitation and Hygiene and the Faculty of Pharmaceutics; there has been an increase in methodical work and a lecture course. Some foreign students are taught in English thanks to teaching assistants N.S. Preobrazhenskaya and E.B. Sabitova. To improve the quality of training, multimedia equipment has been widely used. In particular, each classroom is equipped with a large digital TV and a laptop, the use of which is supported by up-dated manuals for each topic and a large number of visual aids. Modernization of the educational process was much facilitated by Associate Professor R.I. Kitaeva, who was in charge of the academic process, and after her retirement – by Associate Professor N.S. Preobrazhenskaya.

Taking into account his achievements in the field of bioinformatiology, Professor K.M. Reznikov was elected an academician of the International Academy of Informatiology in 1996; in 2006, he was awarded the title of Honoured Scientist by the decree of the President of Russia, "Honorary Professor of Voronezh State Medical University by the order of Rector of Voronezh State Medical University, and in 2017, he was awarded the order of the Academy of Natural Sciences. In total, over the years of his being the head of the Department, he has published more than 500 research papers, including 15 monographs, has made more than 20 inventions, and prepared more than 50 candidates and doctors of science (Reznikov and Kitaeva 2018).

Conclusion

Thus, the principles of experimental pharmacology formulated by R. Buchheim more than 100 years ago have been successfully developed, deepened, confirmed through the improvement of pharmacological science by his students and followers of this specific vector Dorpat (Yuryev) – Voronezh.

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