EDITORIAL

Rus.

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OSWALD SCHMIEDEBERG –THE "FATHER" OF EXPERIMENTAL PHARMACOLOGY

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"Our tribute to the memory of the Teachers and those who were pioneers of pharmacology is an invaluable gift to our descendants"

Abstract

Biography. Oswald Schmiedeberg (1838-1921) was a son of a bailiff and a maid of honour, the eldest of the six children in the family. He was born and educated in the Russian Empire.

Scientific activity. All his life he was completely devoted to science, making experimental pharmacology an independent scientific discipline, and was able to bring it to the international level. O. Schmiedeberg studied the action of muscarine and nicotine, digitoxin, hypnotics and analeptics. He was the first to introduce the concept of "pharmacodynamics" and "pharmacokinetics" of a drug. With his participation, the world's first pharmacological journal was founded, which is still published today.

Science school. Working for many years at the University of Strasbourg, Schmiedeberg managed to educate about 120 students – professors from 20 countries of the world, many of whom later founded experimental pharmacology in their countries, for example, Abel in the USA, and N.P. Kravkov in Russia. Scientific activity of Schmiedeberg influenced scholars of his time and for generations to come, creating the preconditions for new high-profile discoveries and even for receiving Nobel prizes. But Oswald Schmiedeberg failed to obtain this high award himself, though he had been nominated 14 times.

Biography

Oswald Johann Ernst Schmiedeberg (Figure 1) was born on 29.09.1838 (on 11.10.1838 New Style) in Gut-Laizane, in Courland (Laidze parish, Talsi municipality, Latvia), which was at that time part of the Russian Empire.

His father, Wilhelm Ludwig Schmiedeberg was born in 1809 in Vindau (Latvia), a son of Johann Ernst (a mechanic in Libau) and Gertrude Borchet. He worked as a bailiff in Leidzen, later took charge of the forestry in Permisküla, and Paggar (Estonia), died in 1878 in Dorpat. The mother of O. Schmiedeberg, Anna Lucy Bernard, was born in Lausanne (Switzerland) in 1813, a daughter of Johann Bernard, a watchmaker in Lausanne. She worked as a maid of honor and died in 1871. His brother, Johann Julius Rudolf, was born in 1840, worked as a forester in Estonia and was

never married. Oswald Schmiedeberg was the eldest of the six siblings [1, 2].

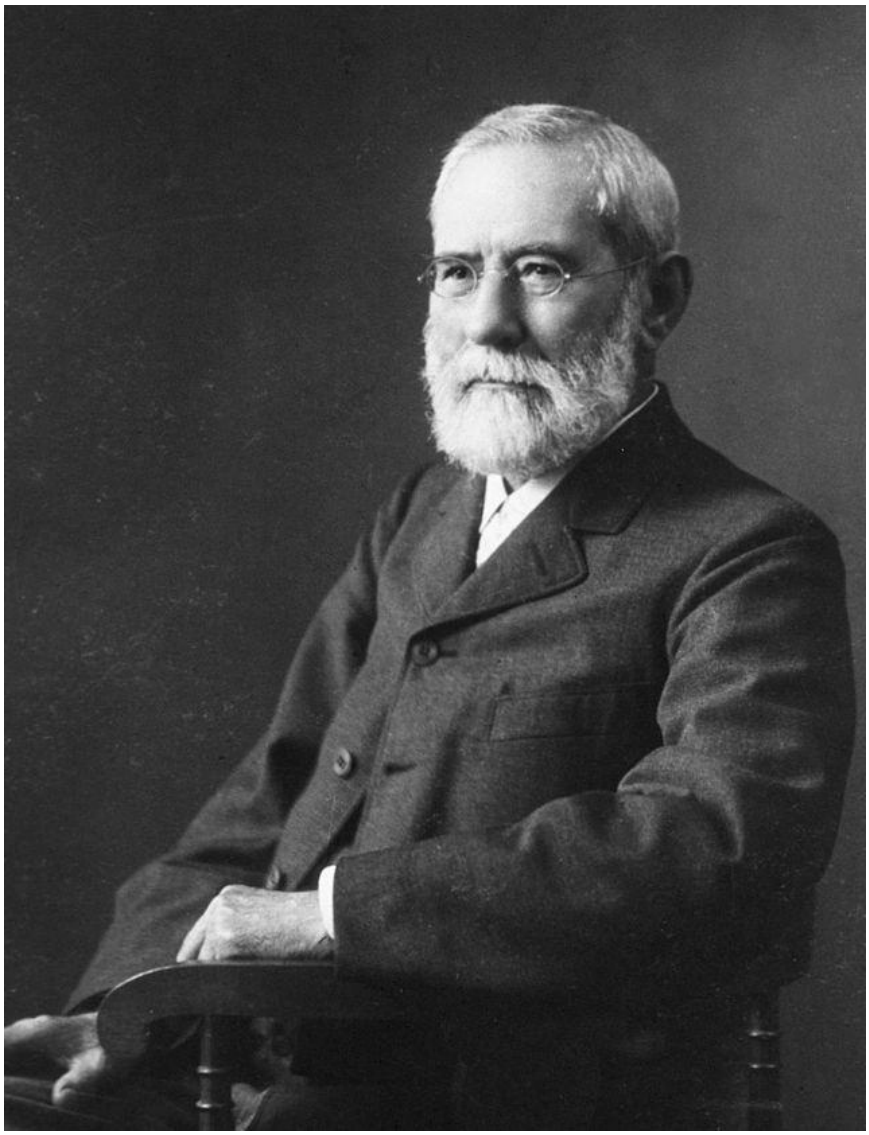


Fig. 1. Oswald Schmiedeberg [3]

After finishing a primary school in Permisküla, Schmiedeberg studied at a district school of Dorpat (today Tartu, Estonia) from 1852 to 1854. In 1855 he studied at the gymnasium in Dorpat, which he successfully finished in 1859, after which he entered the Medical Faculty of the University of Dorpat, where he was a student till 1866. The Imperial University of Dorpat (The Imperial University of Yuryev from 1893 to 1918) was one of the oldest universities in the imperial Russia; nowadays it is The University of Tartu in Estonia (Figure 2) [4, 5, 6].

Schmiedeberg studied at the university at one of the best periods of the Medical Faculty of the University of Dorpat, which was connected with the hey day of Enlightenment in Russia in the second half of the 19th century. In the 1860s, when in all spheres of scientific activity there was a definite change for the better, a system of freelance university lecturers (privat-docents) started to develop at the Medical Faculty, where only after 1863, young scientists (privat-docents) began to work on a constant basis. All this, undoubtedly, was due to the Enlightenment process in Russia at that period. The very development of the system of freelance university lecturers (privat-docents) at Dorpat Medical Faculty proves that at that

time it was in a flourishing condition, there were those who could teach and those who wanted to study [2].

Fig 2. The Imperial University of Dorpat, 1860 [7]

After graduating from the University of Dorpat in 1866, O. Schmiedberg defended his doctoral thesis *On Quantitative Determination of Chloroform in Blood and Its Behavior Towards the Former ("Ueber die quantitative Bestimmung des Chloroforms im Blute u. Sein Verhalten gegen dasselbe")* under the supervision of Professor Rudolf Buchheim [8, 9, 10, 11]. The title page of the dissertation of the scientist can be seen in Fig. 3.

Rudolf Buchheim was elected by the Council of Dorpat University to the Department of Pharmacology on December 30, 1846, and from October 1849 to 1867, he was an ordinary professor at that department. His fruitful professorship and his constant desire to recognize pharmacology as a science independent of therapy, putting it on the experimental research basis, made him so famous that foreign universities such as The University of Breslau, The University of Bonn and The University of Giessen tried to hire him. R. Buchheim was the first scientist who put pharmacology on sound scientific grounds, and the manual that he compiled included for the first time the description of the physiological effect of agents, on which their therapeutic application was based. The vision of Buchheim served as the cornerstone of modern pharmacology. One of the important achievements in Buchheim's scientific life is considered to have been the education of his follower in science, one of the greatest scientists – Oswald Schmiedeberg [2, 13].

Diss. med. 33(1

Ueber die quantitative

Bestimmung des Chloroforms im Blute

und sein Verhalten gegen dasselbe.

Eine mit Bewilligung

der

Hochverordneten Medicinischen Facultät

zu DORPAT

zur Erlangung des

Doctorgrades

verfasste und zur öffentlichen Vertheidigung bestimmte

Abhandlung

von

Oswald Schmiedeberg.

Bayerische Staatsbibliothek München

DORPAT 1866.

Druck von Heinrich Laakmann.

Fig 3. Title page of the thesis by O. Schmiedeberg [12]

While working at Dorpat University, Schmiedeberg actively cooperated in his research with outstanding scientists of that time: a biochemist Karl Schmidt (1822-1894), anatomist Friedrich Heinrich Bidder (1810-1894), physiologist Karl Wilhelm von Kupffer (1829-1902), etc.

Karl Ernst Heinrich Schmidt was a Russian chemist of German-Baltic descent, a professor at the University of Dorpat, and a corresponding member of the Petersburg Academy of Sciences (1873). He supervised a degree project of Wilhelm Ostwald, a Nobel laureate in Chemistry, when the latter was seeking a Doctor of Philosophy degree [2, 14].

Georg Friedrich Carl Heinrich Bidder was a Russian physiologist and anatomist of German-Baltic descent, Professor and Rector of the Imperial University of Dorpat (1857-1864), acorresponding member (1857) and an honorary member (1884) of St. Petersburg Academy of Sciences. In 1869, F.H. Bidder retired as Professor Emeritus [15, 16].

Carl Schmidt and Friedrich Bidder were the first scientists who managed to dispel the doubts of Henry Bence Jones, who had

published an article in *The Lancet magazine* in 1850, in which he wrote: "The gastric juice is a strongly acidic liquid secreted by the stomach ... . Which acid still remains unknown. Salt, phosphoric, acetic, lactic and butyric acids are said to be present in gastric juice" [17]. In 1852, F. Bidder and C. Schmidt published the book *Die Verdauungssaefte und der Stoffwechsel* (Digestive Juices and Metabolism), in which they presented the results of a quantitative analysis of gastric juice collected from various species of live animals, confirming the fact that the stomach normally secretes hydrochloric acid [15].

Karl Wilhelm Kupfer, a German anatomist, histologist and embryologist, was a student of Friedrich Bidder, a prosector and an extraordinary professor at the University of Dorpat (1856–1866). His studies, conducted jointly with Bidder, were on the structure of the spinal cord. In honor of Kupfer, specialized liver macrophages the main function of which is capturing and processing old nonfunctional blood cells were called Kupffer cells [18].

After defending his dissertation in 1866, O. Schmiedberg became Assistant Professor to R. Buchheim at the Pharmacological Institute, and in 1867 he received the title of Privat-docent. When Buchheim left Dorpat after getting an invitation from the University of Giessen, Schmiedeberg was asked to give lectures on pharmacology and dietics. In 1868, he was appointed Full-time Associate Professor, and in 1869 - an Extraordinary Professor of Pharmacology, Dietics and History of Medicine. After being appointed an Extraordinary Professor, Schmiedeber was appointed Director of the Pharmacological Institute, which he had held since the departure of Buchheim.

Together with the renowned scientists of the University of Dorpat, Schmiedeberg made a number of discoveries. Before 1870, his studies on physiological chemistry had led to the discovery of sulfuric acid in the urine of cats and dogs. Together with Ernest Bergman, he conducted research on the poison of rotting substances and discovered sepsin in form of its sulfuric acid salt. Together with Dr. Richard Koppe, Schmiedeberg in 1868 studied the composition of the fly agaric (Agaricus muscarius), which led to the isolation of muscarin, the properties of which were studied in detail by both authors. Over that time, ten scientific dissertations were completed under the supervision by O. Schmiedeberg [2, 5].

In 1870, Schmiedeberg continued his education in Germany, in Leipzig. He spent a whole year at Leipzig University, working together with the outstanding physiologist Karl Friedrich Wilhelm Ludwig (1816-1895). O. Schmiedberg successfully used the kymograph (device for recording blood pressure) invented by K. Ludwig in his scientific experiments and reasonably considered K. Ludwig one of his scientific teachers [19]. Fig. 4 shows a kymogram obtained on smoked paper.

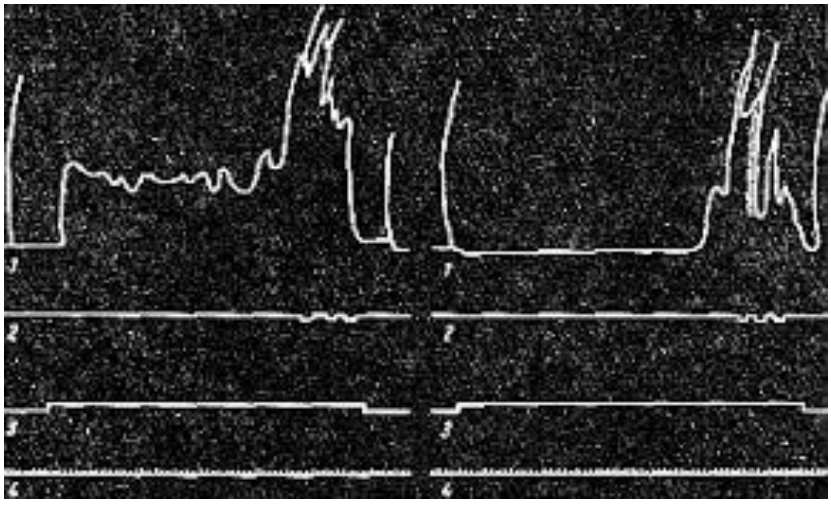


Fig. 4. Example of kymogram on smoked paper [20]

In 1871, Oswald Schmiedeberg became Full Professor of Pharmacology, Dietics and History of Medicine at the University of Dorpat. From 1871 to 1872, Schmiedeberg visited Bern and Kцnigsberg (Prussia), and in 1872, Schmiedeberg resigned from the University of Dorpat after accepting a position at the just-founded University of Strasbourg, where later he was to get engaged in research and teaching for the next 46 years, started his own scientific school and was the Director of the Pharmacological Institute [2].

After arriving at the University of Strasbourg, his scientific laboratory was a very small room in a hospital at Place de l'Нфpital. Along with promoting research in experimental pharmacology, in 1887 the University administration assigned a new spacious building for the laboratory, the building having been designed by Schmiedeberg himself, in cooperation with the architect Otto Warth (1845-1918). Schmiedeberg's office and personal laboratory were on the second floor, the laboratory at the corner with the balcony, the office immediately to the left with the bow window (Figure 5) [21, 22].

The University of Strasbourg was one of the most prestigious and best schools at the time. Along with Schmiedeberg, there worked a number of prominent scientists. Among them was anatomist Heinrich Wilhelm Waldeyer (1836-1921), who was engaged in anatomical, histological, comparative-anatomical and embryological studies. In 1884, he published a paper in which he gave a detailed description of the embryogenesis, structure and functional significance of the pharyngeal lymphoid tissue (*Pirogov-Waldeyer's ring*). In 1888, for the first time he used the term "chromosome", was one of the first supporters of Cajal's neural theory and suggested the term "neuron" [23]. Other famous scholars were Felix Hoppe-Seyler (1825-1895), one of the founders of the Department of Biochemistry and the founder of the journal of physiological chemistry and pathologist Friedrich Daniel von Recklinghausen (1833-1910), whose research papers were on neurofibromatosis, parathyroid osteodystrophy and fibrous ostitis (these diseases, as well as a number of other pathological processes were later called by his name), and who studied rickets and osteomalacies, which later became classical. Schmiedeberg was the youngest among colleague scientists.

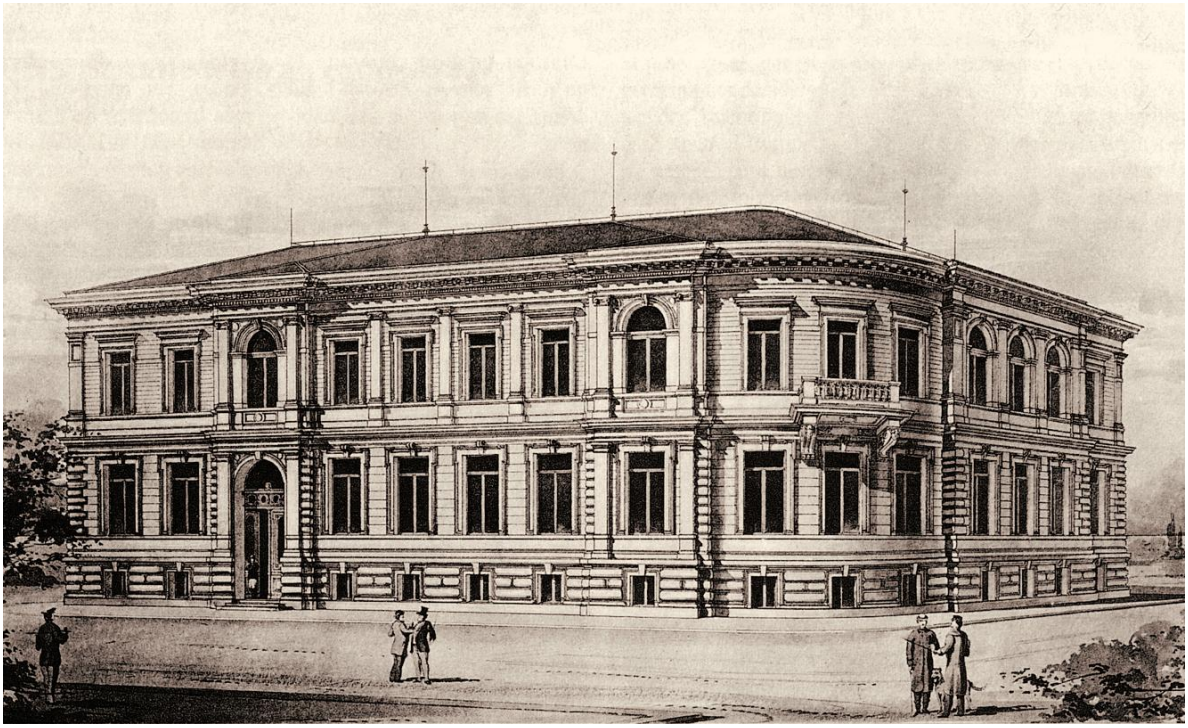


Fig. 5 The Institute of Pharmacology in Strassburg,1877 [21]

In the period from 1918 to 1919, O. Schmiedeberg moved to Baden-Baden, where he lived till his death. His friend in Baden-Baden was B. Naunyn. They were neighbors and often would take a walk along a forest road in Baden-Baden, which is now called Schriever Lane [24].

His view of pharmacology as an independent exact science, O. Schmiedeberg laid in the third edition of his work *Fundamentals of Pharmacology*, for which he tried to provide a rational basis in contrast to purely subjective empiricism [15].

Schmiedeberg's Alma mater, The University of Dorpat, after the fall of the Russian Empire in 1918 was intervened by the Germans. Due to an increase of Russophobia and the First World War, the University faculty members were evacuated to Voronezh, where they made up the basis for Voronezh State University [21, 22, 25].

Oswald Schmiedeberg died on 12.07.1921, at the age of 83.

Scientific activity

The vast knowledge acquired when cooperating with many professors in the field of medicine and chemistry allowed O. Schmiedeberg to make a number of discoveries.

Muscarine, nicotine. In 1869, in the monograph by Oswald Schmiedeberg and paramedic Robert Koppe, there appeared for the first time an article about muscarin as a toxic alkaloid extracted from fly-agarics (Agaricus muscarius L.) [26]. When working together, the scientists isolated pure poison from fly-agarics picked in the vicinity of Dorpat and described its pharmacological effects, named them muscarinic and proved that the poison possessed an antagonistic action towards atropine. Antagonism manifested by atropine against muscarinic receptors was a prototype of competitive antagonism. The work in question was of fundamental importance for pharmacology and medicine as a whole and resulted in the discovery of the chemical transfer of impulse in synapses by Otto Loewi (1873-1961). As O.Shmideberg and R. Koppe wrote: "These effects not only are of high scientific, but also practical interest, since their study has led to the discovery of a physiological antidote to the poison of fly-agaric, which will help avoid the life-threatening consequences of accidental poisoning with this widespread species of mushrooms. Thus, poisoning can probably be completely avoided.

Soon after studying the pharmacological affects of muscarine, O. Schmiedeberg began to study another pharmacological agent – nicotine. The Professor was the first in Dorpat who got interested in this issue, and he further continued his studies in Karl Ludwig's laboratory in Leipzig. Schmiedeberg proved that nicotine suppressed the inhibitory effect of the vagus nerve on the heart and conlcluded that this happened due to ganglionic blockade. That theory was examined thoroughly and was later confirmed in the teachings by John Newport Langley (1852-1925) when studying the autonomic nervous system [27, 28].

About 150 years have passed since the discovery of the pharmacological effects of muscarin and nicotine, but modern textbooks on pharmacology still describe vegetotrophic agents basing on Schmiedeberg's understanding of M- and N-cholinergic receptors, their agonists and antagonists.

Digitalis. One of the most famous works by O. Schmiedeberg and the main direction of his research is rightly considered to have been the study of digitalis, namely alkaloids isolated from this flower. Despite the fact that there was little information about the medicinal properties of digitalis at that time, this topic caused a lot of arguments and controversy. It was O. Schmiedeberg who managed to work out many questions.

In 1874, when Schmiedeberg returned from France, he for the first time isolated a separate substance from the collected red flowers of the digitalis and called it digitoxin. This substance was proved to have a serious effect on the activity of the cardiovascular system. His colleague, Robert Koppe, agreed to conduct an experiment to study the pharmacological effects of digitalis on his own body. During the experiment, R. Koppe recorded the pulse on his wrist (Figure 6). Ingestion of 3.5 mg of digitoxin led to serious poisoning, as well as to the side effects in form of arrhythmia (Pulsus bigeminus).

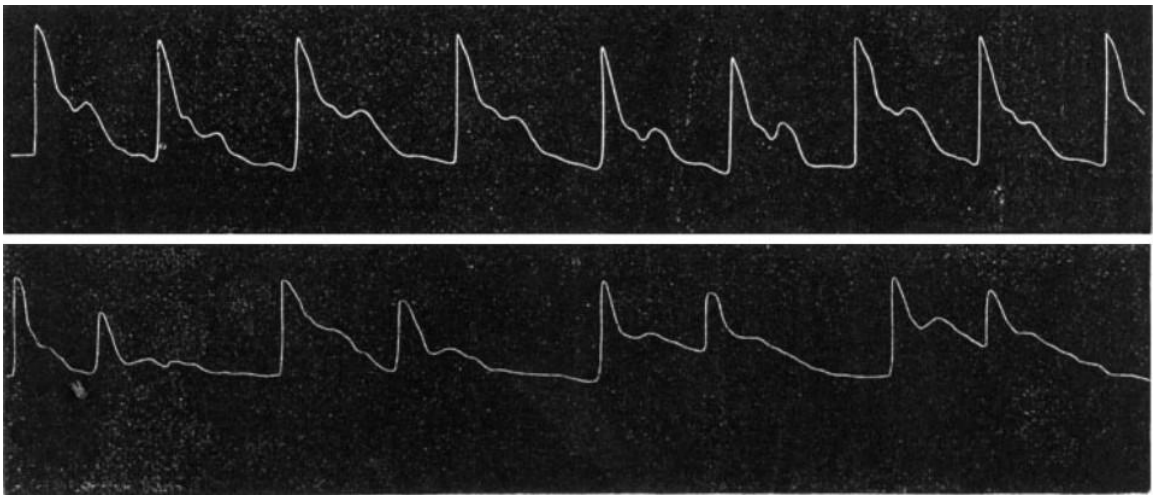


Fig. 6. Radialis pulse curves of R. Koppe before (upper curve) and after (lower curve; pulsus bigeminus) ingestion of3.5 mg digitoxin over five days [21]

Later, R. Koppe described all the pharmacological effects of digitoxin administration in his work, and Arthur Robertson Cushny (1866-1926), Professor of Pharmacology at the University of Edinburgh, who worked with Schmiedeberg in Strasbourg for three years, in 1925 in his monograph - *The Action and Uses in Medicine of Digitalis and Its Allies* called Koppe's publication "the best description of the severe poisoning by digitalis in a healthy person" and also translated the monograph into English [21, 29].

Resulting from his research, Schmiedeberg discovered 19 more alkaloids, including ouabain from parts of the oleander plant, as well as substances from the bear's-foot and lily-of-the-valley, and identified them as a single pharmacological group, which he called a group of digitalis [30].

Metabolism of xenobiotics. The first biochemical synthesis in the history of biochemistry, namely, synthesis of hippuric acid from benzoic acid and glycine, was conducted in the laboratory by Schmiedeberg in 1876, together with the outstanding biochemist of the 19th century Gustav von Bunge, who worked at the University of Dorpat. This fact proves that even after leaving for Strasbourg in 1872 Schmiedeberg maintained scientific networks with the Russian university and collaborated with its scientists in the sphere of his biochemical studies. In 1877, Schmiedeberg clearly demonstrated how this reaction occurred in a dog's kidneys. For the experiment purpose, Schmiedeberg first removed the kidneys from the dog's body, and then, with the help of blood released from fibrinogen, studied kidney perfusion. This experiment was more important for the future of science than simply determining the precise location of the formation of hippuric acid. "The fact that a number of other important issues related to the process of metabolism in the animal's body, in particular, to the place and mechanism of urea formation, were solved with the help of tests on the removed kidney ... allows us to conclude that the value of this study can not be overestimated" , wrote about this Wldemar von Schroeder, Schmeideberg's student (1850-1898) [31, 32].

Camphor. Schmiedeberg and Hans Handful Meyer successfully conducted a study of camphor. They found that camphor was excreted from the body in the form of glucuronide. This study was the first to confirm the chemical transformations of drugs within the body [2].

Sleeping pills. O. Schmiedeberg's dissertation of 1866 was on the anesthetic effect of chloroform. Twenty years later, the scientist continued to develop this idea. He suggested that some alcohols had a narcotic effect and slowed down breathing, whereas ammonia, on the contrary, stimulated breathing. He supposed that some groups of atoms within a chemical compound, especially carbamates, could have analgesic and sedative pharmacological effects. Now, the hypnotic and

anesthetic effects of carbamates along with stimulating the breathing have been confirmed. "This effect can be associated with the carbamate NH2 group, so that the character of the effects of this compound is preserved," Schmiedeberg wrote [33]. This work by Schmiedeberg is noteworthy for three reasons. First, it shows that the pharmacological principles and the biological effects of drugs depend on their chemical structure. Second, this work described a completely new anesthetic which is still used on animals. Third, the discovery led to a number of significant discoveries of sleeping pills and sedatives such as bromisoval, barbiturates, and benzodiazepines.

Synthesis of urea. Schmiedeberg is considered the founder of the synthetic theory of the formation of urea from ammonium carbonate. According to this theory, urea is formed by the dehydration of carbamide-acid ammonium, which can be considered as an intermediate stage of dehydration from ammonium carbonate. When working in Dorpat, Schmiedeberg suggested that ammonium was part of urea. His further experiments in Strasbourg confirmed this suggestion, and his student Waldemar von Schroeder demonstrated that the synthesis of urea from ammonium carbonate took place in the liver [34]. This knowledge was important for understanding the process of reducing the acid-base balance in the formation of urea in the liver in favor of increasing the formation of ammonia in the kidneys in acidosis. The synthetic theory of urea formation in the form in which it was developed and substantiated by the works of scientists of the 19th century, existed with no change until the 30s of the 20th century. In 1932, there appeared a new *theory of Krebs* and Henseleit (1900-1981), which revealed the participation of new compounds in the synthesis of urea. This theory was followed by a further discovery of the Krebs cycle, for which Krebs was awarded the Nobel Prize in Physiology and Medicine in 1953.

Schmiedeberg also gave the first chemical definition of the protein structure free from other impurities, by examining cartilage tissue. He managed to identify the structure of chondroitin [21].

Schmiedeberg Research School

Oswald Schmiedeberg began his research under the supervision of Rudolf Richard Buchheim in Dorpat in the world's first pharmacological research institute. At the beginning of his scientific career, Buchheim turned his own apartment into a research lab. Besides Schmiedeberg, Buchheim supervised about 90 post-graduate students and stated his thoughts in essays and books. However, none of Buchheim's initiatives and ideas would have ever been further developed, if pharmacologist Oswald Schmiedeberg had not become one of his doctoral students. Thanks to Schmiedeberg's own research and the fact that he had approximately 120 disciples from 20 countries – pharmacology and the pharmacological school of Strasbourg got in vanguard and was studied worldwide, and the majority of well-known pharmacologists in the first half of the 20th century were his students (Fig. 7, 8). Schmeideberg's research activity was largely aimed at finding the correlation between the chemical structure of substances and their effectiveness as drugs. During his life, O. Schmiedeberg wrote over 200 scientific books and articles, and his research is sometimes considered a major factor determining the success of the German pharmaceutical industry prior to World War II [5, 24, 35, 36].

Some disciples of Oswald Schmiedeberg [5, 21]:

Otto Loewi (Nobel prize winner) [37], John Jacob Abel (father of American pharmacology) [38], Heinrich Hermann Robert Koch (Nobel prize winner) [39], Rudolf Gottlieb, Hans Horst Meyer, Carl Jacobj, Oskar Minkowski, Alexander Ellinger, Heinrich Dreser, Max Jaffe, George H. Whipple, Corneel Heymans, Carl Ferdinand Cori; Arthur Robertson Cushny, Waldemar von Schroeder, Sigmund Fraenkel, Franz Hofmeister, Alfred Jaquet, Arthur Heffter, Max Arnold Cloetta, Vladimir Lindeman, Dickinson W. Richards, Vincenzo Cervello, Rudolf Eduard Kobert, Hermann Georg Fühner, Wolfgang Heubner, Ferdinand Siegert, Alessandro Baldoni, Edwin Stanton Faust, Louis Lewin.

Fig 7. Schmiedeberg with his disciples at a meeting to commemorate his 70[th] anniversary, Strasbourg, 1908 [21]

1. von Recklinghausen; 2. Reeb; 3. Cloetta; 4. Wallace; 5. Siegert;6. Heubner; 7. Fetzer; 8. Herlant; 9. Lindemann; 10. Faust; 11. Kobert; 12. Meyer; 13. Fühner; 14. Cervello; 15. Straub; 16. Jacobj; 17. Schmiedeberg; 18. Spiro;19. Hofmeister; 20. Harnack; 21. Muffat; 22. Heffter; 23. Cushny; 24. Huldschinsky; 25. His; 26. Minkowski; 27. Gottlieb; 28. Bethe; 29. Zinck.

The disciples of Oswald Schmiedeberg in Russia

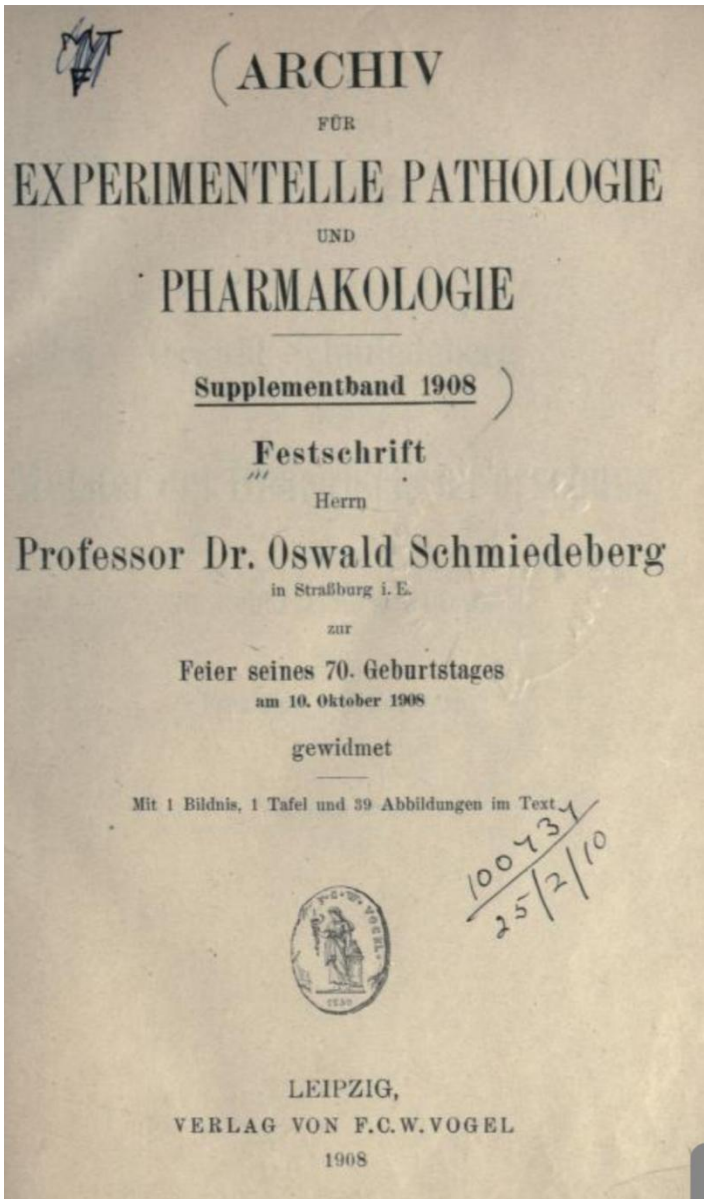
Konstantin F. Arkhangelskyy [40], Nikolay P. Kravkov (1865-1924), the founder of the Russian pharmacology [41, 42], P.V. Bruzinskyy [43], Stanisiaw I. Czyrwicski [44], Vladimir V. Nikolaev [45], Valerian O. Podvysotskiy [46], Dmitryy M. Shcherbachev [47].

Fig 8. O. Schmiedeberg with his disciples, 1905 [5]

O. Schmiedeberg's contribution to enlightenment and his printed works

The idea of mass enlightenment was very important for O. Schmiedeberg, since he considered this an indispensable condition for the development of science and society as a whole. Together with his students, he wrote textbooks and popular books.

With his friend Bernhard Naunyn and pathologist and bacteriologist Edwin Klebs (1834-1913), O. Schmiedeberg founded the first pharmacological journal *Archive of Experimental Pathology and Pharmacology*, which was of paramount importance for promoting the development of theoretical medicine in Germany. In 1873, the first volume of this specialized pharmacological journal was published, which became a symbol of combining physiological chemistry, pathology and clinical science when studying the effects of drugs. For a long time, the journal was the only source with the collection of the best pharmacological studies and remained one of the most important scientific journals. Despite its interdisciplinary approach, O. Schmiedeberg pursued the goal of developing pharmacology as a science independent of clinical and practical medicine. In 1925, the journal got a new name renamed, the modern name of the archive is: *Naunyn-Schmiedeberg's Archives of Pharmacology* and it is still published nowadays (Figure 9) [15, 21, 48].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EXPERIMENTELLE PATHOLOGIE
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Supplementband 1908
Festschrift
Herrn
Professor Dr. Oswald Schmiedeberg
in Straßburg i. E.
zur
Feier seines 70. Geburtstages
am 10. Oktober 1908
gewidmet
Mit 1 Bildnis, 1 Tafel und 39 Abbildungen im Text
LEIPZIG,
VERLAG VON F.C.W.VOGEL
1908

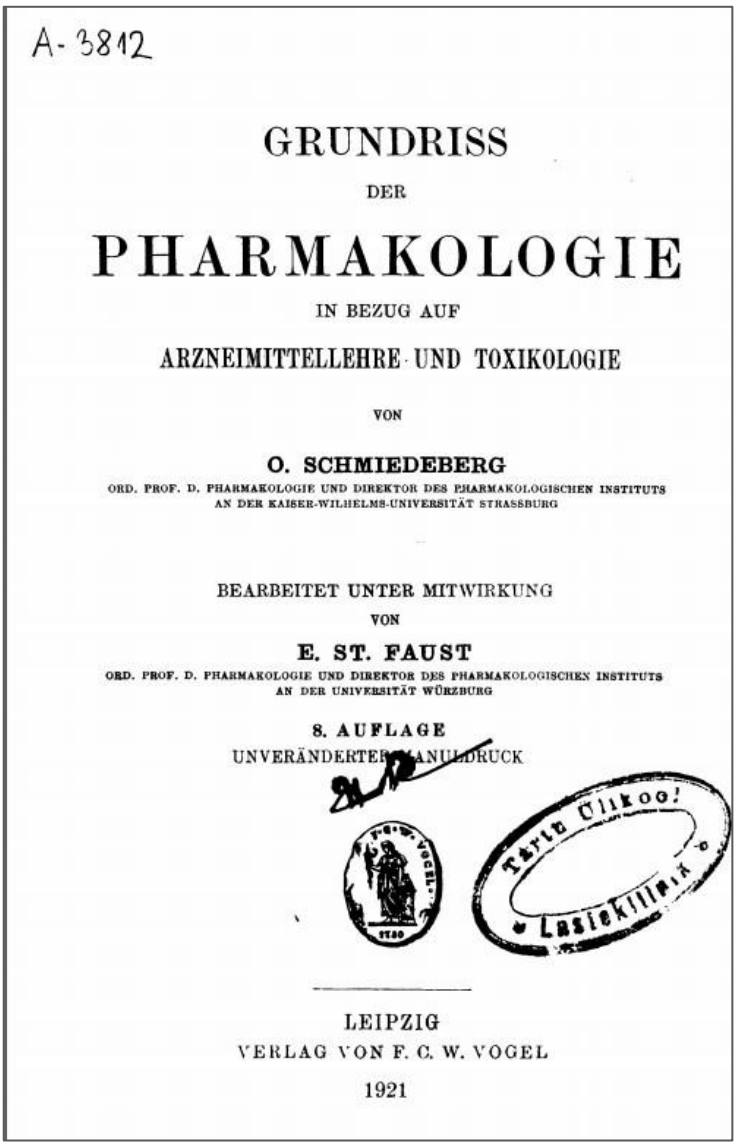
Fig. 9 Title page of *Archive of Experimental Pathology and Pharmacology*, 1908. Leipzig [48]

O. Schmiedeberg also was the author of the book *Grundriss der Pharmakologie in Bezug auf Arzneimittellehre und Toxikologie* (Fundamentals of Pharmacology Through the Doctrine of Medicinal Substances and Toxicology), Leipzig, 1883 (Figure 10). In it, Schmiedeberg developed his basic idea of perceiving the human body "as a chemical laboratory". The book was translated into most languages of the world in accordance with the translation by Hans Horst Mayer [49].

Another work by O. Schmiedeberg was *The Dietetic and Therapeutic Uses of Ferratin*, published in English in Strasbourg in 1893 after he had developed a new drug for treating anemia "Ferratin". In 1894, another work in English by O. Schmiedeberg was published: *Ferratin: the Ferruginous Element of Food*.

Oswald Schmiedeberg wrote the book *Arzneimittel und Genußmittel*. (Medications and Pleasure), a treatise on stimulants, which was published in Leipzig in 1912 [50].

Über die Pharmaka in der Ilias und Odyssee (Iliad and Odysseus in Pharmacology), an essay by O.Schmiedeberg, which was very popular, was published in Strasbourg in 1918 [51].


A-3812

GRUNDRISS

DER

PHARMAKOLOGIE

IN BEZUG AUF

ARZNEIMITTELLEHRE UND TOXIKOLOGIE

VON

O. SCHMIEDEBERG

ORD. PROF. D. PHARMAKOLOGIE UND DIREKTOR DES PHARMAKOLOGISCHEN INSTITUTS AN DER KAISER-WILHELMS-UNIVERSITÄT STRASSBURG

BEARBEITET UNTER MITWIRKUNG

VON

E. ST. FAUST

ORD. PROF. D. PHARMAKOLOGIE UND DIREKTOR DES PHARMAKOLOGISCHEN INSTITUTS AN DER UNIVERSITÄT WÜRZBURG

8. AUFLAGE

UNVERÄNDERTER ANASTATISCHER DRUCK

LEIPZIG

VERLAG VON F. C. W. VOGEL

1921

Fig. 10. Title page of O. Schmiedeberg's book *Grundriss der Pharmakologie in Bezug auf Arzneimittellehre und Toxikologie* (Fundamentals of Pharmacology Through the Doctrine of Medicinal Substances and Toxicology) [49]

Memoirs of the contemporaries about O.Schmiedeberg

Unfortunately, no letters written by O. Schmiedeberg have survived, not to mention his autobiography. Nevertheless, we can learn something about him, as a person, from the memoirs by Bernhard Naunyn and Hans Horst Meyer.

O. Schmiedeberg never married. His disciples said that he had once intended to marry and even bought a wedding cylinder for that purpose, but his rival overtook him, and the cylinder remained "sitting on the shelf" for the rest of his long life. B. Naunyn wrote about Schmiedeberg's attitude towards work: '"This is his whole being, this is his whole life. After having some rest at home, at the beginning of a working day, he was already at his institute, and left his office only for a short lunch break, leaving work late at night, usually being the last to leave".

H.H. Meyer described Schmiedeberg's teaching style: "Schmiedeberg's teaching was not easy, he had a very strict style, he demanded clear answers and clear thoughts. In his lectures to the students, Schmiedeberg was very serious about his teaching. His lectures were, as well as his style of communication, sober, thorough, very rich in content, and in the process there were very bold judgments and

assumptions, so he always impressed the students, despite the fact that he avoided skillful speech patterns. When discussing scientific or political problems in the conversation, Schmiedeberg could expose extensive disproof or he alone could be against everybody, but this exactly was his opinion. This strictness also accounted for his success" [24, 27, 52].

In 1956, the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT) established the highest award, the prize and the medal (Fig. 11) awarded "for outstanding scientific achievements in pharmacology, clinical pharmacology and toxicology". The award is named after Oswald Schmiedeberg and has been presented since 1956 [53].

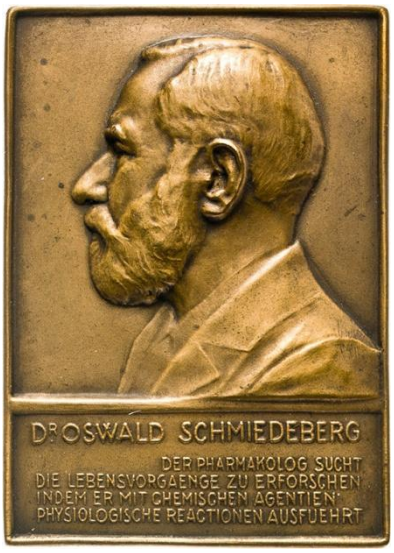


Fig. 11. Medal of Schmiedeberg [53]

Conclusion

All the above proves the outstanding contribution of Oswald Schmiedeberg to the establishment of experimental pharmacology as an independent medical and biological science. It is impossible to overestimate his merits in forming the world school of pharmacologists, 120 professors from which founded departments of pharmacology in Western Europe, the United States, Japan and Russia. His fundamental works on the pharmacology of muscarin and nicotine, digitalis, camphor, sleeping pills, urea are still of value today and are still included in all the guidelines on pharmacology of the 19th-20th centuries. Of great importance is a system of specialized scientific publications on pharmacology which was created with his active participation.

Unfortunately, World War I destroyed Schmiedeberg's Strasbourg Institute of Pharmacology; however, the experimental pharmacology that he had created continued to develop. Such outstanding Schmeideberg's deciples as Heinrich Hermann Robert Koch and Otto Loewi were awarded the Nobel Prize; Hans Horst Meyer, Rudolf Gottlieb, Heinrich Dreser and many others pioneered the industrial revolution in the pharmaceutical industry. Special emphasis should be placed on the fact that in different years at Schmiedeberg's laboratory in Strasbourg there studied and did the internship a number of Russian scientists, such as Konstantin F. Arkhangelskyy, Nikolay P. Kravkov, the founder of the Russian pharmacology, P. V. Bruzinskyy, Stanisiaw I. Czyrwicski, Vladimir V. Nikolaev, Valerian O. Podvysotskiy, Dmitryy M. Shcherbachev who stood at the origins of the Russian pharmacology.

Conflicts of Interest

The authors have no conflict of interest to declare.

References

1. Bäumer B. Schmiedeberg, Oswald. Neue Deutsche Biographie [Internet]. 2007;23:S. 227-228 [cited 2017 Aug 01]. Avialable from: https://www.deutsche-biographie.de/pnd116794720.html#ndbcontent (in Germany)

2. Levickij G.V. Biographical dictionary of professors and teachers of the Imperial Yuryevsky, the former Derpt University for a hundred years of its existence (1802-1902). Vol. 2. YUr'ev: Tipografiya K. Mattisena; 1903. 656 p. (in Russian) [Full text]

3. File: Oswald Schmiedeberg.jpg [Internet]. Wikimedia commons; 2014 July 4 [cited 2017 Aug 01]; Avialable from: https://commons.wikimedia.org/wiki/File:Oswald_Schmiedeberg.jpg

4. Petuhov E.V. The Imperial Yuryevsky, a former Derptsky, a university for a hundred years of its existence (1802-1902). East. essay:

The first and second periods (1802-1865). Vol. 1. YUr'ev: Tipografiya K. Mattisena; 1902. 680 p. (in Russian) [Full text]

5. Muscholl E. The evolution of experimental pharmacology as a biological science: the pioneering work of Buchheim and Schmiedeberg'. *British Joumal of Phamacology*. 1995;116:2155 2159. Doi: 10.1111/j.1476-5381.1995.tb15047.x [Full text] [Abstract]

6. David B. Jack. The University of Tartu (Dorpat), 1632–1982: A review of its contribution to the pharmacological sciences. *Trends in Pharmacological Sciences.* 1983;4:99-101. doi: https://doi.org/10.1016/0165-6147(83)90316-4 [Abstract]

7. File: Album von Dorpat, TKM 0031H 05, crop.jpg [Internet]. Wikimedia commons; 2017 Jan 29 [cited 2017 Aug 01]; Avialable from: https://commons.wikimedia.org/wiki/File:Album_von_Dorpat,_TKM_0031H_05,_crop.jpg

8. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19 Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 36-39. (in Germany) [Full text] [Abstract]

9. Heischkel-Artelt E. Buchheim, Rudolf. Neue Deutsche Biographie [Internet]. 1955;2: S.701 [cited 2017 Aug 01]. Avialable from: https://www.deutsche-biographie.de/pnd119429063.html#ndbcontent (in Germany)

10. Leake ChD. The scientific of pharmacology. *Science.* 1691;134(3496):2069-2079, doi: 10.1126/science.134.3496.2069 [Abstract]

11. Schmiedeberg O. Rudolf Buchheim, sein Leben und seine Bedeutung für die Begründung der wissenschaftlichen Arzneimittellehre und Pharmakologie. *Arch. Exp. Path. Pharmakol.* 1911;67(1):1-54. doi: https://doi.org/10.1007/BF02012802 (in Germany) (in Germany) [Abstract]

12. Ueber die quantitative Bestimmung des Chloroforms im Blute und sein Verhalten gegen dasselbe : Inaug. Diss. Bayerishe StaatsBibliothek digital [Internet]. [cited 2017 Aug 01]. Avialable from: http://reader.digitale-sammlungen.de/de/fs3/object/display/bsb10855892_00003.html (in Germany)

13. Habermann Ernst R. Rudolf Buchheim and the Beginning of Pharmacology as a Science. *Annual Review of Pharmacology.* 1974;14:1-9. Doi: https://doi.org/10.1146/annurev.pa.14.040174.000245. [Abstract]

14. Fischer M. Lebendige Verbindungen. Biobibliographisches Lexikon der Biochemiker zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 12). Aachen; Shaker: 2013, pp. 168-171 (in Germany) [Full text] [Abstract]

15. Bing FC. Friedrich Bidder (1810–1894) and Carl Schmidt (1822– 1894) – a biographical sketch. J Nutr. 1973;103(5):637-648. [Abstract]

16. Rosenfeld L. Gastric tubes, meals, acid, and analysis: rise and decline. *Clinical Chemistry.* 1997;43(5):837-842 [Full text]

17. Jones HB. Diagnosis and treatment of stomach and renal diseases. *Lancet*. 1850;1:69-71.

18. Rosenfeld L. William Prout: Early 19th Century Physician-Chemist. *Clinical Chemistry.* 2003; 49(4):699-705. doi: 10.1373/49.4.699 [Full text]

19. Fischer M. Lebensmuster. Biobibliographisches Lexikon der Physiologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 9). Aachen; Shaker: 2012, pp. 163-165 [Full text]

20. Ed. Petrovsky BV, *Great Medical Encyclopedia.* Kymography. 3rd edition, 10 vol. [Bolshaya meditsinskaya entsiklopediya] [Internet]. [cited 2017 Jul 15] Avialable from: http://xn--90aw5c.xn--c1avg/index.php/%D0%9A%D0%98%D0%9C%D0%9E%D0%93%D0%A0%D0%90%D0%A4%D0%98%D0%AF (In Russian)

21. Starke K. A History of Naunyn-Schmiedeberg's Archives of Pharmacology. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1998;358:1-109 [Abstract]

22. Koch-Weser J, Schechter PJ. Schmiedeberg in Strassburg 1872–1918: The making of modern pharmacology. *Life Sci*.

1978;22:1361-1372. doi.org/10.1016/0024-3205(78)90099-1 [Abstract]

23. Kutya SA. Jubilee dates in the history of morphology in 2011. *Morphologia [Morfologiya]*. 2011;5(1):59-61 (in Russian) [eLIBRARY] [Full text]

24. Naunyn B. Oswald Schmiedeberg †. *Arch Exper Pathol Pharmakol* 1921;90(5-6):I–VII. doi.org/10.1007/BF01864758 [Abstract]

25. Dorpat University [Internet]. [cited 2017 Jul 15]. Avialable from: https://dic.academic.ru/dic.nsf/ruwiki/893131 (InRussian)

26. Schmiedeberg O, Koppe R. Das Muscarin : Das giftige Alkaloid des Fliegenpilzes (Agaricus muscarius L.): seine Darstellung, chemischen Eigenschaften, Physiologischen Wirkungen, Toxicologische bedeutung und Sein Verhaltniss zur Pilzvergiftung im Allgemeinen. Leipzig; Vergalvon F.C.W. Vogel: 1896, 115 pp. [Abstract]

27. Kuum M., Kalda A. Psühhoneurofarmakoloogia loengupäev „Johann Ernst Oswald Schmiedeberg 175". *Eesti Arst.* 2013;92(8):432-43. DOI: 10.15157/ea.v0i0.11409 . [Abstract]

28. Heubner W. Historische Notiz über die Entdeckung der Synapsen im autonomen Nervensystem mit Hilfe des Nikotins. *Archiv f. experiment. Path. u. Pharmakol.* 1947;204(1-3):33-35 Doi: 10.1007/BF00738329 [Abstract]

29. Cushney Arthur R. The action and uses in medicine of Digitalis and its allies. London;Longmans Green: 1925.

30. Schmiedeberg O. Untersuchungen über die pharmakologisch wirksamen Bestandtheile der Digitalis purpurea L. *Archiv für Experimentelle Pathologie und Pharmakologie.* 1970; 3(1):16-43. DOI 10.1007/BF01958772 [Abstract]

31. Martinson E.E. Scientific notes of the Tartu State University. Priority of Russian biochemistry in establishing the structure of urea and its synthesis in the body and the work of the University of Tartu in this field. 6Ed. Tartu; Ehstonskoe gosudarstvennoe izdatel'stvo: 1950, p. 27 [Full text]

32. Bunge G, Schmiedeberg O. Ueber die Bildung der Hippursäure. *Archiv für experimentelle Pathologie und Pharmakologie.* 1877;6(3-4):233-255 [Abstract]

33. Schmiedeberg O. Ueber die pharmakologischen Wirkungen und die therapeutische Anwendung einiger Carbaminsäure-Ester. *Archiv für experimentelle Pathologie und Pharmakologie.* 1885;20(3-4):203-216. doi: https://doi.org/10.1007/BF01918291. (in Germany) [Abstract]

34. Schröder v. W. Ueber die Bildungsstätte des Harnstoffs. *Archiv für experimentelle Pathologie und Pharmakologie.* 1882;15(5-6):364-402. doi: https://doi.org/10.1007/BF01830854. (in Germany) [Abstract]

35. Candler C, Ihnat M, Huang G. Pharmacology education in undergraduate and graduate medical education in the United States. *Clin Pharmacol Ther.* 2007;82(2):134-137. doi: 10.1038/sj.clpt.6100266. [PubMed]

36. Nurmand L. Zur Geschichte der Pharmakologie an der Universität zu Tartu (Dorpat). *DGPT-Mitteilungen.* 1996;19:58-63. (in Germany)

37. Todman D. Otto Loewi (1873–1961). *Journal of Neurology.* 2009;256(2):291–292. doi: https://doi.org/10.1007/s00415-009-0135-8. [Abstract]

38. Dale HH. John Jacob Abel. 1857-1938. *Obituary Notices of Fellows of the Royal Society.* 1939;2(7):577–585. doi:10.1098/rsbm.1939.0019 [Abstract]

39. Wiedeman H. -R. Robert Koch1843–1910. *European Journal of Pediatrics.* 1990;149(4):223-223. Doi: https://doi.org/10.1007/BF02106276. [Abstract]

40. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 6-8 [Full text] [Abstract]

41. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14).

Aachen; Shaker: 2014, pp. 126-132 [Full text] [Abstract]

42. Uzbekova DG. The Importance of Academician N. P. Kravkov's Studies of the Relationship Between Drug Action and Chemical Structure (On The 150TH Birthday of Academician N. P. Kravkov). *Pharmaceutical Chemistry Journal.* 2015;49(2):139-140. Doi: https://doi.org/10.1007/s11094-015-1237-5 [Abstract]

43. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 40-43 [Full text] [Abstract]

44. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 51-54 [Full text] [Abstract]

45. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 154-158 [Full text] [Abstract]

46. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 171-175 [Full text] [Abstract]

47. Fischer M. Akteure und Agentien. Bibliographisches Lexikon der Pharmakologen zwischen Deutschland und Russland im 19. Jahrhundert. (Relationes 14). Aachen; Shaker: 2014, pp. 223-225 [Full text] [Abstract]

48. Schmideberg O, *Archive of Experimental Pathology and Pharmacology.* 1908. Leipzig [Internet].[cited 2017 Jul 17] Avialable from: http://archive.org/stream/festschriftherrn00schmuoft#page/n5/mode/2up

49. Shmideberg O. Grundriß der Pharmakologie in Bezug auf Arzneimittellehre und Toxikologie. 1921. Leipzig. 657 p. [Internet].[cited 2017 Jul 17] Avialable from: http://dspace.ut.ee/handle/10062/22651

50. Schmideberg O. *Arzneimittel und Genußmittel*. Leipzig: 1912, 160p. [Full text]

51. Schmiedeberg O. Über die Pharmaka in der Ilias und Odyssee. Strasbourg; Trübner: 1918, 41 p. [Full text]

52. Meyer HH. Oswald Schmiedeberg. *Naturwissenschaften.* 1922;10(5):105-107. doi: https://doi.org/10.1007/BF01488534 [Abstract]

53. Schmiedeberg-Plakette. Wikipedia. [Internet].[cited 2017 Jul 17] Avialable from: https://de.wikipedia.org/wiki/Schmiedeberg-Plakette

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