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Sanitary-microbiological research at the Hygiene Department of the Pirogov Russian National Research Medical University: the history and the present

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The Department of Hygiene at the Pirogov Russian National Research Medical University is one of the leading schools in the field of sanitary microbiology – its staff have achieved significant scientific results. The bacteriological characteristics, environmental distribution, epidemiology and diagnostics of *C. perfringens, B. cereus, V. parahaemolyticus* have been studied, and preventive measures for the foodborne diseases caused by them have been developed. The methods for using biotechnological strains of genera *Bacillus, Pseudomonas, Candida* have been studied in agriculture and forestry. In connection with the intensive development of biotechnologies, a comprehensive hygienic assessment of biotechnological strains in soil, water in reservoirs, air in workplace areas and atmospheric air has been developed. A set of indices for the evaluation of sensitizing and immunotropic action is proposed, a scheme for toxicological and hygienic studies of biotechnological strains has been optimized, a list of priority microorganisms has been compiled and a classification of microorganisms according to their degree of danger is proposed.

Keywords: *hygiene, sanitation, toxic infections , producing strains of microorganisms, regulation*

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Sanitary microbiology is a branch of preventive medicine that studies environmental microflora. A number of microorganisms of natural and anthropogenic origin are capable of directly or indirectly (via interfering with the natural environment's self-cleaning processes) producing a negative impact on human health [1–6]. Since its opening, the Department of Hygiene's scientific research, conducted at the Pirogov Russian National Research Medical University, has addressed the most pressing issues of hygiene science. The department is one of the leading schools in various areas of sanitary microbiology, and the staff of the department have achieved significant results in this field. Diagnostics and preventive measures for food-borne diseases, safety measures for using bacterial preparations in agriculture, improvement in regulations for biotechnological strains of microorganisms in the air of working areas and natural air – all these scientific fields were the basis for the development of preventive measures aimed at preserving human health.

Since the department's foundation (1908), Professor M.B. Kotsyn's main focus was research in the field of sanitary microbiology. Since 1917, the department has been led by a succession of professors – P.N. Diatropov, N.K. Ignatov and N.N. Litvinov – and its staff's research has been related to food hygiene and communal hygiene. Only in the 1960s, under the guidance of Associate Professor G.I. Sidorenko, was research in the field of sanitary microbiology revived. During this period, its main research field was the study of new causative agents for food-borne human infections. Initial research was devoted to the study of the role of the anaerobic spore-forming bacterium *Clostridium perfringens* in the etiology of these diseases, i.e. toxic infections.

In 1968, Sidorenko's doctoral thesis "Food poisoning caused by *C. perfringens,* and its prevention" was defended. It examined the epidemiology and diagnosis of diseases caused by *C. perfringens*.

Candidate dissertations by Yu.P. Pivovarov ("Epidemiology, clinical practice, diagnosis and prevention of toxic infections caused by *B. cereus*," 1965), E.B. Borovik ("Investigation of the dissemination of *Cl. Rerfringens* of the intestinal contents of healthy people in connection with the study of food-borne diseases," 1967), E.N. Stratonova ("The role of *Cl. rerfringens* type A in the development of intestinal diseases in young children," 1970), A.D. Deriglazov ("On the prevention of food poisoning caused by *Cl. Perfringens* type A, in food service providers," 1970) and L.S. Zinevich ("Development of an experimental model for food-borne diseases caused by *Cl. perrringensens* type A and a study of some pathogenesis issues," 1973) were also associated with the study of the environmental distribution of *C. perfringens*, including in food, with the study of these microorganisms' role in human diseases and with the development of methods for diagnosis and prevention.

Among a number of microorganisms that were little known (or completely unstudied), but widely distributed in the environment, is *Bacillus cereus.* A number of dissertations at the department have been devoted to the study of issues in the identification and role of *B. cereus* as a source of food-borne diseases, its epidemiology, clinical practice and the prevention of diseases associated with it: R.S. Volkova ("Some issues in the prevention of toxic infections caused by *B. cereus,* in food service providers," 1970), A.M. Akimov ("Food as a possible source of food-borne diseases caused by *B. cereus*," 1971), L.P. Sazonova ("Biological characteristics of *B. cereus* strains, causative agents of food toxic infections," 1973), A.I. Sidorenko ("Prevention of food-borne diseases caused by *B. cereus*, in the armed forces," 1974).

In 1971, Pivovarov defended his doctoral thesis "Epidemiology, clinical practice, diagnosis and prevention of toxic infections caused by *B. cereus*," dedicated to an integrated solution to the problems associated with food-borne diseases caused by *B. cereus*. They also developed methodological instructions: "Food poisoning caused by *Bacillus cereus* and its diagnosis," in which the bacteriological characteristics of the microorganism, its spread in the environment, the clinical aspect of poisonings, the diagnosis and recipes for a culture medium for the isolation of *B. cereus* [7] were presented. Professor and Doctor of Medicine Yu.P Pivovarov, a pupil of the Department of Hygiene at the Pirogov Russian National Research Medical University, led the department in 1979. Under his leadership, scientific work on the study of a number of microorganisms capable

of causing human food-borne diseases was expanded and intensified.

Several varieties of halophilic vibrios were of great interest to researchers from numerous countries. They were widely distributed in the environment, above all, in coastal sea waters and aquatic organisms living in them.

In 1974, the staff of the department was asked to study the etiology of the so-called red disease of commercial fishes and to develop recommendations for the use of affected fish. In 1975–1977, three scientific expeditions were undertaken to the north-west Atlantic (the duration of each expedition was three to four months).

In the course of the research, it was discovered that the causative agent of the "red disease" was one of the representatives of the halophilic vibrios group – *Vibrio anguillarum*. In laboratory experiments on fish and frogs, the possibility of such a disease was confirmed. It was also shown that *Vibrio anguillarum* was among microorganisms that were not resistant to environmental factors, it quickly died during storage and cooking, was non-toxic and not dangerous to humans.

On this basis, recommendations were developed for the use of affected fish, which saved many tons of this valuable product for food purposes.

The department's staff thoroughly studied *V. parahaemolyticus*. Methodological recommendations [8] and four Ph.D. theses were prepared in this scientific research field: Yu.I. Grigoriev, ("Distribution of *V.Parahaemolyticus* – a causative agent of food-borne diseases in sea water and seafood," 1975), E.P. Ermolin ("Experimental substantiation of measures for the prevention of toxic infections caused by *V. Parahaemolyticus*," 1976), G.M. Shikalov ("Biological characteristics of strains of halophilic vibrios, possible causative agents of food-borne diseases," 1978), M.I. Lapenkov ("Hygienic assessment [using microbiological indicators] of marine foods contaminated with halophilic vibrios," 1982).

The final work in this scientific field was the summarizations made by Grigoriev in his doctoral dissertation "Regulation of microbiological criteria for assessing the quality of food products from sea fish and invertebrates in the development of new techniques and improvement of traditional techniques for their preparation" (1992).

Based on the results of the scientific research conducted by the department's staff and literature data, the methodological recommendations "Identification of microorganisms of the *Enterobacteriaceae* family" were developed and the "Handbook of Sanitary Microbiology" (1981) [9, 10] was prepared for publication.

Within the sphere of sanitary microbiology, the department conducted research on the prevalence and methods of seeding food products with sanitary-significant and pathogenic microorganisms [11]. L.A. Kharisova[1] studied the problem of pesticides' effect on the sanitary indicator microorganisms of soil – the causative agents of food-borne diseases.

Given the complexity of studying the microflora of any object in the external environment (water, air, soil, food) due to the difficulty of identifying each microorganism, a directory was produced in the department, entitled "A guide to sanitary indicator microorganisms" and a new supplemented edition "Sanitary indicator microorganisms (taxonomic characteristics and differentiation)" [12, 13]. In these publications, the taxonomic characteristics of sanitary indicator microorganisms from more than 30 families are presented, and for their identification, the authors compiled determinants that identify the microorganism, starting with the results of primary isolation through to the definition of its species name.

Later, there was a need to study the safety of microorganisms used in the production of bacterial preparations for pest control in agriculture and forestry. Representatives of the genera *Bacillus, Pseudomonas, Candida* were studied.

It is shown that the uncontrolled use of bacterial insecticides can have an adverse effect on the environment, causing a disturbance in the self-cleaning processes of soil and water bodies.

In experiments on volunteers, it was demonstrated that the mass intake of microorganisms into the body via food could cause intestinal disorders. To prevent adverse

[1] The subject of Kharisova's candidate dissertation was "The influence of residual amounts of pesticides on spore-forming sanitary indicator microorganisms of soil – the causative agents of food-borne diseases" (1995).

effects on the body, hygienic regulations for their use, doses, processing times and more were developed. A number of dissertations on this subject were defended at the department.[2]

One of the important practical results of this field of the scientific work by the department's staff was the creation of methodical documents [14, 15], which ensured the organization of effective sanitary and microbiological control over the production and use of bacterial insecticides. In the second half of the 1970s, the biotechnological industry began to actively develop in the Soviet Union, which made it possible to create using microbiological synthesis a very diverse range of substances needed by the economy. Naturally, there was a need to conduct scientific research on the possible adverse effects of microbiological industry enterprises, as well as the microorganism-producers' effect on human health and environmental objects[3] [16].

In connection with the creation of genetically engineered microorganisms, a new question arose in hygienic science: how dangerous are these strains for the environment and humans? To solve it, the department began research aimed at developing a set of indicators for the initial assessment of biotechnological strains obtained via selection methods and via genetic engineering methods to determine the possible adverse effects on the environment and human beings.

As a result of the research, a set of sufficiently accessible indices was recommended for a single intake into the body: a medium virulent dose, a "threshold" dose, toxicity and toxigenicity, the presence of disease symptoms, dissemination of strains into the organs of experimental animals, the presence of "pathogenicity enzymes" (hyaluronidase, gelatinase, lecithinase and etc.), as well as indicators for assessing the effect of strains on the environment (changes in microbial coenoses, the self-cleaning ability of water and soil, the duration that pathogenic microorganisms were retained in soil). All the research into the microorganisms that were studied was divided into three groups:

The first group – strains recommended for industrial use (strains of genera *Bacillus, Brevibacterium, Micrococcus*);

The second group – strains that verged on risky (strains of genera *Enterobacter, Haemophilus, Escherichia, Acinetobacter*);

The third group – strains not recommended for industrial use (strains of genera *Corinebacterium, Moraxsella, Candida*).

About 250 strains were proposed for use in biotechnology. Only about 40 percent of strains were found to be safe for human health and the environment, about as many strains among those studied were on the verge of risk and 20 percent of strains could not be recommended for use. Most of the strains assigned to the first and second groups were obtained with the help of genetic engineering methods. On the basis of the research conducted, two dissertations[4] and methodological recommendations were prepared [17–19].

Further progress in the scientific field developed by the department's staff (sanitary and microbiological assessment of the environment) was aided by the organization in 2007 of a scientific and educational center (SEC) for ecological and hygienic issues, which included

[2] S.A. Ivashina "Biological and hygienic assessment of entomopathogenic microorganisms from the *B. cereus* group used in the production of bacterial preparations" (1974); V.V. Korolik "Influence of bacterial entobacterin and dendrobacillin insecticides on the processes of soil self-cleaning and the pathogenic enterobacteria survival in it" (1980); T.G. Omelyanets "Hygienic aspects of environmental protection in connection with the use in agriculture of microbial preparations based on non-spore-forming microorganisms" (1982); M.I. Minaeva "Influence of *B. thuringiensis* – based biological preparations on the self-cleaning processes of reservoirs and the death of pathogenic microflora" (1993); K.N. Daburov "The hygienic justification for regulations on the use of *B. thuringiensis* – based bacterial insecticides in agriculture" (1980) and "Hygienic and ecological aspects of applying microbiological products based on *B. thuringiensis* for protecting agricultural plants in Tajikistan" (1997).

[3] Padalkin's thesis "Hygienic regulation of labor at microbiological industrial enterprises" (1985), N.S. Shlyachetsky's "The medico-biological and hygienic justification for the introduction of new technological processes for microbiological synthesis" (1987), V.M. Ostrogolovy's "Influence of microorganisms producers of the *Bacillus, Pse udomonas, Candida* strains on the sanitary state of soil as a criterion of their hygienic standardizations" (1992).

[4] L.I. Mjalina's "Comprehensive hygienic assessment as a criterion for selecting bacterial strains to be used in biotechnology" (1992) and V.V. Korolik's "Integrated hygienic assessment of biotechnological strains of microorganisms in connection with the pollution of their environment" (1999).

the department of hygiene and the department of toxicology at the Russian State Medical University of the Federal Agency for Health and Social Development. Experimental research was carried out as part of the scientific research work of SEC on the topic "Development of a system of safety assessments based on taxonomic and toxicological and hygienic characteristics of industrial microorganisms" under the guidance of Academic Yu.P. Pivovarov and Professor N.G. Ivanov (principal investigator – chief researcher, Dr. N.I. Sheina).

The new data that was acquired on the nature of the adverse effect of biotechnological microorganisms have become an important step in the further development of the theory and practice of hygienic regulation of microbiological factors and the prevention of its adverse effects on human health. An integral indicator for the harmful inhalation effect of microorganisms was a quantitative assessment of the functional metabolic activity of the respiratory tract phagocytes. The microorganisms' action also had specific effects – dysbiotic and sensitizing. In the study, consistencies in intestinal microecology disturbances were revealed during repeated exposure to biotechnological strains, as a result of an increase in opportunistic microflora in the intestine and a decrease in the autochthonous microflora. In order to identify the severity of the sensitizing effect and establish the minimum effectual levels of prolonged exposure to microorganisms, a model of the mast cell population was developed and tested. Mathematically, a linear relationship was demonstrated between mast cell degranulation, the balance of T and B lymphocytes, and the eosinophilia index, which is important for the hygienic regulation of industrial microorganisms.

Based on a set of the studied indicators characterizing the sensitizing and immunotropic action, the procedure for toxicological and hygienic studies was optimized. In the process of studying the character of the harmful effect of more than 40 strains of microorganisms, a list of top-priority industrial microorganisms was created. Taking into account international organizations' recommendations, the authors scientifically substantiated microorganisms' hygienic classification according to the degree of danger to people's health [20, 21].

Based on the results of many years of research, N.I. Sheina's doctoral thesis "Scientific and methodological foundations of hygienic regulation and assessment of occupational exposure to biotechnological strains of microorganisms" (2008), established about 85 maximum permissible concentrations (MPCs) of microorganisms in the air for working areas and natural air in populated areas and 70 methodical guidelines for identifying these microorganisms in these environments.[5]

In 2013, the Academy of Medical Sciences awarded the F.F. Erisman Prize for preventive medicine to the team of authors who were staff of the department of hygiene and the department of toxicology (Yu.P. Pivovarov, N.G. Ivanov, N.I. Sheina, E.G. Skryabin) for a series of works in the field of biosafety of industrial microorganism strains.

Much work has been conducted in the field of sanitary microbiology, including by the staff of the Department of Hygiene at the Pirogov Russian National Research Medical University for the 110th anniversary of the department's existence at the pediatric faculty. A new generation of research staff and teachers continues to actively develop this scientific field. The intensive development of molecular biology and genetics, the production of highly productive genetically engineered modified strains and their use in biotechnology poses new and difficult, but also very interesting, challenges for the department's scientists in their assessment of possible adverse effects on human health and the state of the environment.

[5] Resolution of the Chief State Sanitary Doctor of the Russian Federation of April 18, 2017 No. 56 "On the Approval of Hygienic Norms" GN 2.1.6.3467-17 "Maximum permissible concentrations (MPC) of microorganism-producers and components of bacterial preparations in the natural air of populated areas"; Decree of the Chief State Sanitary Doctor of the Russian Federation of April 18, 2017 No. 56 "On the Approval of Hygienic Norms" GN 2.2.6.3468-17 "Maximum permissible concentration (MPC) of microorganism-producers and components of bacterial preparations in the air of the work areas."

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