

Academician Andrei Dmitrievich Ado and the Kazan Scientific Research Institute of Epidemiology and Microbiology

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Abstract

The article was prepared for the 120th anniversary of the Kazan Scientific — Research Institute of Epidemiology and Microbiology and the 110th anniversary of the birth of the academician, laureate of the USSR State Prize, the author of fundamental guidelines on allergology and pathological physiology, an honorary member of scientific societies of many countries Andrei Dmitrievich Ado who is a representative of the famous dynasty of scientists and doctors of Mislavski-Ado. The paper presents materials about the dynasty — A.A. Mislavsky, N.A. Mislavsky, A.N. Mislavsky and others; information about the Kazan period of A.D. Ado between 1938 and 1952 during his work at Kazan Scientific — Research Institute of Epidemiology and Microbiology (Kazan Institute of Epidemiology and Microbiology until 1942). The article was prepared using documents from the archives of Kazan Scientific — Research Institute of Epidemiology, Microbiology, Kazan Medical University, memoirs of their colleagues. **Keywords:** Kazan Scientific Research Institute of Epidemiology and Microbiology, Andrey Dmitrievich Ado, founder of Russian allergology and immunology.

For citation: Reshetnikova I.D., Dunaev P.D. Academician Andrei Dmitrievich Ado and the Kazan Scientific Research Institute of Epidemiology and Microbiology. *Kazan Medical Journal*. 2021; 102 (1): 115–122. DOI: 10.17816/KMJ2021-115.

Anniversary dates encourage us to draw conclusions from one's life experiences, to reconsider what has been experienced and done, and to remember with gratitude the people who have left a deep mark in history with their deeds and actions throughout their whole life. The best that history leaves to us is a name that inspires with its example. The scientific work of Andrey Dmitrievich Ado, an outstanding Russian scientist, academician, laureate of the USSR State Prize, author of fundamental guidelines on allergology and pathological physiology, and honorary member of scientific societies in many countries, is closely connected with the Kazan Scientific Research Institute of Epidemiology and Microbiology (KSRIEM). On January 12, 2019, the medical community of Russia celebrated the 110th anniversary of his birth.

A.D. Ado was an outstanding representative of the famous Mislavsky–Ado dynasty of scientists and doctors, who were the pride and glory of the Kazan Medical School. He was born and raised

in Kazan, where also worked from 1938 to 1952. One of the streets in the very center of Kazan was named after his grandfather, the late Nikolai Alexandrovich Mislavsky. In 2015, a new street in the Privolzhsky district of Kazan, located within the Lesnoy Gorodok residential complex, was named after A.D. Ado.

For almost two centuries, the Mislavsky–Ado surname has been identified with many glorious chapters of the Kazan Medical School [1–3]. Alexander Andreevich Mislavsky (1828–1914) was the first prominent individual from this famous dynasty, having graduated from the Faculty of Medicine at Kazan University (1852). Working as a doctor in the Urals, he became famous for his successful treatment of eye diseases. A.A. Mislavsky performed surgical interventions during his entire medical career, of which 3264 were conducted for cataracts and 3192 for trachoma. For outstanding achievements in the field of the treatment of eye diseases, A.A. Mislavsky was awarded the degree

of Doctor of Medicine without defending a thesis in 1895. Furthermore, in 1901, by decree of Emperor Nicholas II, A.A. Mislavsky was awarded the title of “Freeman of the City of Yekaterinburg.”

A worthy successor to the work of A.A. Mislavsky was his son, Nikolai Alexandrovich Mislavsky (1854–1928), also a graduate of Kazan University and an outstanding physiologist (Fig. 1). He became famous worldwide for his discovery of the respiratory center in the medulla oblongata (doctorate thesis “On the Respiratory Center,” 1885). N.A. Mislavsky, conferred the titles of Honored Scientist of the RSFSR (1926) and Corresponding Member of the USSR Academy of Sciences (1927), headed the Department of Physiology at the Kazan University from 1891–1909. Under his leadership, the nervous regulation of the work of internal organs (intestines, spleen, endocrine glands, etc.) and the vascular tone was studied. In fact, it was in his laboratory where the famous psychiatrist V.M. Bekhterev studied the pathways of the brain and spinal cord.

Many years later, Alexander Nikolaevich Mislavsky (1880–1958), the son of N.A. Mislavsky, also received medical education at Kazan University (Fig. 2). As a student, he started the scientific work at the Department of Histology. He received a Doctor of Medicine degree, headed the Department of Histology (1921–1958), and was an Honored Scientist of the RSFSR (1939) just like his father before him. His scientific interests and those of his students concerned the study of the morphology of the epithelial tissue of the skin, kidneys, and pancreas. Later on, A.N. Mislavsky became the first chairman of the Tatar branch of the All-Union Scientific Society of Anatomists, Histologists, and Embryologists (founded in 1953).

The future academician, A.D. Ado was born in Kazan on January 12, 1909 and died on October 29, 1997 (Fig. 3). His father, Dmitry Ivanovich Ado (1886–1965), was a teacher of natural science at a gymnasium and was the head of the Department of Teaching Methods of Natural Science at the Kazan Pedagogical Institute. Unfortunately, he left the labor force early due to a serious illness. Dmitry Ivanovich was a chess champion in Kazan. Incidentally, during the tour of A.A. Alekhin in Kazan, he ended the game with him in a draw.

A.D. Ado’s mother, Inna Nikolaevna Mislavskaya (1881–1963) was the daughter of N.A. Mislavsky and the full sister of A.N. Mislavsky. She graduated from two courses of higher medical courses for women at Kazan University. She devoted her life to raising her sons, could speak three main European languages (English, French, and German), and devoted her life imparting such knowledge to children.



Fig. 1. Alexander Andreevich Mislavsky and Nikolai Alexandrovich Mislavsky, photograph taken in the early 19th century.



Fig. 2. Alexander Nikolaevich Mislavsky (1880–1958).

Thus, young Andrey Dmitrievich also became fluent in English and French and was able to develop skills to allow him to read and translate from German.

Andrey Dmitrievich’s brother, Igor Dmitrievich Ado (01/17/1910–06/30/1983), was a professor of mathematics, who received his doctorate after defending his PhD thesis. He was the head of the Department of Higher Mathematics at the Kazan Institute of Chemical Technology. His theorem, referred to as the theory of Lie groups (i.e., matrix theory), is still being studied in modern algebra. His wife, Irina Evgenievna Alatyrtseva, had a PhD in Medicine and served as the director of KSRIEM from 1961 to 1970 before transferring to the laboratory of bacterial allergens in the same Institute.

The wife of Andrey Dmitrievich (1914–1983), Klavdia Mikhailovna Gorbacheva (1909–1997), graduated from the Kazan Medical Institute. She was a neuropathologist who also had a PhD in Medicine. She worked during the Great Patriotic War in the Hospital No. 2778, located in the premises of the Old Clinic of Kazan University. Then, she



Fig. 3. Andrey Dmitrievich Ado (1909–1997).

moved to Moscow and worked as an assistant at the clinic of the I.M. Sechenov First Moscow State Medical University, under the supervision of the famous scientist E.K. Sepp. She also served as a senior researcher at the M.F. Vladimirovsky Moscow Regional Research Clinical Institute. She studied the problem of the influence of infections on higher nervous activity and other forms of nervous regulation. In this experiment, she established the role of microglia in the resistance of animals to the toxin-invasive action of meningococci.

The daughter of A.D. Ado, Marianna Andreevna Ado (born in 1935), has a PhD in Medicine and is a professor, therapist, and a student of academician E.M. Tareev. She currently she lives in Moscow. Meanwhile, his son, Vyacheslav Andreevich Ado (1939–1996) also had a PhD in Medicine and was a professor of allergology at the Department of Allergology of the A.I. Evdokimov Moscow State Institute of Medicine and Dentistry.

Meanwhile, A.D. Ado's niece, Elena Igorevna Ado (born 06/13/1956), has a PhD in Medicine and served as an associate professor at the Department of Propedeutics of Childhood Diseases of the Kazan State Medical Institute (Kazan State Medical University) from 1989–2012. Then, she became the territorial director of a Swiss pharmaceutical company in the field of oncohematology. Currently, she lives and works in Moscow as a chief specialist of the Scientific Research Institute of Health Organization and Medical Management under the Moscow Department of Healthcare.

Elena Igorevna Ado's daughter, Daria Sergeevna Fomina (born in 1980), who also has a PhD in Medicine, is the chief external allergy and immunology specialist in Moscow and is the head of the Center for Allergology and Immunology of the City Clinical Hospital No. 52. Likewise, she is an associate professor at the Department of Clinical Immunology and Allergology of I.M. Sechenov First Moscow State Medical University.

A.D. Ado is justifiably considered the founder of experimental and clinical allergology in the USSR. Through his initiative, the first departments of allergology were organized within several institutes for the advanced training of doctors in Kazan (1970) and Moscow (1971) and later in other cities of the USSR. Through his initiative and active participation, a system of specialized allergological assistance to the population, in the form of a network of allergy rooms and hospitals, was developed and implemented throughout the country. Furthermore, he played a significant role in the production of diagnostic and therapeutic allergens and in the establishment of the country's first scientific research allergological laboratory in 1961. He also led systematic studies on the epidemiology of allergy in various regions throughout the country.

A.D. Ado also made great contributions to the organization of teaching pathophysiology and allergology at medical universities. He was the author of 12 monographs on pathological physiology and allergology and supervised over 150 PhD theses during his time. In 1965, he was awarded the title of Academician of the USSR Academy of Medical Sciences. Moreover, he was a member of the editorial boards of many Russian and international scientific publications, an honorary member of the International Society "Interasthma," the Allergological Society of France, and the J. Purkinje Czechoslovakian Scientific Society, among others.

His initiatives and activities were highly appreciated by the government. For this reason, A.D. Ado was conferred the Order of Lenin, the Order of the October Revolution, the Order of the Red Banner of Labor and the Badge of Honor and also became a laureate of the State Prize (1984) [1,3,4].

A.D. Ado's follower, professor I.M. Rakhmatullin, summed it up well when he said: "Without belittling the scientific work of A.D. Ado in Moscow, for us, citizens of Kazan, we are pleased to note that it was in Kazan that his evolution as a scientific worker took place and the foundation of those scientific fields was laid, which were then developed actively in Moscow" [3].

A.D. Ado started his scientific activities during his student years under the guidance of Professor N.N. Sirotin at the Department of Pathological Physiology of the Kazan Medical Institute. Immediately after his graduation in 1931, A.D. Ado was employed as an assistant at the Department of Pathological Physiology as he was already a trained scientist. In 1938, he was awarded a doctoral degree for his work "Materials for the study of Arthus hyperergic inflammation," when he was just under the age of 30 years. In the same year, Professor Sirotin moved to Kiev and assigned him as the



Fig. 4. Andrey Dmitrievich Ado (left) with a friend and colleague at the Department of Pathological Physiology, Mukhammed Abdullaevich Erzin, who later became a professor and department head. This was taken in front of the 2nd Educational Building of the Kazan State Medical Institute in 1950.



Fig. 5. Kazan Institute of Epidemiology and Microbiology (currently Kazan Scientific Research Institute of Epidemiology and Microbiology), 1940s.

head of the Department of Pathological Pathophysiology, as he was his youngest, but closest student. Concurrently, A.D. Ado became the head of the serological laboratory at the Kazan Institute of Epidemiology and Microbiology (KIEM) until he moved to Moscow in 1952. A photograph of A.D. Ado in Kazan during that period is shown in Fig. 4 [3].

The scientific research conducted at KIEM under the guidance of a young and energetic professor A.D. Ado should be considered to be inextricably connected with the historical realities of that time. Since its foundation in 1900, KIEM had been the leader in the struggle against epidemics in the Volga region. As it was closest to the front, KIEM was the sole scientific microbiological institution that had the necessary equipment and production facilities to assist during the Great Patriotic War (Fig. 5). The first requirement of wartime was a sharp increase in the production of therapeutic and preventive agents and KIEM was able to meet this requirement [5].

According to the materials of the KIEM official report, during the Great Patriotic War, the Institute mastered the production of 14 types of new agents, including four types of antigangrenous sera, trivalent vaccine, and antidysenteric tablets in 1941; anti-tetanus serum in 1942; anti-typhoid tablets, dysentery dry bacteriophage, and dysentery subcutaneous vaccine in 1943; pentovaccine and anti-typhus vaccine in 1944; and gramicidin and agglutinating sera in 1945 [5].

The research subjects at KIEM were very diverse. All of them, quite obviously, were directly related to the problems during wartime, such as the specific prevention of infections, improvement of epidemiological services, development of production technologies, and the microbiological and immunological aspects of the treatment of the wounded. Recalling his scientific work at KIEM during the Great Patriotic War, Andrey Dmitrievich stated, "Together with surgeons, I studied in hospitals the mechanism of septic processes and the aspects of reactivity of the bodies of wounded people affected by gas gangrene. We were able to develop the most rational methods of manufacturing combined antigangrenous sera for the successful treatment of these patients" [6].

The first agents developed at KIEM were therapeutic and prophylactic sera against gangrene, and their production was initiated by the Institute during the Great Patriotic War. Initially, four types of antigangrenous sera were produced for each type of anaerobic bacteria that were considered causative agents of this lethal disease, namely, *Clostridium perfringens*, *Cl. oedematiens*, *Cl. Hystolyticus*, and *Vibrio septicus*. These sera were called monovalent, as other sera were not yet produced at that time. It was necessary to use all these agents together, as it was impossible to predict which microorganisms were present in the wound. Thus, one preventive dose was delivered in four ampoules, which gave rise to many logistical inconveniences and production difficulties. For one, ampoules were then in short supply, and this automatically limited the volume of production. In addition, sera filling and sorting into sets required a great deal of manual labor. There were also difficulties with the delivery of agents. Transport during the war could only be done with extreme exertion, and the antigangrenous serum kits were quite bulky. Finally, and worst of all, there were difficulties in the practical use of monovalent antigangrenous sera. In a front, for example, inconvenience is fraught with fatal errors. In addition, during transportation, some of the ampoules inevitably broke, and the hospital staff often had neither the strength nor the time to re-sort the remaining ones.

For these reasons, already from the beginning of 1942, KIEM set a goal to switch over to the production of polyvalent antitoxigenous serum contained in one preventive dose in one ampoule. The head of production, I.E. Alatyrtseva, and the head of the serum processing department, A.V. Beilinson, were involved in this task.

First of all, it was possible to establish that polyvalent antitoxigenous serum can be prepared in the simplest way, by mixing monovalent ones. Then, a special calculation scheme was developed to ensure the required combination of antitoxins. The resulting mixture fully retained its therapeutic and prophylactic properties and was stable during storage. This rationalization immediately eliminated the most prominent logistical concerns, resulting in great savings and increased significantly labor productivity. Henceforth, the clinical use of agents has become much easier. Thereafter, since the second half of 1942, the institute produced only polyvalent serum.

The quality of antitoxigenous sera has always met the strict requirements for immunobiological preparations. However, the wording of these requirements back then did not provide for clear safety measures in relation to anaphylactic complications, whose causes remained largely unexplained. In relation to this, work was constantly being conducted to improve the quality of agents, based on the results of KIEM's own research.

In this regard, the work of A.D. Ado, "Study of the Antitoxic and Anaphylactogenic Properties of Sera after Peptic Digestion," reported at the KIEM conference in 1943, is especially noteworthy. This study was the first to demonstrate that the combined concentration of sera by peptic digestion and precipitation with ammonium sulfate can destroy most of the allergens, drastically reducing the risk of developing anaphylactic complications in comparison with agents obtained using previously adopted production technology.

The results of this work immediately started to be applied in practice. Young professor A.D. Ado, together with his students at KIEM, developed effective regimens for the use of serum preparations against gas gangrene, tetanus, and other infections. They also revealed the pathophysiological mechanisms and identified the most significant chemical aspects of the development of anaphylactic shock. Furthermore, they showed the inconsistency of the idea of histamine as the only mediator of allergic reactions and established the important role of acetylcholine, serotonin, and other substances. In 1944, the results obtained allowed A.D. Ado to propose a polyergic hypothesis of the development of allergic reactions, which was fully confirmed

later on by the works of Russian and international authors [5].

During the Kazan period, A.D. Ado established that the antigenic (responsible for immunization) and allergenic (causing anaphylaxis) properties of sera are attributed to different structures of biopolymers and that chemical processing can make the agents safer. Thus, Professor Ado, together with Professor A.V. Beilinson (Head of the Serum Processing Department at KIEM during the Great Patriotic War) developed an industrial method for the production of purified native immune sera using peptic digestion. These studies immediately resulted in the improved quality of manufactured immunobiological preparations, saving thousands of human lives in the process. Further improvements in the technology of purification and concentration of sera led to the creation of the famous method "DIAFERM-M" (N.F. Gamaleya Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the USSR).

A.D. Ado also took an active part in anti-epidemic measures in the Volga region in 1943–1945, primarily against typhus, as the scientific work of regional research institutes was focused on the study of its epidemiology. In 1943, KIEM received a government task to launch the production of a typhus vaccine. Work was also actively conducted on other typhoid diseases. In particular, the results of various studies under A.D. Ado and L.A. Spasskaya on the pathogenesis of typhoid fever contributed to the improvement of treatment methods.

The "Report of the Kazan Institute of Epidemiology and Microbiology for the period of the Great Patriotic War 1941–1945" presents the results of studies conducted under the leadership of and with the participation of A.D. Ado [7]: "Study of the Antitoxic and Anaphylactogenic Properties of Sera after Treatment by the Method of Peptic Digestion" (1943), "On the Problem of Antigen Binding by the Organs of a Sensitized Guinea Pig" (1944), "I.I. Mechnikov and Modern Ideas about the Mechanism of Immunity" (1945), and "On the Pathogenesis of Typhoid Infection" conducted by A.D. Ado and L.A. Spasskaya; and "On the Issue of Purification of Anti-Diphtheria Antitoxic Serum from Ballast Proteins by Peptic Digestion" (1943) and "The Value of Albumous Fractions for Determining the Quality of Nutrient Media" conducted by A.D. Ado, I.E. Alatyrtseva, V.N. Sharovskaya, and N.N. Kuznetsova.

In the same period, under the supervision of A.D. Ado, inventions and rationalization proposals were made to improve the quality of nutrient media and preparations, specifically through the study "Regulation of the Amine Nitrogen Content

of the Nutrient Medium for Typhoid-Paratyphoid and Dysentery Cultures in Vaccine Production” conducted by A.D. Ado, I.E. Alatyrtseva, and G.G. Akhmadullina.

In the post-war years, issues of immunity and allergies, as well as problems of regional epidemiology were still essential in the research activities of the Institute. The immunological subject was developed in the following fields:

- study of general patterns and mechanisms of immunity and allergies;
- improvement of the technological process of serum production (immunization of horse producers and the processing, purification, and concentration of sera), study of their protective and allergenic properties, stability during storage, etc.;
- improvement of agents and methods of active immunization against various infections (diphtheria, pertussis, tetanus, etc.), study of their reactivity and immunological and epidemiological effectiveness;
- study of the diagnostic value of various methods for the recognition of infectious diseases and the improvement of some diagnostic preparations (diagnostic sera of the intestinal group, influenza diagnostic agents, and diagnostic sera);
- study of the immunological structure of the population in relation to various infections;
- development of new agents of bacterial allergens.

In studies on the physiological mechanisms of immunity, which were performed in the 1940s under the supervision of Professor Ado, the following topics were also studied:

- the effects of bacterial and serum antigens on the sensitive nerve endings of various parts of the nervous system in a normal, immunized, and sensitized organism;
- the state of excitability of the immunogenic apparatus of antitoxic sera horses at different periods of immunization and under different feeding conditions (A.M. Volkova-Borzunina, I.E. Alatyrtseva, A.M. Khomyakov, and L.M. Ishimova).

Under the supervision of Professor Ado, experiments to study the possibility of reflex antibody production were conducted. The study results revealed that the existing production of antibodies can be changed and regulated by a reflex pathway (G.G. Akhmadullina et al.).

Based on these studies, the so-called sparing scheme of equine immunization to obtain anti-influenza serum was subsequently developed and introduced into production in 1960 (G.G. Akhmadullina et al.). In addition to Kazan, this scheme was also used in the production in the Leningrad, Ufa, and Stavropol institutes of vaccines and sera.

The method was subsequently applied in the production of anti-tetanus and anti-diphtheria sera.

In 1964, upon the initiative of Professor Ado and the director of the institute I.E. Alatyrtseva, a new scientific field was established at KSRIEM, and the country’s first scientific laboratory for the study of allergies in infectious diseases was opened (headed by K.S. Zobnina, PhD in Biology).

For the first time in the country, from 1966–1975, the KSRIEM and the L.A. Tarasevich State Scientific Research Institute for Standardization and Control of Biological Medicines mastered the industrial production of 18 types of diagnostic and 4 types of medicinal bacterial allergens. In fact, the basis for their development was already established by Professor Ado as far back as in the war years.

After that, KSRIEM received the task to expand research in this area with the aim of introducing new bacterial and fungal allergens for use in healthcare practice. Indeed, there was an urgent need for such agents. For the further improvement of diagnostic preparations and the development of therapeutic allergens, it was necessary to create a clinical base that can undertake the systematic monitoring of patients with infectious and allergic diseases of the upper respiratory tract, lungs, digestive tract, and skin. At the same time, such a base facilitated the exploration of the possibilities of specialized care for patients with infectious and allergic diseases in the Tatar Autonomous Soviet Socialist Republic and throughout the Middle Volga region. For these reasons, in 1976, a specialized consultative and diagnostic polyclinic for infectious and allergic diseases was opened at KSRIEM for 13 medical workers. A polyclinic of this profile was, at that time, the only one in the Middle Volga region.

In 1980, the KSRIEM practically began the development of technologies for obtaining fungal allergens. Allergens from yeast-like and mold fungi were developed, successfully passed clinical trials, and then advanced to production. Furthermore, the stages of purification from mycotoxins and control for their absence were included in the technology. The development program for each of these agents included a wide range of mycological studies of strains and their antigenic spectrum as well as studies on the general composition and molecular parameters of the agents, the production of hyperimmune sera, the development of a model of fungal sensitization in guinea pigs, and the elaboration of the optimal dose for skin-allergic reactions in a specialized allergic polyclinic. Cross-reactions between species and genera of fungi were also studied.

The polyclinic of KSRIEM and the Department of Allergology of the Kazan State Institute

for Advanced Training of Physicians, which was established through the initiative of Academician A.D. Ado, actively performed clinical testing of the agents developed. The polyclinic also introduced new diagnostic schemes and specific immunotherapy with fungal and bacterial allergens. At present, the polyclinic for infectious and allergic diseases operates as a structural subdivision of the Institute and continues and has the primary function of developing the scientific traditions of our great fellow countryman.

The genuine devotee of science, Andrey Dmitrievich Ado, left us—the descendants and successors of his scientific prospects—an inestimable heritage of his thoughts, ideas, and initiatives. As such, his memory will forever remain in the grateful hearts of his many students and followers as well as fellow scientists and doctors.

Author contributions. I.D.R. was responsible for the collection and analysis of the research results; P.D.D. collected research results.

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

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