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I. A. Kuzmenko[1], PhD, Assoc. Prof.
ORCID ID: 0009-0001-6206-1920
I. P. Gurkalova[2], PhD, Assoc. Prof.
ORCID ID: 0009-0005-8449-8129
A. I. Gozhenko[3], Dr. Sc. (Med.), Prof.
ORCID ID: 0000-0001-7413-4173

THE FIRST STEPS OF ACADEMICIAN O. O. BOGOMOLETS AT ODESA MEDICAL UNIVERSITY AND HIS PATHOPHYSIOLOGICAL SCIENTIFIC SCHOOL

[1,3]Ukrainian Scientific and Advanced Research Institute of Transport Medicine,
[2]International Humanitarian University, Odesa, Ukraine

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І. А. Кузьменко[1], І. П. Гуркалова[2], А. І. Гоженко[3]
ПЕРШІ КРОКІ АКАДЕМІКА О. О. БОГОМОЛЬЦЯ, ЗРОБЛЕНІ В ОДЕСЬКОМУ МЕДИЧНОМУ УНІВЕРСИТЕТІ, ТА ЙОГО ПАТОФІЗІОЛОГІЧНА НАУКОВА ШКОЛА
[1,3]Український науково-дослідний інститут медицини транспорту МОЗ України, Одеса, Україна
[2]Міжнародний гуманітарний університет, Одеса, Україна

У статті висвітлено Одеський період навчання та роботи академіка О. О. Богомольця (1901–1911). Його перші вчителі, професори В. В. Підвисоцький, О. Ф. Маньковський, Л. О. Тарасевич, Н. Г. Ушинський, В. В. Воронін, які залишили значний внесок у більшості галузей медицини, особливо в загальній патології та клінічній патофізіології, безпосередньо вплинули на формування наукових поглядів Богомольця. Завдяки своїм любим учителям він став ближчим до всесвітньо відомої патофізіологічної школи та проблем медицини того часу. Одеський період навчання й роботи Богомольця показав, як і чому він був натхненний внести частку себе у створення найбільшої в країні школи патофізіології і в найбільш значущі сфери досліджень (ендокринології, реактивності організму, алергії та імунітету, концепції фізіологічної і патологічної ролі сполучної тканини та мезенхіми в патогенезі захворювань).
Ключові слова: академік Богомолець, Одеський медичний університет, сполучна тканина, надниркики, імунологія, цитотоксична терапія.

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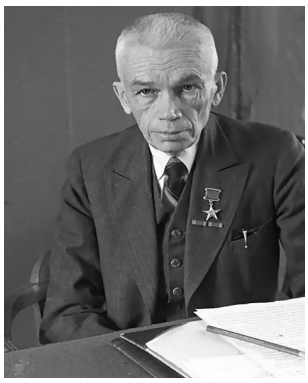
[1,3]Ukrainian Scientific and Advanced Research Institute of Transport Medicine of Ministry of Health of Ukraine, Odesa, Ukraine
[2]International Humanitarian University, Odesa, Ukraine

The article highlights the Odessa period of study and work of Academician O. O. Bogomolets (1901–1911). His first teachers were professors V. V. Pidvysotsky, O. F. Manikovsky, L. O. Tarasevich, N. G. Ushinsky and V. V. Voronin, who left significant contributions in most areas of medicine, especially in general pathology and clinical pathophysiology, which influenced the formation of scientific views of Bogomolets. Thanks to his teachers, he becomes closer to the world-famous pathophysiological school and the problems of medicine of that time. The Odessa period of Bogomolets' studies and work shows how and why he was inspired to contribute to the creation of the country's largest school of pathophysiology and to the most significant areas of research (endocrinology, body reactivity, allergy and immunity, as well as the concept of the physiological and pathological role of connective tissue, and mesenchyme in the pathogenesis of diseases).
Key words: academician Bogomolets, Odessa Medical University, connective tissue, adrenal glands, immunology, cytotoxic therapy.

Introduction. Year 1900 was the start of a new century, opening of a long-awaited Medical University in Odessa. Among the first students was a young Bogomolets, who came from Kyiv with professor V. Podvysotskiy – the first dean of the Medical University and the Head of the Department of General Pathology and Bacteriology.



All of this was not by chance, as it was in Odessa, in the city, where "everything breathes and smells of Europe" and where intellectual life was welcome and was developing. During a short period, despite, as usual, some financial difficulties and lack of money, the first-class Richelieu Lyceum (1817) was opened, and the University was created on its basis (1865). World famous scientists, such as Mechnikov, Sechenov, Kovalevskiy, were working there, due to which the University became a prestigious reference for development of biological sciences [1, p. 23–28]. Finally, after long and painful years of fight, the Medical University was opened in 1900. The same year student recruitment started and outstanding scientists came to chair the Departments by the invitation of Pidvysotskiy for Bogomolets the way of education and formation as a scientist took 10 years [1, p. 35–44]. In Odessa he got married to Olga Georgievna Tikhotskaya and created a family. On receiving a position of an associate professor at the Department of General Pathology and Bacteriology, he started delivering a course of lectures on immunology. In 1911, O. Bogomolets was sent on a traineeship to France for one year [1, p. 45–56].

From this moment a fruitful period of his state, scientific and research and pedagogical activity started. In all this multifaceted activity of Bogomolets one can see ideas, absorbed by him during Odessa period (1901–1911) from the leading figures of domestic medicine, enabling him to create the biggest school of pathophysiologists. To learn ideas of I. Mechnikov and I. Sechenov through V. Pidvysotskiy and L. Tarasevich, to learn ideas of Pashutin and Botkin, and to learn ideas of Babukhin and Zakharin through V. Voronin. All of this contributed to developing the solutions for the issues of modern medicine up till today.

Young Oleksander Bogomolets arrived from Kyiv to Odessa in January 1901 and immediately immersed himself into educational process [1, p. 67–71]. He worked very hard, because, except for mandatory curriculum, he started his first researches at the Departments of Histology and Pathology. The Heads of those Departments were a world-known scientist, professor V. Pidvysotskiy, and his student, a brilliant experimenter Mankovskiy. Thanks to them, young Bogomolets continued studying experimental research at the University for a long time.

Who were his first guidance? O. Bogomolets met professor V. Pidvysotksiy for the first time in Kyiv University, when he came to his lecture and was excited about interesting information on the problems of world medicine at those times. V. Pidvysotskiy recommended him to join the Faculty of Medicine, which O. Bogomolets did. However, at that time V. Pidvysotskiy was supposed to start working in the newly built Odessa University, and O. Bogomolets together with some other followers came with him to Odessa [1, p. 71–75].

V. V. Pidvysotskiy was born in 1857 in Chernigiv region. His mother graduated from Kyiv Institute of Noble Maidens. His father was a lawyer. After some time he graduated from the Faculty of Medicine and began to work as a professor-pharmacologist. Podvysotskiy first studied in the foreign languages college in Switzerland in Geneva, afterwards – in the gymnasium in Zhitomir, and in 1877 he joined the Faculty of Medicine of Kyiv University. After graduation from Kyiv University, he passed state exams with excellent marks, and, thanks to this received a right to go for advanced training in Munchen and Paris, where he worked with L. Paster. After defending his doctoral thesis in Kyiv, in 1888 he was appointed as an extraordinary professor of the Medical University. He was a brilliant teacher and lecturer and delivered lectures on the latest problems in medicine in the whole world. He wrote a Guidance on General Pathology, which was published 4 times in the country and 17 times in different countries of the world in foreign languages. V. Podvysotskiy was well known in different countries thanks to his deep and original researches, which deeply explained sensitive topics of medicine at those times (pathogenesis of infectious diseases, bacteriology, immunology, etiology and pathogenesis of a tumor) [2, p. 19–21]. In 1887, he was a correspondent member of the Anatomical Society in Paris, and in 1888 he was awarded with the prize of Karl Baer of the Academy of Sciences for his work "Regeneration of the liver and salivary glands". In Kyiv he created a school, from where in the future came famous scientists – D. Zabolotnyi, O. Mankovskyi, L. Tarasevich, V. Stefanskiy, S. Schastnyi – epidemiologist, infectologist, pathophysiologist. V. Pidvysotskiy began studies of endocrine glands while understanding a big role of inner glands for a healthy and for a sick organism (endocrinology as a part of theoretical and practical medicine was absent at that time). In 1886, he published works: "Current state of the tissue of functioning adrenal glands" and "Adrenal glands as a source of cardiac excitement". When in 1900 there came a question who could resolve the issue of building Medical University in Odessa, the Rector of Odessa University, professor, physicist Shvedov invited Pidvysotskiy, who later cooperated with the construction company and became the first Dean and Head of the Department of Pathology and Bacteriology. He was a real professor, who built a European analogue of

the Medical University and attracted progressive scientists from different cities [2, p. 22–23]. Pidvysotskiy arrived to Odessa with his followers, who used to work with him in Kyiv. One of them was O. Mankovskiy.

O. F. Mankovskiy (1868–1946) after graduation from the excellent Kyiv Medical University worked at the Department of Pathology and Bacteriology in Kyiv. Thanks to recommendations of his teacher, professor Pidvysotskiy, he began studies of endocrine glands. In 1902, he wrote a big article on the "problems of cell poisons (cytotoxins), thyrotoxins and the simplest methods of obtaining adrenal extract and its effect" [3, p. 28–44]. He was one of the pioneers in studying an adrenal function, and in 1902 he became the Head of the Department of Histology of Odessa Medical University. It is obvious that young Bogomolets made the first steps in the science after contacts and communication with very intellectual and competent persons. During this period the main issues were immunity, inflammation, infectology, bacteriology, reactivity, endocrine glands (structure and function). That is why Bogomolets, being a first-year student, started studying morphology and physiology of adrenal glands with pleasure [5, 6]. This topic in the future became a part of his doctoral thesis. He published these works in 1902 and in 1905 in his country and in Germany – "On issues of the structure and microphysiology of Brunner's glands" [4, p. 572–574].

In 1905, in Odessa there was published his student scientific work "On issues of a microscopic structure of an adrenal gland in connection to its functions" (Odessa, 1905). In Germany – "Zur Frage uber die Veranderungen der Nebennieren bei experimenteller Diphterie. In his researches he used not only histological techniques, but also experimental researches, which improved the received data and made it more convincing. In his first experiments Bogomolets showed adrenal glands in their evolution aspect and that mammals and humans have the same morphological structure and excretory function of the glands [4, p. 575–576]. Today it is known to everybody with a medical knowledge, but more than 100 years ago it was a new idea and information on adrenal glands. Bogomolets understood and showed that adrenal glands have high reactive ability and that irritant of the cortex of adrenal glands, accompanied by exertion of incretin function, could influence other organs. However, a deeper understanding of adrenal glands in organism came only in the future. E. London, a great pathochemist, published material on hemolysins and spermolysins in 1900, 1901, 1903 and defended a thesis "On the doctrine of hemolysins" [4, p. 577–579]. In 1902, at Odessa Medical University O. Mankovskiy got "thyrotoxin" thanks to immunization of cats by the thyroid gland of a dog and then using these sera in dogs, getting a model of hypothyroidism. In 1902, in Odesa a young student of Mechnikov and Pidvysotskiy, L. Tarasevich defended a doctoral thesis on hemolysins, which he prepared at Pasteur Institute. At that time the future world-known ophthalmologist Filatov was working at the Department of Pathology of Odessa University. He made an experimental study on the effect of blood sera on the eye (ophtalmotoxin), and in 1908 he defended a doctoral thesis on the "Doctrine of cellular poisons in ophthalmology". All this information had an influence on the young experimenter O. Bogomolets. When O. Mankovskiy gave him a lucky idea to research the effect of anti-adrenal serum, he did such experiments, and the topic of adrenal glands was his first love, which he further developed in his doctoral thesis [5, p. 12–22]. But then the time passed, and in 1905 he had to finish the University course. However, revolution of 1905 to protests and excitement, agitation among people, students and their teachers, and the University was closed. Only in 1906 the attestation commission started working, and O. Bogomolets received a diploma with honours. Pidvysotskiy was very depressed at that time, because his staff was at the opposite side. He left Odessa in 1906 and became the director of the Institute of Experimental Medicine. During 1907–1908, O. Bogomolets was working at the Department of Pathology as a laboratory technician and continued studying scientific literature and making experimental research for a doctoral thesis. At this time Heads of Departments changed, and he continued communicating and studying with influential figures in different areas of medicine (Tarasevich, Ushinskiy, Voronin) [6, p. 135].

L. O. Tarasevich was the main person at the Department of Pathology (1906–1907). His teachers were Pidvysotskiy and Mechnikov. Bogomolets and Tarasevich had friendly relations. In 1907, Bogomolets was working as a laboratory technician of the Department and was in close contact with L. Tarasevich and S. Schastnyi, while performing new researches.

Tarasevich (1868–1927) was born in Tiraspol (Moldova). He graduated from the Department of Biology of the Faculty of Physics and Mathematics of Odessa University. He continued studying at the Medical Faculty in Paris, where he was working with I. Mechnikov and met V. Pidvisotskiy, who very often visited Pasteur Institute and invited Tarasevich, after he finished his studies, to Kyiv. However, at that time Pidvysotskiy was participating in construction of the Medical University in Odessa and became the first Dean and the Head of the Department of Pathology of Odessa Medical University. Therefore, followers of Pidvysotskiy moved with him from Kyiv to Odessa to the newly constructed Medical University with European standards. As a result of a close contact with Tarasevich from Mechnikov school, Bogomolets made studies and wrote research on the role of sensibilizing substances and specific serum in phagocytosis (1907), and on lipoid anaphylaxy (1910), published in the country and in Germany [6, p. 136–137]. In 1902, Tarasevich defended his doctoral thesis on hemolysin, which stimulates progress in immunology, in Odessa. Bogomolets proved by experiments that phagocytes absorbing target cells, provoked agglutination, bacteriolysis, opsonization, precipitation, which depend

only on pathogen. At that time it was a critical and destroying dogma for immunity, which was experimentally proved.

Bogomolets was the first to write about lipoid anaphylaxis and explain the role of cells in this mechanism, connected with inactivating enzyme in cells complemented by anaphylatoxins. In 1907, professor M. Ushinskiy, a follower of a prominent pathophysiologist Pashutin and a clinicist Botkin, arrived to Odessa from Warsaw. Ushinskiy drew attention of Bogomolets to bacteriology, as during Saratov period he created a clinical and diagnostic laboratory and special bacteriology laboratory for acute infectious diseases. Under the guidance of Ushinskiy, Bogomolets researched in Odessa blood and lungs changes with the presence of carboxide [7, p. 100].

Later Ushinskiy and Bogomolets maintained friendly contacts as two great scientists. Stefanskiy and Schastnyi, well-known scientiscs, maintained an interest to bacteriology and infectiology. They worked with Pidvysotskiy for a long time and were co-workers with Bogomolets, who discussed with them and drew their attention to the actual problem of a widespread infectious disease at that time. In 1908, the Head of the Department of Pathology and Bacteriology in Odessa was a young professor of pathophysiology and a great erudite in medicine, professor V. Voronin (1870–1960). He was a student of a brilliant histologist, professor Babukhin and of a therapist, professor G. Zakharin.

V. V. Voronin was born in 1870 in Nikolskoe, Tula province. His father was an agronomist. After finishing a classical gymnasium, he entered the Medical Department of University. During his studies, he took part in student researches at the Department of Histology. In 1893, he graduated from the University with honours. Afterwards he had his traineeship as a doctor at the therapeutical clinics. For some time, he was working at the bacteriological laboratory. He was sent on study visits to France and Germany in 1895 and defended his doctoral thesis "On inflammation" in 1897. In 1898 he worked as a doctor of medicine and a doctor of philosophy at the University and taught a course on bacteriology. In Odessa he was the Head of the Department of Pathology and Bacteriology and raised distinguished scientists in theoretical and clinical medicine. O. Bogomolets met V. Voronin with great interest and was in a friendly contact with him all his life. Thanks to Voronin, Bogomolets used microscope technique for studying elements of connective tissue. After a while the topic of "connective tissue" will be his "second love". In the future he made a great contribution to the development of the doctrine of the constitution and its classification. It proved the role of the constitution in reactivity of a healthy and a sick organism and pathogenesis of different diseases. The study of the most sensitive topics of constitution makes it possible to prognoses their traumatic consequences, to determine disease predisposition, to prognoses disease course and to have an individual approach to the treatment course.

In 1908, Bogomolets continued experimental researches at the Department of Pathology in Odessa. He showed physiological activity of vessels wall in permeability in gastric space. The research was published in Kharkov Medical Journal. However, he developed a deeper understanding of the mechanism after being in contact with Voronin as a co-worker. In 1909, Bogomolets successfully defended a doctoral thesis. His official opponent was a well-known academician and physiologist I. Pavlov (1849–1936), who highly appreciated the thesis and made a short conclusion about the future work of Bogomolets and predicted that Bogomolets will be a great scientist, who will have his own school. It will be the truth. However, on the basis of experiments with suprarenotoxins, Bogomolets coined ideas that adrenocorticocytes might produce lipids essential for maintaining of other organs' functions, which was far ahead of that time. He experimentally proved physiological significance of adrenal glands in a healthy and in a sick organism that was far ahead of Selye stress-syndrome. His early interest provoked a massive contribution into adrenalin research [8, p. 361]. He returned to Odessa Medical University and was delivering the course on immunology for students. The way towards this Department was connected with having a traineeship in Pasteur Institute and improving his knowledge about immunology culture and the history of France. While understanding a universal role of the connective tissue, Bogomolets combined reticuloendothelial system, which includes only cells, with all the elements of connective tissue (fibers, micro- and macrophages, parenchymal substrate) into "physiological system of connective tissue", and then studied anti-reticular cytotoxic serum (ACS) and its functions [8, p. 362]. It was an attractive idea, because connective tissue plays a very important role in plastic, protective and trophic function of an organism. O. Bogomolets all the time dreamed about the practical use of ACS, but at that time it was a "locus minoris" ability to prepare an antigen and minimize the damage for the cells when antibodies are staying on their surface. This problem disappeared after introduction of the new technology, which showed that ACS did not have a specific effect on connective tissue [9, p. 191–200].

Conclusions. Due to technological progress and development era of immunofluorescence (IF) and immunohistochemistry (IHC), the concept of physiological regularity of immunity, which was accordingly present in researches of Mechnikov and Bogomolets, would need changes. It was necessary for building a bridge, that would lead to the past and also would give the way to the future. At this time there were two scientists, who had a significant influence on the modern view of cytotoxin in experimental immunology, namely professor L. Perelman (1900–1969) and professor O. Zaichik (1938–2014). According to O. Zaichik and his group and D. Alarcon Segovia's studies of the antibody cells penetration, cytotoxin can be an equal partner in the treatment process. With adjustments of antigen specific preparation, stimulation of

connective tissue might be effective only for a part of the treatment. The loss of cytotoxicity and achieving specificity is a key for IF and IHC technology. In modern immunology, cytotoxins are a part of humoral immunity with some stipulations [9, p. 200–207]. However, the final reaction occurs at the cell. Nowadays there is very interesting information on functional autoantibodies in a healthy organism and on possible protective role of some autoantibodies against dysautonomic disorders.

Therefore, O. Bogomolets contribution to solving acute scientific topics is significant and relevant to this day. This stimulated the emergence of new technologies in medicine and scientific progress.

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