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Kazan Scientific Research Institute of Epidemiology and Microbiology — the stages of a long journey

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Abstract

This article was prepared for the 120th anniversary of the Kazan Scientific Research Institute of Epidemiology and Microbiology. The paper describes the main stages of the institute's development since its founding as the Kazan Bacteriological Institute at Kazan University in 1900. Until 2005, the institute belonged to the system of the Ministry of Health, and later, among 28 Federal State Institutions of Science, it entered the Rospotrebnadzor system. The information on priority research and the contribution of the institute to the achievements of domestic health care and the federal service for supervision in the field of consumer protection over the 120-year history of its activity are presented. The data on ongoing research and development, development prospects also are presented. The article was prepared using documents from the archives of Kazan Scientific Research Institute of Epidemiology and Microbiology, Kazan Medical University and Kazan Federal University, the National Archives of the Republic of Tatarstan, and the memoirs of employees of the Kazan Research Institute of Epidemiology and Microbiology.
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Kazan Scientific Research Institute of Epidemiology and Microbiology (KSRIEM) is the oldest institution of this kind in Russia. It was founded in the 1900s as a leader in the struggle against epidemics in the Volga region. Since the time of its inception as a bacteriological institute at the Kazan University, it was renamed several times, and until 2005 it came under the purview of the Ministry of Health. Subsequently, it was registered under the Rospotrebnadzor system among 28 other federal state scientific institutions (Table 1).

The need to create a bacteriological institute arose due to the spread of various mortiferous epidemics in all parts of the country. In the 1880s, the most severe and prolonged outbreak of diphtheria occurred in the Volga region that killed almost all the peasant children under the age of fifteen in the three neighboring provinces of Samara, Saratov, and Simbirsk.

In 1889, the Faculty of Medicine of Kazan University elected a commission composed of professors N.F. Vysotsky, S.M. Levashov, and N.M. Lyubimov "for development, joint with the city and zemstvo, of the decision on the establishment of a bacteriological station in Kazan" [1]. The chairman of the commission was Professor Nikolai Fedorovich Vysotsky, a surgeon by profession and a passionate enthusiast for the development of bacteriology, which was still in its nascent stage during those years. He was well-versed with this new science and had exceptional energy and great authority. It was N.F. Vysotsky who went on to become the first director of the institute (Fig. 1)

The foundation stone of the building was laid down in a solemn ceremony on May 14, 1897, on the first anniversary of the crowning of Nikolay II. The attic of the building has the Roman numerals MDCCCXCVII (1897) inscribed along with the date of the building's erection, MDCCCXCVIII (1898). The institute was officially opened on February 10, 1900, four years after the day Nikolay II allocated the funds for its construction. In 1896,

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Table 1. Kazan Scientific Research Institute of Epidemiology and Microbiology since its inception

Institute name	Years	Full name of the head, years of management
Bacteriological Institute at the Kazan University	1900–1925	N.F. Vysotsky (1900–1904), I.G. Savchenko (1904–1918), V.M. Aristovsky (1918–1932)
Regional Microbiological Institute of the People's Commissariat of Public Health of the Tatar Autonomous Soviet Socialist Republic (TASSR)	1925–1934	S.F. Nemshilov (1932–1937), P.A. Vershilova (1941–1943), A.R. Konova (1943–1945), A.M. Volkova-Borzunina (1945–1954)
Kazan Institute of Epidemiology and Microbiology of the People's Commissariat of Public Health of the Tatar Autonomous Soviet Socialist Republic	1935–1941	
Kazan Scientific Research Institute of Epidemiology and Microbiology of the People's Commissariat of Public Health (Ministry of Health) of the Russian Soviet Federative Socialist Republic	1942–1951	
Kazan Scientific Research Institute of Vaccines and Sera, Ministry of Health of the Union of Soviet Socialist Republics	1952–1955	N.A. Nemshilova (1954–1961)
Kazan Scientific Research Institute of Epidemiology and Hygiene, Ministry of Health of the Russian Soviet Federative Socialist Republic	1956–1965	I.Ye. Alatyrtseva (1961–1970)
KSRIEM of the Ministry of Health of the Russian Soviet Federative Socialist Republic	1966–2003	T.A. Bashkirev (1970–1983), V.I. Kurochkin (1983–1985), I.Z. Mukhutdinov (1986–1990), F.Z. Kamalov (1990–1996), V.M. Lukashkov (1996–2000), S.Kh. Iskhakova (2000–2003)
State Institution KSRIEM of the Ministry of Health of the Russian Soviet Federative Socialist Republic	2003–2005	R.S. Fassakhov (2003–2016)
Federal State Scientific Establishment KSRIEM, Rospotrebnadzor	2005–2011	
Federal budgetary institution of science KSRIEM, Rospotrebnadzor	since 2011	G.Sh. Isaeva (2016–2019), V.B. Ziatdinov (2019–present)

the rector of Kazan University notified the dean of the medical faculty of the receipt of 25 thousand rubles, allocated "by royal command" for the construction of the institute building. Fifteen thousand rubles were collected through private donations, while 20 thousand rubles were additionally received from the state treasury [1]. The building was constructed in the neoclassical style (Fig. 2). The design of the building was inspired by the famous Pasteur Institute in Paris.

In 1904, the institute was headed by Ivan Grigorievich Savchenko, a former employee of the Paris Pasteur Institute, who worked under the guidance of I.I. Mechnikov, the scientist who proposed the phagocytic theory of immunity (Fig. 3). I.G. Savchenko was the first to establish that the process of phagocytosis proceeded in phases; namely, the phase of adsorption of bacteria on the surface of the phagocyte that depended on the environmental factors (temperature, pH, etc.) and the phase of absorption of adsorbed microbial bodies, wherein the enzymes within the cytoplasm of the phagocyte played an important role. In 1902, he also discovered that the phagocytic reaction was enhanced in the presence of specific antibodies, which he called "immunisins" (a year later, such antibodies were described by Wright and called opsonins). These discoveries by I.G. Savchenko played an important role in the experimental substantiation of the theory of I.I. Mechnikov.

In 1905, I.G. Savchenko isolated a specific scarlet fever toxin of the hemolytic streptococcus and developed a method for obtaining anti-scarlet fever therapeutic serum, the production of which was immediately started in the serum department of the institute. Savchenko's serum received wide practical applications and reduced the number of complications (cases of the so-called "serum sickness" or anaphylaxis) by almost a factor of two. Twelve years later, a similar serum was offered by the American scientist couple George and Gladys Dick.

From 1902 to 1910, the scientific department of the institute published 36 works, a significant part of which was written by I.G. Savchenko. The thesis papers of Vyacheslav Mikhailovich Aristovsky "On the influence of the environment on cytolysis in the

Fig. 1. Nikolay Fedorovich Vysotsky

Fig. 2. The building of the bacteriological institute in the early XX century.

Fig. 3. Ivan Grigorievich Savchenko

Fig. 4. Vyacheslav Mikhailovich Aristovsky

presence of alexin and fixative" and other employees of the institute were also issued in these years. By decision of the Faculty of Medicine of Kazan University, V.M. Aristovsky was appointed as the director of the institute in 1918, and in 1920, he became the first head of the newly created department of microbiology at Kazan University (Fig. 4).

During the initial few years itself, the researchers of the institute produced tens of thousands of therapeutic doses of anti-diphtheria serum that was consumed not only in Kazan, but also by zemstvo administrations and hospitals in other provinces. This resulted in the eradication of the annual diphtheria epidemics in the Volga region. During the revolution, the Civil War, and the post-war devastation, the institute continued to function almost continuously, a fact confirmed by the information about the medicinal preparations introduced into production by the institution during these years (anti-diphtheria serum, anti-rabies vaccine, anti-scarlet fever serum in 1917, cholera vaccine, murine typhus vaccine in 1919, scarlet fever vaccine according to Gabrichevsky in 1922, and staphylococcal and streptococcal vaccines in 1924).

In 1925, the bacteriological institute at the Kazan University was reorganized; it withdrew from the structure of the university, and was transformed into the Regional Microbiological Institute of the People's Commissariat for Health of the TASSR. It was joined by the Variolation and Chemical and Bacteriological Institutes that existed at that time in the city. As a result of this merger, the Regional Microbiological Institute was formed. At that time, there were four departments in its structure (diagnostic, serum-vaccine, Pasteur, and sanitary-hygiene) and a smallpox sub-department.

In 1927, the sanitary-hygiene department, located in the building on the Pokrovskaya Street (now Shchapova St.), was transformed into an independent Institute of Social Hygiene. In its place, a department of epidemiology was created in the structure of the Regional Microbiological Institute, and the smallpox sub-department increased its status and became a full-fledged department. Thus, by the end of 1927, there were already five departments in the Microbiological Institute.

In 1927, the institute mastered the production of the diphtheria toxoid. In 1928, the production of typhoid-cholera divaccine was mastered, and two anti-dysenteric agents were developed, serum and dry vaccine in tablets. Since 1930, the institute began to prepare agglutinating sera, namely typhoid, paratyphoid, diphtheria, cholera, and meningococcal sera. Work continued on the improvement of the BCG vaccine and specific prophylaxis of tuberculosis.

Along with production and scientific activities, the institute organized the teaching of bacteriology and immunology for medical practitioners who

underwent advanced training at the State Institute for Advanced Medical Education (created in 1920).

Classes were held to train smallpox vaccine doctors and familiarize health care workers with the preventive vaccinations against rabies. Later, lectures were conducted on various aspects of microbiology (plague, cholera, anti-rabies vaccinations, etc.). In 1935, scarlet fever toxin was added to the existing range of bacterial preparations produced by the institute. In 1936, the institute was one of the first in the country to start the production of concentrated immune sera. In 1937, the institute first mastered the production of an anti-dysentery bacteriophage.

During the Great Patriotic War, the institute mastered the production of 14 types of new drugs, namely four types of anti-gangrenous sera, trivaccine, and anti-dysentery tablets in 1941, anti-tetanus serum in 1942, anti-typhoid tablets, dysentery dry bacteriophage, and subcutaneous dysentery vaccine in 1943, pentovaccine and typhus vaccine in 1944, and agglutinating sera in 1945. For the first time in the USSR, industrial production of an antibiotic (gramicidin) was launched. The raw material for the vaccines and sera was the blood of immunized animals, mainly horses. At the beginning of the war, their livestock numbers exceeded one hundred. Since 1942, the entire livestock of the producer horses was stationed at the Laishevsky district, where grazing was organized, and in one of the villages (first in Taneevo, then in Teteyevo), a facility for immunization and a laboratory for primary blood processing were established.

In addition to the infectious diseases, new scientific frontiers including the phenomena of anaphylaxis and allergies (mainly in the field of studying skin sensitivity as an indicator of immunity) were explored. During the Great Patriotic War, a young professor Andrei Dmitrievich Ado, who worked at the institute, revealed the physiological mechanisms and identified the most important chemical aspects of the development of anaphylactic shock. It turned out that the antigenic (responsible for immunization) and allergenic (causing anaphylaxis) properties of sera were due to different structures of biopolymers, and chemical treatment could make the preparations safer. These studies immediately enabled an improvement in the quality of the immunobiological agents that were manufactured and saved many human lives. The scientific results obtained by A.D. Ado during 1941–1945, became the basis of the contemporary allergology and immunology. Subsequently, through his initiative, the specialty of allergy-immunology appeared, and the first department of allergology was organized in Kazan.

In 1964 at KSRIEM, through an initiative of Academician A.D. Ado and the director of the institute I.E. Alatyrtseva, a new scientific field was established in the country and the first scientific laboratory for the study of allergies in infectious diseases was opened (headed by K.S. Zobnina, D.Bi.Sci.). Subsequently, the laboratory was transformed into a research and production complex for the development, clinical study, and production of bacterial and fungal allergens. As early as in 1965, the industrial production of the first five allergens from opportunistic bacteria (hemolytic staphylococcus, hemolytic streptococcus, *E. coli*, *Proteus mirabilis*, and enterococcus) was mastered. The production of allergens was based on the method of Ando-Verzhikovsky (1929–1936) modified by P.P. Sakharov and E.I. Gudkova (1963). In 2000, the assortment of the bacterial preparations included 13 items of diagnostic and therapeutic bacterial allergens for *in vivo* reactions and 6 items for *in vitro* reactions.

In the 1980s, the institute represented a modern scientific and industrial complex where various biological preparations were developed and produced, including blood preparations, in particular anti-staphylococcal immunoglobulin. Additionally, scientific and technical documentation for production of immunoglobulin preparation against hemorrhagic fever with renal syndrome (HFRS) was developed and prepared for implementation. It was the only institute in the USSR that developed and manufactured bacterial and fungal allergens. Furthermore, a specialized infectious and allergic diseases clinic was established therein for the testing and implementation of the allergens.

In 1997, the scientific research institute (SRI) and the production unit were divided into two separate legal entities. In 2005, during the process of administrative reform, the research institute was transferred to Rospotrebnadzor and the production unit was assigned to Roszdrav. Since 1997, the SRI was financed only under the article “Healthcare”. Funding under the article “Science” was restored only in 2004.

Currently, four research laboratories are functioning at the institute.

The laboratory of epidemiology and zoonotic diseases performs work on the zoonotic diseases most relevant for the region; namely HFRS, tick-borne viral encephalitis, and ixodic tick-borne borreliosis. An important part of the laboratory scientific work comprises detection and study of nosological forms of zoonotic diseases “new” for the republic, such as the West Nile viral fever, human granulocytic anaplasmosis, and human monocytic ehrlichiosis.

Taking into account the epidemiological significance of these infections, first described in Tatarstan [tick-borne viral encephalitis in 1949 (G.L. Khasis, 1950), HFRS in 1957 (F.T. Bashkirev, 1957), ixodic tick-borne borreliosis in 1992 (official registration)]; since 1955, the institute became a pioneer in the country to conduct comprehensive studies of natural foci of these infections and their epidemic manifestations [1].

In 1979, the KSRIEM mastered and began to successfully utilize the indirect application of fluorescent antibodies to indicate the antigen of the HFRS virus and the antibodies against it (M.A. Zakharova, S.B. Bogdanova, and M.E. Ermolaeva). A method for obtaining a sufficient amount of highly concentrated antigens of the HFRS virus from naturally infected bank voles with their group management was worked out and applied in practice. Consequently, since 1980, all studies were conducted under the control of a specific diagnostic test [2]. Antigenic agents were obtained from the cultures and the biological properties of the virus were studied in the samples of the infected people in the Middle Volga region. Since 1986, KSRIEM has been preparing series of immunoglobulins against the Puumala virus serotype. Serum samples of people who had a history of HFRS in the endemic regions of Tatarstan were used as raw materials.

Since 1957, under the guidance of Professor V.A. Boyko, the researchers at the institute have been conducting research on landscape-epidemiological zoning of forest-covered territories of Tatarstan; enzootic for HFRS, ixodic tick-borne borreliosis, and tick-borne viral encephalitis. They have been able to determine zones with high infection based on the observations of the elements of focal complexes in expeditions to municipal areas of Tatarstan, through stationary research process in key natural-territorial complexes, and during targeted missions to decipher group diseases and outbreaks of HFRS among civilian and military contingents. To study the immunological response to HFRS viruses they conducted large-scale laboratory studies of rodents, the main carriers of the HFRS pathogen, as well as serological studies of human blood serum samples. According to the results of the research, four groups of nosociological foci with different epizootic activity were identified; namely, a high-risk area in a typical forest-steppe landscape subzone of the Trans-Kama region, middle-risk area in the sub-taiga and broad-leaved subzones of the Fore-Kama region, and a low-risk area in the southern forest-steppe subzone of the Volga region.

In 2014, studies were initiated for the second stage of landscape-epidemiological zoning that included ranking of forested areas in the format of district forestries of the state forest fund of Tatarstan with different phytocenotic compositions. Since 2016, KSRIEM, together with the Kazan (Volga) Federal University, has been conducting research using modern molecular methods to study the genovariants of the HFRS Hantavirus, taking into account the infection rate of bank vole populations in the regions of the Republic of Tatarstan located in various landscape zones that are characterized by high incidence of HFRS. It has been established that genovariants of the Puumala virus circulate among bank voles on the territory of the republic in various landscape-geographical zones.

In December 2017, in accordance with the order of Rospotrebnadzor dated 01.12.2017 No. 1116 "On improving the system of monitoring, laboratory diagnostics of infectious and parasitic diseases and indication of pathogenic biological agents in the Russian Federation", a reference center for monitoring HFRS was created at the KSRIEM.

The main activities of the reference center include the following:

– monitoring of the epidemiological situation for HFRS throughout the territory of the Russian Federation as a whole and in individual regions;

– drawing up reviews, short-term and long-term prognoses for the epidemiological situation;

– study of circulating varieties of HFRS viruses using contemporary laboratory research methods;

– conducting serological monitoring among the population of endemic territories;

– preparation and publication of information and analytical materials on epidemiology, diagnostics and prevention of HFRS;

– improvement of epidemiological surveillance, as well as preventive and anti-epidemic measures, and methods of laboratory diagnostics of HFRS.

The laboratory of microbiology (the laboratory of intestinal infections until 2002) is one of the oldest divisions, organized based on the laboratory of intestinal infections. In 1948, the Kazan Institute started research on the circulating Shigella strains. A change in the dominant type of dysentery bacillus was revealed, and the variability of Shigella under the influence of antimicrobial drugs was studied (E.N. Kulikova, Yu.T. Kuzmina, E.I. Vaiman, Yu.D. Egorova). Together with the practical health care workers, they studied the issues of colibacillosis in children, and investigated the prevalence of enteropathogenic Escherichia. In accordance with the recommendation of the KSRIEM, mandatory microbiological examinations of the employees at children's institutions for pathogens of acute intestinal infections were introduced into practice. After the war, with the

increase in the number of intestinal diseases of unknown etiology, studies were performed to analyze this infection with an active participation of N.A. Nemshilova, R.B. Donskaya, D.A. Yakobson, E.I. Vayman, and E.N. Kulikova. The use of the indirect hemagglutination reaction enabled an increase in the detectability of carriers of typhoid fever (E.N. Kulikova, K.F. Firsova, L.A. Spasskaya, and T.A. Lobak) [3].

Since 1970, the laboratory started research on the etiology of serological groups of Escherichia, and continued the study of epidemiology of dysentery in various population groups in preschool institutions (E.I. Vayman, D.A. Yakobson). In the 1980s, at the laboratory of intestinal infections of KSRIEM, under the supervision of O.P. Galeeva in close cooperation with the staff of the Leningrad L. Pasteur Research Institute of Epidemiology and Microbiology, the study of aspects of the epidemic process of dysentery in the TASSR was started. Bacteriological studies were conducted to analyze the cytotoxicity of Shigella on the model of an FL cell culture and the degree of biochemical activity of the microorganism cultures was determined using an extended set of carbohydrates.

Laboratory specialists worked in close cooperation with the Sanitary and Epidemiological Service of the TASSR, provided scientific and methodological assistance in identifying and assessing the severity of pathogenic factors of clinical isolates of Shigella delivered to the intestinal infections laboratory of the KSRIEM from the bacteriological laboratories of Kazan and the regions of TASSR. During these years, studies were conducted to investigate the nature of the colon microflora in patients with intestinal dysbiosis, as well as to analyze the effectiveness of lactic acid eubiotics (coli- and bifidumbacterinum) for the correction of dysmicrobiocenosis in patients with various pathologies (O.P. Galeeva, L.T. Bayazitova, O.F. Tyupkina., and T.A. Chazova).

The 1990s were characterized by an increase in the incidence of hepatitis B and C infections. Studies were launched to examine the relationship between intestinal microflora and the pathogenesis of parenteral hepatitis. During 1992–1993, in the laboratory of intestinal infections, studies of the microflora of the gastrointestinal tract in patients with parenteral hepatitis were commenced. These studies were conducted jointly with the Department of Infectious Diseases of the Kazan State Medical Institute (Professor D.Sh. Enaleeva, Professor V.Kh. Fazylov). Concurrently, the characteristics of the microbiota of various human biotopes in normal and dysbiotic conditions were also studied (L.T. Bayazitova, O.F. Tyupkina).

In the first decade of the XXI century, under the supervision of Professor R.S. Fassakhov, a number of new scientific studies were commenced. The role of microorganisms in the pathogenesis of allergic diseases (allergic rhinitis, atopic dermatitis) raised particular interest in the staff at the KSRIEM laboratory of microbiology (L.T. Bayazitova, O.F. Tyupkina, T.A. Chazova) together with the personnel of the consultative and diagnostic polyclinic of KSRIEM (I.D. Reshetnikova, A.A. Sharifullina), and the staff at the laboratory of immunology and the development of allergens (Yu.A. Tyurin, S.N. Kulikov).

Studies that analyzed the properties of the skin microbiota in various forms of atopic dermatitis in pediatric patients revealed severe pathological changes and the eventual development of atopic dermatitis in those with skins colonized by *Staphylococcus aureus*. In such cases, topical therapy with zinc pyrithione was found to be highly efficient, due to its antibacterial effect that promoted the elimination of *S. aureus* from the skin of patients and the decreased virulence of the pathogen (L.T. Bayazitova). Further research was initiated to study the virulence factors of opportunistic bacteria in the pathogenesis of infectious, somatic, and allergic diseases, the optimal complete biological and epidemiological characteristics of opportunistic bacterial species, and etiopathogenetic aspects of infections caused by pathogenic and opportunistic bacteria, in order to improve laboratory diagnostics.

One of the main fields of activity was monitoring the antibiotic resistance of *Streptococcus pneumoniae* in risk groups for bacterial carriage, assessing the effect of vaccination with pneumococcal vaccine on bacterial carriers, and studying the serotypic composition of epidemiologically relevant strains of pneumococci.

The relevance of studying the aspects of colonization of the nasopharynx by pneumococci was based on the relationship between the strains colonizing the nasopharynx and strains that caused invasive infections, otitis media, and rhinosinusitis. It was revealed that nasopharyngeal strains of pneumococci in children-carriers were a reservoir of microorganisms with genetic mechanisms for the development of antibiotic resistance. In light of this, monitoring of the prevalence of nasopharyngeal pneumococci in children and monitoring over the increase in antibiotic resistance of *S. pneumoniae* strains in the pediatric population became an important link in controlling the epidemic process in relation to pneumococcal infections.

Within this field, the prevalence of nasopharyngeal carriage of *S. pneumoniae* in children in Kazan and the Republic of Tatarstan were assessed.

The microbiological characteristics of nasopharyngeal strains of pneumococci were studied; namely, the severity of pathogenicity factors, sensitivity to antimicrobial drugs, and bacteriophages. Monitoring of the regional data on seroepidemiology of *S. pneumoniae* with a description of the serotype composition was performed that enabled the assessment of the trends in the spread of epidemically significant strains in the region to determine the completeness of coverage of children with pneumococcal conjugate vaccines used for vaccination.

In 1977, a new subdivision was created at KSRIEM, the *laboratory of immunology and biochemistry*, headed by MD, PhD A.N. Mayansky. The laboratory activities were aimed at studying the molecular parameters of allergenically active fractions of bacteria, assessing cellular reactivity to bacterial metabolites, and studying the mechanisms of specific and nonspecific immunity in bacterial allergies (M.E. Viksman, R.A. Parshakova, V.I. Vershinina, and M.B. Kuravskaya). Methods of allergy diagnostics of sensitization in *in vitro* reactions were actively developed. Consequently, the micro-test method with nitro blue tetrazolium was introduced (M.E. Viksman, E.A. Pazyuk) and a lymphocytic mitogen of *Staphylococcus aureus* was obtained for the blast transformation reaction (V.A. Ilyushin). The study of allergenically active fractions of bacteria enabled the production of purified bacterial allergens and complex allergens aimed at detecting immediate and delayed types hypersensitivity reactions *in vivo*, as well as to develop preparations for determining the index of neutrophil damage, the reaction of leukocyte migration inhibition, and the reaction of destruction of mast cells with bacterial allergens (O.D. Zinkevich, S.Kh. Iskhakova, V.A. Ilyushin, M.G. Bykova, S.Yu. Egorova, T.V. Pavlova, N.B. Hardina) [1, 3].

In 1982, O.D. Zinkevich (Ph.D. in Biology) became the head of the laboratory of immunology and biochemistry. Under his guidance, a new blood product, fibronectin was developed and its properties, methods of detection, and application were actively studied. A new drug in the form of eye drops, composed of fibronectin, was also created (A.F. Kharrasov, N.A. Safina, and I.G. Mustafin).

During 2000–2005, in the laboratory of immunology and biochemistry, together with the laboratory of microbiology and in close cooperation with the department of children's infections and hospital pediatrics of the Kazan State Medical University, and the departments of pediatrics and neonatology of the Kazan State Medical Academy (V.A. Anokhin, T.P. Makarova, I.V. Nikolaeva, N.A. Safina, Yu.A. Tyurin, A.A. Babintseva, O.D. Zinkevich, A.V. Kuznetsova), work was started on the study of the activity of enzymes of pathogenic and opportunistic bacteria capable of specifically cleaving human protective factors; namely, immunoglobulins of various classes. This line of research was developed with the cooperation and support of the head of the laboratory of genetics of virulence of bacteria, N.F. Gamaleya Research Institute of Epidemiology and Microbiology (Moscow), Professor V.M. Bondarenko.

During 2000–2001, in the laboratory of immunology and biochemistry, practical surgeons along with the graduate students of the surgical departments of the Kazan State Medical Academy (V.Yu. Tereshchenko, D.E. Volkov, and R.G. Mingazov) studied the relationship between the level of systemic endotoxinemia, antiendotoxin immunity, and bilirubinemia in patients with acute diseases of the extrahepatic biliary tract, accompanied by a disorder of the passage of bile into the intestine.

In 2004, the laboratory for immunology and biochemistry was renamed the *laboratory for immunology and allergen development*. The primary scientific activity of the laboratory was the production and study of the immunological and biochemical properties of bacterial antigens, as well as the study of pathogenic factors and their genes in bacteria. The laboratory included a parasitological group involved in improving the methods for diagnosing parasitological diseases.

As part of the cooperation of laboratories for microbiology and immunology and the development of allergens, the following activities were conducted:

– comprehensive epidemiological monitoring of the prevalence of pathogenic factors (toxin production, genetic toxigenic profile, the ability to form invasive enzymes, and other factors that counteract the factors of innate and adaptive immunity);

– monitoring the profile of resistance to antimicrobial drugs, bacteriophages and disinfectants of opportunistic bacterial strains colonizing various biotopes of individuals from decreed groups (such as catering workers, medical workers, frequently ill children, patients with underlying chronic diseases, patients with allergic dermatoses, etc.) as well as strains associated with infections related with the provision of medical care in various surgical hospitals of multidisciplinary healthcare facilities;

– study of the genetic mechanisms of antibiotic resistance of opportunistic bacterial strains in order to identify them and compile a genotypic profile (using molecular genetic methods of analysis);

– identification of key genetic risk factors for the development of long-term carriage of opportunistic bacterial taxa associated with the peculiarities of gene polymorphisms that control innate and

acquired mechanisms of antibacterial and antimicrobial protection of the skin and mucous membranes, and control colonization resistance.

Mycology laboratory. The development of mycological studies at KSRIEM started during 1978–1980 with the formation of a scientific group for the development of fungal allergens. One of the reasons for the attention to the problem of fungal (mycogenic) allergy was the outbreak of allergic diseases in factories for the production of yeast-based protein-vitamin concentrates. The main task of the scientific group was the study of the allergenic active properties of yeast-like and filamentous fungi. In 1985, it was established as an independent laboratory for the development of fungal allergens, headed by V.M. Lukashkov [1, 3].

An important field of the laboratory activities was the development of specific agents from the fungi-producers of biotechnological production, which was performed under contracts with the All-Union Institute of Biosynthesis of Protein Substances. For the first time, in the laboratory, allergens were created, and that enabled a distinction between sensitization to pathogenic and non-pathogenic species of the genus *Candida* (*C. maltoza* and *C. albicans*). Also, experimental laboratory series of agents from the species used in the production of protein-vitamin concentrates (*Candida scottii* and *Candida utilis*) were obtained. Cross-reactions between the main types of yeast-like fungi of interest for medicine were studied (a total of about 30 species of 6 genera). This enabled to substantiate theoretically the range of allergens produced in the laboratory.

Similar work was conducted for all genera of mold fungi. In particular, E.N. Shahbazova showed the antigenic isolation of *Penicillium tardum*, *Penicillium chryzogenum*, *Penicillium expansum*, and *Penicillium digitatum,* and the need to develop individual allergens from these species. A.A. Vershinin studied in detail the antigenic relationships and the composition of the antigens obtained from fungi of the genus *Aspergillus* (1985–1990).

Since 1985, when the laboratory became organizationally independent, its staff and scientific topics expanded significantly. Senior researchers M.A. Zakharova and E.A. Pazyuk, junior researcher L.E. Efimova, senior laboratory assistants, and then research workers T.R. Grebyonkin and F.T. Abdullina joined the laboratory. They started to perform work on the specific diagnostics of sensitization in *in vitro* methods (the reaction of degranulation of basophils, an indicator of damage to neutrophils; the reaction of inhibition of migration of leukocytes, etc.).

Doctors of the KSRIEM polyclinic (A.A. Lodi, L.R. Smirnova, F.A. Fattakhova, A.M. Gumerova, etc.) launched a comprehensive study of the developed fungal allergens in the clinic for the diagnostics and treatment of adults and children. The results obtained formed the basis for a number of thesis papers on the clinical aspects of the use of fungal allergens.

After 1987, began the development of new fungal allergens, which included those from the pathogenic fungi *Trichophyton rubrum* and *Aspergillus fumigatus*. This work required significant changes in the technology, and was successfully performed by N.I. Glushko and L.E. Efimova. T.R. Grebyonkina continued work on obtaining allergens from yeast-like fungi, as well as baker's yeast, *Saccharomyces cerevisia*. By the beginning of the 1990s, normative and technical documentation for 15 names of yeast-like and mold fungi was compiled.

In the late 1990s, the laboratory headed by N.I. Glushko started to master a new field, which was laboratory diagnostics of fungal infections. It soon gathered great demand by practical healthcare, especially by otorhinolaryngologists and dermatologists. The study of mycotic complications of allergic diseases, in particular atopic dermatitis and bronchial asthma, conducted during 2000–2012 in KSRIEM polyclinic, was of great importance.

In the early 2000s, another direction associated with the identification of fungi-biodestructors appeared in the laboratory activities, which became especially relevant in connection with the large-scale work on the restoration and reconstruction of historical buildings, including the objects of the Kazan Kremlin in preparation for the celebration of 1000-year anniversary of Kazan (2005), and then for the World Student Games (2013). Later, the experience gained by the laboratory turned out to be in demand when assessing the prevalence of micromycete fungi in residential buildings, health facilities, cultural, and sports facilities.

In 2005, after reorganization into the laboratory of mycology, the development of these fields continued and received new impetus after moving to new premises in 2012. Efforts were directed to improve the laboratory diagnostics of fungal diseases, taking into account contemporary ideas about the morphophysiological, biochemical, and genetic characteristics of fungi. Studies of the virulence factors of clinically significant and potentially pathogenic fungi (adhesion, biofilm formation, enzymatic and antigenic properties, etc.) and their resistance to antimycotics, including those in biofilms, were conducted. An important direction was the study of the processes of biofilm formation of *Candida albicans* on the surface of medical products.

The research area of the mycology laboratory also covered the problems of mycogenic contami-

Fig. 5. The team of the Kazan Scientific Research Institute of Epidemiology and Microbiology in 2019

nation and mycological monitoring of the modern urban environment as one of the topical hygienic fields, as well as the search for new compounds with antifungal activity.

One of the structural units of the KSRIEM was a *specialized consultative and diagnostic polyclinic for infectious and allergic diseases* established in 1976 as a clinical base for testing the diagnostic and therapeutic bacterial and fungal allergens developed at that time at the Institute [1]. A great contribution to the creation of the polyclinic was made by the director of the institute T.A. Bashkirev, head of the laboratory for the development of bacterial allergens, professor B.A. Molotilov, and Ph.D. F.Z. Kamalov who became the first head of the clinic, (later the head of production at KSRIEM, director of an independent enterprise organized on its basis), as well as L.R. Smirnova, who headed the polyclinic until 2012.

In 1978, an immunological laboratory (currently clinical diagnostic) was established within the polyclinic. It was organized to a large extent by Professor, A.N. Mayansky; Senior Researcher, Ph.D. M.E. Vicksman; head of the laboratory for the development of bacterial allergens, PhD in Medicine B.A. Molotilov; and later the head of the laboratory, Ph.D. E.V. Agafonova.

Currently, the polyclinic aims at the provision of primary, including pre-medical, medical, and specialized health care to patients with a number of immune-mediated diseases (somatic, infectious, immunopathological, allergic) at the specialties of doctors of medical institutions or independent requests from patients in Kazan, the Republic of Tatarstan, and other regions of the Russian Federation.

Polyclinic personnel took part in the development of the following scientific topics of the institute:

– "Early detection of patients with latex allergy among medical workers of the Republic of Tatarstan, development of a set of diagnostic and preventive measures aimed at reducing morbidity and treatment costs";

– "Epidemiology of chronic respiratory diseases and risk factors for their development in the adult population with an assessment of effectiveness of educational programs for the management of patients with respiratory pathology in primary health care institutions in the Russian Federation";

– "Epidemiological surveillance of viral hepatitis B among medical workers and children with a burdened allergic history and helminth infestations immunized against hepatitis B";

– "Factors of virulence of opportunistic bacteria and various human microbial ecosystems in the pathogenesis of infectious and allergic diseases in children and adults";

– "Improvement of coproscopic and serological methods of diagnostics and prevention of geohelminthosis; improvement of the algorithm for laboratory diagnostics and epidemiological monitoring of parasitosis";

– "Research on serological monitoring of zoonotic diseases in the Republic of Tatarstan, namely hemorrhagic fever with renal syndrome, tick-borne encephalitis, West Nile fever, ixodic tick-borne borreliosis";

– "Studies to assess the strength of post-vaccination immunity against measles and rubella among risk groups (medical workers)."

KSRIEM employees are proud of the glorious history of the institute. They feel a deep sense of gratitude and respect for its good traditions, founders, and outstanding teachers in bringing up young worthy specialists. They strive to constantly improve their professional skills, dedicating all their knowledge, energy, and experience to ensure the sanitary and epidemiological well-being of the population (Fig. 5).

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