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THE MOST IMPORTANT TASKS OF USSR MEDICAL VIROLOGY

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Among scientific disciplines which deal with infectious diseases, a prominent place is occupied by medical virology. It is sufficient to recall that among the most common infectious diseases are such virus infections as influenza, measles, epidemic hepatitis, poliomyelitis, encephalitides, hemorrhagic fevers, papataci fever, chicken pox, epidemic hepatitis, choriomeningitis, etc.

During recent years the virological institutions which are active in our country have developed and become stronger. In addition to the Institute of Virology imeni E. I. Ivanovskiy, Academy of Medical Sciences USSR, and other virological laboratories located in Moscow, important research on virus infection is being conducted at Leningrad, Tashkent, Khar'kov, Kiev, Tomsk, Alma-Ata, Odessa, Molotov, Yerevan, and other cities of the Soviet Union. The organization of virological laboratories at some sanitary-epidemiological stations has been launched. As the scope of the investigations develops, practical measures for the control of virus infections, which are based on contemporary scientific data, are expanded. For that reason it is expedient to give a brief review of the most important tasks to be solved by general and special virology.

In the field of general virology, problems pertaining to the modifiability, morphology, and biochemistry of viruses and to the experimental chemotherapy of virus infections command particular attention.

The strict tissue parasitism (intracellular parasitism) of viruses, which distinguishes viruses from other microorganisms, requires special methods for the study of their modifiability. Investigations which have been carried out during recent years established that such biological characteristics as virulence, antigenic structure, and immunological properties are determined by the characteristics of the medium [or environment] in which the development of the viruses takes place.

The most stable property is the antigenic structure of the viruses, which, as a rule, was found unchanged after passage through the organism of different animals or cultivation of the viruses in cultures of animal tissues. This was clearly demonstrated in the examples of the viruses of influenza, tick encephalitis, epidemic parotitis, and vaccinia. The antigenic structure of even a relatively labile virus such as that of influenza, could be changed under laboratory conditions only by subjecting it to the action of specific immunity factors. The investigations in question make possible an understanding of such contradictory phenomena as the existence of viruses which function as causative factors of different diseases but nevertheless have a similar antigenic structure (e.g., the viruses of tick encephalitides and the viruses of the psittacosis-lymphogranuloma group), as well as the occurrence of several serological types among the causative factors of identical diseases (e.g., the viruses of influenza and poliomyelitis).

Results which differ from those outlined above were obtained in the investigation of the immunogenic characteristics of viruses. In the case of the influenza virus, these characteristics depend on the species of the animal or the nature of the isolated tissues used. For that reason, prolonged passages through mice, chicken embryos, or cultures of tissues derived from these animals [mice and chickens] bring about an attenuation of the immunogenic properties of the

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strain with respect to human beings. On the other hand, when the virus is passed through cultures of human tissues, its immunogenic properties are preserved.

Passages of the virus of tick encephalitis, Japanese encephalitis, or rabies do not bring about a loss of immunogenicity in human beings.

The pathogenic properties were found to be the least stable. These properties (i.e., virulence) could be weakened or strengthened by cultivating the viruses under different environmental conditions. Specifically, it was established that in the process of adaptation of a number of viruses to a definite species of animal the virulence increases with reference to the species in question and is modified with reference to human beings.

The regularities in the modification of viruses which have been indicated above deserve the closest attention and require further study because understanding of these regularities and an ability to control them are necessary prerequisites for the production of live vaccines. Practical application of the regularities involved has already proved successful in the search for live vaccines, particularly vaccines for the prophylaxis of influenza. There can be no doubt that further development of the investigations in question will form a basis for the production of live vaccines that are effective against a number of additional virus infections.

One must also concentrate on investigations dealing with the morphology and biochemistry of viruses. It must be admitted that research on the morphology of viruses is not being carried out to an adequate extent. Nevertheless, investigation of the morphology of viruses and of virus occlusions by means of electron microscopy and phase-contrast microscopy is of great importance both for the clarification of the nature of viruses and the diagnosis of virus diseases.

The contemporary biochemistry of viruses develops along two principal lines. Chemical methods are used in order to investigate the nature of the causative factors as such. Parallel to this the biochemical processes which take place during the reaction of viruses with sensitive tissues of the macroorganism are being investigated.

The first line of research is not being pursued to an adequate extent in our laboratories. Expansion of this type of work depends on the availability of the necessary equipment and requires that serious attention be paid to this type of research.

Groups of biochemists and virologists who are active under the direction of V. L. Ryzhkov and V. I. Tovarnitskiy are engaged in work of the second type. Among investigations carried out by these groups of investigators one may mention research on the mechanism of the reaction of the influenza virus with erythrocytes and with the structural elements of the cytoplasm, as well as the role of the so-called inhibitors. In this work the significance of the functional group of proteins, of the salt content of the medium, of the temperature, and of other factors was demonstrated. Using the results of the work in question, simple and promising methods for the preparation of agents used in laboratory diagnosis have been developed.

Of great interest are the investigations of biochemical processes taking place during the propagation of pathogenic and nonpathogenic strains of the influenza virus. It was established that the pathogenesis of experimental influenza does not depend so much upon the propagation of the virus as on disturbances of various types of metabolism (carbohydrate, phosphorus, and protein metabolism) brought about by the pathogenic strains and interference

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of these strains with enzymatic functions pertaining to internal organs. The energetic aspects of the propagation of viruses and their disturbances during the process of infection are also being subjected to investigation. This line of biochemical research touches closely upon the pathophysiological investigations that deal with pathogenesis and immunity in virus diseases being carried out in the laboratory of A. D. Ado. In this laboratory the action of viruses as specific irritants of the nervous system is being investigated.

The study of biochemical processes which take place during the interaction of viruses with the tissues of the macroorganism is also important because it opens up possibilities of finding methods which make it possible to influence the process of infection by chemotherapeutic means.

One must emphasize that chemotherapeutic investigations are being carried out in the USSR on an entirely inadequate scale. Considerable expansion of work in this field is necessary. The work in question must include the synthesis of new therapeutic agents and the search for antibiotics which counteract virus infections.

We do not consider it possible to delve into general problems of pathogenesis and immunity in virus infections, assuming that these problems should not be detached from the development of a more general problem, namely that of pathogenesis and immunity in infectious diseases considered on the basis of I. P. Pavlov's physiological teaching. At the same time, in working on the latter problem, one must not forget that the phenomena of pathogenesis and immunity in virus diseases are so diverse that it is practically impossible to draw on the basis of the study of individual diseases general conclusions which are valid for all virus infections. Work on the systematic classification of viruses is one of the problems of general virology. The publication of work by V. L. Ryzhkov, Sh. D. Moshkovskiy, and V. M. Zhdanov on this subject, in combination with the discussion on this problem which has developed at the Moscow Society of Microbiologists, Epidemiologists, and Infectionists, as well as on the pages of the periodical Mikrobiologiya, will undoubtedly contribute to the development of a unified USSR systematization and nomenclature of viruses.

The most important task which confronts Soviet virology is the practical solution of the problem of influenza. The intensive scientific work which has been carried out on this subject during recent years at the Institute of Virology, the Institute of Experimental Medicine, and the Moscow Institute imeni Mechnikov has culminated in the development, testing, and introduction into practical use of live anti-influenza vaccines. Immunization with these vaccines has become one of the principal methods for the prophylaxis of influenza. An appropriate place in the system of measures for the control of influenza must be occupied by the anti-influenza serum developed by A. A. Smorodintsev at the Institute of Experimental Medicine and the Institute of Virology. The investigations which have been carried out hitherto do not, of course, exhaust the possibilities for the specific prophylaxis of influenza. Further work on the perfection of available vaccines and sera and of the methods of their application is required.

One of the aspects of the problem of influenza which remains unsolved is that pertaining to the diagnosis of the disease and above all, an early and rapid differential diagnosis of it. As far as methods of early diagnosis of influenza are concerned, particular attention should be paid to the reaction of hemagglutination for the detection of the influenza antigen in washings from the nasopharynx. Although this reaction was proposed for practical use without adequate methodological preparation, it should not

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have been forgotten after the extensive but unsuccessful use which had been made of it. There are adequate reasons for the belief that this reaction may be considerably perfected, its sensitivity increased, and the nonspecific reactions accompanying it suppressed.

Less promising is the reaction of complement fixation, because any method of diagnosing influenza must be simple and suitable for application on a mass scale. Serological procedures which enable one to detect increases of the amount of specific antibodies in the blood remain the most reliable methods for the laboratory diagnosis of influenza. However, methods of this type are purely retrospective. Furthermore, in order to apply methods of this type one must dispose of assorted type antigens (diagnostica) which have been tested and approved. These antigens must include the principal variants of viruses, i.e., A. B. and A₁. One must further improve the clinical-laboratory methods for the diagnosis of influenza (i.e., rhinocytoscopy, testing of the blood) and check more thoroughly the microscopic methods of investigation (i.e., viroscopy, investigation of occlusions).

In view of the fact that the progressing modification of the antigenic structure of influenza viruses which participate in the epidemic process has been firmly established, observation of strains which circulate among the population acquires great significance. This observation must be carried out to include these strains in the composition of vaccines and diagnostic antigens. The investigations in question must be conducted in different areas of the country according to a unified plan devised by the Institute of Virology. At the same time, one must carry out observation on the indices of immunity among the population. There can be no doubt that the investigations mentioned above, when combined with epidemiological investigations, will clarify the genesis of influenza epidemics and thus enable us to set an epidemiological prognosis and take prophylactic measures in good time.

The problem of acute catarrhs of the upper respiratory tract requires particular attention. In this field a number of problems have not yet been solved, although the connection of this group of diseases with weather factors and with chilling of the body is evident. This applies particularly to cold catarrhs which are not complicated by any other condition or complicated solely by an autogenous infection. Furthermore, it is now known that one often registers under the classification of acute catarrhs aggravations of chronic pathogenic conditions of the throat, pharynx, nose, and adjacent regions. Such aggravated conditions also depend primarily on chilling and colds. Among young children a considerable portion of contagious catarrhs of the respiratory tract has a staphylococcus etiology. According to statistical data which have been accumulated during a number of years, there are fluctuations of the indices of incidence of acute catarrhs among workers, depending on the branch of industry in which these workers are active. This testifies to the fact that occupational conditions have an effect on the incidence of catarrhs. The facts that have been observed form a basis for subsequent work on the subject of acute catarrhs of the upper respiratory tract and make possible development of a system of therapeutic and prophylactic measures against this type of affliction.

The so-called atypical or interstitial pneumonias also belong to the group of virus diseases of the respiratory organs. It is clear that these diseases do not comprise an etiologically homogeneous group. Some of them have been found to be Q-fever infections, while others are due to infection with ornithosis. Solution of the problem of atypical pneumonias will be advanced by the practical possibilities of differentiating them by identifying etiologically distinct forms in the laboratory.

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In order to accomplish this one must develop within the shortest possible time, and introduce into practical use, diagnostic antigens for serological reactions and skin tests. The experimental investigation on epidemic parotitis which has been conducted at the laboratory directed by A. K. Shubladze made it possible to check from every standpoint the data obtained earlier by foreign investigators and to conduct work which sheds new light on many aspects of the clinical course and epidemiology of this disease. One must expand the investigations, which have already shown a promise of success, and subject the virus of parotitis to a more thorough study. On the other hand, the data which have already been accumulated must be applied practically. These data will aid in solving the various problems of diagnosis and prophylaxis.

Virologists should also concentrate on still another common infection, namely measles. Investigations carried out in the laboratories directed by P. G. Sergiyev and V. I. Ioffe established that it is possible to isolate the virus of measles and pass it through susceptible animals and chicken embryos. In Sergiyev's laboratory the characteristics of the virus and its modifiability have been thoroughly investigated. Work on the development of a live vaccine against measles has progressed in this laboratory to a considerable extent. Ioffe has carried out investigations on a minor scale on the use as a vaccine of a strain grown on chicken embryos. However, the extent of work being done on measles, and what is more important, the practical application of the results of research on measles which has been completed, are definitely inadequate. It is necessary to dispose of reliable methods for the cultivation of the virus in order to be able to solve more rapidly the basic problems involved in the development of an effective live vaccine and the mass production of this vaccine.

In solving these problems it is expedient to consider the experience accumulated in work on the development of anti-influenza vaccines. At the same time one should not underevaluate the difficulties that confront investigators who work on measles. These difficulties are connected with the characteristics of the measles virus. The virus of measles is strictly adapted to human beings and is not pathogenic to any experimental animals with the exception of simians.

The problem of epidemic hepatitis proved to be still more refractory. Notwithstanding the great interest in this problem, and the considerable number of investigations on the subject carried out both in the USSR and abroad, research on epidemic hepatitis has stopped because no reliable methods of cultivating the virus or laboratory models for its investigation exist.

Here we have an example of an investigation which has been delayed because no reliable methods are available, so that the problem in question can not be solved. The history of virology shows that it has not developed at a uniform rate and that the rate of its development varied depending on the discovery of new methods of investigation which facilitated the solution of scientific problems. It is well known that the study of infections for which susceptible experimental animals were found progressed most rapidly. The use of chicken embryos for the cultivation of viruses sharply advanced research on a number of virus infections. This opened up new possibilities as far as the production of the virus vaccines for prophylaxis is concerned. The extensive investigation to which the viruses of poliomyelitis and the Coxsackie virus were subjected became possible because the viruses could be passed through newly born mice and cotton rats.

Viruses for which no susceptible animals could be found, which cannot be cultivated on chicken embryos, or can be cultivated on this medium only with difficulty, and for which no indicative reactions aiding in detection have been found, remain least investigated. To these viruses belong the causative factors of epidemic hepatitis, of polyseasonal neuroinfections, and of chicken pox. The viruses of many skin diseases, i.e., pemphigus, psoriasis, herpetic dermatitis, etc., also apparently belong to this class. The viruses of human

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tumors definitely belong to it. A characteristic which these viruses have in common is their strict adaptation to human beings. One must assume that for the cultivation of these viruses, cultures of human tissues in vitro will serve as the most suitable medium. The advisability of applying this method has been demonstrated in the example of other causative factors of diseases which also affect human beings only, namely influenza and poliomyelitis. However, the main difficulty in this case will consist in finding a good indicator reaction which will make it possible to detect the virus in the culture. For the influenza virus, passage through chicken embryos serves as an indicator reaction of this type. The virus can be readily detected in the chicken embryos by the method of hemagglutination. The virus of poliomyelitis, when cultured in a fibroblast tissue culture in vitro, brings out distinct morphological changes of a degenerative character. Furthermore, the virus can be detected by passing it through susceptible animals. Such specific indicator reactions have not been found for the infections mentioned above. Every effort must be bent to find such reactions.

Important problems must also be solved by virologists in the field of viral neuroinfections. This refers particularly to poliomyelitis. Significant progress in the experimental investigation of the virus of poliomyelitis will make it possible to initiate research on methods for the laboratory diagnosis of this disease and to develop methods for its treatment and prophylaxis. Some of the epidemiological characteristics of poliomyelitis are determined by the wide occurrence of atypical and indistinct forms of this disease, as well as participation in the epidemic process of three serologically distinct types of the virus with different characteristics.

At present it is known that not only simians are susceptible to poliomyelitis but also some species of rodents. Newly born white mice are suitable experimental animals for work on this disease. Furthermore, data have been obtained on the successful isolation and propagation of the virus in vitro in tissue cultures by the method of rotating test tubes. Particular attention should be paid to the investigations on active immunization against poliomyelitis which are carried out under experimental conditions by subcutaneous or the oral administration of antigen.

The achievements of Soviet investigators in work on virus neuroinfections, particularly transmissible encephalitides, are widely known. However, it would be a mistake to assume that all problems in this field have been solved. Further investigations on the geographic distribution of natural reservoirs of spring-summer encephalitis and the parasitological and virological characteristics of these reservoirs are necessary. One must concentrate one's efforts on the investigation and perfection of the therapeutic and prophylactic methods which are already available and develop new methods for the control of encephalitides. Although the specific serum and vaccine for spring-summer encephalitis were first subjected to practical tests 10 years ago, no improvements have been made since then in the production of these preparations. The production of the serum can be improved by replacing the brain antigen (which is currently used and) which brings about the appearance in the blood of agents that have cytotoxic properties. Furthermore, the antibodies contained in the serum can be concentrated and purified further. It is necessary to achieve rapid progress in the practical application of new preparations for the prophylaxis of transmissible encephalitides by immunization [literally "vaccination"]. Among the advances in this field, one must first of all mention the egg vaccine proposed by A. K. Shubladze and O. G. Andzhaparidze. This vaccine has already been tested under epidemiological conditions and found satisfactory.

The advances made in the field of virology indicate the timeliness of applying on a practical scale a number of measures for the control of virus infections.

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One of the most important measures would be organization of the laboratory diagnosis of virus infections. As a result of scientific research carried out during recent years, a number of preparations for the diagnosis of virus infections has been developed and tested on a practical scale. These preparations include antigens for serological diagnosis and type-specific sera for the detection of the antigen by means of the hemagglutination reaction in the case of influenza, diagnostic preparations for serological tests in epidemic parotitis, and diagnostic preparations for the reaction of complement fixation in tick encephalitis, Japanese encephalitis, and choriomeningitis.

One might express the hope that the Institute of Virology imeni Ivanovskiy would develop the production and the release of these preparations for the use of sanitary-epidemiological stations. As the preparations are developed and released, considerable work will become necessary in training virologists to diagnose virus infections. This work can be successfully carried out by the institutes of vaccines and sera and the institutes of epidemiology, microbiology, and hygiene.

At the present time the industrial production of a number of vaccines and sera for the prophylaxis of virus infections has been developed. In addition to antismallpox vaccine, antirabies vaccine, and antimeasles serum, which have been supplied for many years, the production of gamma globulin, influenza vaccine, anti-influenza serum, vaccines and sera against encephalitis, and vaccines against papapataci fever, Omsk hemorrhagic fever, and multiple sclerosis have been developed. It is necessary to expand and improve the production of these preparations at the institutes of vaccines and sera to an extent which would result in a supply fully satisfying the needs of therapeutic-prophylactic institutions. The preparations in question should be made popular among medical workers. All this will make possible correct planning and organization of the specific prophylaxis and therapy of virus infections. The problems of the prophylaxis of virus infections is not solved by the application of immunizing agents alone, especially since vaccines have not been developed against a number of virus diseases. However, the scientific knowledge which has been accumulated makes possible improvements in the prophylaxis and control of many virus infections. For that reason medical workers must be informed of new results pertaining to the etiology, pathogenesis, immunity, clinical aspects, diagnosis, therapy, and prophylaxis of virus infections as soon as this knowledge becomes available and the information should be summarized in the form of instructions, published articles, booklets, monographs, and handbooks.

Expedient introduction into practical use of scientific achievements in the field of virology is the most important task of scientific research institutes. The efficient execution of this task will make possible important advances in the control of virus infections.

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