



Pharmacology, From Rudolf Buchheim to Arnold Holste: the Founding of the Institute of Pharmacology at the Faculty of Medicine, University of Belgrade

Zoran Todorović,^{1, 2} Sonja Vučković,¹ Nevena Divac¹

Abstract

The School of Medicine at the University of Belgrade celebrates its centennial anniversary. The Institute of Pharmacology and Toxicology, founded in 1924, played an important role in the School's life and development. It is not just about the scientific achievements, but above all, the exceptional personalities of our predecessors. If they spent their academic careers somewhere else, they would certainly have been among the most respected researchers in the world. The courage to stay in the turbulent Balkans and maintain successful communication with colleagues from abroad deserves respect and admiration. One German and one Serb, professors Arnold Holste and Radivoje Pavlović, the latter with severely impaired sight, did an extraordinary job. They established a distinct pharmacological school, equipped research labs and provided their students with generous support despite the adverse circumstances (two world wars and persistent economic crisis, above all). Their younger associates, future professors Dimitrijević and Bogdanović, followed in the footsteps of their predecessors. Their example and sacrifice oblige us to keep pace with the extremely rapid development of pharmacology in the world.

Key words: Pharmacology; School of medicine; Centennial anniversary.

1. Department of Pharmacology, Clinical Pharmacology and Toxicology, University of Belgrade School of Medicine, Belgrade, Serbia.
2. University Medical Centre "Bežanijska kosa", Belgrade, Serbia.

Correspondence:
ZORAN TODOROVIĆ
E: zoran.todorovic@med.bg.ac.rs

ARTICLE INFO

Received: 28 December 2021
Revision received: 8 March 2022
Accepted: 8 March 2022

Establishment of the University Medical School in Belgrade - the first hundred years

The end of the nineteenth and the beginning of the twentieth century in Serbia were marked by numerous debates and opposing views regarding the need to establish a medical faculty in Belgrade. On one side stood physicians Milan Jovanović Batut (1847-1940) and Đoka Nikolić, a member of the General Sanitary Council and on the other equally distinguished doctors - Vladan Đorđević and senior military officer Mihajlo Petrović, to mention only the most prominent among them. The former advocated the establishment of the faculty of medicine in Belgrade and supported the transformation of the Great

School to the level of a university. They had a role model in the successful organisation of the University of Zagreb, where the initiative to establish a medical faculty has come a long way. However, the latter strongly opposed the establishment of the first medical faculty in Serbia, arguing that it was more reasonable to educate young doctors abroad and that the medical faculty was an expensive and complicated institution that required decades of investment in scientific staff and equipment. The need for medical staff was more than obvious - the situation in Serbian health care was challenging, but the conflict

between supporters and opponents of the establishment of the faculty was very sharp and was conducted both in the National Assembly and in the most prestigious medical journal of the time - Serbian Archives.

At the end of the nineteenth century, Belgrade had four hospitals (general/state-, military-, prison-, and mental hospital, with almost 800 beds) and 54 civilian and 10 military doctors. The situation in those hospitals was extremely difficult, as the press from that time testifies. Despite the conflicting views of the medical professionals and general public, surgeon Dr Vojislav Subotić ("senior", 1859-1923) managed to adopt an initiative in the Serbian Medical Association in 1914 to establish a medical school in Belgrade. The former Prime Minister, Stojan Protić, then accepted such an initiative. The report was written by a commission composed of Dr Milan Jovanović Batut, Dr Vojislav Subotić and Dr Edward Muhl who had already visited 17 European medical schools in order to find the best model. However, the faculty could not be established before World War I. Unfortunately, the Great War brought enormous suffering and death of a huge number of civilian victims, which strengthened arguments for the establishment of one of the first medical faculties among the South Slavs.

In 1876, Josif Pančić, the first Chairman of the Serbian Royal Academy, initiated the transformation of the Great School into the University of Belgrade and in 1898 the National Assembly of Serbia decided to adopt this initiative, which was accomplished seven years later. Unfortunately, this law did not provide for the establishment of the Faculty of Medicine within the University of Belgrade. Only after the end of World War I, the energetic Minister of Education Ljuba Davidović initiated an adjustment of the 1905 University Act enabling the establishment of the School of Medicine within the University of Belgrade. Professor Batut was the first appointed Dean and Dr Vojislav Subotić Sr., former Head of the Surgical Department of the General State Hospital, the first Vice-Dean. The Faculty began its work on 20 February 1920. The first decision of the Board of Directors was the appointment of Professor Đorđe Joannović from the Medical Faculty in Vienna as a Full Professor of Pathology. Thus, the appointment of the first full professors was successfully completed and the Administration was able to dedicate itself to the organisation of the work of the Faculty. The Faculty was officially opened on 9 December 1920, with a Dean's speech. The first lecture was given by a former French surgeon Dr Niko Miljanić, the newly appointed Full Professor of Anatomy in Belgrade.^{1,2}

A brief history of pharmacology

Pharmacology was first defined in 1791 by the German chemist and physicist Friedrich Albrecht Karl Gren (1760-1798), distinguishing between pharmacology as a science of drugs and *materia medica* as a list and description of drugs.³ In the mid-1800s, pharmacology emerged as a separate scientific discipline, positioned between physiology and experimental pathology.⁴ The founder is considered to be the German pharmacologist Rudolf Buchheim (1820-1879), who founded the first Institute of Pharmacology (in his own basement) in the Russian city of Dorpat (now Tartu, Estonia). Buchheim became the first Head of the Department of Materia Medica, Dietetics and History and Encyclopaedia of Medicine in 1847 when he was only 27 years old. Indeed, he did a lot:

- Buchheim defined the essential parts of pharmacology, pharmacokinetics, and pharmacodynamics.

- Also, he explained the term "drug mechanism of action".
- Last but not least, he introduced the experimental method in drug testing through animal experiments and bioassay.

Thus, it might be said that he was the real founder of experimental pharmacology. Before Buchheim, science of drugs was limited to collecting pharmacognostic information without in-depth analysis. The foundation of the Dorpat Institute of Pharmacology in the mid-nineteenth century dates back eight years before Virchow established cell theory and fourteen years before Paster's theory of germs. Buchheim also translated Jonathan Pereira's *Materia Medica* from English into German. Accordingly, Buchheim was not the first expert in therapeutic agent armamentarium. However, he was the first experimental

pharmacologist in the modern sense of the term. Moreover, Buchheim improved Pereira's publication by adding a lot of new drugs and completed his own textbook of pharmacology (*Lehrbuch der Arzneimittellehre*) in 1848. It should be emphasised that the first clinical trials also gave impetus to the further development of pharmacology, such as the investigation of the effects of lemon in sailors with scurvy by Lind (published in 1753) or Wihering's research on the impact of foxglove in heart failure (1785).

Buchheim was active as a mentor - between 1847 and 1867, he supervised 90 papers, including 80 doctoral theses. His probably most successful student was Oswald Schmiedeberg (1838-1921), a Baltic German who established the first pharmacological journal, *Archives of Experimental Pathology and Pharmacology* (1873), the world-famous

founder of the German pharmaceutical industry.³ As a scientist, he discovered the importance of the chemical structure of drugs for their pharmacological action (structure-activity relationship). If Buchheim laid the foundations of experimental pharmacology, emphasising that drugs should be examined by pharmacologists, not chemists and physicists, then Schmiedeberg popularised pharmacology worldwide, becoming known as the "Father of Pharmacology." During his prosperous, nearly half-century-long scientific career at the University of Strasbourg, he had 120 students from twenty countries who later held approximately forty pharmacology chairs worldwide. Many of his students became world-famous, such as Hans Horst Meyer (1853-1939), who set up the famous Meyer-Overton theory of narcosis and mentored four future Nobel laureates.

Institute of Pharmacology in Belgrade

Among Oswald Schmiedeberg's younger associates was Arnold Holste (1863-1937), a future founder of the Institute and first Full Professor of Pharmacology in Serbia. Holste came to Belgrade in the early 1920s upon the invitation of Prof. Joannović and the recommendation of H.H. Meyer (both were professors at the Vienna Medical School and the latter was a collaborator of Schmiedeberg himself). Arnold Holste was elected as a Full Professor of Pharmacology and Toxicology in 1923 and took the chair in 1924. Previously, Holste was an Associate Professor at the Medical Faculty of the University of Jena,

Germany. His collaboration with Schmiedeberg occurred from 1911-1913 when he was his assistant in Strasbourg.

Arnold Holste was born in Hanover, Germany, on 28 August 1863. He studied medicine in Göttingen and Berlin. From 1888, when he was promoted to MD. Then, he worked at the Internal Medicine Clinic in Göttingen and then moved to Hannover, where he worked at the obstetrics school and as a general practitioner. From 1904-1906 he worked at the Institute of Physiology in Göttingen and then spent three years at a phar-

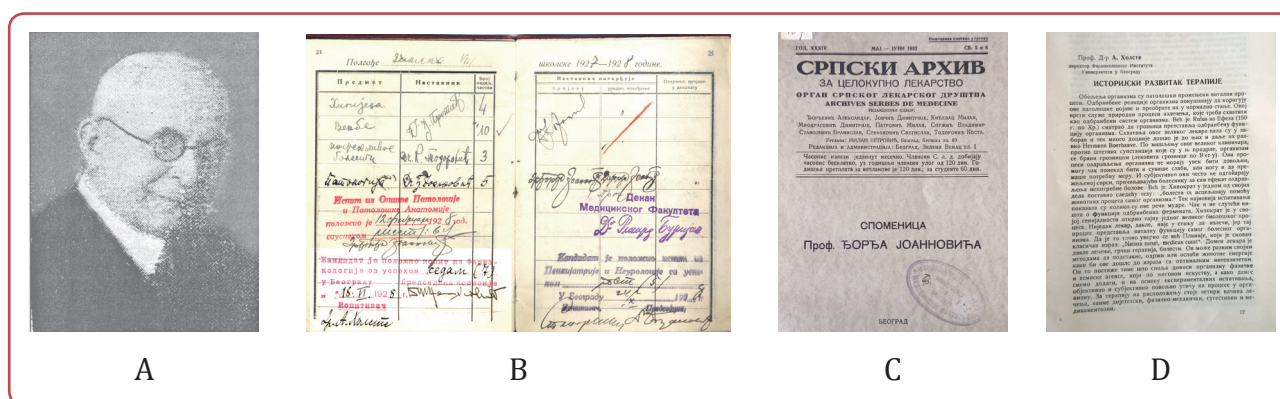


Figure 1: Panel A: The portrait of Professor Arnold Holste (adapted from ref. 6). Panel B: Medical student's Index (Gradebook) from the 1920s signed by Professor Holste in Cyrillic, University of Belgrade School of Medicine (author's collection). Panel C: The cover page of the Serbian Archive of Medicine (issue 5-6 published in June 1932) with the paper entitled: "Historical development of therapy" written by Arnold Holste.

maceutical company in Switzerland. Holste subsequently moved to Strasbourg, Jena and finally Belgrade.^{5,6}

Upon his arrival in Belgrade, Professor Holste faced problems such as lack of Serbian language skills, the flawed premises of the Institute and lack of financial support. Such obstacles temporarily prevented him from continuing his scientific research. Three years later, when Pharmacology Institute moved to the new establishment, Holste continued his previous research on the interplay between calcium and digitalis, pharmacology of bile acids, etc. Holste wrote his papers in German, French, Italian and Serbian, which he soon mastered well. This native German, who did not know a single Serbian word after arriving in Belgrade, signed in Cyrillic after a few years and gave lectures fluently without an interpreter (Figure 1).

Holste's research opus focused on the pharmacological effects of the active ingredients of herbal drugs (foxglove, peony, etc.), aspirin's vasodilatory properties and others. He was a distinguished scientist of his time, whose results were cited decades later.⁷ However, Holste regularly submits manuscripts to the *Medical Review* journal (*Medicinski pregled* in Serbian), a respected international scientific journal published at the Medical Faculty in Belgrade between 1926 and 1940 that was edited by his younger collaborator, Prof. Radivoje Pavlović (see below). Professor Holste's research interests were broad, ranging from a historical overview of different types of therapy to experimental research of active principles of herbal drugs. In 1926 he published a paper on heavy metal poisoning in German⁸ and in 1930 a textbook entitled: "Fundamentals of Toxicology" in Serbian. Holste's lectures had a broad and large audience, despite being often held in unconditional rooms. The professor was kind, helpful and ready to explain the complex matter quickly and clearly. At the same time, he was very precise and meticulous in his scientific research. He learned experimental work from the most outstanding researchers of his time, such as Oswald Schmiedeberg and he studied pharmacology only after he acquired basic knowledge of clinical medicine. In particular, his experience in the pharmaceutical industry has helped him gain a critical view of drug development. The Institute of Pharmacology of the Medical Faculty in Belgrade is immensely grateful to him, above all, for his endless enthusiasm and dedicated efforts. Professor Arnold

Holste passed away and was buried in Belgrade in April 1937.

Professor Radivoje Pavlović (1893-1938) was the first Serbian pharmacologist. Like Holste, Pavlović was an experienced clinician before devoting himself to pharmacology at the newly established institute in Belgrade. Pavlović was born in Hungary, where he graduated from Medicine in Budapest as a Tekelianum scholarship holder. He expanded his medical education in Berlin, studying biochemistry and specialising in internal medicine. He gained clinical experience in Subotica and Novi Sad, first as a military and then a civil physician. In 1922, he was employed as an assistant at the First Internal Medicine Clinic in Belgrade. Then, he became an associate of Professor Holste, simultaneously translating his lectures from German into Serbian. He was elected Teaching Assistant in Pharmacology and Toxicology in 1926 and Assistant Professor the following year. The introductory lecture of the young Assistant Professor was entitled: "Subjectivity in therapy", which was Pavlović's original contribution, but not without the influence of his teacher. Of note, Professor Pavlović emphasised the issue of dogmatism in therapy from the very beginning of his academic career. In 1929, Pavlović founded a pharmacotherapeutic seminar for clinicians, the first of its kind in our region and in 1933 he became the Head of the Institute and Associate Professor at the Medical Faculty in Belgrade. As a researcher, he was unique and versatile and as a lecturer, he was beloved and respected by students and doctors. This is not unusual, considering that Pavlović's life motto was: "I always want to be surrounded by satisfied and happy people." A particular achievement of Professor Radivoje Pavlović was the founding and editing of a prestigious international journal entitled: *Medical Review* (*Medicinski pregled* in Serbian) for 12 years (1926-1938). Professor Pavlović's exceptional personality can also be portrayed by the fact that he was almost blind during the most productive years of his career, between 1926 and 1938, when he died at the age of 45. The loss of sight did not stop him from the numerous activities he performed with enormous enthusiasm and the generous support of his wife.

The title page of the paper from this journal is shown in Figure 2.

The *Medical Review* journal was published between 1926 and 1940. The founding board con-

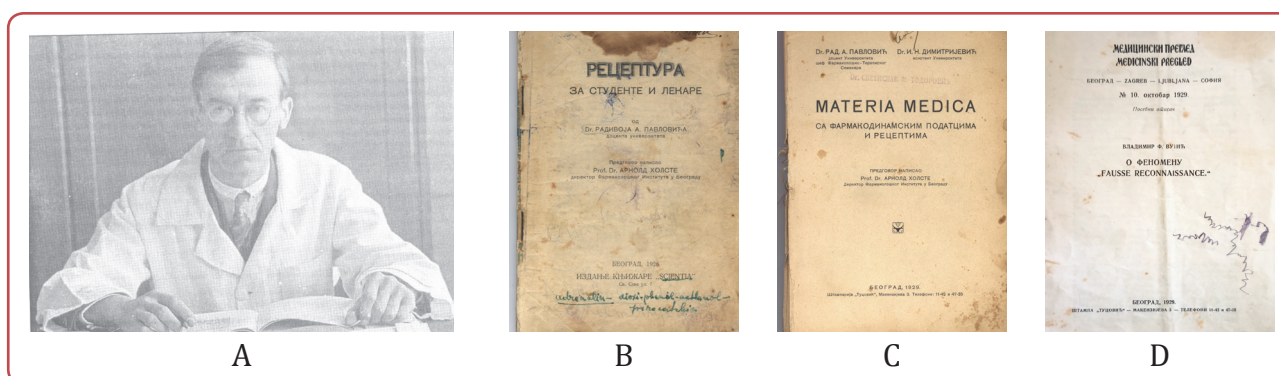


Figure 2: Panel A: The portrait of Professor Radivoje Pavlović (adapted from ref. 6). Panel B: Principles of Prescription (in Serbian) by Prof. Pavlović. Panel C: Materia Medica (in Serbian) by Radivoje Pavlović and Ilija Dimitrijević. Panel D: Paper published in the Medical Review journal.

sisted of distinguished professors, deans and future rectors from Belgrade, Zagreb, Ljubljana and Sofia (Dr Đorđe Joannović, Dr Božidar Špišić, Dr Radoje Šerko, and Dr Vasilij Molov.⁹ The project's soul (*spiritus movens*) was, above all, Radivoje Pavlović, then a Teaching Assistant at the Faculty of Medicine in Belgrade and the future Editor-in-Chief of 156 issues published during the subsequent thirteen years. The editorial board also consisted of Pavlović's associates and friends, future eminent doctors - Arnovljević, Brašovan, Dimitrijević, Spužić, Šahović, etc. The first journal issue was published on 22 April 1926, in Serbian, Bulgarian (Cyrillic), Croatian and Slovenian. The multilingual editorial policy of the journal was maintained until the end of its publication. *Medical Review* had a comprehensive profile of topics, from current reviews and original articles to examples from medical practice, something like the *BMJ* or *JAMA*. Health workers from Serbia and abroad supported the journal with at notable subscription; 600 copies were sent to Bulgaria. His peers selflessly and with admiration paid tribute to Professor Pavlović: "He had a superb family upbringing ... he acquired a humanistic education in the Serbian high school in Novi Sad ... Gifted by nature with many talents ... Made of goodness, optimists and idealists ... He shared his impressive knowledge from all fields of science and art ... He was a great worker and endless source of enthusiasm ... He used the strength of his intellect and the warmth of his Slavic soul ... He believed in truth, justice, progress ... He was a good connoisseur of all human weaknesses ... Always consistent, always with a clear opinion, without hesitation in decisions ... At the beginning of his university career, he lost his sight - with undiminished enthusiasm and energy, he continued his work..."¹⁰ Last but not least, Prof. Pavlović wrote the first *Principles of Pre-*

scription and Materia Medica (with Ilija Dimitrijević) in Serbian (in 1928, and 1929, respectively). The associates and successors of Professors Holste and Pavlović were no less capable and worthy of respect. Professors Ilija Dimitrijević and Siniša Bogdanović continued their predecessors' comprehensive scientific and pedagogical work in challenging times before, during and immediately after World War II (Figure 3).

They studied abroad in top-level medical school and were loved and respected both by their peers and students. They established pharmacology departments at related higher education institutions, faculties of dentistry, veterinary medicine and pharmacy within the University of Belgrade. It is a great honour to work in the same institute as our dear professors and teachers and to continue their work.

Ilija Dimitrijević (1896-1968) graduated from the Faculty of Medicine in Geneva, specialising in chemistry in Berlin, microbiology in Paris and pharmacology in Belgrade. He spoke five languages and being erudite, edited numerous books and dictionaries (such as *Materia Medica* and *Medical Dictionary*). He was a quiet, decent person and a successful scientist, endowed with extraordinary pedagogical skills. He made a great personal sacrifice - during World War II, he was imprisoned in the Banjica Nazi concentration camp. After the war, he was expelled from the Medical Faculty in Belgrade due to political persecution (1953) and half a century later, he was rehabilitated at the same faculty.

Siniša Bogdanović played a crucial role in developing the Institute of Pharmacology: he was first employed as a teaching assistant before World War II, met the founders of the Institute, and

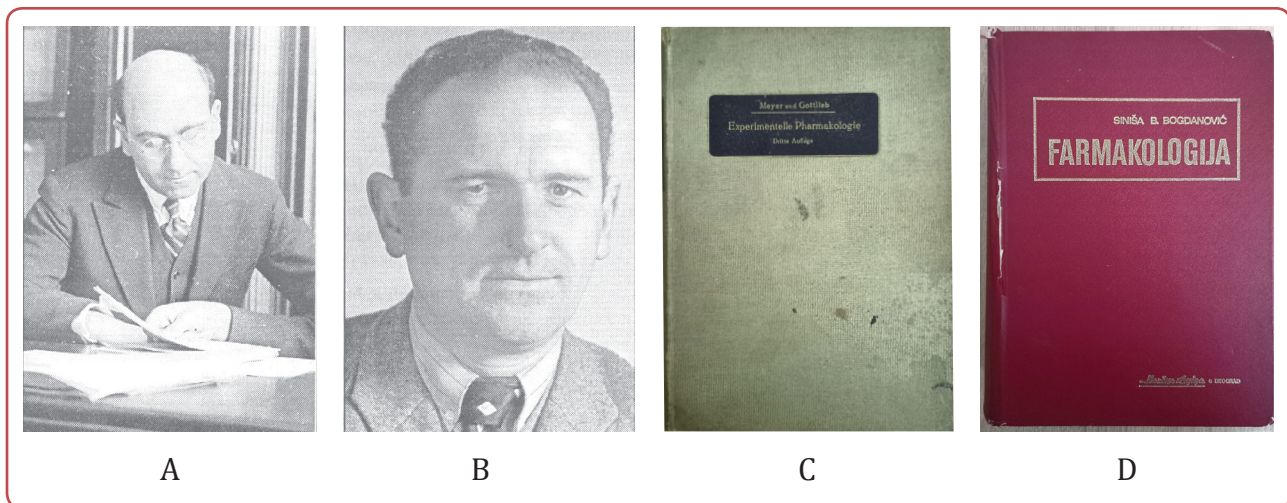


Figure 3: The portraits of Professors Ilija Dimitrijević and Siniša Bogdanović (Panels A and B, respectively; adapted from ref. 6). *Experimental Pharmacology* (in German) by Dr. Hans H. Meyer and Dr. R. Gottlieb, the first pharmacology textbook used by medical students in Belgrade (panel C). *Pharmacology* (in Serbian) by Siniša Bogdanović (panel D).

gained exceptional training abroad (France, USA - Yale, etc). He later became a Visiting Professor at Rockefeller University in New York. After the War, he successfully led our Institute for more than two decades, giving impetus to a highly successful development called the “golden age of the Institute.” He was highly professional, authoritative, with pronounced pedagogical skills and a parental attitude towards the younger associates. His broad publishing activity deserves particular attention: he wrote the first textbook in pharmacology in Serbian with an original chapter on hormones, the first of its kind in Serbian pharmacotherapy. He was highly dedicated to teaching - everyone was afraid of “Professor Bogdanović’s index finger,” which would point out the mistakes of younger associates during the prescription exercises. His exams were like theatrical performances that have been remembered for a long time. He often examined students from various faculties at the same time: medicine, veterinary medicine and others. Professor Bogdanović talked to doctors, students and laypeople equally clearly and vividly. He sent his younger associates for training to the world’s leading centres and carefully pursued personnel policy.¹¹

Conclusion

It is difficult to remain indifferent to the picture of the rapid development of pharmacology at the Faculty of Medicine in Belgrade. The professors mentioned with the most profound respect in this text have brought us closer to world science without sparing themselves and often sacrificing their entire lives to it. Their example inspires and obliges us today, not only now when our faculty is celebrating a centennial anniversary in the turbulent region of the Balkans.

Acknowledgements

None.

Conflict of interest

None.

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