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SCIENTIFIC AND PRODUCTION ACTIVITIES AND FUTURE TASKS OF USSR INSTITUTES OF VACCINES AND SERA

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The institutes which produce bacterial preparations have grown out of bacteriological and sanitary-hygienic laboratories. The first national institute of this type was opened at Odessa in 1886. During the next 30 years, 12 more institutes which produced antirabies and smallpox vaccines were opened in major centers of the country. After the October Revolution the number of institutes began to grow rapidly. By 1930, there were more than 50 institutes of epidemiology and microbiology in the USSR. These institutes combined the production of bacterial preparations with scientific research work and antiepidemic activities.

In 1952, some institutes of epidemiology and microbiology were reorganized into institutes of vaccines and sera, while others became institutes of epidemiology, microbiology, and hygiene. The production of bacterial preparations was concentrated in the first type of institute while the second type was charged primarily with antiepidemic activities. The production activity of the latter was restricted to two or three preparations (antimeasles serum, antirabies vaccine, and smallpox vaccine or antituberculosis vaccine). In 1954, the institutes of vaccines and sera were included in the activity of the network of antiepidemic institutions in the capacity of organizational and methodological centers. Thus, bacterial preparations are at present partly produced by institutes of vaccines and sera and partly by the institutes of epidemiology, microbiology, and hygiene. The institutes of vaccines and sera produce 68.5% of all bacterial preparations, and 31.5% are produced by the institutes of epidemiology, microbiology, and hygiene and by sanitary-epidemiological stations. The sanitary-epidemiological stations produce antimeasles serum.

The range of preparations supplied by the institutes of vaccines and sera has expanded from year to year. In the 1930s the assortment of bacterial preparations that was supplied consisted of killed vaccines of intestinal diseases, smallpox vaccine, and several sera. By 1940 the assortment was complete with regard to the types of products and comprised vaccines, bacteriophages, anatoxins, sera, and diagnostic preparations. A particularly rapid increase in the number of bacterial preparations being released took place in the past 10 years. During this period, a number of the most important preparations were introduced into practical use. Some of these preparations are STI vaccine, encephalitis vaccine, brucellosis vaccine, tularemia vaccine, leptospirosis vaccine, influenza vaccine, cutaneous BCG [Bacillus Calmette-Guerin] vaccine, gammaglobulin, antiencephalitis serum, antiinfluenza serum, antibrucellosis serum, and a number of diagnostic preparations such as brucellin, tularin, etc. Vaccines against Q fever and measles and a number of other preparations have been developed on an experimental basis. As a result, the assortment of therapeutic and prophylactic preparations has increased to 50, while the assortment of diagnostic preparations exceeds 100. In accordance with the tasks with which the institutes are charged and which are aimed at the elimination of infectious diseases, the institutes constantly carry out scientific research on the perfection of available preparations and development of new preparations for bacteriological and serological diagnosis and for the prophylaxis and therapy of infectious diseases. However, the efficiency of the work of the institutes is limited to a considerable extent by the state of their technical equipment.

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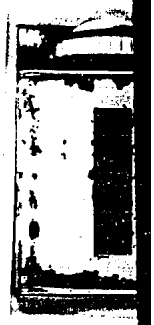

Until recently, laboratory methods rather than industrial methods were used in the production of bacterial preparations. In connection with the production of vaccines, culturing in small glass vessels was carried out, while in the production of sera, separation by mechanical means and release of the sera in the natural state were practiced. Almost all preparations were supplied in a liquid state, were therefore inconvenient for transportation, and had only a short useful life.

The use of complex technical equipment in the production of bacterial preparations was begun long ago. At present, glass vessels have been replaced by reactors in the production of vaccines and to some extent in the production of anatoxins. Serum production is now carried out with [large-scale] equipment for purification, concentration, and fractionation. Furthermore, the institutes have at their disposal drying equipment and refrigerator installations of varying capacity.

Introduction of technological production methods made it possible to improve the quality of some preparations, particularly to produce these preparations in the dry state, to expand the production program, and to achieve a reduction in costs. Introduction of technological methods has also contributed to the expansion and extension of scientific research and led to the development of new bacterial preparations, particularly virological preparations, in the production of which the availability of equipment for carrying out processes at low temperatures is of decisive importance.

However, there are serious obstacles to supplying large-scale equipment to institutes which produce bacterial preparations. First, industry cannot undertake the production of special equipment of this type because it cannot be mass-produced. As a result, the institutes themselves must often construct relatively complicated equipment at their own workshops or assemble it from parts supplied by industrial plants. It is obvious that this equipment cannot be perfect. Also, the institutes have only a few highly qualified technologists with adequate training, because such technologists are not provided for in the personnel setup of the institutes and are not being trained at any technical educational institutions.

Finally, modern technical equipment requires additional space, which as a rule is not available at the institutes because the institutes are located in the original buildings assigned to them at the time of their founding.

The effectiveness of the preparations supplied by the institutes therefore does not satisfy the requirements of public health work. It is necessary to effect without delay a radical improvement in the work of the institutes of vaccines and sera so that in the next few years they will assure to the country a sufficient supply of high-quality bacterial preparations.

In addition to technical equipment, there are other conditions on which the quality of bacterial preparations depends.

One of these conditions is the availability of appropriate bacterial cultures at the institutes. It is known that the state of the live bacterial cultures from which bacterial preparations are produced is of great importance for the quality of these preparations. Nevertheless, the situation with regard to live cultures is not satisfactory. The principal deficiency in the organization of work pertaining to the cultures is the absence of a single center engaged in the collection, recording, and identification of strains of bacteria, viruses, and protozoa. The local collections of cultures at the institutes, with few exceptions, are not equipped with vacuum apparatuses for lyophilic drying. Furthermore, not all of them have refrigerator installations. Thus, appropriate conditions for storage are not being provided. As a result, the cultures change, dissociate, and lose important properties. All this interferes with the scientific research work and the search for the most suitable strains, thus exerting an undesirable effect on the quality of the bacterial preparations produced by the institutes.

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One must therefore regard as urgent measured aiming at the improvement of the quality of bacterial preparation, the organization of a central collection of cultures, compilation of a special catalog of bacterial cultures available in the USSR and abroad, and development of standard sera. Th task of supplying the institutes with cultures has been assigned to the State Control Institute of Sera and Vaccines imeni Tarasevich. For this reason, it would be expedient to organize the permanent collection ("museum") of cultures at this institute.

The quality of the most important preparations supplied by the institutes and the ways of improving the preparations should also be discussed.

Among these preparations are therapeutic sera. At present, the institutes prepare at least 13 kinds of sera.

As a result of numerous investigations carried out at the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, Academy of Medical Sciences USSR, the method of enzymatic (proteolytic) purification and concentration ("diaferm") has been introduced in the production of antitoxic sera. Many-sided investigations carried out at the institute with the participation of biochemists and mechanical engineers have made it possible to construct special equipment which assures the mechanization of the most important production processes. As a result, the time needed for carrying out the over-all process has been shortened to 6-7 days from 45 days and the titers of the sera have been improved by a factor of 5-8. However, many problems which have a bearing on the improvement of the quality of the sera remain unsolved and require urgent study. Among these problems are the reduction of the percentage of wasted anti-toxin, improvement of titers, and an increase in the yields of sera obtained from producer animals.

One must also mention the attempts of the Moscow Institute of Vaccines and Sera imeni I. I. Mechnikov to purify the therapeutic equine sera by separating definite fractions of globulins. At present, gamma globulins have been obtained under experimental conditions from the antidiphtheria, antitetanus, antien-cephalitis, and antiplague sera. The institute should expedite the development of this highly effective type of preparation which can be used and stored con-veniently.

Particular attention should be paid to the problem of obtaining sera in the dry state. Using ordinary drying equipment, the Khar'kov Institute of Vaccines and Sera imeni I. I. Mechnikov has developed a method of obtaining anaerobic equine sera in the dry state. At the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, Academy of Medical Sciences USSR, special equipment is being developed for the drying of large volumes of sera. It is necessary to expedite this work so that it will be possible to pass from ex-perimental investigations to the production of large quantities of dried sera in the shortest possible time.

One must also mention another serum preparation, the antimeasles gamma globulin. This preparation, although it has been thoroughly introduced into practical use, is applied for the prophylaxis of measles but not for the pro-phylaxis of other infectious diseases (poliomyelitis, hepatitis, and dysentery) because it is produced in only limited quantities. The production of gamma globulin should be greatly expanded by using placental blood and also placenta, by applying more efficient equipment in its production, and by organizing its production at a number of additional institutes.

Among vaccine preparations, the vaccines against intestinal infections should be mentioned first. At present, the institutes supply both corpuscular and chemical typhoid-paratyphoid-dysentery vaccines. The method of culturing in depth [i.e., the method of submerged culture] has been firmly introduced into the technology of their production. However, the use of this method is not assured by the availability of sufficiently effective equipment provided with an automatic air supply, recording instruments, etc.

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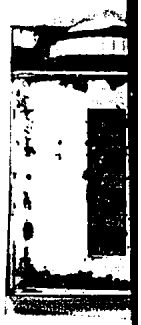

The production of vaccines effective against intestinal diseases depends on the solution of a number of special problems, among which are the selection of the most highly immunogenic strains, a type of treatment which has the least harmful effect on bacterial suspensions (replacement of formalin with Merthiolate), and development of methods for the standard laboratory testing of the quality of vaccine preparations. One must especially emphasize the necessity of the rapid introduction into production of a method of treatment with alcohol which has been developed by the Moscow Institute of Epidemiology, Microbiology, and Hygiene in connection with the production of therapeuty dysenteria vaccine.

In the production of corpuscular vaccines for the prophylaxis of intestinal infections, the institutes are faced with the following tasks: more concentrated work on strains, the replacement of formalin with a milder preservative, and further perfection of the equipment and technology applied in connection with culturing in depth.

The production of a chemical vaccine (the NIISI polyvaccine) has been completely developed by the Moscow Institute imeni I. I. Mechnikov. However, the quality of this preparation has been criticized for the low effectiveness of individual components and the high tendency of the vaccine to produce reactions. The institute must exert every effort to improve this preparation as soon as possible.

It is urgent that associated vaccines against infectious diseases be developed which will be effective after a minimum number of injections (one, or in an extreme case, two injections).

Bacteriophage, particularly dysentery bacteriophage, used to be important. During the past few years, however, this preparation has not been produced by the institutes of vaccines and serums because its quality did not satisfy the organs of public health. However, experimental data are now available which testify to the possibility of improving the bacteriophage by special selection and adaptation to definite strains. It is expedient, therefore, to summarize the results of the experimental investigations on the subject and settle the question of the possibility of producing highly effective bacteriophages against the causative factors of intestinal diseases and possibly against the causative factors of other infections (e.g., pyophages and wound [infection] phages).

In virus infections, particular attention has been paid by investigators during recent years to influenza, encephalitis, poliomyelitis, infectious hepatitis, hemmorhagic fever, etc. Numerous investigations have resulted in the development of a number of prophylactic preparations which have now been introduced into practical public health work. Among these are the live influenza vaccine, dry antiinfluenza serum, a vaccine against spring and autumn encephalitis, and a vaccine against acute encephalomyelitis and multiple sclerosis. However, all of these preparations are being produced in inadequate quantities as yet and require further improvement.

One of the old vaccines against virus infections, i.e., antirabies vaccine deserves particular attention. This vaccine is produced in large quantities not only by the institutes of vaccines and sera and the institutes of epidemiology, microbiology, and hygiene but also by sanitary-epidemiological stations.

This vaccine has one substantial drawback: its useful life is brief, so that planned supplying with this preparation is difficult. During the past 2-3 years, a number of institutes have successfully developed methods for the production of a dry antirabies vaccine. However, this preparation has not yet been introduced into production. This problem must be solved quickly.

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Live vaccines developed by Soviet scientists are used in the prophylaxis of particularly dangerous infections. It is necessary to develop the production of these vaccines at several institutes.

The problem of the quality of the anatoxins being supplied by the institutes of vaccines and sera must also be considered. Antiepidemic practice indicates that the diphtheria anatoxin is not sufficiently effective. Some investigators feel the reason for its inadequate effectiveness lies in shortcomings connected with the methods of inoculation, while others accuse the preparation. This imposes on the institutes a number of problems the solution of which would establish the reasons for the inadequate effectiveness of antidiphtheria inoculations and make possible the improvement of the quality of the diphtheria anatoxin. Work on these problems should comprise the selection of new strains, the development of optimal nutrient media, and the introduction of the use of purified and adsorbed preparations. Purified adsorbed preparations have been developed by the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, Academy of Medical Sciences USSR. Although they are supplied for use on a mass scale, they have not yet been applied extensively in practice.

Everything that has been said in regard to purified and adsorbed preparations applies to tetanus anatoxin, which should be supplied only in a purified and concentrated state.

It has been mentioned above that the institutes produce more than 100 kinds of diagnostic preparations. At some institutes both sera and diagnostic preparations are produced in the dry state. It is obvious that the quality of diagnostic preparations depends on the quality of the initial bacterial cultures. The unsatisfactory state of the permanent collections for the storage of cultures has been adequately described above. It is only necessary to add that the sera and diagnostic preparations must be supplied in complete assortments and that they should be accompanied by clear instructions as to their use.

In summary therefore, in the production of bacterial preparations, the following measures are essential as far as the future development of the institutes of vaccines and sera is concerned: First and most important is the reinforcement of the material and technological basis of the institutes. Second is the organization of an expedient use of technology; for this purpose special experimental and technical laboratories must be organized at the institutes, and highly qualified specialists must be provided. Third is the creation of a central collection of live cultures and organization of the industrial production of nutrient media and special laboratory glassware.

In an evaluation of the activity of institutes which produce microbiological preparations, it can be concluded that the institutes have carried out extensive work on the development and introduction into practical use of new therapeutic and prophylactic preparations and also of new technical methods which have made it possible to improve the quality of these preparations and to increase their quantity considerably. There is every reason to believe that the institutes of vaccines and sera in their future work will supply the country with still more perfect preparations and in doing so will contribute to the rapid elimination of infectious diseases.

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